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

(1) *For eyewash products intended for use with an eyecup.* Rinse cup with clean water immediately before each use. Avoid contamination of rim and inside surfaces of cup. Fill cup half full and apply the cup to the affected eye, pressing tightly to prevent the escape of the liquid, and tilt the head backward. Open eyelids wide and rotate eyeball to ensure thorough bathing with the wash or lotion. Rinse cup with clean water after each use.

(2) *For eyewash products intended for use with a nozzle applicator.* Flush the affected eye as needed, controlling the rate of flow of solution by pressure on the bottle.

§ 349.79 Labeling of permitted combinations of active ingredients.

Statements of identity, indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable.

(a) *Statement of identity.* For a combination drug product that has an established name, the labeling of the product states the established name of the combination drug product, followed by the statement of identity for each ingredient in the combination, as established in the statement of identity sections of this part. For a combination drug product that does not have an established name, the labeling of the product states the statement of identity for each ingredient in the combination, as established in the statement of identity sections of this part.

(b) *Indications.* The labeling of the product states, under the heading ''Indications,'' the indication(s) for each ingredient in the combination, as established in the indications sections of this part.

(c) *Warnings.* The labeling of the product states, under the heading ''Warnings,'' the warning(s) for each ingredient in the combination, as established in the warnings sections of this part.

(d) *Directions.* The labeling of the product states, under the heading ''Directions,'' directions that conform to the directions established for each ingredient in the directions sections of this part. When the time intervals or age limitations for administration of the individual ingredients differ, the directions for the combination product may not exceed any maximum dosage limits established for the individual ingredients in the applicable OTC drug monograph.

§ 349.80 Professional labeling.

The labeling of any OTC ophthalmic demulcent drug product provided to health professionals (but not to the general public) may contain instructions for the use of these products in professional eye examinations (i.e. gonioscopy, electroretinography).

PART 352—SUNSCREEN DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Subpart B—Active Ingredients

Subpart C—Labeling

Subpart D—Testing Procedures

AUTHORITY: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

SOURCE: 64 FR 27687, May 21, 1999, unless otherwise noted.

EFFECTIVE DATE NOTE: At 64 FR 27687, May 21, 1999, part 352 was added, effective May 21,

2001. At 65 FR 36319, June 8, 2000, the effective date was delayed through Dec. 31, 2002.

Subpart A—General Provisions

§ 352.1 Scope.

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

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

§ 352.3 Definitions.

As used in this part:

(a) *Minimal erythema dose (MED).* The quantity of erythema-effective energy (expressed as Joules per square meter) required to produce the first perceptible, redness reaction with clearly defined borders.

(b) *Product category designation (PCD).* A labeling designation for sunscreen drug products to aid in selecting the type of product best suited to an individual's complexion (pigmentation) and desired response to ultraviolet (UV) radiation.

(1) *Minimal sun protection product.* A sunscreen product that provides a sun protection factor (SPF) value of 2 to under 12.

(2) *Moderate sun protection product.* A sunscreen product that provides an SPF value of 12 to under 30.

(3) *High sun protection product.* A sunscreen product that provides an SPF value of 30 or above.

(c) *Sunscreen active ingredient.* An active ingredient listed in § 352.10 that absorbs, reflects, or scatters radiation in the UV range at wavelengths from 290 to 400 nanometers.

(d) *Sun protection factor (SPF) value.* The UV energy required to produce an MED on protected skin divided by the UV energy required to produce an MED on unprotected skin, which may also be defined by the following ratio: SPF value = MED (protected skin (PS))/MED (unprotected skin (US)), where MED (PS) is the minimal erythema dose for protected skin after application of 2 milligrams per square centimeter of the final formulation of the sunscreen product, and MED (US) is the minimal erythema dose for unprotected skin, i.e., skin to which no sunscreen product has been applied. In effect, the SPF value is the reciprocal of the effective transmission of the product viewed as a UV radiation filter.

Subpart B—Active Ingredients

§ 352.10 Sunscreen active ingredients.

The active ingredient of the product consists of any of the following, within the concentration specified for each ingredient, and the finished product provides a minimum SPF value of not less than 2 as measured by the testing procedures established in subpart D of this part:

(a) Aminobenzoic acid (PABA) up to 15 percent.

(b) Avobenzone up to 3 percent.

(c) Cinoxate up to 3 percent.

(d) [Reserved].

(e) Dioxybenzone up to 3 percent.

(f) Homosalate up to 15 percent.

(g) [Reserved].

(h) Menthyl anthranilate up to 5 percent.

(i) Octocrylene up to 10 percent.

(j) Octyl methoxycinnamate up to 7.5 percent.

(k) Octyl salicylate up to 5 percent.

(l) Oxybenzone up to 6 percent.

(m) Padimate O up to 8 percent.

(n) Phenylbenzimidazole sulfonic acid up to 4 percent.

(o) Sulisobenzone up to 10 percent.

(p) Titanium dioxide up to 25 percent.

(q) Trolamine salicylate up to 12 percent.

(r) Zinc oxide up to 25 percent.

§ 352.20 Permitted combinations of active ingredients.

The SPF of any combination product is measured by the testing procedures established in subpart D of this part.

(a) *Combinations of sunscreen active ingredients.* (1) Two or more sunscreen active ingredients identified in § 352.10(a), (c), (e), (f), and (h) through (r) may be combined with each other in a single product when used in the concentrations established for each ingredient in § 352.10. The concentration of each active ingredient must be sufficient to contribute a minimum SPF of not less

than 2 to the finished product. The finished product must have a minimum SPF of not less than the number of sunscreen active ingredients used in the combination multiplied by 2.

(2) Two or more sunscreen active ingredients identified in § 352.10(b), (c), (e), (f), (i) through (l), (o), and (q) may be combined with each other in a single product when used in the concentrations established for each ingredient in § 352.10. The concentration of each active ingredient must be sufficient to contribute a minimum SPF of not less than 2 to the finished product. The finished product must have a minimum SPF of not less than the number of sunscreen active ingredients used in the combination multiplied by 2.

(b)–(c) [Reserved]

Subpart C—Labeling

§ 352.50 Principal display panel of all sunscreen drug products.

In addition to the statement of identity required in § 352.52, the following labeling statements shall be prominently placed on the principal display panel:

(a) *For products that do not satisfy the water resistant or very water resistant sunscreen product testing procedures in § 352.76.* (1) *For products with SPF values up to 30.* ''SPF (insert tested SPF value of the product up to 30).''

(2) *For products with SPF values over 30.* ''SPF 30'' (select one of the following: ''plus'' or ''+''). Any statement accompanying the marketed product that states a specific SPF value above 30 or similar language indicating a person can stay in the sun more than 30 times longer than without sunscreen will cause the product to be misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (the act).

(b) *For products that satisfy the water resistant sunscreen product testing procedures in § 352.76.* (1) (Select one of the following: ''Water,'' ''Water/Sweat,'' or ''Water/Perspiration'') ''Resistant.''

(2) ''SPF (insert SPF value of the product, as stated in paragraph (a)(1) or (a)(2) of this section, after it has been tested using the water resistant sunscreen product testing procedures in § 352.76).''

(c) *For products that satisfy the very water resistant sunscreen product testing procedures in § 352.76.* (1) ''Very'' (select one of the following: ''Water,'' ''Water/Sweat,'' or ''Water/Perspiration'') ''Resistant.''

(2) ''SPF (insert SPF value of the product, as stated in paragraph (a)(1) or (a)(2) of this section, after it has been tested using the very water resistant sunscreen product testing procedures in § 352.76).''

§ 352.52 Labeling of sunscreen 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 a ''sunscreen.''

(b) *Indications.* The labeling of the product states, under the heading ''Uses,'' all of the phrases listed in paragraph (b)(1) of this section that are applicable to the product and may contain any of the additional phrases listed in paragraph (b)(2) of this section, as appropriate. Other truthful and nonmisleading statements, describing only the uses that have 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 act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) *For products containing any ingredient in § 352.10.* (i) ''[bullet][1] helps prevent sunburn [bullet] higher SPF gives more sunburn protection''.

(ii) *For products that satisfy the water resistant testing procedures identified in § 352.76.* ''[bullet] retains SPF after 40 minutes of'' (select one or more of the following: ''activity in the water,'' ''sweating,'' or ''perspiring'').

(iii) *For products that satisfy the very water resistant testing procedures identified in § 352.76.* ''[bullet] retains SPF after 80 minutes of'' (select one or more of the following: ''activity in the water,'' ''sweating,'' or ''perspiring'').

[1] See § 201.66(b)(4) of this chapter.

(2) *Additional indications.* In addition to the indications provided in paragraph (b)(1) of this section, the following may be used for products containing any ingredient in § 352.10:

(i) *For products that provide an SPF of 2 to under 12.* Select one or both of the following: [''[bullet]'' (select one of the following: ''provides minimal,'' ''provides minimum,'' ''minimal,'' or ''minimum'') ''protection against'' (select one of the following: ''sunburn'' or ''sunburn and tanning'')], or ''[bullet] for skin that sunburns minimally''.

(ii) *For products that provide an SPF of 12 to under 30.* Select one or both of the following: [''[bullet]'' (select one of the following: ''provides moderate'' or ''moderate'') ''protection against'' (select one of the following: ''sunburn'' or ''sunburn and tanning'')], or ''[bullet] for skin that sunburns easily''.

(iii) *For products that provide an SPF of 30 or above.* Select one or both of the following: [''[bullet]'' (select one of the following: ''provides high'' or ''high'') ''protection against'' (select one of the following: ''sunburn'' or ''sunburn and tanning'')], or ''[bullet] for skin highly sensitive to sunburn''.

(c) *Warnings.* The labeling of the product contains the following warnings under the heading ''Warnings:''

(1) *For products containing any ingredient in § 352.10.* (i) ''When using this product [bullet] keep out of eyes. Rinse with water to remove.''–

(ii) ''Stop use and ask a doctor if [bullet] rash or irritation develops and lasts''.

(2) *For products containing any ingredient identified in § 352.10 marketed as a lipstick.* The external use only warning in § 201.66(c)(5)(i) of this chapter and the warning in paragraph (c)(1)(i) of this section are not required.

(d) *Directions.* The labeling of the product contains the following statements, as appropriate, under the heading ''Directions.'' More detailed directions applicable to a particular product formulation (e.g., cream, gel, lotion, oil, spray, etc.) may also be included.

(1) *For products containing any ingredient in § 352.10.* (i) ''[bullet] apply'' (select one or more of the following, as applicable: ''liberally,'' ''generously,'' ''smoothly,'' or ''evenly'') ''(insert appropriate time interval, if a waiting period is needed) before sun exposure and as needed''.

(ii) ''[bullet] children under 6 months of age: ask a doctor''.

(2) *In addition to the directions provided in § 352.52(d)(1), the following may be used for products containing any ingredient in § 352.10.* ''[bullet] reapply as needed or after towel drying, swimming, or'' (select one of the following: ''sweating'' or ''perspiring'').

(3) *If the additional directions provided in § 352.52(d)(2) are used, the phrase ''and as needed'' in § 352.52(d)(1) is not required.*

(4) *For products marketed as a lipstick.* The directions in paragraphs (d)(1) and (d)(2) of this section are not required.

(e) *Statement on product performance—*(1) *For products containing any ingredient identified in § 352.10, the following PCD labeling claims may be used under the heading ''Other information'' or anywhere outside of the ''Drug Facts'' box or enclosure.*

(i) *For products containing active ingredient(s) that provide an SPF value of 2 to under 12.* (Select one of the following: ''minimal'' or ''minimum'') ''sun protection product.''

(ii) *For products containing active ingredient(s) that provide an SPF value of 12 to under 30.* ''moderate sun protection product.''

(iii) *For products containing active ingredient(s) that provide an SPF value of 30 or above.* ''high sun protection product.''

(2) *For products containing any ingredient identified in § 352.10, the following labeling statement may be used under the heading ''Other information'' or anywhere outside of the ''Drug Facts'' box or enclosure.* ''Sun alert: Limiting sun exposure, wearing protective clothing, and using sunscreens may reduce the risks of skin aging, skin cancer, and other harmful effects of the sun.'' Any variation of this statement will cause the product to be misbranded under section 502 of the act.

(f) *Products labeled for use only on specific small areas of the face (e.g., lips, nose, ears, and/or around eyes) and that meet the criteria established in § 201.66(d)(10) of this chapter.* The title, headings, subheadings, and information described in § 201.66(c) of this chapter

shall be printed in accordance with the following specifications:

(1) The labeling shall meet the requirements of § 201.66(c) of this chapter except that the title, headings, and information described in § 201.66(c)(1), (c)(3), and (c)(7) may be omitted, and the headings, subheadings, and information described in § 201.66(c)(2), (c)(4), (c)(5), and (c)(6) may be presented as follows:–

(i) The active ingredients (§ 201.66(c)(2) of this chapter) shall be listed in alphabetical order.

(ii) The heading and the indication required by § 201.66(c)(4) may be limited to: ''Use [in bold type] helps prevent sunburn.''

(iii) The ''external use only'' warning in § 201.66(c)(5)(i) of this chapter may be omitted.

(iv) The subheadings in § 201.66(c)(5)(iii) through (c)(5)(vii) of this chapter may be omitted, provided the information after the heading ''Warnings'' states: ''Keep out of eyes.'' and ''Stop use if skin rash occurs.''

(v) The warning in § 201.66(c)(5)(x) of this chapter may be limited to the following: ''Keep out of reach of children.''

(vi) For a lipstick, the warnings ''Keep out of eyes'' in § 352.52(f)(1)(iv) and ''Keep out of reach of children'' in § 352.52(f)(1)(v) and the directions in § 352.52(d) may be omitted.

(2) The labeling shall be printed in accordance with the requirements of § 201.66(d) of this chapter except that any requirements related to § 201.66(c)(1), (c)(3), and (c)(7), and the horizontal barlines and hairlines described in § 201.66(d)(8), may be omitted.

§ 352.60 Labeling of permitted combinations of active ingredients.

Statements of identity, indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable.

(a) *Statement of identity.* For a combination drug product that has an established name, the labeling of the product states the established name of the combination drug product, followed by the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC drug monographs. For a combination drug product that does not have an established name, the labeling of the product states the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC drug monographs.

(b) *Indications.* The labeling of the product states, under the heading ''Uses,'' the indication(s) for each ingredient in the combination as established in the indications sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph. Other truthful and nonmisleading statements, describing only the indications for use that have been established in the applicable OTC drug monographs or listed in this paragraph (b), may also be used, as provided by § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) In addition, the labeling of the product may contain any of the ''other allowable statements'' that are identified in the applicable monographs.

(2) For permitted combinations containing a sunscreen and a skin protectant identified in § 352.20(b).

(c) *Warnings.* The labeling of the product states, under the heading ''Warnings,'' the warning(s) for each ingredient in the combination, as established in the warnings section of the applicable OTC drug monographs. For permitted combinations containing a sunscreen and a skin protectant identified in § 352.20(b).

(d) *Directions.* The labeling of the product states, under the heading ''Directions,'' directions that conform to the directions established for each ingredient in the directions sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph. When the time intervals or age limitations for administration of the

individual ingredients differ, the directions for the combination product may not contain any dosage that exceeds those established for any individual ingredient in the applicable OTC drug monograph(s), and may not provide for use by any age group lower than the highest minimum age limit established for any individual ingredient. For permitted combinations containing a sunscreen and a skin protectant identified in § 352.20(b).

Subpart D—Testing Procedures

§ 352.70 Standard sunscreen.

(a) *Laboratory validation.* A standard sunscreen shall be used concomitantly in the testing procedures for determining the SPF value of a sunscreen drug product to ensure the uniform evaluation of sunscreen drug products. The standard sunscreen shall be an 8-percent homosalate preparation with a mean SPF value of 4.47 (standard deviation = 1.279). In order for the SPF determination of a test product to be considered valid, the SPF of the standard sunscreen must fall within the standard deviation range of the expected SPF (i.e., 4.47 ± 1.279) and the 95-percent confidence interval for the mean SPF must contain the value 4.

(b) *Preparation of the standard homosalate sunscreen.* (1) The standard homosalate sunscreen is prepared from two different preparations (preparation A and preparation B) with the following compositions:

COMPOSITION OF PREPARATION A AND PREPARATION B OF THE STANDARD SUNSCREEN

Ingredients———	Percent by weight
Preparation A	
Lanolin	5.00
Homosalate	8.00
White petrolatum	2.50
Stearic acid	4.00
Propylparaben	0.05
Preparation B	
Methylparaben	0.10
Edetate disodium	0.05
Propylene glycol	5.00
Triethanolamine	1.00
Purified water U.S.P	74.30

(2) Preparation A and preparation B are heated separately to 77 to 82 °C, with constant stirring, until the contents of each part are solubilized. Add preparation A slowly to preparation B while stirring. Continue stirring until the emulsion formed is cooled to room temperature (15 to 30 °C). Add sufficient purified water to obtain 100 grams of standard sunscreen preparation.

(c) *Assay of the standard homosalate sunscreen.* Assay the standard homosalate sunscreen preparation by the following method to ensure proper concentration:

(1) *Preparation of the assay solvent.* The solvent consists of 1 percent glacial acetic acid (V/V) in denatured ethanol. The denatured ethanol should not contain a UV radiation absorbing denaturant.

(2) *Preparation of a 1-percent solution of the standard homosalate sunscreen preparation.* Accurately weigh 1 gram of the standard homosalate sunscreen preparation into a 100-milliliter volumetric flask. Add 50 milliliters of the assay solvent. Heat on a steam bath and mix well. Cool the solution to room temperature (15 to 30 °C). Then dilute the solution to volume with the assay solvent and mix well to make a 1-percent solution.

(3) *Preparation of the test solution (1:50 dilution of the 1-percent solution).* Filter a portion of the 1-percent solution through number 1 filter paper. Discard the first 10 to 15 milliliters of the filtrate. Collect the next 20 milliliters of the filtrate (second collection). Add 1 milliliter of the second collection of the filtrate to a 50-milliliter volumetric flask. Dilute this solution to volume with assay solvent and mix well. This is the test solution (1:50 dilution of the 1-percent solution).

(4) *Spectrophotometric determination.* The absorbance of the test solution is measured in a suitable double beam spectrophotometer with the assay solvent and reference beam at a wavelength near 306 nanometers.

(5) *Calculation of the concentration of homosalate.* The concentration of homosalate is determined by the following formula which takes into consideration the absorbance of the sample of the test solution, the dilution of the 1-percent solution (1:50), the weight of the sample of the standard homosalate sunscreen preparation (1 gram), and the standard absorbance

value (172) of homosalate as determined by averaging the absorbance of a large number of batches of raw homosalate:

Concentration of homosalate = absorbance x 50 x 100 x 172 = percent concentration by weight.

§ 352.71 Light source (solar simulator).

A solar simulator used for determining the SPF of a sunscreen drug product should be filtered so that it provides a continuous emission spectrum from 290 to 400 nanometers similar to sunlight at sea level from the sun at a zenith angle of 10° it has less than 1 percent of its total energy output contributed by nonsolar wavelengths shorter than 290 nanometers; and it has not more than 5 percent of its total energy output contributed by wavelengths longer than 400 nanometers. In addition, a solar simulator should have no significant time-related fluctuations in radiation emissions after an appropriate warmup time, and it should have good beam uniformity (within 10 percent) in the exposure plane. To ensure that the solar simulator delivers the appropriate spectrum of UV radiation, it must be measured periodically with an accurately-calibrated spectroradiometer system or equivalent instrument.

§ 352.72 General testing procedures.

(a) *Selection of test subjects (male and female).* (1) Only fair-skin subjects with skin types I, II, and III using the following guidelines shall be selected:

Selection of Fair-skin Subjects
Skin Type and Sunburn and Tanning History (Based on first 30 to 45 minutes sun exposure after a winter season of no sun exposure.)
I—Always burns easily; never tans (sensitive).
II—Always burns easily; tans minimally (sensitive).
III—Burns moderately; tans gradually (light brown) (normal).
IV—Burns minimally; always tans well (moderate brown) (normal).
V—Rarely burns; tans profusely (dark brown) (insensitive).
VI—Never burns; deeply pigmented (insensitive).

(2) A medical history shall be obtained from all subjects with emphasis on the effects of sunlight on their skin. Ascertain the general health of the individual, the individual's skin type (I, II, or III), whether the individual is taking medication (topical or systemic) that is known to produce abnormal sunlight responses, and whether the individual is subject to any abnormal responses to sunlight, such as a phototoxic or photoallergic response.

(b) *Test site inspection.* The physical examination shall determine the presence of sunburn, suntan, scars, active dermal lesions, and uneven skin tones on the areas of the back to be tested. The presence of nevi, blemishes, or moles will be acceptable if in the physician's judgment they will not interfere with the study results. Excess hair on the back is acceptable if the hair is clipped or shaved.

(c) *Informed consent.* Legally effective written informed consent must be obtained from all individuals.

(d) *Test site delineation*—(1) *Test site area.* A test site area serves as an area for determining the subject's MED after application of either the sunscreen standard or the test sunscreen product, or for determining the subject's MED when the skin is unprotected (control site). The area to be tested shall be the back between the beltline and the shoulder blade (scapulae) and lateral to the midline. Each test site area for applying a product or the standard sunscreen shall be a minimum of 50-square centimeters, e.g., 5 × 10 centimeters. The test site areas are outlined with ink. If the person is to be tested in an upright position, the lines shall be drawn on the skin with the subject upright. If the subject is to be tested while prone, the markings shall be made with the subject prone.

(2) *Test subsite area.* Each test site area shall be divided into at least three test subsite areas that are at least 1 square centimeter. Usually four or five subsites are employed. Each test subsite within a test site area is subjected to a specified dosage of UV radiation, in a series of UV radiation exposures, in which the test site area is exposed for the determination of the MED.

(e) *Application of test materials.* To ensure standardized reporting and to define a product's SPF value, the application of the product shall be expressed on a weight basis per unit area which establishes a standard film. Both the test sunscreen product and the standard sunscreen application shall be 2 milligrams per square centimeter. For oils and most lotions, the viscosity is such that the material can be applied with a volumetric syringe. For creams, heavy gels, and butters, the product shall be warmed slightly so that it can be applied volumetrically. On heating, care shall be taken not to alter the product's physical characteristics, especially separation of the formulations. Pastes and ointments shall be weighed, then applied by spreading on the test site area. A product shall be spread by using a finger cot. If two or more sunscreen drug products are being evaluated at the same time, the test products and the standard sunscreen, as specified in § 352.70, should be applied in a blinded, randomized manner. If only one sunscreen drug product is being tested, the testing subsites should be exposed to the varying doses of UV radiation in a randomized manner.

(f) *Waiting period.* Before exposing the test site areas after applying a product, a waiting period of at least 15 minutes is required.

(g) *Number of subjects.* A test panel shall consist of not more than 25 subjects with the number fixed in advance by the investigator. From this panel, at least 20 subjects must produce valid data for analysis.

(h) *Response criteria.* In order that the person who evaluates the MED responses does not know which sunscreen formulation was applied to which site or what doses of UV radiation were administered, he/she must not be the same person who applied the sunscreen drug product to the test site or administered the doses of UV radiation. After UV radiation exposure from the solar simulator is completed, all immediate responses shall be recorded. These include several types of typical responses such as the following: An immediate darkening or tanning, typically greyish or purplish in color, fading in 30 to 60 minutes, and attributed to photo-oxidation of existing melanin granules; immediate reddening, fading rapidly, and viewed as a normal response of capillaries and venules to heat, visible and infrared radiation; and an immediate generalized heat response, resembling prickly heat rash, fading in 30 to 60 minutes, and apparently caused by heat and moisture generally irritating to the skin's surface. After the immediate responses are noted, each subject shall shield the exposed area from further UV radiation for the remainder of the test day. The MED is determined 22 to 24 hours after exposure. The erythema responses of the test subject should be evaluated under the following conditions: The source of illumination should be either a tungsten light bulb or a warm white fluorescent light bulb that provides a level of illumination at the test site within the range of 450 to 550 lux, and the test subject should be in the same position used when the test site was irradiated. Testing depends upon determining the smallest dose of energy that produces redness reaching the borders of the exposure site at 22 to 24 hours postexposure for each series of exposures. To determine the MED, somewhat more intense erythemas must also be produced. The goal is to have some exposures that produce absolutely no effect, and of those exposures that produce an effect, the maximal exposure should be no more than twice the total energy of the minimal exposure.

(i) *Rejection of test data.* Test data shall be rejected if the exposure series fails to elicit an MED response on either the treated or unprotected skin sites, or if the responses on the treated sites are randomly absent (which indicates the product was not spread evenly), or if the subject was noncompliant (e.g., subject withdraws from the test due to illness or work conflicts, subject does not shield the exposed testing sites from further UV radiation until the MED is read, etc.).

§ 352.73 Determination of SPF value.

(a)(1) The following erythema action spectrum shall be used to calculate the erythema effective exposure of a solar simulator:

$V_i\ (\lambda) = 1.0\ (250 < \lambda < 298\ nm)$

V_i (λ) = $1.0^{0.094\ (298\ -\ \lambda)}$ (298 < λ < 328 nanometers)

V_i (λ) = $1.0^{0.015\ (139\ -\ \lambda)}$ (328 < λ < 400 nanometers)

(2) The data contained in this action spectrum are to be used as spectral weighting factors to calculate the erythema effective exposure of a solar simulator as follows:

$$E = \sum_{250}^{400} V_i(\lambda) * I(\lambda) * t_{exp}$$

where: E = Erythema Effective Exposure (dose: Joules per square meter)

V_i = Weighting Factor (Erythema Action Spectrum)

I = Spectral Irradiance (Watts per square meter per nanometer)

t_{exp} = exposure time (seconds)

(b) *Determination of MED of the unprotected skin.* A series of UV radiation exposures expressed as Joules per square meter (adjusted to the erythema action spectrum calculated according to § 352.73(a)) is administered to the subsite areas on each subject with an accurately calibrated solar simulator. A series of five exposures shall be administered to the untreated, unprotected skin to determine the subject's inherent MED. The doses selected shall be a geometric series represented by (1.25^n), wherein each exposure time interval is 25 percent greater than the previous time to maintain the same relative uncertainty (expressed as a constant percentage), independent of the subject's sensitivity to UV radiation, regardless of whether the subject has a high or low MED. Usually, the MED of a person's unprotected skin is determined the day prior to testing a product. This MED(US) shall be used in the determination of the series of UV radiation exposures to be administered to the protected site in subsequent testing. The MED(US) should be determined again on the same day as the standard and test sunscreens and this MED(US) should be used in calculating the SPF.

(c) *Determination of individual SPF values.* A series of UV radiation exposures expressed as Joules per square meter (adjusted to the erythema action spectrum calculated according to § 352.73(a)) is administered to the subsite areas on each subject with an accurately-calibrated solar simulator. A series of seven exposures shall be administered to the protected test sites to determine the MED of the protected skin (MED(PS)). The doses selected shall consist of a geometric series of five exposures, where the middle exposure is placed to yield the expected SPF plus two other exposures placed symmetrically around the middle exposure. The exact series of exposures to be given to the protected skin shall be determined by the previously established MED(US) and the expected SPF of the test sunscreen. For products with an expected SPF less than 8, the exposures shall be the MED(US) times 0.64X, 0.80X, 0.90X, 1.00X, 1.10X, 1.25X, and 1.56X, where X equals the expected

SPF of the test product. For products with an expected SPF between 8 and 15, the exposures shall be the MED(US) times 0.69X, 0.83X, 0.91X, 1.00X, 1.09X, 1.20X, and 1.44X, where X equals the expected SPF of the test product. For products with an expected SPF greater that 15, the exposures shall be the MED(US) times 0.76X, 0.87X, 0.93X, 1.00X, 1.07X, 1.15X, and 1.32X, where X equals the expected SPF of the test product. The MED is the quantity of erythema-effective energy required to produce the first perceptible, unambiguous redness reaction with clearly defined borders at 22 to 24 hours postexposure. The SPF value of the test sunscreen is then calculated from the dose of UV radiation required to produce the MED of the protected skin and from the dose of UV radiation required to produce the MED of the unprotected skin (control site) as follows:

SPF value = the ratio of erythema effective exposure (Joules per square meter) (MED(PS)) to the erythema effective exposure (Joules per square meter) (MED(US)).

(d) *Determination of the test product's SPF value and PCD.* Use data from at least 20 test subjects with n representing the number of subjects used. First, for each subject, compute the SPF value as stated in § 352.73(b) and (c). Second, compute the mean SPF value, $\bar{x}$, and the standard deviation, s, for these subjects. Third, obtain the upper 5-percent point from the t distribution table with n-1 degrees of freedom. Denote this value by t. Fourth, compute $ts/\sqrt{n}$. Denote this quantity by A (i.e., $A = ts/\sqrt{n}$). Fifth, calculate the SPF value to be used in labeling as follows: the label SPF equals the largest whole number less than $\bar{x} - A$. Sixth and last, the drug product is classified into a PCD as follows: if $30 + A < \bar{x}$, the PCD is High; if $12 + A < \bar{x} < 30 + A$, the PCD is Moderate; if $2 + A < \bar{x} < 12 + A$, the PCD is Minimal; if $\bar{x} < 2 + A$, the product shall not be labeled as a sunscreen drug product and shall not display an SPF value.

§ 352.76 Determination if a product is water resistant or very water resistant.

The general testing procedures in § 352.72 shall be used as part of the following tests, except where modified in this section. An indoor fresh water pool, whirlpool, and/or jacuzzi maintained at 23 to 32 °C shall be used in these testing procedures. Fresh water is clean drinking water that meets the standards in 40 CFR part 141. The pool and air temperature and the relative humidity shall be recorded.

(a) *Procedure for testing the water resistance of a sunscreen product.* For sunscreen products making the claim of ''water resistant,'' the label SPF shall be the label SPF value determined after 40 minutes of water immersion using the following procedure for the water resistance 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) 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

Subpart B—Active Ingredients

Subpart C—Labeling

Subpart D—Testing Procedures

AUTHORITY: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

SOURCE: 60 FR 52507, Oct. 6, 1995, unless otherwise noted.

Subpart A—General Provisions

§ 355.1 Scope.

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

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

§ 355.3 Definitions.

As used in this part:

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

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

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

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

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

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

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

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

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

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

(k) *Treatment rinse concentrated solution.* A fluoride treatment rinse in a