

§ 352.70

21 CFR Ch. I (4–1–11 Edition)

“Warnings,” the warning(s) for each ingredient in the combination, as established in the warnings section of the applicable OTC drug monographs, except that the warning for skin protectants in § 347.50(c)(3) of this chapter is not required for permitted combinations containing a sunscreen and a skin protectant identified in § 352.20(b). For products marketed as a lip protectant or lipstick, § 352.52(f)(1)(iii), (f)(1)(iv) (except “Keep out of eyes,” which may be omitted), and (f)(1)(vi) apply.

(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), the directions for sunscreens in § 352.52(d) should be used. For products marketed as a lip protectant or lipstick, § 352.52(d)(4) applies.

[64 FR 27687, May 21, 1999, as amended at 68 FR 33380, June 4, 2003]

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:

$$\text{Concentration of homosalate} = \frac{\text{absorbance} \times 50 \times 100 \times 172}{\text{concentration by weight}}$$

§ 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.

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§ 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:

$$V_i(\lambda) = 1.0 \quad (250 < \lambda < 298 \text{ nm})$$

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

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

(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:

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

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 (1.25ⁿ), 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 than 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

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355.70 Testing procedures for fluoride dentifrice drug products.

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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