the monograph SPF test is probably adequate for products with low SPF values, it is not adequate for testing high SPF products because differences in solar simulators can provide as much as a 200 percent variation in results depending on the formulation. The comment further argued that an impossibly high number of subjects would be required for the current SPF method to obtain a 95 percent confidence level and that the test exposes subjects to a potentially dangerous condition, sunburn.

According to the comment, the average MED for each skin type can be predicted from existing solar simulator calibration data. During the pass/fail test, each test subject is screened for skin type and then given a first day range of energy that does not exceed the expected MED. The comment proposed using a panel of five subjects. Using the MED information obtained on the first day, each subject is given four UV radiation exposures corresponding to the expected SPF value. Each subsite is then evaluated for erythema. If six or more of the 20 subsites show perceptible erythema, the product fails, as there would be less than a 95 percent probability the actual SPF value was higher than the expected SPF value. If less than six subsites show perceptible erythema, the product passes, as there would be greater than a 95 percent probability that the actual SPF value was more than the expected SPF value. The comment proposed the following:

TABLE 2.—PROBABILITY TABLE

No. of subjects	Maximum no. of failures	Probability
1 (n=4)	0	0.0625[1]
2 (n=8)	2	0.0352
3 (n=12)	3	0.0200
4 (n=16)	5	0.0383
5 (n=20)	5	0.0207

[1] n is not sufficient to make a 95 percent prediction

The comment further proposed that if all eight subsites of the first two subjects pass, then the product passes and the remaining three subjects would not be

evaluated. The probability of this happening would be 1/256 unless the product is over the expected SPF value.

FDA agrees that, currently, there may not be enough experience and test data for products with SPF values of 30 and over on which to determine the sample size needed to obtain an acceptable 95 percent confidence interval. As discussed in section III.L, comment 37 of this document, to account for increased variability in SPF values for sunscreens with SPF values over 30, FDA proposes to increase the sample size to at least 25 subjects. Therefore, the comment may be correct in arguing that large numbers of subjects may be required for testing products with high SPF values. FDA believes that the pass/fail test has merit and could provide a reasonable substitute for the current SPF method for products with expected SPF value of 30 or higher. However, before the method can be accepted, method validation data are required that demonstrate the method can be performed satisfactorily by multiple laboratories using the same sunscreen formulation(s). FDA invites such data.

If the pass/fail method is accepted, FDA may stipulate that the method be used only for products with SPF values of 30 and higher because of the large number of subjects that would be required for high SPF products under the current test method. A pass/fail method would require fewer test subjects. Low SPF products can be adequately tested under the current method without large numbers of subjects. In addition, FDA would likely require that all 20 subsites be evaluated even if the first 2 subjects pass. Further, using standard probability computer software, FDA calculates that the values for the maximum number of failures in table 2 of this document for subjects one

through five should be 0, 1, 2, 4, and 5, respectively, rather than the values provided by the comment.

FDA would also consider three modifications to the method described by the comment and invites comment. First, each subject may have test successes and failures due to multiple subsites on each subject. Statistically, these will not be independent observations, which is a condition needed for a binomial probability calculation. Therefore, FDA is considering that a test panel should consist of 20 to 25 subjects and that only one site be tested on each subject. A pass/fail determination would be made for each individual.

Second, as an alternate, a double sampling plan based on Taylor's *Guide to Acceptance Sampling* may replace the five-layered plan proposed by the comment (Ref. 64). With the double sampling plan, two subjects are tested simultaneously with up to a maximum of four subjects, each having four subsites tested. If no more than one of the first eight subsites has perceptible erythema, the product passes. If three to eight subsites have perceptible erythema, the product fails. If exactly two of the eight subsites have perceptible erythema, then the second group of two subjects is tested. If two to four subsites from four subjects have perceptible erythema, the product passes. Otherwise, the product fails. According to this scheme, if probability $p = 0.10$ that the product tested would produce any recognizable erythema, then the probability = 0.95 that the product will pass. If probability $p = 0.5$ that the product tested would produce any recognizable erythema, then the probability = 0.05 that the product will pass.

Third, an alternative to the probability calculation is a margin of error approach. With this method, a margin of error for the expected SPF value is defined before testing. The margin of error is used to determine the tolerability

interval around the expected SPF value. The 90 percent confidence interval for the product's test result (one result per subject) must fall within the tolerability interval to be labeled with that SPF value. For example, if a 10 percent margin of error is claimed for a product with an expected SPF value of 40, then the tolerability interval would be 40 ± 4, or 36 to 44. If the related 90 percent confidence interval is from 37 to 43, an SPF value of 40 is assigned to the product. If the related 90 percent confidence interval is from 35 to 45, an SPF value of 40 could not be assigned to the product and the product may be retested at an expected SPF of 30.

FDA invites discussion of these suggested modifications to the comment's pass/fail method for testing sunscreen drug products having an SPF value of 30 or higher.

(Comment 25) One comment described an in vitro method it developed for simultaneously predicting SPF and assessing photostability. The method utilizes a 150 watt xenon arc lamp to irradiate sunscreen applied at a level of 1 to 2 mg/cm^2 to a flat collagen membrane substrate placed in the opening of an integrating sphere attached to a spectroradiometer. The spectral irradiance of the source and the spectral irradiance of the substrate alone are measured from 290 to 400 nm, at 1 nm intervals. The spectral irradiance transmitted by the sunscreen/substrate combination is measured at 1 minute intervals until the total erythemal-effective dose transmitted by the sunscreen exceeds 1 MED, where 1 MED equals 0.02 erythema-effective Joules (J)/cm^2. Each 1 minute interval represents two to three MEDs. The time course of the sunscreen's SPF is then computed (Ref. 65). This information reveals the photostability of a sunscreen. If a sunscreen is photostable, it will not decompose when exposed to UV radiation, and the SPF will not change with

increasing UV exposure. If a sunscreen is not photostable, it will decompose when exposed to UV radiation, and the SPF will decrease with increasing UV exposure. Another comment asked FDA to consider replacing the human SPF test with equivalent in vitro technology and chemical engineering, but did not suggest a suitable method.

FDA does not agree that an in vitro method is adequate to replace the in vivo SPF test. In vitro tests are generally inadequate as the sole measure of SPF because substrates cannot mimic sweating, skin absorption, or certain interactions with skin that influence SPF. Some sunscreen ingredients do not behave similarly in vitro and in vivo. At this time, the comment's method has not been validated, and the chosen substrate has not been demonstrated to possess penetration characteristics and surface chemistry similar to human skin.

The described in vitro method does have potential utility for measuring photostability of a sunscreen product. Measuring the erythemal-effective dose transmitted through the sunscreen in vitro over time seems like a reasonable approach. However, portions of the method require further exploration. Items such as the cut-off to define photostability need further explanation and validation. It should also be pointed out that the current SPF test method does not directly measure photostability, but it accounts for photostability. More specifically, the SPF value is determined after a sunscreen is exposed to UV radiation, so the SPF represents UVB protection provided by whatever fraction of the sunscreen has not decomposed.

FDA agrees that in vitro tests are generally rapid and less expensive than in vivo tests and, for SPF measurements, would reduce exposure of human subjects to UV radiation. FDA is willing to consider alternate methods for SPF

testing if they are adequately supported with data and are shown to be equivalent to established in vivo methods by collaborative studies. If the methods are equivalent, then the same SPF values should be determined for each sunscreen tested according to the SPF method and the alternate method. The comments have not provided data from such studies. Therefore, FDA is not proposing to include the described in vitro method in the monograph at this time.

(Comment 26) Several comments urged FDA to revise § 352.72(h) and reinstate the requirement for determining MED at 16 to 24 hours after exposure, rather than 22 to 24 hours. The comments submitted data showing that, for an SPF 30 product and for the 8 percent homosalate standard, determining the MED at 16 or 24 hours does not result in any clinical or statistical difference in the SPF (Refs. 66 and 67). Comments argued that immediate pigmentation fades rapidly and does not interfere with MED readings. One comment further argued that the 16 to 24 hour time is universally accepted by the European Union, Australia, and Japan and FDA should adopt this time in the interest of international harmonization.

The Panel recommended that the MED be evaluated 16 to 24 hours after exposure (43 FR 38206 at 38262). FDA proposed a post exposure time of 22 to 24 hours based upon information provided by comments to the Panel's report that immediate pigmentation may persist with higher doses of UV radiation up to 24 hours or, in some cases, for 36 to 48 hours after prolonged exposure (58 FR 28194 at 28268 to 28269). Comments had indicated that immediate pigmentation might interfere with an investigator's perception of minimally perceptible erythema.

FDA agrees that these new data show no significant difference in MED readings at 16 and 24 hours. Thus, FDA is proposing to revise the MED determination time in §§ 352.72(h) and 352.73(c) (proposed §§ 352.70(c)(8) and 352.70(d)(3), respectively) from "22 to 24 hours" to "16 to 24 hours."

J. Comments on the Sunscreen Standard for SPF Testing Procedure

(Comment 27) Several comments suggested that standard controls with SPF values of 15 or higher be developed to test high SPF sunscreen products. One comment stated that such standards would improve test accuracy and provide a consistent and adequate benchmark for compliance. One comment mentioned use of a control SPF 15 formula routinely in SPF evaluation and considered it a more valuable control than the 8-percent homosalate SPF 4 standard. Another comment supplied "round-robin," collaborative SPF testing data from 7 laboratories on a total of 153 subjects with 2 potential SPF 15 sunscreen standard preparations, "Formulation A" on 147 subjects and "Formulation B" on 146 subjects (Refs. 13, 68, and 69). The comment concluded that differences between the two preparations were not significant (p=0.653) but "Formulation B" was preferred due to its less complex formula and slightly more consistent results. The comment added that the data showed that different laboratories can obtain valid, reproducible results when testing high SPF sunscreens. Another comment stated that it provided test results on 20 subjects using an SPF 25 product as the control (Ref. 70). Three comments suggested that the European Cosmetic, Toiletry, and Perfumery Association (COLIPA) "European low SPF Standard Code Number COL492/1 (formerly the DIN standard)" be included in the OTC sunscreen drug product monograph as a permissible standard sunscreen preparation, in addition to the 8-percent homosalate standard, and that either standard should be allowed in the SPF

testing procedures. The comments contended that this approach will serve to permit international marketing and eliminate duplicative testing. Another comment asked FDA to adopt the JCIA SPF 15 "P3" standard, but did not provide supporting data.

The comment concerning the SPF 25 control provided data from comparative tests on 20 subjects, using the 8-percent homosalate standard, an SPF 15 sunscreen drug product, and an SPF 25 sunscreen drug product (Ref. 70). FDA finds that this study is inadequate to support the comment's request because the study did not do the following:

- Include sufficient numbers of subjects,
- Address suitability of the standard across different laboratories, and
- Document some properties required in a sunscreen standard to test high SPF sunscreen products.

The following properties of a sunscreen standard were not addressed but need to be addressed:

- Low level of interlaboratory variation,
- Sensitivity to experimental error, and
- Ease of preparation with a reasonable degree of accuracy.

These data are also needed for the JCIA standard.

Although comments provided data on 20 subjects in each of 4 laboratories using the COLIPA COL492/1 standard, FDA is not proposing to include this standard as an alternate to the 8-percent homosalate standard because we do not believe that using the COL492/1 standard will make the monograph method comparable to the European method, as other differences exist between the two methods. For example, the monograph method requires 20 evaluable subjects, while the European method requires only 10 evaluable subjects.

Therefore, the COL492/1 standard is a valid standard under the European method but may not be a valid standard under the monograph method. Finally, FDA finds that the 8-percent homosalate standard is a suitable control for testing sunscreen drug products with SPF 15 or below (see section III.J, comment 28 of this document).

FDA agrees with the comment that the submitted collaborative data from seven laboratories support "Formulation B" as an appropriate SPF 15 sunscreen standard. The mean SPF for "Formulation B" was 16.3 in 146 subjects tested, with 1.7 percent standard error of the mean, and laboratory means ranging from SPF 15.6 to 18.5. Therefore, FDA is proposing to include the "Formulation B" SPF 15 standard in the FM to be used for sunscreen drug products with an SPF value over 15 (optional for SPF values of 2 to 15).

(Comment 28) One comment noted that there are two recognized standard control formulations:

1. An 8-percent homosalate preparation with an SPF value of 4 (§ 352.70(b) of the FM), and

2. Formulation B (padimate O/oxybenzone) with an SPF value of 15.

The comment stated that the function of the standard formulation is quality assurance for method control and not as a calibration standard to bracket specific SPF ranges. The comment claimed that the 8-percent homosalate SPF 4 standard is appropriate to test products at any SPF level and that the choice of whether to use the SPF 4 or SPF 15 control formulation should rest with the manufacturer. Several other comments agreed with this comment.

Another comment provided data using the 8-percent homosalate standard to test product formulations with estimated SPF values of 15, 30, and 45 on 20 subjects (Ref. 67). The comment concluded that the data showed testing

procedures in the FM can differentiate high SPF sunscreens using the homosalate SPF 4 standard. The comment requested that the homosalate SPF 4 standard be allowed to be used for products with an SPF value over or below 15.

FDA does not consider the data adequate to support the suggestion that the 8-percent homosalate standard currently used to evaluate sunscreen drug products with SPF values up to 15 is equally applicable to products with SPF values over 15 (Ref. 67). The study had the following deficiencies:

- Did not include sufficient numbers of subjects,
- Did not address suitability of the standard across different laboratories, and
- Did not document certain properties required in a sunscreen standard to test high SPF sunscreen products.

The following sunscreen standard properties were not addressed but need to be addressed:

- Low level of interlaboratory variation, and
- Sensitivity to experimental error.

FDA agrees that the two standards are method controls rather than calibration tools. As such, the standard used should approximate the expected SPF of the product being tested to better verify that all aspects of the testing method are performing properly at the expected SPF level.

Using the SPF 4 standard to measure SPF values over 15 is more likely to produce erroneous results than using a standard with an SPF of 15. In measuring SPF values over 15, much higher light energies (J/cm^2) are used in comparison to measuring SPF values below 15. Problems in the accurate quantitation of high light intensities may not be detected if the SPF 4 standard

is used for SPF values over 15. While the SPF 4 standard may give acceptable results for products with SPF values over 15 in some studies, the extrapolation of these results to approximately 4 to 13 fold higher light energies used to test products with SPF values over 15 may be erroneous in other studies. Better assurance of an accurate SPF value is obtained by using a standard that is closer in SPF value to the sunscreen product being tested.

The use of an SPF 15 standard would be reasonable to test products with SPF values below 15. SPF 15 is in the middle (geometrically) of the 4 to 50 range. The ratio of SPF 15 to SPF 4 is 3.75, and the ratio of SPF 50 to SPF 15 is 3.33. Thus, there would be equal coverage of all ranges. Therefore, FDA is proposing that Formulation B may be used to test sunscreen drug products with SPF 2 and over, and is required for testing sunscreen drug products with SPF over 15 (proposed § 352.70(a)(1)(ii)). The 8-percent homosalate standard may be used for testing sunscreen drug products with SPF of 2 to 15.

(Comment 29) Several comments suggested that a modern, HPLC method is superior to the older spectrophotometric assay in § 352.70(c) of the FM. One comment provided technical information about the HPLC method and stated that it is now commonly used by analytical laboratories to assay sunscreen formulations (Ref. 71). Although this HPLC assay method was used in the study of two SPF 15 sunscreen standard preparations (see section III.J, comment 27 of this document), one comment noted that there are limited data on this method with the SPF 15 control formulation because FDA has not yet published this formula as an accepted standard.

FDA agrees that an HPLC method is superior to the spectrophotometric method, which was originally published by FDA in 1978, in specificity and

precision. Validation data provided by the comment documented the following:

- Specificity,
- Accuracy,
- Limit of detection,
- Linearity,
- Precision, and
- Reproducibility of the method.

The validation data included chromatograms and demonstrated that the HPLC method is suitable for both the SPF 4 and SPF 15 standards. Further, FDA validated the method in its laboratories and concludes that the method is acceptable for quality control and regulatory purposes (Ref. 72). Finally, the spectrophotometric method has not been validated for the SPF 15 standard, and the HPLC method has been validated for both the SPF 4 and SPF 15 standards. Therefore, FDA is proposing to revise § 352.70 to replace the outdated spectrophotometric method with the HPLC method and to use the HPLC method to assay both the SPF 4 and SPF 15 standards.

(Comment 30) Two comments disagreed with the requirement in § 352.70(a) for concomitant use of a standard sunscreen for each SPF test. One comment suggested that a standard could be run twice yearly. Another comment suggested that data to evaluate proper laboratory test procedures could be obtained from panels of a standard run as part of "the ongoing laboratory operation." A third comment stated that a standard preparation should be run each time an SPF determination is made.

FDA discussed this issue in comment 78 of the TFM (58 FR 28194 at 28253 to 28254). FDA disagreed with one comment that the standard could be run

once or twice a year and reaffirmed the Panel's recommendation that concomitant testing is necessary in SPF determinations to ensure uniform evaluation of OTC sunscreen drug products and to serve as an internal indicator of experimental errors. The comments requesting a change did not provide any supporting data. In the absence of supporting data, FDA is not persuaded to change the concomitant use requirement in § 352.70(a).

(Comment 31) One comment suggested that there is a need for a specific source to maintain and supply sunscreen standards. The comment contended that a few testing laboratories are reporting differences in the tested SPF of the 8-percent homosalate standard preparation depending on whether the standard is prepared by the laboratory or purchased from one company that manufactured this standard. The comment stated that either the testing procedures or the standard itself have changed since the original formula was published (earlier standard SPF values were 3.7/3.8 to 4.2/4.3 with an average of 4.1, while current values are 4.3 to 4.9/5.0).

Data supporting the reliability and wide acceptance of the 8-percent homosalate standard preparation were previously discussed in the TFM (58 FR 28194 at 28250 through 28252). The comment did not provide any data to support its contention concerning discrepancies in the SPF of 8-percent homosalate standard preparations and FDA is not aware of any new data that support the need for a specific source to maintain and supply this standard. The standard is a control to validate the testing procedure, equipment, and facilities rather than a calibration tool for setting SPF values of sunscreen products. FDA considers the parameters established in § 352.70 of the FM adequate to assure a uniform standard and is not requiring that a specific source maintain and supply the sunscreen standard at this time.

K. Comments on Artificial Light Sources for SPF Testing Procedure

(Comment 32) Several comments suggested that FDA replace the specifications in § 352.71 that state "sun at a zenith angle of 10°" and "less than 1 percent of its total energy output contributed by nonsolar wavelengths shorter than 290 nm" with the COLIPA table of "percent erythemal contribution" as the spectral power distribution standard for the light source used in the SPF test procedures (Ref. 73). The comments suggested that the spectra of currently used solar simulators (especially around 290 nm and above 350 nm) could cause overestimation of SPF values for high SPF sunscreens. Because shorter wavelengths can make a very large contribution to erythema, the comments stated that small errors in the 290 nm region of solar simulator spectra could have considerable effects. The comments noted that spectral power deficiencies above 350 nm may give artificially high SPF values for sunscreen drug products that absorb poorly in the long wavelength UVA region.

The comments added that there is general agreement in the industry that § 352.71 should be revised to permit compliance with the COLIPA standard for solar simulators. The comments further recommended one modification to the COLIPA standard: The energy for wavelengths below 290 nm should be limited to "less than 0.1 percent" rather than "less than 1.0 percent," as stated in the COLIPA standard. The comments stated that a more restrictive specification of "0.01 percent," as mentioned by FDA (65 FR 36319 at 36321), would result more in testing the limits of the measurement spectroradiometer rather than the true output of the solar simulator. One comment that supported the COLIPA standard subsequently suggested that the spectral limits be further

narrowed to prevent excessive variability of SPF values for certain sunscreen products (Ref. 74).

One comment discussed the calculations to obtain the source spectral specification according to COLIPA (Ref. 73). In the COLIPA table, the source spectral specification is described in terms of cumulative erythemal effectiveness by successive wavebands. The erythemal effectiveness of each waveband is expressed as a percentage of the total erythemal effectiveness from 250 nm to 400 nm, or as the Percentage Relative Cumulative Erythemal Effectiveness (%RCEE). According to the COLIPA specifications and consistent with § 352.71, wavelengths below 290 nm should be excluded from any source by appropriate filters. Likewise, wavelengths above 400 nm should be limited as much as possible and are not included in the calculation of %RCEE. Because RCEE values are calculated as relative percentages, measuring the spectral irradiance in absolute energy units is not necessary. Relative units are sufficient. The spectral irradiance of the source is multiplied by the Commission International de L'Eclairage (CIE) (1998) standard skin erythemal action spectrum to obtain the erythemal effectiveness of the source. The spectral erythemal effectiveness values of the source spectrum are then integrated from 250 nm to the various successive reference wavelength values shown in the COLIPA table in order to produce the cumulative erythemal effectiveness for each spectral waveband, and the total erythemal effectiveness is calculated up to 400 nm. Finally, the %RCEE is calculated at the reference waveband as the percentage ratio of the cumulative erythemal effectiveness in each of these wavebands to the total integrated value from 250 nm to 400 nm.

Based on these calculations, the COLIPA table includes limits up to 400 nm. In contrast, when FDA requested comments on this issue, we included a modified COLIPA table that includes limits up to 350 nm (65 FR 36319 at 36321). However, the modified COLIPA table published by FDA was erroneous. FDA agrees with the comment (and COLIPA) that it is necessary to include all UV erythemal wavelengths (i.e., up to 400 nm) when standardizing solar simulator output. As argued by the comment, the erythemal contribution from long-wavelength UVA radiation (i.e., 350 nm to 400 nm) can become important when a high SPF product is tested. However, FDA believes that the limits for the 290 to 350 waveband should be changed from 93.5 to 99.0 percent to 93.5 to 98.5 percent. This modification will address some of the errors in SPF that are attributed to the lack of match between the solar simulator and actual solar spectra. FDA invites comments on these proposed changes.

FDA does not agree, at this time, with the comment's suggestion to further narrow the COLIPA standard to the spectral limits that it proposed. The comment based its suggestion on a theoretical argument and did not supply the complete emission spectra of the four solar simulators used in its two referenced studies. There may be significant differences in the 290 to 350 nm range in these studies that can account for the reported differences in SPF test results. Further, FDA has concerns about the ability of currently used solar simulators to meet the comment's suggested spectral standard and invites comments on the changes suggested by the comment.

FDA agrees with the comments that the COLIPA approach provides a more appropriate description for solar simulators. FDA's original proposal that solar simulators have a spectral power distribution "similar to sunlight at a zenith

angle of 10°" is nonquantitative and may not be practical, considering the types of solar simulators that are generally available. Accordingly, FDA is proposing to revise the first part of § 352.71 (proposed § 352.70(b)) as follows:

(b) *Light source (solar simulator)*—(1) *Emission spectrum.* 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 (nm) with * * * the following percentage of erythema-effective radiation in each specified range of wavelengths:

SOLAR SIMULATOR EMISSION SPECTRUM

Wavelength range (nm)	Percent erythemal contribution
< 290	< 0.1
290–310	46.0–67.0
290–320	80.0–91.0
290–330	86.5–95.0
290–340	90.5–97.0
290–350	93.5–98.5
290–400	93.5–100.0

(Comment 33) Several comments suggested the following revisions to the light source (solar simulator) requirements in § 352.71:

- Delete the "out of band" specification that not more than 5 percent of a solar simulator's total energy output can be contributed by wavelengths longer than 400 nm.
- In place of this 5 percent "out of band" limitation, allow a limit such as 1,250 to 1,500 watts/square meter (W/m^2) on the total solar simulator irradiance delivered to the skin for all wavelengths.

One comment provided data comparing solar simulators with and without a 50 percent neutral density filter to demonstrate that there is no measurable impact of heat load on the outcome of SPF testing (Ref. 13). The comment stated that thermal overload does not occur for COLIPA-compliant solar simulators operated at or below a total irradiance limit of 1,500 W/m^2. The comments added that the "out of band" specification is not possible with

existing solar simulators and new systems would need to be designed, tested, manufactured, and distributed to provide equipment capable of meeting this specification. The comments concluded that replacing the "out of band" specification with a limit would improve the testing of all products, including high SPF products.

FDA believes that it is important to limit total energy delivered to the skin during the SPF test so that skin temperature does not reach a point that may compromise dose reciprocity. FDA concurs with the comments and is proposing to replace the "out of band" specification in § 352.71 (proposed § 352.70(b)) with a limit of 1,500 W/m^2 on total solar simulator irradiance between 250 and 1,400 nm.

(Comment 34) Two comments recommended that FDA change the solar simulator specification in § 352.71 from "good beam uniformity (within 10 percent) in the exposure plane" to "the delivered dose to the UV exposure sites be within 10 percent of the prescribed dose with good beam uniformity" (without defining "good beam uniformity"). The comments contended that although "reasonable" or "good" beam uniformity is desirable, beam uniformity within 10 percent is virtually impossible to measure or achieve for the vast majority of solar simulators.

FDA agrees that "dose" accuracy is a critical variable and the delivered dose to the UV exposure sites should be within 10 percent of the prescribed dose. Because FDA considers quantification of "good beam uniformity" to be an important issue, it is keeping a specification for this parameter. However, FDA believes that a specification of 20 percent is more achievable than the proposed 10 percent. Beam uniformity can be measured with broadband UV detectors that have been modified to provide a small input aperture to the

detector. For example, for a single beam simulator with a subsite exposure area of approximately 1 cm^2, an appropriate input aperture would be 0.25 cm^2. Beam uniformity can then be checked by making a measurement in the center of each of the four quadrants of the exposure field. These readings should be within 20 percent of the peak reading. The same principle can be applied to larger exposure fields. Additionally, the average of these four readings should be within 10 percent of the prescribed dose for a given exposure site. In addition, FDA is proposing a requirement that places a quantifiable limit of 20 percent on time related fluctuations of the radiation emissions of the solar simulator.

Accordingly, FDA is proposing to revise portions of § 352.71 (proposed § 352.70(b)(2)) to read as follows:

(2) *Operation.* A solar simulator should have no significant time related fluctuations (within 20 percent) in radiation emissions after an appropriate warmup time and good beam uniformity (within 20 percent) in the exposure plane. The average delivered dose to the UV exposure site must be within 10 percent of the prescribed dose.

(Comment 35) Several comments recommended that the last sentence of § 352.71 be modified to include additional requirements for the periodic testing of solar simulators. The comments suggested that periodic measurements be made twice a year and that measurements be done after changes in the optical filtering components.

FDA agrees with the comments and is proposing to revise the last part of § 352.71 (proposed § 352.70(b)(3)) to read as follows:

(3) *Periodic measurement.* To ensure that the solar simulator delivers the appropriate spectrum of UV radiation, the emission spectrum of the solar simulator

must be measured every 6 months with an appropriate and accurately calibrated spectroradiometer system (results should be traceable to the National Institute for Standards and Technology). In addition, the solar simulator must be recalibrated if there is any change in the lamp bulb or the optical filtering components (i.e., filters, mirrors, lenses, collimating devices, or focusing devices). Daily solar simulator radiation intensity should be monitored with a broadband radiometric device that is sensitive primarily to UV radiation. The broadband radiometric device should be calibrated using side by side comparison with the spectroradiometer at the time of the semiannual spectroradiometric measurement of the solar simulator. If a lamp must be replaced due to failure or aging during a phototest, broadband device readings consistent with those obtained for the original calibrated lamp will suffice until measurements can be performed with the spectroradiometer at the earliest possible opportunity.

L. Comments on the Design/Analysis of SPF Testing Procedure

(Comment 36) Several comments contended that the series of seven exposure doses in § 352.73(c) should be modified to eliminate the two doses placed symmetrically around the middle exposure. One comment provided data comparing the seven-exposure series against the five-exposure series and concluded that the seven-exposure series did not increase the precision of the test (Ref. 66). Comments also argued that the seven-exposure series would require longer testing times, thus increasing exposure risk and discomfort to subjects, and that the five-exposure series is as accurate as the seven-exposure series even at high SPF values.

FDA discussed its rationale for seven versus five exposure doses in the TFM (58 FR 28194 at 28269 to 28272). FDA sought an exposure format that would provide better accuracy and precision to SPF measurements, particularly at higher SPF values. FDA reasoned that the seven-exposure series

in § 352.73(c), with two additional exposures symmetrically placed around the middle exposure of the geometric series, would increase precision and eliminate possible overestimation of the true SPF value of a product with a high SPF.

FDA has evaluated the data and other information submitted by the comments and agrees they demonstrate that the additional two exposure doses do not make the test more precise. Therefore, FDA is proposing to modify § 352.73(c) (proposed § 352.70(d)(3)) as follows:

* * * Administer a series of five UV radiation doses expressed as J/m^2-eff (adjusted to the erythema action spectrum calculated according to paragraph (d)(1) of this section) to the subsites within each test site on a subject using an accurately calibrated solar simulator. The five UV doses will be a geometric series as described in paragraph (d)(2) of this section, where the middle exposure represents the expected SPF. For products with an expected SPF less than 8, use exposures that are the product of the initial unprotected MED times 0.64X, 0.80X, 1.00X, 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, use exposures that are the initial unprotected MED times 0.69X, 0.83X, 1.00X, 1.20X, and 1.44X, where X equals the expected SPF of the test product. For products with an expected SPF greater that 15, use exposures that are the initial unprotected MED times 0.76X, 0.87X, 1.00X, 1.15X, and 1.32X, where X equals the expected SPF of the test product. * * *

(Comment 37) Several comments suggested changes to the number of subjects per test panel in § 352.72(g). One comment suggested deletion of the phrase "with the number fixed in advance by the investigator." The comment reasoned that if the first 20 subjects provided data that can be evaluated, risk to human subjects could be curtailed by not impaneling another 5 subjects. Other comments recommended using 10 to 20 subjects, arguing that the

criterion for accuracy should not be the number of subjects, but the relative deviation of individual SPF measurements. One comment used absorbance instead of the SPF value to calculate the number of subjects required for high SPF products and proposed a binomial test method to reduce the number of subjects (see section III.I, comment 24 of this document). Another comment stated that the 20 of 25 subject limitation may be an issue for products with high SPF values due to the high variability in the responses obtained and suggested that the number of subjects be increased when evaluating sunscreen products with high SPF values.

As discussed in section III.I, comment 24 of this document, the binomial test method deserves further investigation and may prove to be a reasonable approach as additional data and experience become available. In addition, based on the current SPF test method, FDA agrees with the comment recommending deletion of the requirement to fix the number of subjects per panel in advance. This requirement is unnecessary because the panel is limited to a range of 20 to 25 subjects (under current § 352.72(g)). Thus, if 20 subjects produce valid data in accordance with proposed § 352.70(c)(9), then it would be unnecessary to test additional subjects. In addition, some subjects may not produce valid data in accordance with proposed § 352.70(c)(9) (e.g., no erythema produced), requiring testing of additional subjects (not exceeding 25 subjects). FDA agrees that the number of subjects should be based on error about the mean SPF, but disagrees that the minimum number of subjects can be lowered to 10. As described later in this comment, FDA has reevaluated the proposed minimum number of subjects based on error about the mean SPF.

FDA agrees with one comment that more subjects are needed when testing products with high SPF values. FDA believes that a minimum sample size of

20 subjects is adequate for products with an expected SPF value of 30 or less. However, current data and experience with products having SPF values over 30 are not sufficient to determine an appropriate sample size. Therefore, to account for increased variability in SPF values for sunscreens with SPF values over 30, FDA proposes to increase the sample size to at least 25 subjects. FDA invites data demonstrating an appropriate panel size for sunscreens with SPF values over 30. At this time, FDA is proposing to revise § 352.72(g) (proposed § 352.70(c)(7)) as follows:

(7) *Number of subjects*—(i) *For products with an expected SPF value under 30.* A test panel shall consist of 20 to 25 subjects with at least 20 subjects who produce valid data for analysis. Data are valid unless rejected in accordance with paragraph (c)(9) of this section. If more than 5 subjects are rejected based on paragraph (c)(9) of this section, the panel is disqualified, and a new panel must be created.

(ii) *For products with an expected SPF of 30 or over.* A test panel shall consist of 25 to 30 subjects with at least 25 subjects who produce valid data for analysis. Data are valid unless rejected in accordance with paragraph (c)(9) of this section. If more than 5 subjects are rejected based on paragraph (c)(9) of this section, the panel is disqualified, and a new panel must be created.

In the 1978 advance notice of proposed rulemaking (ANPRM), the Panel recommended that studies enroll at least 20 subjects, adding that "the standard error shall not exceed ± 5 percent of the mean" (43 FR 38206 at 38261). Following publication of the ANPRM, FDA held a public meeting on January 26, 1988 (52 FR 33598 at 33600 to 33601). During that meeting, attendees argued the following four points related to the number of subjects:

1. Test panels should consist of at least 20 subjects.

2. The size of the test panel should be fixed in advance.

3. The limitation that the standard error should be less than ± 5 percent should not apply.

4. The testing procedures should make it clear that the addition of subjects to the test panel to achieve the desired minimum is acceptable under specific conditions (58 FR 28194 at 28267).

In the 1993 TFM, FDA based § 352.72(g) on these comments and the Panel's recommendation.

The calculations of the sample size and confidence interval in § 352.72(g) are based on the assumption that there is a normal distribution about the mean (i.e., a bell curve). Based on this assumption, the t-test is used for statistical analysis. Based on the t-test, FDA calculated that a panel of 20 subjects should result in an acceptable error about the mean. However, in some cases, a panel of 10 subjects would probably result in an error about the mean that is unacceptably large. There is inherently higher variability in testing and, consequently, larger error about the mean for products with high SPF values. Therefore, FDA believes a greater number of subjects is necessary when testing products with high SPF values. FDA believes a panel of 25 to 30 subjects should result in an acceptable error about the mean for products with high SPF values. FDA invites additional data demonstrating adequate numbers of subjects, especially for products with high SPF values.

(Comment 38) One comment stated that one factor affecting the SPF of a product is the erythemal threshold of the skin, or MED(US). The comment argued that SPF decreases with increasing erythemal threshold. The comment maintained that, because MED(US) varies only with skin type, the MED(US) of each subject in a test group should be within reasonably similar limits. The comment suggested that the MED(US) of each subject should be 50 to 150

percent of the median MED(US). The comment also suggested that subjects with an MED(US) that is twice the median should be excluded regardless of skin type.

FDA is not proposing the revisions suggested by the comment. FDA based § 352.73(b), which describes determination of an MED(US), on the Panel recommendation in the ANPRM. The procedure for determining MED(US) requires irradiation of subjects with a geometric series of UV doses. When developing this procedure, the Panel explained that the geometric series provides the same relative level of uncertainty independent of the subject's sensitivity to UV light (i.e., independent of skin type) (43 FR 38206 at 38266). Thus, the Panel disagreed that skin type affects MED(US). The comment did not provide any data or other information demonstrating that skin type, in fact, affects MED(US). FDA is not aware of any data demonstrating this phenomenon. FDA will revise the proposed test criteria if we receive data or information demonstrating that the criteria are not appropriate or other criteria are more suitable.

(Comment 39) Several comments urged FDA to reduce the minimum 1 cm^2 test subsite area in § 352.72(d)(2). One comment proposed the minimum test subsite area be decreased to 0.5 cm^2. Two comments suggested that the test subsite area be defined by minimum diameters of 0.8 cm (circular area of 0.5 cm^2) and 0.15 cm (circular area of 0.017 cm^2), respectively.

The comment supporting the 0.5 cm^2 test subsite area referenced a study published in 1987 (Ref. 75) that was mentioned in relation to artificial light sources in comment 86 of the TFM (58 FR 28258 to 28261). This study was designed to evaluate the FDA sequential technique of dosing using a single-port solar simulator (SPSS), a series sequential method using a multi-port

xenon arc solar simulator (MPSS), and the Deutsches Institut für Normung (DIN) simultaneous technique of dosing using an Osram Ultravitalux lamp. Five sunscreen formulations with SPF values from 4 to 15 were tested. The authors suggested that there was little systematic difference in estimates obtained using the SPSS and MPSS, but there was a large systematic deviation between the FDA and DIN methods. As this study was not designed specifically to compare irradiation areas, three different test subsite areas were used, and none was 0.5 cm^2. FDA cannot determine the suitability of a 0.5 cm^2 test subsite area compared to a 1 cm^2 test subsite area based on this study.

The comment advocating the 0.8 cm test subsite diameter argued that setting a lower area limit has the following four benefits:

- Does not preclude the use of larger irradiation areas,
- Will not affect the accuracy of resulting measurements,
- Permits lower wattage lamps as well as liquid light guides that have apertures of 0.8 cm diameter, and
- Provides more skin area for testing.

The comment provided statistical analysis of a study comparing multi-port and single-port solar simulators (Ref. 66). SPF 15 or SPF 4 products were tested along with the homosalate standard sunscreen. Two subsite areas were exposed to the multi-port solar simulator, and two were exposed to the single-port solar simulator. The comment concluded that similar SPF values are determined using the two types of solar simulators. However, the study report did not include details such as subject selection, product application, or specifications for the solar simulators. More importantly, the study report did not specify the size of each subsite. Thus, FDA cannot draw any conclusions regarding appropriate test subsite area from the submitted study.

The comment supporting the 0.15 cm test subsite diameter referenced two studies (Ref. 76). Significant discrepancies in the information submitted for the first study prevented evaluation of this study. The comment did not submit full details of the second study. Therefore, FDA could not reach any conclusions from the submitted studies.

FDA agrees, in principle, with the advantages of a smaller test subsite area. The Panel stated that, depending on instrumental design, irradiation test subsite areas less than 1 cm^2 can be utilized and that test subsite diameters greater than 0.4 cm present no difficulty in determining skin erythema (43 FR 38206 at 38260). While FDA does not consider the information provided by the comments adequate to support the suggested test subsite areas, it recognizes that considerable advances have been made since the Panel met. However, FDA requires data demonstrating that the monograph test produces valid and reproducible results using a smaller test subsite area before amending the monograph test. FDA will consider a reduction in test subsite area if adequate supporting data are provided. The studies should do the following:

- Compare the smaller subsite area to 1 cm^2 on the same subjects,
- Utilize high SPF products as well as products with SPF values below 15, and
- Demonstrate comparable results among several laboratories.

(Comment 40) Several comments either agreed or disagreed with the blinding procedures for the application of test materials described in § 352.72(e). One comment stated that unblinded SPF testing is bad science, and that exposure sites within test areas should always be randomized no matter how many products are being tested. Another comment stated that the blinding procedure is an unnecessary complication and does not contribute

to the accuracy of the test. One comment agreed that, in order to approximate true blinding, the individual who grades erythemal responses should not be the same clinician who applied the test materials. Another comment contended that it is not reasonable to randomly irradiate test sites with varying doses of UV radiation. One comment recommended making the use of finger cots optional because some product vehicles are incompatible with finger cot material. Another comment suggested that the amount of product remaining on the finger cot is a source of variability in the SPF test and suggested that the extent of this variability be fully evaluated.

FDA agrees with the comments that favor blinding and randomization and is not proposing to remove the blinding and randomization requirements from § 352.72(e) (proposed § 352.70(c)(5)). According to § 352.72, blinding and randomization is required only when two or more sunscreen drug products are being evaluated at the same time. Because a test product is always tested in conjunction with the standard sunscreen, FDA proposes to delete the statement, "If only one sunscreen drug product is being tested, testing subsites should be exposed to varying doses of UV radiation in a randomized manner." Section 352.72(h) (proposed § 352.70(c)(8)) specifies that the person who evaluates the MED responses must not be the same person who applied the sunscreen or administered the dose of UV radiation. The comments that disagreed did not provide evidence demonstrating that these requirements are unnecessary.

With regard to the suggestion that the use of finger cots be made optional, the Panel's review of data found that numerous investigators have obtained more reproducible results by spreading a product using a finger cot than by spreading with a glass or plastic rod (43 FR 38206 at 38261). FDA agrees with

the comment that some formulations may be chemically incompatible with latex finger cots, but there are finger cots composed of other materials that should be compatible with these sunscreens. Therefore, to increase reproducibility in sunscreen application, FDA is proposing to revise the application requirement in § 352.72(e) (proposed § 352.70(c)(5)) to read as follows:

* * * Use a finger cot compatible with the sunscreen to spread the product as evenly as possible. Pretreat the finger cot by saturating with the sunscreen and then wiping off material before application. Pretreatment is meant to ensure that sunscreen is applied at the correct density of 2 mg/cm^2.

FDA urges manufacturers of sunscreen drug products to investigate the extent of variability in the SPF test that may be caused by various applicators.

(Comment 41) One comment addressed illumination at the test site in § 352.72(h) and recommended that a level of at least 1,000 lux be used. The comment contended that 450 to 550 lux is too low to provide adequate illumination for reading erythema.

As discussed in the TFM, the Panel recommended an incandescent or warm fluorescent illumination source but did not specify a required illumination level (58 FR 28194 at 28269). In the TFM, FDA agreed with the Panel about the illumination source. FDA also proposed that the illumination level be 450 to 550 lux. The comment did not provide any data to support its contention that 1,000 lux is the appropriate illumination level. Thus, FDA is not revising the lux range in § 352.72(h) (proposed § 352.70(c)(8)) at this time. FDA invites data and information on levels of illumination currently used to evaluate MED responses in SPF testing laboratories and will consider adequately supported alternatives.

(Comment 42) One comment stated that the third sentence in § 352.73(b) should be modified to read: "* * * wherein each exposure dose is 25 percent greater than the previous exposure dose to maintain the same relative uncertainty * * *." The comment explained that defining the exposure dose in terms of "time" is incorrect.

FDA discussed the Panel's definition of dose in terms of time intervals in comment 84 of the TFM (58 FR 28194 at 28256 to 28257). FDA stated that it is more accurate to express dose as the "erythema-effective exposure," in units that define the total amount of erythema-effective energy applied to the testing subsite (i.e., as J/m^2). FDA discussed replacing "exposure time interval" with "erythema-effective exposure (dose)," but inadvertently used "exposure time interval" instead of "dose" in § 352.73(b). FDA agrees that § 352.73(b) (proposed § 352.70(d)(2)) should be modified and is amending this section as the comment suggested.

(Comment 43) Several comments suggested an alternative statistical procedure for calculating product SPF values and PCD in current § 352.73(d). The comments argued that the procedure described in the FM would result in significant lowering of SPF values. The comments advocated clinical equivalency testing (i.e., using a lower one-sided 95 percent confidence interval or a one-sided t test, with a delta of 5 percent). The comments noted that an upper and lower bound equivalency procedure with a delta of 20 percent would be an appropriate procedure. The comments added that SPF is not a precise value, but rather a valid estimate of product performance. Another comment suggested using the mean of the results to find the actual number and then round-off (either up or down) to the nearest whole number.

FDA is not proposing to modify the calculation of product SPF values and PCD in § 352.73(d) (proposed § 352.70(d)(4)) at this time. The distinct advantage of the t-test is that it provides a simple computational procedure for a statistical test that makes inferences about the population. The SPF is determined to be the largest whole number that is excluded by a lower one-sided 95 percent confidence interval. Simply finding a mean value, as one comment suggested, is not adequate because such a value does not provide information about the validity of the test (e.g., standard deviation) that should be taken into consideration.

FDA's evaluation of the equivalency testing approach for calculating SPF values indicates the method is less stringent than the FM method. The proposed equivalency test is essentially testing the following hypothesis:

H_0: $\mu \leq 0.95L$ versus H_a: $\mu > 0.95L$

where: H_0 = null hypothesis

H_a = alternative hypothesis

μ = population mean

L = confidence limit

FDA acknowledges that the equivalency test may be a valid method for determining SPF. In many cases, the same SPF would be determined for a sunscreen using either the equivalency test or the FM method. However, in some cases, a higher SPF would be determined for a sunscreen using the equivalency test than would be determined using the FM method. By contrast, a higher SPF would never be determined for a sunscreen using the FM method than would be determined using the equivalency test. Thus, the FM method results in a more conservative SPF value than the equivalency test. FDA believes it is in the best interest of public health to label sunscreens with the

more conservative SPF value. If FDA adopted the equivalency test after over 30 years of using the FM method, consumers may, in some cases, overestimate the protection provided by a sunscreen based on a higher SPF number resulting from the equivalency test.

M. General Comments on UVA Testing Procedure

(Comment 44) Many comments discussed UVA radiation action spectra and skin damage (erythema, photocarcinogenesis, DNA damage, photosensitivity reactions, photoaging, mutagenicity, and immunosuppression). Some comments described various types of solar-induced skin damage and the wavelengths contributing to the specific biological events. Some comments stated that UVA II radiation (320 to 340 nm) is much more damaging than UVA I radiation (340 to 400 nm).

Other comments stated that there is presently no convincing evidence that the action spectra for damage from UV radiation have been clearly defined. One comment stated that until the separate dangers and risks of each portion of the UVB and UVA radiation action spectra are precisely and scientifically identified and quantified, FDA should consider the entire UVA radiation range as having significant biological risk. Another comment stated that protection against all UVA radiation wavelengths would seem to be both desirable and prudent considering the present state of our knowledge.

FDA agrees that the action spectra for various harmful effects on human skin from chronic UVA radiation have not been clearly defined and that it may be misleading to associate damage with any specific action spectrum based upon current knowledge. Information provided by comments suggests a relatively greater role for UVA radiation than UVB radiation in long-term sun damage even though there is little consensus about the amount of UVA

radiation protection required. Therefore, FDA is proposing UVA radiation test methods that assess protection throughout the UVA spectrum (see section III.N, comment 45 of this document).

N. Comments on UVA Testing Procedure Design and Testing Criteria

(Comment 45) FDA is proposing that both an in vitro and an in vivo test be conducted to determine UVA radiation protection. The proposed in vitro test is the ratio of long wavelength UVA absorbance (UVA I) to total UV absorbance (i.e., UVB + UVA). The proposed in vivo test is the PPD test, which is similar to the SPF test except the endpoint is pigment darkening rather than erythema. FDA is proposing that UVA labeling consist of a UVA rating reflecting both the in vitro and in vivo test results. The rating will be the lowest "high" protection, then the sunscreen would be labeled as providing "medium" UVA protection.

FDA is proposing these UVA testing requirements based on many comments submitted in response to the TFM that contained data and information on possible test methods (and combinations or modifications of these methods). The comments discussed the following in vivo and in vitro test procedures:

- IPD,
- PPD,
- PFA,
- Photosensitivity methods,
- UVA radiation protection percent,
- Diffey/Robson method and modifications of that method,
- Standards Association of Australia,
- Diffuse reflectance method,

- Skin[2] method, and
- Psoralen photoadduct method.

On May 12, 1994, FDA held a public meeting to discuss these UVA radiation testing procedures (Ref. 77).

One comment suggested using either or both PPD and erythema skin responses to measure the UVA radiation protection effectiveness of OTC sunscreen drug products. The comment maintained that these two test methods have the following similarities:

- Same UVA radiation source,
- Same dose range, and
- Similar post exposure time lags for observation.

The only difference is in the skin types used, thus giving a variable balance in PPD and erythema responses. The comment added that such a combination of methods has the following advantages:

- Reproducibility and stability,
- Relevance,
- Persistence of skin response through 1 to 24 hours,
- Independence of source flux and accuracy,
- Utilization for static as well as for water resistance photoprotective predictions, and
- Practicability, convenience, and safety.

Stating that there is currently no convincing evidence that the action spectrum for UVA radiation damage has been clearly defined, another comment suggested that protection from UV radiation be measured using two factors based on the degree of attenuation of UV radiation across the full spectrum. One factor, the SPF value, is erythemally weighted and gives an

indication of the power of protection provided by the product. The second factor should take into account the shape of the transmittance curve measured by either in vivo or in vitro means. The comment stated that it is potentially dangerous to associate skin damage with any single action spectrum (e.g., IPD, PPD, or PFA). The comment argued that all of these indicators are wavelength-specific and protection from specific wavelengths does not mean protection from damage. The comment added that if only the erythema action spectrum is used, it virtually ignores the effects of wavelengths over 320 nm. The comment contended that using an SPF value augmented by the shape of the transmission curve would give consumers the information necessary to make an effective and safe judgment about the protection provided by a sunscreen drug product. For example, the comment noted that a product with a high SPF and a uniform high level of attenuation across the spectrum (i.e., equal attenuation at all UVB and UVA wavelengths) will provide the most protection. The comment added that, at a later date, if sufficient evidence becomes available to describe a credible UVA radiation damage spectrum, this combined system could be used by convoluting the attenuation curve with the action spectrum curve.

One comment proposed a modification ("critical wavelength") of the Diffey/Robson test method (Refs. 78 and 79). The comment noted that, when people are outdoors, they are not exposed to only UVB or UVA radiation but are exposed to solar UV radiation, which always contains both. In addition, biological effects against which people may wish to be protected are caused by all wavelengths in the solar UV radiation spectrum. The comment contended that investigators should not be exposing subjects to sources of

radiation with spectra that have no practical application and using irrelevant biological effects as endpoints (e.g., IPD).

The comment proposed to assess the UVA radiation protection potential of an OTC sunscreen drug product by first spectrophotometrically determining the absorption spectrum of the product throughout the UV radiation range. Then, one calculates the wavelength value λ_c (the "critical wavelength"), where the area under the absorption spectrum from 290 nm to λ_c is 90 percent of the integral of the absorption spectrum from 290 to 400 nm, and uses a five-point scale to classify products as follows:

TABLE 3.—BROAD SPECTRUM RATING BASED ON CRITICAL WAVELENGTH

Critical Wavelength (nm)	Broad Spectrum Rating
$\lambda_c < 325$	0
$325 \leq \lambda_c < 335$	1
$335 \leq \lambda_c < 350$	2
$350 \leq \lambda_c < 370$	3
$370 < \lambda_c$	4

The comment concluded that this test method makes no underlying assumptions about the form of action spectra for either acute or chronic photobiological damage. Because the efficiency of UV radiation to induce a given photobiological endpoint tends to decrease with increasing wavelength, the method utilizes wavelength intervals for classifying the "broad spectrum" rating, which increases in an approximately logarithmic manner.

One comment submitted a protocol for the "critical wavelength" (CW) modification of the Diffey/Robson method for classifying the relative degree of UVA radiation protection of sunscreen drug products (Ref. 80). The comment addressed product photostability by pre-irradiation of the sunscreen product with a UV radiation dose corresponding to one-third the labeled SPF value. The comment reported recommendations based on the results of a round-robin evaluation of the proposed CW method involving six laboratories

using four test sunscreen formulations with various substrates. The comment concluded that the CW method is a convenient, reproducible in vitro method for measuring the uniformity of sunscreen absorbance spectra across the UV radiation spectrum to classify products into broad UVA radiation protection categories.

In response to the June 8, 2000, reopening of the administrative record for the rulemaking for OTC sunscreen drug products (65 FR 36319), FDA received additional comments on UVA radiation testing methods. While all comments supported some type of testing to differentiate the UVA radiation protection potential of sunscreen products, they disagreed about the use of in vivo versus in vitro testing methods.

Comments from a group of sunscreen product manufacturers contended that an in vivo test method, such as PPD or PFA, best describes the photoprotective characteristics of a sunscreen drug product. These comments stated that an in vivo method measures the actual effect of UVA radiation on the skin and estimates the expected product performance under actual use conditions.

One comment presented test data that suggested PPD and PFA values are comparable (Ref. 6). The comment stated that an advantage of the PFA method is that it allows inclusion of skin type I, whereas the PPD test is conducted on darker skin types (II and III). However, the comment added that the PPD test has been accepted since 1996 by the JCIA for the assessment of UVA radiation protection efficacy of sunscreen products.

One comment contended that the PPD test should be used for the following reasons:

- It requires a relatively low dose of UV radiation.

- The reaction is stabilized in 2 to 4 hours.
- The test subject is left with no mark of irradiation and receives little or no injury.
- The test can be conducted with high precision.

Another comment stated that PPD values demonstrate the same correlative benefits that exist for SPF values and, therefore, do not give false impressions of magnitude. Another comment stated that products with the same SPF can have different levels of UVA radiation protection. Thus, PFA or PPD is not redundant with the SPF value.

Comments from other sunscreen product manufacturers opposed an in vivo method to determine UVA radiation protection. One of these comments stated that in vivo tests expose human subjects to doses of UVA radiation with unknown human health consequences. The comment added that because exposure to UVA radiation alone is never encountered in nature, full spectrum light is most relevant for product evaluations. This comment contended that PFA values are redundant with SPF testing because of an overemphasis on short wavelength UVA radiation (UVA II), and PFA values give a false impression of the magnitude of absorption differences. For example, the comment stated that two products with PFA values of 5 and 10 may attenuate 80 and 90 percent of UVA radiation, respectively. Thus, the real difference is small. The comment further stated that the proposed in vivo methods modeled after the SPF test generate protection factors that are protocol dependent and of indeterminate clinical relevance, as none are surrogates for long term concerns like cancer and photoaging. Another comment added that the PPD and PFA tests do not adequately assess the breadth of UVA radiation

protection and that the biologic effects of full spectrum UV radiation differ from the effects of isolated wavelengths.

Several comments recommended using an in vitro method, and most considered the CW method as appropriate. One comment stated that CW allows for broad spectrum activity regardless of SPF so that, if consumers use a low SPF product, they will at least have the option of choosing one that provides a wide breadth of activity. Another comment stated that CW provides a simple, reproducible, and adaptable method that can account for sunscreen photostability and insure UVA radiation protection that is both commensurate with and independent from the SPF value. Another comment added that CW accounts for proportionality because, in order for a sunscreen to maintain a given CW, protection from both long and short UVA radiation wavelengths must increase as UVB radiation protection increases.

Several comments stated that the CW threshold should be 370 nm for a "broad spectrum" claim on a sunscreen. Other comments recommended a threshold of 360 nm. One comment stated that if FDA were to arbitrarily select a standard higher than 360 nm, it would cause a major reformulation effort within the industry, higher prices to consumers, and a shortage of "broad spectrum" products in the OTC marketplace. The comments did not provide data to support the use of a specific threshold number in relation to the prevention of specific photobiological effects.

Other comments opposed the CW method as not appropriate. One comment, which favored an in vivo method, stated that the CW method, based on an arbitrary, nonbiological criterion, fails to provide an accurate measure of the protection efficacy of a sunscreen product. This comment provided data to demonstrate that a significant failure of the CW method is its inherent

inability to differentiate UVA radiation protection levels of sunscreen products relative to biological endpoints (e.g., premature skin aging) (Ref. 23). A second comment agreed with this assertion, while a third comment expressed concern that CW measurements may be misleading because two products can have the same CW with very different UVA radiation absorbance curves and, thus, provide different protection for consumers.

Some comments stated that a combination of methods may be appropriate for assessing the complete UVA radiation protection potential of a sunscreen product. One comment suggested combining either the PPD or PFA method with an in vitro method for a meaningful and rigorous test of both the magnitude and breadth of the biological protection (i.e., the level of protection and the UVB and UVA wavelengths that are protected against) provided by a sunscreen product. Another comment stated that complete assessment of a sunscreen product's UVA radiation protection must include both of the following:

- An in vitro measurement of the absorbance above 360 nm (i.e., demonstrate adequate breadth of absorbance), and
- An in vivo measurement of the quantity of UV radiation protection (i.e., demonstrate adequate magnitude of absorbance).

Other comments stated that a combination of the in vivo SPF method and the in vitro CW method provide a complete description of a product's inherent photoprotective characteristics with the SPF value describing the amplitude of protection and CW providing a reliable measure of the product's spectral absorption capability.

One comment suggested a UVA/UVB radiation proportionality scheme. The comment referred to FDA's previous discussions about UVA/UVB

radiation proportionality (Refs. 11 and 81) and a recommendation from the AAD that "an increase in SPF of a sunscreen must be accompanied by a proportional increase in the UVA protection value" (Ref. 82). The comment added that the proportional contribution to sunburn from solar UVB and UVA radiation is 80 to 20 (4 to 1), respectively, and that this relationship gives the minimum UVA radiation attenuation needed to provide proportional UVA/UVB radiation protection for any SPF value. The comment concluded that a minimum UVA protection value of 2 should be required even at low SPF levels with proportionately higher UVA protection values for higher SPF values.

One comment suggested that the UVA protection value should be determined with an in vivo method while CW is appropriate to determine spectral broadness. Another comment stated that CW accounts for proportionality because both long and short UVA radiation protection must increase as UVB radiation protection increases in order for a sunscreen to maintain a given CW. Another comment provided data (Ref. 23) for two products with the same CW value but different SPF values and concluded that the product with the higher SPF value did not provide greater UVA protection. Other comments stated that there is no biological basis for establishing strict UVB/UVA radiation proportionality and that the establishment of this kind of ratio is arbitrary.

The AAD (Ref. 83) referenced an international consensus conference on UVA radiation protection of sunscreens and recommended the following:

1. Both an in vitro and an in vivo testing method must be used to measure UVA radiation protection.

2. CW is the preferred method of in vitro testing for a broad spectrum claim (with a threshold for this claim at 370 nm).

3. CW must be combined with an in vivo method such as either PPD or PFA.

4. There must be a minimum four-fold increase in PPD or PFA value in the presence of a sunscreen (relative to the absence of sunscreen).

In the **Federal Registers** of May 12, 1993 (58 FR 28194 at 28248 to 28250), September 16, 1996 (61 FR at 48645 at 48652), and October 22, 1998 (63 FR 56584 at 56587), FDA discussed photosensitivity and erythemal UVA radiation testing procedures for OTC sunscreen drug products. Criteria discussed for UVA radiation claims included the requirement for an absorption spectrum extending to 360 nm or above, plus the demonstration of meaningful UVA radiation protection via testing procedures. IPD/PPD, PFA, photosensitivity, and in vitro UVA radiation testing methodologies were also discussed at a public meeting on May 12, 1994 (Ref. 77).

The selection of an appropriate UVA radiation testing procedure for OTC sunscreen drug products has been difficult for a number of reasons. The scientific community does not agree on which testing procedure is most appropriate. For example, Cole discusses the virtues and shortcomings of a variety of in vivo and in vitro test methods (Ref. 84). In addition, each test procedure has its own distinct advantages and disadvantages, as discussed in the following paragraphs.

FDA believes the IPD test method provides an appropriate endpoint for determining UVA protection, because pigment darkening is caused primarily by UVA (and not UVB) radiation. This method is advantageous over other suggested test methods in that it uses low doses of radiation and, therefore, exposes subjects to less risk than other suggested test methods. On the other hand, the IPD response has not been shown to represent a direct or surrogate

endpoint for biological damage. The IPD response is also extremely difficult to read.

The PFA test method uses endpoints that reflect actual damage that can occur to normal skin as a result of UVA radiation exposure (i.e., erythema or tanning). The erythema action spectra may be similar to the action spectra of known chronic skin damage (e.g., solar elastosis) (Ref. 85). However, the PFA test method may not determine protection against skin melanoma or other skin damage thought to be caused by chronic exposure to UVA radiation (Refs. 29 and 86).

The CW method can assess how broadly a sunscreen can absorb across the UV radiation spectrum, but provides no information concerning product performance after interaction with human skin. While in vivo methods to assess UVA radiation protection may have possible sources of variability similar to the SPF test (e.g., test product application, differences in light sources, etc.), in vitro methods also possess possible sources of inherent variability (e.g., test product evaporation time, substrate orientation, instrumentation, use with color change sunscreen formulations, etc.).

In general, FDA would prefer the standard UVA radiation test method to have a clinically significant endpoint. After reviewing the data and information provided by the comments, FDA agrees that there is no convincing evidence that the action spectra for all possible types of UVA-induced damage have been clearly defined and that no one method is without disadvantages. At this time, FDA agrees with the recommendation provided by the AAD and other comments that an in vivo method is appropriate in combination with an in vitro testing method to assess the UVA radiation protection.

Because the action spectrum for UVA-induced skin damage is not clearly known, FDA considers it necessary to measure both the magnitude and breadth of UVA protection. The magnitude of UVA absorbance is a measure of how well a product absorbs UVA radiation. The magnitude of UVA absorbance is best measured by an in vivo method. An in vivo method measures a biological response on the skin (e.g., pigment darkening) and, therefore, correlates to actual use conditions. The breadth of the UVA absorbance is a measure of how broadly a product absorbs UVA radiation across the entire UVA radiation spectrum. Breadth can best be determined by appropriate in vitro test methods.

At this time, FDA believes a combination of existing in vivo and in vitro UVA radiation testing methods addresses the inadequacies of either method when used alone and provides a more complete UVA radiation attenuation profile for use in labeling OTC sunscreen drug products. Requiring the two test methods will ensure that both the magnitude and breadth of UVA protection is determined. As discussed later in this response, the proposed UVA labeling will reflect the results of both tests and, therefore, will reflect magnitude and breadth of UVA protection. FDA believes that the methods and labeling currently being proposed provide the best assurance for consumers to receive adequate protection across the entire UVA radiation spectrum.

FDA is proposing the PPD method as the in vivo part of the test to determine UVA radiation protection of a sunscreen drug product. This test assesses UVA radiation attenuation by measuring UVA radiation-induced tanning, a direct effect induced by UVA exposure. The PPD test is relatively easy to perform and relies on a stable, biological endpoint that can describe the magnitude of UVA radiation protection of sunscreen products. It is similar to the SPF determination as it is a ratio of a minimum pigmenting dose (MPD)

on unprotected skin to that on protected skin. The endpoint is the PPD response, which is the stable, lasting residual part of the immediate pigment darkening or blue gray pigment that develops immediately during exposure to UVA radiation and quickly fades at the end of exposure. It provides consumers with a means to specifically compare the amount of UVA radiation protection between products and select an appropriate sunscreen product. The PPD test has been shown to produce reliable, reproducible data and to distinguish between varying levels of UVA radiation attenuation (Refs. 87 and 88). It has been shown to detect protection provided by "broad spectrum" sunscreens against both short and long wavelength UVA radiation. The endpoint is a stable skin response that is linearly dependent on the amount of UVA radiation that enters the viable epidermis. FDA also agrees with one comment that a UVA protection value of 2 should define the lowest end of acceptable PPD test results relative to the consideration of acceptable UVA radiation claims (see proposed § 352.72(d)(3)). FDA considers it desirable to incorporate measurable UVA radiation protection at all SPF levels for products that claim to protect against both UVB and UVA radiation.

As one comment noted, the PPD test has been accepted and validated as the JCIA method since 1996 (Ref. 23) and is one of two in vivo methods suggested by the AAD (Ref. 83). Although data provided to FDA indicate that the PPD and PFA in vivo tests provide comparable results (Ref. 6), the PPD test provides the practical benefit of a shorter post exposure reading time. FDA agrees with the comments that PPD values are not redundant with SPF values as sunscreen drug products with the same SPF value can have very different levels of UVA radiation protection as measured by the PPD test. Accordingly, FDA is including the PPD method in proposed § 352.72 as part of the testing

to determine the UVA radiation protection potential of an OTC sunscreen drug product.

FDA agrees with the comments that suggested modifications to the PPD method (i.e., the JCIA standard). Therefore, FDA is proposing modifications to the PPD method. One group of sunscreen manufacturers suggested that the previously validated "high SPF" padimate O/oxybenzone standard sunscreen under consideration by FDA (see section III.J, comment 27 of this document) should also be used as the control formulation for in vivo UVA radiation testing (Ref. 6). Based upon data provided by the comment, FDA is proposing the referenced "high SPF" padimate O/oxybenzone standard sunscreen for use as the standard sunscreen in the in vivo UVA radiation test in proposed § 352.72. FDA invites comment on the suitability of this formulation as a UVA radiation test standard, on alternative standards, and on preparation/assay/ validation data for any suggested alternatives.

FDA also notes that the JCIA light source specification states that "UV rays shorter than 320 nm shall be excluded through the use of an appropriate filter." FDA considers it important to set an exact limit for this specification and is proposing that optical radiation from the light source between 250 and 320 nm be less than 0.1 percent of the optical radiation between 320 and 400 nm. Also, the observation of pigment darkening in the JCIA standard is at 2 to 4 hours post irradiation. FDA notes that it appears the pigment darkening is most stable about 3 hours or more after post irradiation (Ref. 89), and is thus proposing that this observation occur at 3 to 24 hours post irradiation. This time range provides increased flexibility in the test method without sacrificing accuracy.

As the current state of technology allows for an instrumental measurement/quantification of skin color via spectral reflectance, FDA also invites comments regarding colorimetry as a method of evaluating pigment darkening. By avoiding the subjectivity of detecting pigment change by the human eye, the reproducibility of the PPD method should increase. Colorimetry could likewise be used in SPF testing if submitted data demonstrated increased accuracy and reproducibility of colorimetry over visual inspection.

As the PPD method is similar, overall, to the SPF method, FDA is also proposing that the directions for the PPD method be similar to those for the SPF test for determining MPDs on unprotected skin, individual UVA protection factors, test product UVA protection factors, and PCDs. Further, as discussed in section III.L, comment 37 of this document regarding the SPF test, FDA is proposing that a PPD test panel consist of 20 subjects who produce valid data, similar to the panel size for sunscreens having SPF values less than 30.

FDA is concerned, however, that use of the PPD method alone could result in some products yielding high UVA radiation protection factors without having broad absorbance throughout the UVA radiation spectrum due to strong absorbance in the UVA II region. In other words, a sunscreen could absorb high levels of UVA II but very little UVA I and achieve a high UVA rating under the PPD method. Therefore, FDA is proposing that an in vitro method be used (to assess the breadth of absorbance across the UV radiation spectrum) in conjunction with the PPD method to more completely assess a product's UVA radiation protection.

FDA disagrees with the comments that the CW method should be used as the in vitro testing method and proposes using a modification of the Boots adaptation of the Diffey/Robson method (Ref. 90). Both the CW and the in vitro test proposed by FDA measure the absorbance of a sunscreen product using in vitro spectrophotometry. However, FDA's proposed method calculates the ratio of long wavelength UVA absorbance (UVA I) to total UV absorbance to provide a measure of the relative UVA I radiation protection provided by a sunscreen drug product. FDA believes that this test, in combination with the PPD method, provides a better assessment of overall UVA radiation protection.

The Boots adaptation of the Diffey/Robson test method assesses the absorbance of a sunscreen drug product over the UV radiation range from 290 to 400 nm by measuring the quantity of UV radiation transmitted through surgical tape (Transpore™ tape) before and after application of a sunscreen drug product. The test product (2 mg/cm^2) is applied to the textured surface of the Transpore™ tape. A xenon arc solar simulator is used as the UV radiation source. Transmitted UV energy is collected and measured at 5 nm intervals over the UVB and UVA radiation range, which provides a profile of UV radiation absorbance. Mathematical calculations are made separately of the areas under the UVB and UVA radiation parts of the curve. The ratio below the curve is determined as follows:

$$\frac{\text{UVA area under curve per unit wavelength}}{\text{UVB area under curve per unit wavelength}}$$

As the ratio increases, the degree of UVA radiation protection increases.

FDA is concerned that this method, as described in previous paragraphs, determines the ratio of the entire UVA to UVB radiation spectra. Therefore, a sunscreen drug product that absorbs strongly in the UVA II radiation area, but does not absorb strongly in the UVA I radiation area, might still have an adequate ratio of UVA to UVB radiation protection to fulfill the test requirements, but would not provide adequate protection in the UVA radiation region where absorbance is lacking. FDA believes that this deficiency can be corrected by revising the calculations to take into account the ratio of UVA I and/or UVA II individually to UV radiation. Some comments were concerned that UVA II radiation may be the portion of the UVA spectrum most represented in the PPD test. FDA agrees that the UVA II spectrum is well represented by the PPD test. Therefore, to provide for a more balanced method, FDA is proposing that the in vitro component of the monograph UVA radiation method only need provide a measure of the relative UVA I radiation absorbance.

FDA is proposing to measure UVA I radiation absorbance relative to UV radiation absorbance rather than relative to UVB radiation absorbance. If UVA I radiation protection is measured relative to UVB radiation, then the test does not account for UVA II radiation protection. FDA's proposed modification of the Boots adaptation of the Diffey/Robson method accounts for the entire UV radiation spectrum. Further, the ratio of UVA I radiation to UV radiation has a convenient finite range and allows for the use of defined values to categorize UVA radiation protection.

FDA is proposing a modified Boots adaptation of the Diffey/Robson method instead of the CW method. The CW determination only reveals the

shortest wavelength at which 90 percent of total UVB and UVA radiation is absorbed by a sunscreen. Thus, this method does not directly reveal the breadth of UV absorption, whereas the modified Boots adaptation of the Diffey/ Robson method does. This point is demonstrated by data submitted by one comment (Ref. 23). The comment submitted the UV absorption spectra of two sunscreens having nearly identical SPF and CW values. The absorption spectra demonstrate that two sunscreens with similar CWs can have significantly different UVA absorption spectra. The ratios of UVA I/UV radiation absorbance for these formulations were markedly different: 0.85 and 0.52. Thus, FDA believes that the ratio method generally allows for better discrimination of products with these types of absorbance spectra.

FDA is also concerned that the activity of the sunscreen ingredients in the product may be diminished by exposure to UV radiation, i.e., that the sunscreen ingredients in the product might not be photostable. Therefore, in order to account for changes in absorbance as a function of UV radiation exposure, FDA is proposing to revise the Boots modification of the Diffey/ Robson method by incorporating pre-irradiation dose (PID), which is defined as follows (see section III.O, comment 46 of this document):

PID (J/m^2-eff) = SPF * 1 MED * 2/3,

where 1 MED = 200 J/m^2-eff

FDA is also concerned about specifying the use of Transpore™ tape (used in the original Diffey/Robson method), an artificial substrate that mimics the surface topography of human stratum corneum. When sunscreen emulsions are applied to Transpore™ tape (Refs. 7 and 77), the emulsions may experience a micro environment that differs from human skin in several key aspects, including the following:

- Lack of electrolyte effect,
- Lack of moisturization/humectant plasticization of the substrate,
- Differences in pH and wetting effects, and
- Different degrees of sunscreen penetration and retention by the substrate.

The fourth aspect, different degrees of penetration and retention, is especially significant for oil soluble sunscreen ingredients. One comment suggested that either roughened quartz plates or a synthetic collagen should be used as the substrate, noting that COLIPA has used quartz plates for its in vitro studies and that quartz plates are reusable and inert. Diffey et al. have also used quartz plates as the substrate for the CW method (Ref. 91). Accordingly, at this time, FDA is proposing that roughened quartz plates be specified as the substrate in the in vitro portion of its UVA test method. FDA requests comment regarding the suitability and availability of quartz plates and other possible substrates.

FDA agrees with one comment that there is no biological basis for establishing a strict UVA to UVB ratio and that such a ratio would be arbitrary. FDA is proposing that data from the proposed in vitro and in vivo tests be integrated into a single labeled UVA rating. Similar to suggestions from some comments, FDA is proposing the categories of low, medium, high, and highest (corresponding to one, two, three, and four "stars," respectively). Based on test data submitted by one comment (Ref. 6), FDA is proposing that test results for each in vitro or in vivo test be categorized as follows:

TABLE 4.—UVA RATING CATEGORIES

Category	In vitro result	In vivo result
Low	0.2 to 0.39	2 to under 4
Medium	0.40 to 0.69	4 to under 8
High	0.70 to 0.95	8 to under 12
Highest	greater than 0.95	12 or more

FDA is aware of the difficulty for current sunscreen formulations to meet the "highest" category and believes that allowing such a category will foster additional research and development in this area.

FDA is proposing that the overall UVA radiation category for use in product labeling be the lowest category determined by the in vitro and in vivo test results. For example, if the test results for a sunscreen indicate an in vitro category of "low" and an in vivo category of "high" (or the reverse), then the overall UVA classification on the sunscreen product label would be "low" (i.e., the lower of the two categories). FDA believes that using the lower of the two categories takes into account the following situations:

- A product that has a high in vivo rating because of substantial UVA II absorbance, but a low in vitro rating because of poor UVA I absorbance, or
- A product that has a low in vivo rating because of poor UVA II absorbance, but a high in vitro rating because of substantial UVA I absorbance.

FDA is further proposing that each overall UVA radiation category correspond to and (on product labeling) be used with the following number of graphical representations in the form of solid "stars":

TABLE 5.—GRAPHICAL UVA RATING BASED ON CATEGORY

Combined Category Rating	Star Rating
Low	★☆☆☆
Medium	★★☆☆
High	★★★☆
Highest	★★★★

FDA invites comment on these proposed test methods/criteria and encourages the continued development of biologically meaningful test procedures.

O. Comments on the Photostability of Sunscreen Drug Products

(Comment 46) Various comments discussed the photostability of OTC sunscreen formulations and active ingredients. One comment stated that photostability is important because many sunscreen ingredient combinations with avobenzone are not believed to be photostable. This comment stressed that a sunscreen drug product should maintain most of its UVA and UVB radiation protection throughout the expected consumer time in the sun. Another comment stated that the integrity of a sunscreen drug product depends on its degree of photostability and that a photostable product should maintain its protection over a wide range of UV radiation spectra.

Some comments supported a standard method using pre-irradiation to account for photostability of sunscreen ingredients. One comment favoring the CW method for measuring UVA radiation protection submitted a formula to establish a pre-irradiation dose to assess photostability (Ref. 7). This comment stated that pre-irradiation provides a reasonable estimate of what a consumer might expect when using the product and stressed that the dose should be both full spectrum (290 to 400 nm) and sufficient to detect significant changes in CW as a function of UV radiation exposure. This comment considered its pre-irradiation dose of solar-simulated UV radiation to be equivalent to about 1 1/2 hours of noonday sun or 3 hours of sun exposure in the early morning or late afternoon. One comment noted that avobenzone-containing formulations can be photostabilized by the addition of suitable ingredients and supported a protocol developed by Sayre and Dowdy for measuring UVA radiation protection following a measured exposure of the test formulation to solar radiation (290 to 400 nm) (Ref. 92).

Another comment stressed the importance of a standard pre-irradiation dose and included data suggesting that a "UVB-only" sunscreen product formulation, at high pre-irradiation doses, could qualify for UVA "broad spectrum" labeling by the CW method (Ref. 23). This comment concluded that pre-irradiation does not always account for photostability and appears to be very formulation specific.

Another comment submitted an in vitro method for simultaneously predicting SPF and assessing photostability of sunscreen formulas (Ref. 65). The comment stated that pre-irradiation with measured UV radiation doses has permitted more accurate in vitro estimates of SPF.

FDA agrees that it is important to address the photostability for sunscreen drug product formulations. Unstable product formulations present the problem of degradation of product effectiveness during actual use. The assessment of overall protection provided by such formulations is difficult due to product effectiveness being heavily dependent on the UV radiation exposure dose. Sayre and Dowdy demonstrated, through a series of in vitro studies, how the UV radiation transmission of an avobenzone containing formula changes with UV radiation exposure and that most of the loss of protection occurred in the UVA radiation spectrum (Ref. 92).

FDA is proposing to address photostability by adding a pre-irradiation step to the in vitro test method for measuring UVA radiation protection (see section III.N, comment 45 of this document). As noted in the scientific literature, the choice of a pre irradiation dose is "somewhat arbitrary, yet critical to the outcome of the test" (Ref. 84). FDA received one comment with supporting data for a proposed pre-irradiation dose (Ref. 7). The comment suggested using a dose equivalent to the SPF times 2 J/cm^2 multiplied by a factor of 2/3. The

comment stated that 2 J/cm^2 from a xenon arc solar simulator with 1 millimeter (mm) WG-320 and 1 mm UG-5 filters was equivalent to one MED. Because all solar simulators used by the industry may not use this exact filter combination and the spectral transmittance of filters can vary from lot to lot, FDA is proposing to specify the pre-irradiation dose in terms of "erythemal effective dose." The erythemal effective dose of a solar simulator can by calculated as described in proposed § 352.70(d) by weighting the output spectrum of the solar simulator with the reference action spectrum for erythema as defined by CIE. A typical weighted value (J/m^2-eff) for an MED in a Skin Type II individual is 200 J/m^2-eff (Ref. 93). Thus, FDA is proposing to use the following formula to determine the required pre-irradiation dose:

PID (J/m^2-eff) = SPF * 1 MED * 2/3

where 1 MED = 200 J/m^2-eff

In considering the selection of the appropriate pre-irradiation dose of solar-simulated UV radiation, FDA agrees that the maximum pre-irradiation exposure would be a dose of UV radiation that equaled the SPF of the product times the MED. However, FDA believes that this calculated dose is probably greater than the dose that a sunscreen product would incur during typical consumer usage. Thus, the dose was reduced by a factor of one-third to represent a more reasonable exposure condition.

IV. FDA's Tentative Conclusions and Proposals

FDA tentatively concludes that the FM for OTC sunscreen drug products should be amended to include the combinations of avobenzone with ensulizole and avobenzone with zinc oxide when used in the concentrations established for each ingredient in § 352.10 (see section III.C, comment 7 of this document). However, before marketing may begin, the comment period for this proposal

must end and FDA must publish another **Federal Register** notice setting forth our determination concerning interim marketing before publication of the final rule for OTC sunscreen drug products. FDA followed this procedure previously for avobenzone as a single active ingredient and in combination with some GRASE active ingredients other than ensulizole or zinc oxide (62 FR 23350).

FDA considers the UVA-related labeling in this proposal to supersede the labeling proposed in the TFM and its amendments of September 16, 1996, and October 22, 1998. While the prior proposed labeling can continue to be used until a FM is issued, FDA encourages manufacturers of OTC sunscreen drug products to voluntarily implement the UVA-related labeling changes as soon as possible after publication of this proposal, especially if product relabeling occurs in the normal course of business. We note, though, that any relabeling prior to issuance of the FM is subject to the possibility that FDA may change some of the labeling requirements as a result of comments filed in response to this proposal.

Mandating warnings in an OTC drug monograph does not require a finding that any or all of the OTC drug products covered by the monograph actually caused an adverse event, and FDA does not so find. Nor does FDA's requirement of warnings repudiate the prior OTC drug monographs and monograph rulemakings under which the affected drug products have been lawfully marketed. Rather, as a consumer protection agency, FDA has determined that warnings are necessary to ensure that these OTC drug products continue to be safe and effective for their labeled indications under ordinary conditions of use as those terms are defined in the act. This judgment balances the benefits of these drug products against their potential risks (see 21 CFR 330.10(a)).

FDA's decision to act in this instance need not meet the standard of proof required to prevail in a private tort action (*Glastetter* v. *Novartis Pharmaceuticals Corp.*, 252 F.3d 986, 991 (8th Cir. 2001)). To mandate warnings, or take similar regulatory action, FDA need not show, nor do we allege, actual causation. For an expanded discussion of the case law supporting FDA's authority to require such warnings without evidence of actual causation, see Labeling of Diphenhydramine-Containing Drug Products for Over-the-Counter Human Use, final rule (67 FR 72555, December 6, 2002).

V. Analysis of Impacts

FDA has examined the impacts of this proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (2 U.S.C. 1501 *et seq.*). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation).

FDA believes that this proposed rule is consistent with the principles set out in the Executive Order 12866 and in these two statutes. The proposed rule

is not a significant regulatory action as defined by the Executive order and, therefore, is not subject to review under the Executive order. Further, because this proposed rule is not expected to result in any 1-year expenditure that would exceed $100 million adjusted for inflation, FDA need not prepare additional analyses under the Unfunded Mandates Reform Act. Because the rule may have a significant economic impact on a substantial number of small entities, this section of the preamble constitutes FDA's regulatory flexibility analysis.

An analysis of the costs and benefits of this regulation, conducted under Executive Order 12866, was discussed in the FM (64 FR 27666 at 27683 to 27686), which was later stayed (66 FR 67485). This analysis reflects the incremental costs of the revised or new requirements in this proposed amendment of the FM.

A. Background

The purpose of this document is to amend the conditions under which OTC sunscreen drug products are generally recognized as safe and effective (GRASE) and not misbranded. This amendment addresses formulation, labeling, and testing requirements for both UVB and UVA radiation protection.

Manufacturers would not need to reformulate their sunscreen products to comply with the proposed requirements. Manufacturers also would not need to retest their sunscreen products for UVB protection (i.e., they would not need to retest for SPF). The labeled SPF value determined from the SPF test in the FM would not likely change if a sunscreen product was retested using the modifications to the SPF test proposed in this document. In addition, manufacturers who have tested and labeled their sunscreen products as "SPF

30+" can relabel their products with the specific SPF value above 30 (but no greater than 50) without retesting.

However, all manufacturers would incur some relabeling costs due to proposed revisions to both the PDP and the Drug Facts section of the product label. If manufacturers wish to label their sunscreen products as providing UVA protection, then manufacturers of those sunscreen products would also incur UVA testing costs. Because UVA testing is not required, some manufacturers will choose not to test for UVA protection and the labeling for those sunscreens will state, "No UVA Protection."

B. Number of Products Affected

Estimating the number of products affected is difficult because we lack data on the number of products currently marketed. Our Drug Listing System currently does not have accurate information on the number of marketed OTC sunscreen products, especially the drug-cosmetic combination products. Proprietary databases that track retail sales of OTC drugs and other products do not distinguish cosmetics containing sunscreens from other cosmetic products and their surveys do not include many of the outlets where sunscreen products are sold. Based on earlier estimates (64 FR 27666 at 27684) and our knowledge of the industry, we assume there are about 3,000 OTC sunscreen drug products (different formulations, not including products that differ only by color), including drug-cosmetic combinations, and about 12,000 individual stock keeping units (SKUs) (individual products, packages, and sizes). All 12,000 SKUs will need to be relabeled, but manufacturers can choose whether to test their sunscreen products for UVA protection. We assume that about 75 percent (2,250) of the sunscreen products would be tested for UVA protection. We request comment on the accuracy of this assumption.

C. Cost to Relabel

The cost to relabel varies greatly depending on the printing method and number of colors used. The majority of sunscreen products are packaged in plastic bottles or tubes with the label printed directly on the container or applied as a decal or paper label during the packaging process. The proposed labeling requirements impact both the PDP and the Drug Facts section of the package and would be considered a major redesign.

Frequent label redesigns are typical for OTC sunscreen products, with redesigns generally implemented every 1 to 2 years for a product. To the extent that a scheduled redesign coincides with the regulatory-mandated relabeling, the impact on the manufacturer will be negligible.

We used a model developed for FDA by the consulting firm RTI to derive an estimate of the cost to relabel sunscreen products (Ref. 94). The model was developed to estimate the cost of food labels. However, we believe that the graphic and design estimates from that study are an appropriate proxy for the costs that would be incurred by OTC sunscreen manufacturers. RTI estimated that graphic design and prepress and engraving costs would range from $1,970 to $13,800 per SKU depending on the type of packaging and printing method used. There would also be administrative costs to account for contracting costs and obtaining final approvals for the new labels. RTI estimated administrative costs to range from $360 to $880 depending on the size of the firm. For this analysis, we are assuming an average design price of $7,000 per SKU and average administrative costs of $600 per SKU.[1] Therefore, the total relabeling cost per SKU would be $7,600 (i.e., $600 + $7,000).

[1] We did not select the midpoint of the ranges because of the large number of private label products that have lower design and administrative costs than branded goods.

While all sunscreen SKUs would need to be relabeled to comply with the proposed rule, we estimate that the timing of the scheduled relabeling would coincide with the regulatory-mandated changes for 50 percent of the SKUs (i.e., 6,000 SKUs). We estimate the total labeling cost of the proposed labeling changes for the SKUs with the coinciding scheduled redesign would be 50 percent of the administrative cost (i.e., $300). Therefore, the total one-time cost to industry for relabeling would be about $47.5 million (i.e., (6,000 x $7,600) + (6,000 x $300)).

D. Cost to Test or Retest Products for UVA Protection

This proposed rule will result in testing costs for products that make UVA protection claims. The approximate costs are $2,200 for in vivo UVA testing and $200 for in vitro UVA testing. Based on the number of sunscreen products currently labeled as providing UVA protection, we estimate that 75 percent (2,250) of the sunscreen products will be tested according to the proposed UVA tests. Therefore, FDA estimates a one-time UVA testing cost of approximately $5.4 million (i.e., 2,250 x $2,400).

E. Total Incremental Costs

The estimated total one-time incremental cost of this proposed rule is $53 million (i.e., $47.5 million + $5.4 million). The incremental cost for the UVA testing could be less should the rule become final because many manufacturers may voluntarily comply with the proposed rule when reformulating current products or marketing new products. Although the FM is not effective, manufacturers of sunscreen products comply with the UVB (SPF) test in the FM for nearly all sunscreen products. Therefore, it is likely that manufacturers of sunscreen products will also voluntarily comply with the proposed UVA tests in this document.

It should also be noted that sunscreen products that are already distributed by the effective date of the FM will not be required to be relabeled or retested in conformity with these FM conditions, unless these products are subsequently relabeled or repackaged after the effective date. Therefore, there is no one-time cost associated with disposing of sunscreens that are already on the market at the time of the rule's effective date.

F. Small Business Impact

In the FM (64 FR 27666 at 27685), FDA estimated that 78 percent of the 180 domestic companies that manufacture OTC sunscreen products would be considered a small business (defined as fewer than 750 employees). FDA cannot estimate with certainty the number of small firms that will need to test or retest their OTC sunscreen products to provide for UVA protection claims, but projects that approximately 75 percent of all products may need to be tested for UVA protection. Costs will vary by firm, depending on the number of products requiring testing. The firm-specific impact may vary inversely with the volume of product sales, because per unit costs will be lower for products with high volume sales. Thus, the relative economic impact of product retesting may be greater for small firms than for large firms. Because the OTC drug industry is highly regulated, all firms are expected to have access to the necessary professional skills on staff or to have contractual arrangements to comply with the testing requirements of this rule.

G. Analysis of Alternatives

FDA could have proposed only an in vivo or an in vitro test for UVA. FDA recognizes that requiring only the in vitro test would mean significantly less cost to manufacturers. However, the proposed in vivo test measures the magnitude of UVA protection. The proposed in vitro test measures the breadth

of UVA protection. FDA believes it is important to conduct both tests to determine the magnitude and breadth of UVA protection.

FDA plans to grant an extended compliance period when this proposed rule is finalized. Given the seasonal nature of these products, FDA is concerned that some manufacturers may not have sufficient time to incorporate labeling changes without disrupting their production schedules. By providing an additional 6 months to implement the changes, compliance costs to manufacturers will be reduced.

In addition, FDA reduced compliance costs when we chose to stay the labeling requirements for the FM (64 FR 27666), sparing industry the cost of an additional regulatory-mandated label change. In the stay, FDA estimated a cost savings of $1.5 million to industry. It should be noted that labeling costs were significantly less in the FM than in this proposed rule primarily because we assumed in the FM that the majority of relabeling would coinside with scheduled voluntary label redesigns at no additional cost. Manufacturers were also able to avoid or postpone incurring an additional industry total of $5 million when FDA chose to stay the UVB testing requirements of the FM.

FDA invites public comment regarding any substantial or significant economic impact that this proposed rule would have on manufacturers of OTC sunscreen drug products. Comments regarding the impact of this rulemaking on such manufacturers should be accompanied by appropriate documentation. FDA is providing a period of 90 days from the date of publication of this proposed rule in the **Federal Register** for comments to be developed and submitted. FDA will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the final rule.

VI. Paperwork Reduction Act of 1995

FDA tentatively concludes that the labeling requirements in this document are not subject to review by the Office of Management and Budget because they do not constitute a "collection of information" under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the proposed labeling statements are a "public disclosure of information originally supplied by the Federal Government to the recipient for the purpose of disclosure to the public" (5 CFR 1320.3(c)(2)).

VII. Environmental Impact

FDA has determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule, if finalized as proposed, would have a preemptive effect on State law. Section 4(a) of the Executive order requires agencies to "construe * * * a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute." Section 751 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 379r) is an express preemption provision. Section 751(a) of the act (21 U.S.C. 379r(a)) provides that "no State or political subdivision of a State may establish or continue in effect any requirement—* * * (1) that relates to the regulation of a drug that is not subject to the requirements of section 503(b)(1) or

503(f)(1)(A); and (2) that is different from or in addition to, or that is otherwise not identical with, a requirement under this Act, the Poison Prevention Packaging Act of 1970 (15 U.S.C. 1471 *et seq.*), or the Fair Packaging and Labeling Act (15 U.S.C. 1451 *et seq.*)." Currently, this provision operates to preempt States from imposing requirements related to the regulation of nonprescription drug products. Section 751(b) through (e) of the act outlines the scope of the express preemption provision, the exemption procedures, and the exceptions to the provision.

This proposed rule, if finalized as proposed, would amend the labeling and include new UVA testing for OTC sunscreen drug products. Any final rule would have a preemptive effect in that it would preclude States from issuing requirements related to the labeling and testing of OTC sunscreen drug products that are different from or in addition to, or not otherwise identical with a requirement in the final rule. This preemptive effect is consistent with what Congress set forth in section 751 of the act. Section 751(a) of the act displaces both State legislative requirements and State common law duties. We also note that even where the express preemption provision in section 751(a) of the act is not applicable, implied preemption may arise (see *Geier* v. *American Honda Co.*, 529 US 861 (2000)).

FDA believes that the preemptive effect of the proposed rule, if finalized as proposed, would be consistent with Executive Order 13132. Section 4(e) of the Executive order provides that "when an agency proposes to act through adjudication or rulemaking to preempt State law, the agency shall provide all affected State and local officials notice and an opportunity for appropriate participation in the proceedings." FDA is providing an opportunity for State and local officials to comment on this rulemaking.

IX. Request for Comments

In the **Federal Register** of January 10, 2005 (70 FR 1721), FDA announced the availability of a final guidance for industry entitled "Labeling for Topically Applied Cosmetic Products Containing Alpha Hydroxy Acids as Ingredients." The purpose of this guidance is twofold:

- To educate consumers about the potential for increased skin sensitivity to the sun from the topical use of cosmetics containing alpha hydroxy acids (AHAs) as ingredients.
- To educate manufacturers to help ensure that their labeling for cosmetic products containing AHAs as ingredients is not false or misleading.

As discussed in the guidance, AHAs may increase skin sensitivity to UV radiation. Therefore, FDA recommends that manufacturers of cosmetic products containing AHAs include the following warning:

Sunburn Alert: This product contains an alpha hydroxy acid (AHA) that may increase your skin's sensitivity to the sun and particularly the possibility of sunburn. Use a sunscreen and limit sun exposure while using this product and for a week afterwards.

The guidance addresses only cosmetic products containing AHAs and does not address sunscreen drug products containing AHAs (i.e., drug-cosmetic products). FDA is considering an additional warning or direction for sunscreen drug products containing AHAs similar to the warning for the cosmetic products described in the guidance for industry. However, FDA invites interested parties to submit comments and data regarding such labeling. In particular, FDA would like the following questions addressed:

1. Does the body of existing evidence on AHAs and skin sensitivity warrant voluntary or mandatory labeling on OTC sunscreen drug products

containing AHAs regarding possible risks of increased sun damage (e.g., sunburn)?

2. If additional labeling is warranted, what information should be conveyed in the labeling and why?

Comments along with supporting data will help enable FDA to determine how and what information, if any, related to UV hypersensitivity due to AHAs in sunscreen-cosmetic products should be communicated to consumers. FDA will also be evaluating any comments or data submitted in response to the final guidance for cosmetic products containing AHAs.

In addition to AHAs, FDA seeks comment on titanium dioxide and zinc oxide formulated in particle sizes as small as a few nanometers. FDA addressed issues concerning micronized sunscreen ingredients in the FM (64 FR 27666 at 27671 to 27672). The FM stated that FDA did not consider micronized titanium dioxide to be a new ingredient but rather a specific grade of the same active ingredient. The FM also stated that FDA was aware of concerns about potential risks associated with increased dermal penetration of such small particles. However, the FM explained that, based on the safety data submitted to FDA before publication of the FM, FDA was not aware of any evidence at that time demonstrating a safety concern from the use of micronized titanium dioxide in sunscreen products (64 FR 27666 at 27671 to 27672).

FDA recognizes that more sunscreens containing small particle size titanium dioxide and zinc oxide ingredients enter the market each year. FDA is interested in receiving comments and data about these sunscreen ingredients and products that contain these ingredients, their safety and effectiveness, and how they should be regulated. FDA received a citizen petition shortly before publication of this document that, among other things, raises these issues. FDA

is currently evaluating the citizen petition, which is filed as CP17 in Docket No. 1978N–0038. FDA encourages other parties to submit additional data or information on the safety and effectiveness of sunscreen ingredients formulated in particle sizes as small as a few nanometers.

On April 14, 2006, FDA announced in the **Federal Register** that we were planning a public meeting on FDA-regulated products containing nanotechnology materials (71 FR 19523). As explained in the notice, the purpose of the meeting was to help FDA further its understanding of developments in nanotechnology materials that pertain to FDA-regulated products. The meeting was held on October 10, 2006, and FDA has received comments from interested members of the public which have been filed in the docket for this public meeting (Docket No. 2006N– 0107). Some of these comments concern sunscreen ingredients formulated with nanotechnology materials. FDA will file any comments concerning sunscreen ingredients formulated in nanometer particle sizes received in response to this proposed rule in the docket for this rulemaking and the citizen petition (Docket No. 1978N–0038) and the docket for the nanotechnology meeting.

X. Proposed Effective and Compliance Dates

FDA is proposing that any final rule that may issue based on this proposal become effective 18 months after its date of publication in the **Federal Register**. The compliance date for products with annual sales less than $25,000 would be 24 months after publication of the final rule in the **Federal Register**.

XI. References

The following references are on display in the Division of Dockets Management (see **ADDRESSES**) under Docket No. 1978N–0038 and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Comment No. CP6.

2. Comment Nos. CP8, C548, SUP22, and C555.

3. Comment Nos. LET166 and LET169.

4. Comment No. C538.

5. Comment No. C576.

6. Comment No. C565.

7. Comment No. C581.

8. Comment No. C567.

9. Comment No. C515.

10. Comment No. C597.

11. Comment No. MM22.

12. Comment No. MM21.

13. Comment No. C573.

14. Autier, P. et al., "Sunscreen Use and Duration of Sun Exposure: a Double-blind, Randomized Trial," *Journal of the National Cancer Institute*, 91(15):1304–1309, 1999.

15. Reynolds, K.D. et al., "Predictors of Sun Exposure in Adolescents in a Southeastern U.S. Population," *Journal of Adolescent Health*, 19(6):409–415, 1996.

16. Robinson, J.K., D.S. Rigel, and R.A. Amonette, "Summertime Sun Protection Used by Adults for Their Children," *Journal American Academy of Dermatology*, 42(5):746–753, 2000.

17. Gallagher, R.P. et al., "Broad-spectrum Sunscreen Use and the Development of New Nevi in White Children: A Randomized Controlled Trial," *Journal of the American Medical Association*, 283(22):2955–2960, 2000.

18. Stender, I.M., J.L. Andersen, and H.C. Wulf, "Sun Exposure and Sunscreen Use among Sunbathers in Denmark," *Acta Dermato-Venereologica*, 76:31–33, 1996.

19. Zitser, B.S. et al., "A Survey of Sunbathing Practices on Three Connecticut State Beaches," *Connecticut Medicine*, 60(10):591–594, 1996.

20. Green, A. et al., "Daily Sunscreen Application and Betacarotene Supplementation in Prevention of Basal-cell and Squamous-cell Carcinomas of the Skin: a Randomized Controlled Trial," *The Lancet*, 354:723–729, 1999.

21. *IARC Handbooks of Cancer Prevention Volume 5 Sunscreens*, H. Vainio, ed., International Agency for Research on Cancer, Lyon, France, p. 62, 2001.

22. Diffey, B.L. et al., "In Vitro Assessment of the Broad-spectrum Ultraviolet Protection of Sunscreen Products," *Journal of the American Academy of Dermatology*, 43(6):1024–1035, 2000.

23. Comment No. C572.

24. Gasparro, F.P., "Sunscreens, Skin Photobiology, and Skin Cancer: the Need for UVA Protection and Evaluation of Efficacy," *Environmental Health Perspectives*, 108 Suppl 1:71–78, 2000.

25. Garland, C.F., F.C. Garland, and E.D. Gorham, "Lack of Efficacy of Common Sunscreens in Melanoma Prevention" in *Epidemiology, Causes and Prevention of Skin Diseases*, Grob, J.J. et al. eds., Blackwell Science Ltd., Malden, MA, pp. 151–159, 1997.

26. Lowe, N.J. et al., "Low Doses of Repetitive Ultraviolet A Induce Morphologic Changes in Human Skin," *Journal of Investigative Dermatology*, 105(6):739–743, 1995.

27. Seite, S. et al., "Effects of Repeated Suberythemal Doses of UVA in Human Skin," *European Journal of Dermatology*, 7:204–209, 1997.

28. Lavker, R.M. et al., "Quantitative Assessment of Cumulative Damage from Repetitive Exposures to Suberythemogenic Doses of UVA in Human Skin," *Photodermatology, Photoimmunology, and Photomedicine*, 62(2):348–352, 1995.

29. Lavker, R.M. et al., "Cumulative Effects from Repeated Exposures to Suberythemal Doses of UVB and UVA in Human Skin," *Journal of the American Academy of Dermatology*, 32(1):53–62, 1995.

30. Elmets, C.A., A. Vargas, and C. Oresajo, "Photoprotective Effects of Sunscreens in Cosmetics on Sunburn and Langerhans Cell Photodamage," *Photodermatology, Photoimmunology, and Photomedicine*, 9(3):113–120, 1992.

31. Lavker, R., and K. Kaidbey, "The Spectral Dependence for UVA-induced Cumulative Damage in Human Skin," *Journal of Investigative Dermatology*, 108(1):17–21, 1997.

32. Seite, S. et al., "A Full-UV Spectrum Absorbing Daily Use Cream Protects Human Skin Against Biological Changes Occurring in Photoaging," *Photodermatology, Photoimmunology, and Photomedicine*, 16(4):147–155, 2000.

33. Boyd, A.S. et al., "The Effects of Chronic Sunscreen Use on the Histologic Changes of Dermatoheliosis," *Journal of the American Academy of Dermatology*, 33(6):941–946, 1995.

34. Comment No. CP15.

35. Center for Disease Control and Prevention, "Guidelines for School Programs To Prevent Skin Cancer" in *Morbidity and Mortality Weekly Report*, 1–18, 2002.

36. Ries, A.G. et al., "The Annual Report to the Nation on the Status of Cancer, 1973–1997, with a Special Section on Colorectal Cancer," *Cancer*, 88(10):2398–2424, 2000.

37. Cancer Facts and Figures 2007, American Cancer Society, Inc., 2007.

38. Sun Safety Tips, The American Academy of Dermatology, 1999.

39. Skin Cancer: Preventing America's Most Common Cancer 2001 Choose Your Cover, Centers for Disease Control and Prevention, 2001.

40. The Sun, UV, and You: A Guide to SunWise Behavior, Environmental Protection Agency, 1999.

41. Sun Protection Facts to Help You Prevent Skin Cancer, American Cancer Society, 2000.

42. What You Need to Know About Skin Cancer, National Cancer Institute, 1998.

43. Committee on Environmental Health, American Academy of Pediatrics, "Ultraviolet Light: A Hazard to Children," *Pediatrics*, 104:328–333, 1999.

44. Green, A. et al., "Site Distribution of Cutaneous Melanoma in Queensland," *International Journal of Cancer*, 53:232–236, 1992.

45. Franceschi, S. et al., "Site Distribution of Different Types of Skin Cancer: New Aetiological Clues," *International Journal of Cancer*, 67:24–28, 1996.

46. Raasch, B. et al., "Body Site Specific Incidence of Basal and Squamous Cell Carcinoma in an Exposed Population, Townsville, Australia," *Mutation Research*, 422:101–106, 1998.

47. Osterlind, A., K. Hou-Jensen, and O.M. Jensen, "Incidence of Cutaneous Malignant Melanoma in Denmark 1978–1982. Anatomic Site Distribution, Histologic Types, and Comparison with Non-melanoma Skin Cancer," *British Journal of Cancer*, 58:385–391, 1988.

48. Neale, R., G. Williams, and A. Green, "Application Patterns Among Participants Randomized to Daily Sunscreen Use in a Skin Cancer Prevention Trial," *Archives of Dermatology*, 138:1319–1325, 2002.

49. Comment No. C584.

50. Steinberg, C., and O. Larko, "Sunscreen Application and its Importance for Sun Protection Factor," *Archives of Dermatology*, 121:1400–1402, 1985.

51. Stokes, R., and B. Diffey, "How Well Are Sunscreen Users Protected?," *Photodermatology, Photoimmunology, and Photomedicine*, 13:186–188, 1997.

52. Sayre, R.M. et al., "Product Application Technique Alters the Sun Protection Factor," *Photodermatology, Photoimmunology, and Photomedicine*, 8:222–224, 1991.

53. Azurda, R.M. et al., "Sunscreen Application Technique in Photosensitive Patients: a Quantitative Assessment and the Effect of Education," *Photodermatology, Photoimmunology and Photomedicine*, 16:53–66, 2000.

54. Bech-Thomsen, N., and H.C. Wulf, "Sunbather's Application of Sunscreen is Probably Inadequate to Obtain Sun Protection Factor Assigned to the Preparation," *Photodermatology, Photoimmunolology and Photomedicine*, 9:242–244, 1992.

55. Diffey, B., "People Do Not Apply Enough Sunscreen for Protection," *British Medical Journal*, 313:942, 1996.

56. Wright, M.W. et al., "Mechanisms of Sunscreen Failure," *Journal of the American Academy of Dermatology*, 44:781–784, 2001.

57. Rigel, D. et al., "American Academy of Dermatology's Melanoma/Skin Cancer Detection and Prevention Month Press Release," April 25, 2001.

58. The ABCs for Fun in the Sun Educational Pamphlet, The American Academy of Dermatology, 1999.

59. Ultraviolet Index—What You Need to Know, The American Academy of Dermatology, 1996.

60. Sun Basics-Skin Protection Made Simple for Everyone Under the Sun, American Cancer Society, Inc., 1999.

61. Skin Protection Guide for Everyone Under the Sun. A Parents Guide to Sun Protection, American Cancer Society, Inc., 1999.

62. Can Melanoma Be Prevented?, American Cancer Society, Inc., 2001.

63. Diffey, B., "Has the Sun Protection Factor Had Its Day?," *British Medical Journal*, 320:176–177, 2000.

64. Taylor, W.A., "Double Sampling Plan" in *Guide to Acceptance Sampling*, R. R. Donnelly & Sons, U.S.A., pp. 117–142, 1992.

65. Comment No. C574.

66. Comment No. C405.

67. Comment No. C404.

68. Comment No. C111.

69. Comment No. RPT7.

70. Comment No. C442.

71. Comment No. SUP29.

72. Memorandum from W.H. DeCamp, FDA, to C. Ganley, FDA, July 7, 2000.

73. Comment No. CP12.

74. Comment No. SUP33.

75. Gabriel, K.L. et al., "Sun Protection Factor Testing: Comparison of FDA and DIN Methods," *Journal of Toxicology-Cutaneous and Ocular Toxicology*, 6:357–370, 1987.

76. Comment No. C491.

77. Comment No. TR2.

78. Diffey, B.L., "A Method for Broad Spectrum Classification of Sunscreens," *International Journal of Cosmetic Science*, 16:47–52, 1994.

79. Diffey, B.L., and J. Robson, "A New Substrate to Measure Sunscreen Protection Factors Throughout the Ultraviolet Spectrum," *Journal of the Society of Cosmetic Chemists*, 40:127–133, 1989.

80. Comment No. RPT9.

81. Comment No. LET170.

82. Press Release: "The Future of Sunscreen Labeling: Recommendations of the Consensus Conference on UVA Protection of Sunscreens Convened by the American Academy of Dermatology," New York, NY, April 26, 2000.

83. Lim, H.W. et al., "American Academy of Dermatology Consensus Conference on UVA Protection of Sunscreens: Summary and Recommendations," *Journal of the American Academy of Dermatology*, 44:505–508, 2001.

84. Cole, C., "Sunscreen Protection in the Ultraviolet A Region: How to Measure Effectiveness," *Photodermatology, Photoimmunology, and Photomedicine*, 17:2–10, 2001.

85. Comment No. C137.

86. Setlow, R.B., et al., "Wavelengths Effective in Induction of Malignant Melanoma," *Proceedings of the American Academy of Science, U.S.A.*, 90:6666–6670, 1993.

87. Moyal, D. et al., "UVA Protection Efficacy of Sunscreens Can Be Determined by the Persistent Pigment Darkening (PPD) Method (Part 2)," *Photodermatology, Photoimmunology, and Photomedicine*, 16:250–255, 2000.

88. Moyal, D. et al., "Determination of UVA Protection Factors Using the Persistent Pigment Darkening (PPD) Method as the Endpoint (Part 1) Calibration of the Method," *Photodermatology, Photoimmunology, and Photomedicine*, 16:245–249, 2000.

89. Chardon, A. et al., "Persistent Pigment-Darkening Response as a Method for Evaluation of Ultraviolet A Protection Assays" in *Sunscreens: Development, Evaluation, and Regulatory Aspects*, 2nd edition, Marcel Dekker, Inc., New York, NY, pp. 559–582, 1997.

90. Comment No. TS3.

91. Diffey, B.L. et al., "Suncare Product Photostability: a Key Parameter for a More Realistic In Vitro Efficacy Evaluation," *European Journal of Dermatology*, 7:226–228, 1997.

92. Sayre, R.M., and J. Dowdy, "Photostability Testing of Avobenzone," *Cosmetics and Toiletries*, 114:85–86, 88, 90–91, 1999.

93. Urbach, F., "Man and Ultraviolet Radiation" in *Human Exposure to Ultraviolet Radiation: Risks and Regulations*, Passchier, W.F. and Bosnjakovic, B.F.M. (eds.), Elsevier Science, New York, NY, pp. 3–6, 1987.

94. RTI International, "FDA Labeling Cost Model, Final Report," prepared by Mary Muth, Erica Gledhill, and Shawn Karns, RTI. Prepared for Amber Jessup, FDA Center for Food Safety and Applied Nutrition, Revised January 2003.

List of Subjects

21 CFR Part 347

Labeling, Over-the-counter drugs.

21 CFR Part 352

Labeling, Over-the-counter drugs, Incorporation by reference.

Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 347 and 352 be amended as follows:

PART 347—SKIN PROTECTANT DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation for 21 CFR part 347 continues to read as follows:

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

2. FDA is proposing to lift the stay of § 347.20(d) as published at 68 FR 33362, June 4, 2003.

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

3. The authority citation for 21 CFR part 352 continues to read as follows:

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

4. FDA is proposing to lift the stay of 21 CFR part 352 as published at 68 FR 33362, June 4, 2003.

5. Section 352.3 is amended by redesignating paragraphs (b) through (d) as (c) through (e), respectively; revising newly redesignated paragraphs (c) and (e); and adding new paragraph (b) to read as follows:

§ 352.3 Definitions.

* * * * *

(b) *Minimal pigmenting dose (MPD).* The quantity of erythema-effective energy (expressed as Joules per square meter) required to produce the first perceptible pigment darkening.

(c) *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) *Low UVB sunburn protection product.* A sunscreen product that provides a sunburn protection factor (SPF) value of 2 to under 15.

(2) *Medium UVB sunburn protection product.* A sunscreen product that provides an SPF value of 15 to under 30.

(3) *High UVB sunburn protection product.* A sunscreen product that provides an SPF value of 30 to 50.

(4) *Highest UVB sunburn protection product.* A sunscreen product that provides an SPF value over 50.

* * * * *

(e) *Sunburn 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.

6. Section 352.20 is amended by revising paragraph (a)(2) to read as follows:

§ 352.20 Permitted combinations of active ingredients.

* * * * *

(a) * * *

(2) Avobenzone in § 352.10(b) may be combined with one or more sunscreen active ingredients identified in § 352.10(c), (e), (f), (i) through (l), (n), (o), (q), and (r) 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.

* * * * *

7. Section 352.50 is revised to read as follows:

§ 352.50 Principal display panel of all sunscreen drug products.

(a) *UVB sunburn protection designation*—(1) *For products with an SPF of 2 to under 15.* The labeling states "UVB SPF [insert tested SPF value of the product] low".

(2) *For products with an SPF of 15 to under 30.* The labeling states "UVB SPF [insert tested SPF value of the product] medium".

(3) *For products with an SPF of 30 to 50.* The labeling states "UVB SPF [insert tested SPF value of the product] high".

(4) *For products with an SPF over 50.* The labeling states "UVB SPF 50 [select one of the following: 'plus' or '+'] highest". Any statement

accompanying the marketed product that states a specific SPF value over 50 or similar language indicating a person can stay in the sun more than 50 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) (21 U.S.C. 352).

(b) *UVA protection designation*—(1) *For products not providing UVA protection according to § 352.73.* The labeling states "no UVA protection".

(i) The UVA protection designation shall appear on the principal display panel along with the UVB protection designation in an equally prominent manner that does not conflict with the UVB protection designation.

(ii) The font size of the UVA protection designation shall be the same size as the UVB protection designation.

(2) *For products providing UVA protection according to § 352.73.* The labeling states "UVA [select one of the following in accordance with § 352.73: '★☆☆☆ Low,' '★★☆☆ Medium,' '★★★☆ High,' or '★★★★ Highest']".

(i) The UVA protection designation shall appear on the principal display panel along with the UVB protection designation in an equally prominent manner that does not conflict with the UVB protection designation.

(ii) The font size of the UVA protection designation shall be the same size as the UVB protection designation.

(iii) All star borders and the color inside a solid star shall be the same while the color of "empty" stars must be lighter and distinctly different than solid stars. The color inside a solid star should be distinctly different than the background color.

(iv) The stars are to be filled in starting with the first star on the left and are to appear in a straight horizontal line.

(c) Select one of the following: "UV rays from the sun are made of UVB and UVA. It is important to protect against both UVB & UVA rays." or "UV rays from the sun are made of UVB and UVA. It is important to protect against both UVB & UVA rays to prevent sunburn and other skin damage."

(d) *For products that satisfy the water resistant sunscreen product testing procedures in § 352.76.* The labeling states (select one of the following: "water," "water/sweat," or "water/perspiration") "resistant."

(e) *For products that satisfy the very water resistant sunscreen product testing procedures in § 352.76.* The labeling states "very" (select one of the following: "water," "water/sweat," or "water/perspiration") "resistant."

8. Section 352.52 is amended by revising paragraphs (b), (c), (d), (e), the heading of paragraph (f), paragraphs (f)(1)(ii) through (f)(1)(vi) to read as follows:

§ 352.52 Labeling of sunscreen drug products.

* * * * *

(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 (21 U.S.C. 352) relating to misbranding and the prohibition in section 301(d) of the act (21 U.S.C. 331(d)) against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act (21 U.S.C. 355(a)).

(1) *For products containing any ingredient in § 352.10.* (i) *For products with an SPF of 2 to under 15.* The labeling states "[bullet][1] low UVB sunburn protection".

(ii) *For products with an SPF of 15 to under 30.* The labeling states "[bullet] medium UVB sunburn protection".

(iii) *For products with an SPF of 30 to 50.* The labeling states "[bullet] high UVB sunburn protection".

(iv) *For products with an SPF over 50.* The labeling states "[bullet] highest UVB sunburn protection".

(v) *For products not providing UVA protection according to § 352.73.* The labeling states "[bullet] no UVA protection."

(vi) *For products providing UVA protection according to § 352.73.* The labeling states "[bullet] [select one of the following in accordance with § 352.73: 'Low,' 'medium,' 'high,' or 'highest'] UVA protection".

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

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

(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:

[1] See § 201.66(b)(4) of this chapter for definition of bullet symbol.

(i) *For products with an SPF of 2 to under 15.* Select one or both of the following: "[Bullet] provides low protection against [select one of the following: 'sunburn' or 'sunburn and tanning']" or "[bullet] for skin that sunburns minimally".

(ii) *For products with an SPF of 15 to under 30.* Select one or both of the following: "[Bullet] provides medium protection against [select one of the following: 'sunburn' or 'sunburn and tanning']" or "[bullet] for skin that sunburns moderately".

(iii) *For products with an SPF of 30 to 50.* 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".

(iv) *For products with an SPF over 50.* Select one or both of the following: "[Bullet] [select one of the following: 'provides highest' or 'highest'] protection against [select one of the following: 'sunburn' or 'sunburn and tanning']" or "[bullet] for skin extremely sensitive to sunburn".

(v) If the UVA descriptor in § 352.52(b)(1)(vi) is the same as the SPF descriptor in § 352.52(b)(1)(i) through (b)(1)(iv), then the statement in § 352.52(b)(1)(i) through (b)(1)(iv) may be combined with the statement in § 352.52(b)(1)(vi) as follows: "[Bullet] [select one of the following descriptors in accordance with §§ 352.70 and 352.73: 'low,' 'medium,' 'high,' or 'highest'] UVB sunburn/UVA protection".

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

(1) The labeling states in bold type "UV exposure from the sun increases the risk of skin cancer, premature skin aging, and other skin damage. It is

important to decrease UV exposure by limiting time in the sun, wearing protective clothing, and using a sunscreen."

(2) The labeling states "When using this product [bullet] keep out of eyes. Rinse with water to remove."

(3) The labeling states "Stop use and ask a doctor if [bullet] skin rash occurs".

(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) The labeling states "[bullet] apply [select one of the following: 'liberally' or 'generously'] [and, as an option: 'and evenly'] [insert appropriate time interval, if a waiting period is needed] before sun exposure".

(ii) The labeling states "[bullet] apply and reapply as directed to avoid lowering protection".

(iii) As an option, the labeling may state "[bullet] apply to all skin exposed to the sun".

(iv) The labeling states "[bullet] children under 6 months of age: ask a doctor".

(2) *For products that satisfy the water resistant or very water resistant testing procedures identified in § 352.76.* The labeling states "[bullet] reapply after [select one of the following: '40 minutes of' or '80 minutes of' for products that satisfy either the water resistant or very water resistant test procedures in § 352.76, respectively] swimming or [select one or more of the following: 'sweating' or 'perspiring'] and after towel drying. Otherwise, reapply at least every 2 hours".

(3) *For products that do not satisfy the water resistant or very water resistant testing procedures identified in § 352.76.* The labeling states "[bullet] reapply at least every 2 hours and after towel drying, swimming, or [select one of the following: 'sweating' or 'perspiring']".

(e) *Statement on product performance*—(1) *For products containing any ingredient identified in § 352.10.* The following product category designation (PCD) labeling claims may be used under the heading "Other information" or anywhere outside of the "Drug Facts" box or enclosure and shall not be intermixed with the information required under § 352.50(a).

(i) *For products with an SPF of 2 to under 15.* The labeling states "low sunburn protection product".

(ii) *For products with an SPF of 15 to under 30.* The labeling states "medium sunburn protection product".

(iii) *For products with an SPF of 30 to 50.* The labeling states "high sunburn protection product".

(iv) *For products with an SPF over 50.* The labeling states "highest sunburn 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 and shall not be intermixed with the information required under § 352.50(a). The labeling states "higher SPF products give more sun protection, but are not intended to extend the time spent in the sun".

(3) *For products containing any ingredient identified in § 352.10 and that satisfy the requirements in § 352.73 for a labeled UVA protection value.* The following labeling statements may be used anywhere outside of the "Drug

Facts" box or enclosure and shall not be intermixed with the information required under § 352.50(a).

(i) The labeling states "broad spectrum sunscreen".

(ii) The labeling states "provides [select one of the following: 'UVA and UVB,' or 'broad spectrum'] protection".

(iii) The labeling states "protects from UVA and UVB [select one of the following: 'rays' or 'radiation']".

(iv) The labeling states "[select one of the following: 'absorbs' or 'protects'] within the UVA spectrum".

(f) *Products, including cosmetic-drug products, containing any ingredient identified in § 352.10 labeled for use only on specific small areas of the face (e.g., lips, nose, ears, and/or around the eyes) and that meet the criteria established in § 201.66(d)(10) of this chapter.* * * *

(1) * * *

* * * * *

(ii) The indication required by § 201.66(c)(4) of this chapter may be limited to the following: "Use [in bold type] helps prevent sunburn."

(iii) The warnings required by § 201.66(c)(5)(i) through (c)(5)(ix) of this chapter may be limited to the following: "UV exposure from the sun increases the risk of skin cancer, premature skin aging, and other skin damage. It is important to decrease UV exposure by limiting time in the sun, wearing protective clothing, and using a sunscreen. [in bold type]" "[bullet] keep out of eyes" "[bullet] stop use if skin rash occurs."

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

(v) *For lip protectant products containing any ingredient identified in § 352.10.* The heading and the indication required by § 201.66(c)(4) of this

chapter may be limited to "Use [in bold type] helps prevent sunburn and chapped lips". The warnings required in paragraph (f)(1)(iii) of this section may be limited to the following: "Stop use if skin rash occurs." The warning required in paragraph (f)(1)(iv) of this section may be omitted. The directions in paragraphs (d)(2) and (d)(3) of this section may be limited to the following: "apply liberally and reapply at least every 2 hours for sunburn protection".

(vi) *For lipsticks, lip products to prolong wear of lipstick, lip gloss, and lip balm containing any ingredient identified in § 352.10 and identified in § 720.4(c)(7) of this chapter.* The labeling is identical to that in paragraph (f)(1)(v) of this section except the heading and the indication required by § 201.66(c)(4) of this chapter are limited to "Use [in bold type] helps prevent sunburn".

* * * * *

9. Section 352.60 is amended by revising paragraphs (c) and (d) to read as follows:

§ 352.60 Labeling of permitted combinations of active ingredients.

* * * * *

(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, 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 with sunscreen, § 352.52(f)(1)(vi) applies.

(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) must be used. For products marketed as a lip protectant with sunscreen, § 352.52(f)(1)(vi) applies.

10. Sections 352.70 through 352.73 are revised as follows:

Subpart D—Testing Procedures

Sec.

352.70 SPF testing procedure.

352.71 UVA in vitro testing procedure.

352.72 UVA in vivo testing procedure.

352.73 Determination of the labeled UVA protective value.

* * * * *

§ 352.70 SPF testing procedure.

(a) *Standard sunscreens*—(1) *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.

(i) *For products with an SPF of 2 to 15.* The standard sunscreen shall be an 8-percent homosalate preparation with a mean SPF value of 4.47 (standard deviation = 1.28). 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 ± 1.28). Optionally, the standard sunscreen in paragraph (a)(1)(ii) of this section may be used.

(ii) *For products with an SPF over 15 (optional for SPF values of 2 to 15).* The standard sunscreen shall be an SPF 15 formulation containing 7 percent padimate O and 3 percent oxybenzone with a mean SPF value of 16.3 (standard deviation = 3.43). 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., 16.3 ± 3.43).

(2) *Standard homosalate sunscreen*—(i) *Preparation of the standard homosalate sunscreen.* (A) 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 HOMOSALATE 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 USP	74.30

(B) 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.

(ii) *High performance liquid chromatography (HPLC) assay of the standard homosalate sunscreen.* Assay the standard homosalate sunscreen preparation by the following method to ensure proper concentration:

(A) *Reagents.* (*1*) Acetic acid, glacial, ACS grade.

(*2*) Isopropanol, HPLC grade.

(*3*) Methanol, HPLC grade.

(*4*) Homosalate, USP reference standard.

(B) *Instrumentation.* Equilibrate a suitable liquid chromatograph to the following or equivalent conditions:

Column	Ultrasphere ODS 150 x 4.6 millimeters (5 microns), or Ultrasphere ODS 250 x 4.6 millimeters (5 microns)
Mobile Phase	85:15:0.5 methanol:water:acetic acid
Flow Rate	1.5 milliliters per minute
Temperature	Ambient
Detector	UV spectrophotometer at 308 nanometers
Attenuation	As needed
Injection Amount	10 microliters

(C) *Standard preparation.* (*1*) Accurately weigh 0.50 gram of homosalate USP reference standard into a 250-milliliter volumetric flask. Dissolve and dilute to volume with isopropanol. Mix well.

(*2*) Accurately pipet 20.0 milliliters of the homosalate solution (described in paragraph (a)(2)(ii)(C)(*1*) of this section) into a 100-milliliter volumetric flask. Dilute to volume with isopropanol and mix well. This is the standard preparation.

(D) *Sample preparation.* (*1*) Accurately weigh 2.0 grams of sample into a 100-milliliter volumetric flask.

(*2*) Add approximately 75 milliliters of isopropanol and heat with swirling until the sample is evenly dispersed.

(*3*) Cool to room temperature (15 to 30 °C) and dilute to volume with isopropanol. Mix well.

(*4*) Pipet 25.0 milliliters of this sample preparation into a 100-milliliter volumetric flask and dilute to volume with isopropanol. Mix well.

(E) *System suitability.* (*1*) Three replicate injections of the standard preparation (described in paragraph (a)(2)(ii)(C)(*2*) of this section) will yield a relative standard deviation of not more than 2.0 percent calculated on peak areas for homosalate.

(*2*) In case a system fails to meet this criterion, adjusting the mobile phase or replacing the column may be necessary to obtain suitable chromatography.

(F) *Analysis.* (*1*) Inject 10 microliters of the standard preparation (described in paragraph (a)(2)(ii)(C) of this section) in triplicate and collect data for about 15 minutes or until both homosalate (two isomers) peaks have completely eluted.

(*2*) Similarly inject 10 microliters of each sample preparation.

(*3*) The system suitability requirements must be met.

(G) *Calculation.* Sum the peak areas of the two homosalate isomers for each injection and calculate the percent (weight/weight) homosalate content in the sample preparation as follows:

$$\frac{\text{(Total homosalate peak area for sample) (Standard weight}^{1}\text{) (DF}^{2}\text{)}}{\text{(Average total homosalate peak area for standard) (Sample weight}^{1}\text{)}}$$

[1] weight in grams
[2] DF is a dilution factor calculated as follows:

$$\frac{WStd}{Vd} \times \frac{AStd}{Vd} \times \frac{Vd}{WSmp} \times \frac{Vd}{ASmp} \times 100 = \text{percent weight/weight}$$

where:
WStd = standard weight (in grams)
Vd = volume of dilution
AStd = aliquot of prepared standard solution
WSmp = sample weight (in grams)
ASmp = aliquot of prepared sample solution

(3) *Standard padimate O/oxybenzone sunscreen*—(i) *Preparation of the standard padimate O/oxybenzone sunscreen.* The standard sunscreen is prepared from four different parts (parts A, B, C, and D) with the following compositions:

COMPOSITION OF THE PADIMATE O/ OXYBENZONE STANDARD SUNSCREEN

Ingredients	Percent by weight
Part A	
Lanolin	4.50
Cocoa butter	2.00
Glyceryl monostearate	3.00
Stearic acid	2.00
Padimate O	7.00
Oxybenzone	3.00
Propylparaben	0.10
Part B	
Purified water USP	71.60
Sorbitol solution	5.00
Triethanolamine, 99 percent	1.00
Methylparaben	0.30
Part C	
Benzyl alcohol	0.50
Part D	
Purified water USP	QS[1]

[1] Quantity sufficient to make 100 grams

(A) *Step 1.* Add the ingredients of Part A into a suitable stainless steel kettle equipped with a propeller agitator. Mix at 77 to 82 °C until uniform.

(B) *Step 2.* Add the water of Part B into a suitable stainless steel kettle equipped with a propeller agitator and begin mixing and heating to 77 to 82 °C. Add the remaining ingredients of Part B and mix until uniform. Maintain temperature at 77 to 82 °C.

(C) *Step 3.* Add the batch of Step 1 at 77 to 82 °C to the batch of Step 2 at 77 to 82 °C, and mix until smooth and uniform. Slowly cool the batch to 49 to 54 °C.

(D) *Step 4.* Add the benzyl alcohol of Part C to the batch of Step 3 at 49 to 54 °C. Mix until uniform. Continue to cool batch to 35 to 41 °C.

(E) *Step 5.* Add sufficient water of Part D to the batch of Step 4 at 35 to 41 °C to obtain 100 grams of standard sunscreen preparation. Mix until uniform. Cool batch to 27 to 32 °C.

(ii) *HPLC assay of the standard padimate O/oxybenzone sunscreen.* To ensure that the standard sunscreen contains proper amounts of padimate O and oxybenzone, analyze it against USP reference standards for padimate O and oxybenzone in a high performance liquid chromatography procedure using the following parameters:

(A) *Reagents.* (*1*) Acetic acid, glacial, ACS grade.

(*2*) Isopropanol, HPLC grade.

(*3*) Methanol, HPLC grade.

(*4*) Oxybenzone, USP reference standard.

(*5*) Padimate O, USP reference standard.

(B) *Instrumentation.* Equilibrate a suitable liquid chromatograph to the following or equivalent conditions:

Column	Ultrasphere ODS 250 x 4.6 millimeters (5 microns), or Supelcosil LC-18 DB 250 x 4.6 millimeters (5 microns)
Mobile Phase	85:15:0.5 methanol:water:acetic acid
Flow Rate	1.5 milliliters per minute
Temperature	Ambient
Detector	UV spectrophotometer at 308 nanometers
Attenuation	As needed
Injection Amount	10 microliters

(C) *Standard preparation.* (*1*) Weigh 0.50 gram of oxybenzone reference standard into a 250-milliliter volumetric flask. Dissolve and dilute to volume with isopropanol. Mix well.

(*2*) Weigh 0.50 gram of padimate O reference standard into a 250-milliliter volumetric flask. Dissolve and dilute to volume with isopropanol. Mix well.

(*3*) Pipet 3.0 milliliters of the oxybenzone solution and 7.0 milliliters of the padimate O solution into a 100-milliliter volumetric flask. Dilute to volume with isopropanol and mix well. This is the standard preparation.

(D) *Sample preparation.* (*1*) Weigh 1.0 gram of sample into a 50-milliliter volumetric flask.

(*2*) Add approximately 30 milliliters of isopropanol and heat with swirling until the sample is evenly dispersed.

(*3*) Cool to room temperature (15 to 30 °C) and dilute to volume with isopropanol. Mix well.

(*4*) Pipet 5.0 milliliters of this sample preparation into a 50-milliliter volumetric flask and dilute to volume with isopropanol. Mix well.

(E) *System suitability.* (*1*) Three replicate injections of the standard preparation (described in paragraph (a)(3)(ii)(C) of this section) will yield a relative standard deviation of not more than 2.0 percent calculated on peak areas for oxybenzone and padimate O.

(*2*) A calculated resolution between the oxybenzone and padimate O peaks will be not less than 3.0.

(*3*) In case a system fails to meet this criterion, adjusting the mobile phase or replacing the column may be necessary to obtain suitable chromatography.

(F) *Analysis.* (*1*) Inject 10 microliters of the standard preparation (described in paragraph (a)(3)(ii)(C) of this section) in triplicate and collect data for about 15 minutes or until the padimate O peak has completely eluted. Elution order is oxybenzone, then padimate O.

(*2*) Similarly inject 10 microliters of each sample preparation.

(*3*) The system suitability requirements must be met.

(G) *Calculation.* Calculate the percent (weight/weight) of each sunscreen ingredient in the sample preparation as follows:

(*1*) Oxybenzone (percent weight)

$$\frac{\text{(Sample oxybenzone peak area)(Standard oxybenzone weight}^{1}\text{)(DF}^{2}\text{)}}{\text{(Standard oxybenzone peak area)(Sample weight}^{1}\text{)}}$$

[1] weight in grams
[2] DF is a dilution factor calculated as in paragraph (a)(2)(ii)(G) of this section.

(*2*) Padimate O (percent weight)

$$\frac{(\text{Sample padimate O peak area})(\text{Standard padimate O weight}^{1})(\text{DF}^{2})}{(\text{Standard padimate O peak area})(\text{Sample weight}^{1})}$$

[1] weight in grams
[2] DF is a dilution factor calculated as in paragraph (a)(2)(ii)(G) of this section.

(b) *Light source (solar simulator)*—(1) *Emission spectrum.* 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 (nm) with a limit of 1,500 watts per square meter (W/m^2) on total solar simulator irradiance for all wavelengths between 250 and 1400 nm and the following percentage of erythema-effective radiation in each specified range of wavelengths:

SOLAR SIMULATOR EMISSION SPECTRUM

Wavelength range (nm)	Percent erythemal contribution
< 290	< 0.1
290–310	46.0–67.0
290–320	80.0–91.0
290–330	86.5–95.0
290–340	90.5–97.0
290–350	93.5–98.5
290–400	93.5–100.0

(2) *Operation.* A solar simulator should have no significant time related fluctuations (within 20 percent) in radiation emissions after an appropriate warmup time and good beam uniformity (within 20 percent) in the exposure plane. The average delivered dose to the UV exposure site must be within 10 percent of the prescribed dose.

(3) *Periodic measurement.* To ensure that the solar simulator delivers the appropriate spectrum of UV radiation, the emission spectrum of the solar simulator must be measured every 6 months with an appropriate and accurately calibrated spectroradiometer system (results should be traceable to the National Institute for Standards and Technology). In addition, the solar simulator must be recalibrated if there is any change in the lamp bulb or the optical filtering components (i.e., filters, mirrors, lenses, collimating devices, or focusing devices). Daily solar simulator radiation intensity should be monitored with a broadband radiometric device that is sensitive primarily to UV radiation. The broadband radiometric device should be calibrated using