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Food and Drug Administration

**21 CFR Parts 347 and 352
Sunscreen Drug Products for Over-the-
Counter Human Use; Proposed
Amendment of Final Monograph;
Proposed Rule**

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 347 and 352

[Docket No. 1978N-0038] (formerly Docket No. 78N-0038)

RIN 0910-AF43

Sunscreen Drug Products for Over-the-Counter Human Use; Proposed Amendment of Final Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a proposed rule that would amend the final monograph (FM) for over-the-counter (OTC) sunscreen drug products as part of FDA's ongoing review of OTC drug products. This amendment addresses formulation, labeling, and testing requirements for both ultraviolet B (UVB) and ultraviolet A (UVA) radiation protection. FDA is issuing this proposed rule after considering public comments and new data and information that have come to FDA's attention. This rule proposes to lift the stays of 21 CFR 347.20(d) and 21 CFR Part 352 when FDA publishes a final rule based on this proposed rule.

DATES: Submit written or electronic comments by November 26, 2007. Submit written or electronic comments on FDA's economic impact determination by November 26, 2007. Please see section X of this document for the effective and compliance dates of any final rule that may publish based on this proposal.

ADDRESSES: You may submit comments, identified by Docket No. 1978N-0038 and RIN number 0910-AF43, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following ways:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.
- Agency Web site: <http://www.fda.gov/dockets/ecomments>. Follow the instructions for submitting comments on the agency Web site.

Written Submissions

Submit written submissions in the following ways:

- FAX: 301-827-6870.
- Mail/Hand delivery/Courier (for paper, disk, or CD-ROM submissions): Division of Dockets Management (HFA-

305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal or the agency Web site, as described in the *Electronic Submissions* portion of this paragraph.

Instructions: All submissions received must include the agency name, docket number and regulatory information number (RIN) for this rulemaking. All comments received may be posted without change to <http://www.fda.gov/ohrms/dockets/default.htm>, including any personal information provided. For additional information on submitting comments, see the "Request for Comments" heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to <http://www.fda.gov/ohrms/dockets/default.htm> and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Matthew R. Holman, Office of Nonprescription Products, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 5414, Silver Spring, MD 20993, 301-796-2090.

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I. Background

In the **Federal Register** of May 12, 1993 (58 FR 28194), FDA published a notice of proposed rulemaking in the form of a tentative final monograph (TFM) for OTC sunscreen drug products. In the TFM, FDA proposed the conditions under which OTC sunscreen drug products would be considered generally recognized as safe and effective (GRASE), under section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)), and not misbranded, under section 502 of the act (21 U.S.C. 352).

In the **Federal Register** of April 5, 1994 (59 FR 16042), FDA reopened the administrative record until July 31, 1994, to allow additional submissions on UVA-related issues and announced a public meeting for May 12, 1994, to discuss UVA testing procedures. As explained in that **Federal Register** notice, the TFM included proposed UVB (i.e., 290-320 nm) testing and labeling. The sun protection factor (SPF)

test and corresponding labeling reflects the level of protection against sunburn, which is caused primarily by UVB radiation. The TFM also explained the importance of protection against UVA radiation (i.e., 320–400 nm), the other UV component of sunlight (58 FR 28194 at 28232 and 28233). The TFM referenced published UVA test methods but did not propose a method (58 FR 28194 at 28248 to 28250). Rather, the TFM stated that a product could be labeled as “broad spectrum” or a similar claim if it protected against UVA radiation. Thus, FDA held the 1994 public meeting to gather further information about an appropriate UVA test method and labeling.

In the **Federal Register** of June 8, 1994 (59 FR 29706), FDA proposed to amend the TFM (and reopened the comment period until August 22, 1994) to remove five proposed sunscreen ingredients from the TFM because of lack of interest in establishing United States Pharmacopeia—National Formulary (USP–NF) monographs. FDA also reiterated that all sunscreen ingredients must have a USP–NF monograph before being included in the FM for OTC sunscreen drug products.

In the **Federal Register** of August 15, 1996 (61 FR 42398), FDA reopened the administrative record until December 6, 1996, to allow additional submissions on zinc oxide and titanium dioxide as well as sunscreen photostability. FDA also announced a public meeting for September 19 and 20, 1996, to discuss the safety and efficacy of these two ingredients and photostability of sunscreens in general.

In the **Federal Registers** of September 16, 1996 (61 FR 48645) and October 22, 1998 (63 FR 56584), FDA amended the TFM to add the UVA-absorbing sunscreen ingredients avobenzene and zinc oxide to the proposed list of monograph ingredients. FDA also proposed indications for these ingredients. As a result of this amendment to the TFM, in the **Federal Register** of April 30, 1997 (62 FR 23350), FDA announced an enforcement policy allowing interim marketing of OTC sunscreen drug products containing avobenzene.

On November 21, 1997, Congress enacted the Food and Drug Administration Modernization Act of 1997 (FDAMA). Section 129 of FDAMA stated that “Not later than 18 months after the date of enactment of this Act, the Secretary of Health and Human Services shall issue regulations for over-the-counter sunscreen products for the prevention or treatment of sunburn.” FDA identified the UVB portions of the monograph (and related provisions on

water resistant test methods and cosmetic labeling) as items that could be finalized within the timeframe set by FDAMA. Because of outstanding issues related to the development of testing standards and labeling for UVA radiation protection, FDA deferred final action on these items.

Therefore, in the **Federal Register** of May 21, 1999 (64 FR 27666), FDA published the FM for OTC sunscreen drug products in part 352 (21 CFR part 352) with an effective date of May 21, 2001, but deferred UVA testing and labeling for future regulatory action. FDA stated that more time was required to review comments from interested parties on active ingredients, labeling, and test methods for products intended to provide UVA protection. This proposed amendment to the FM for OTC sunscreen drug products will complete the FM by addressing both UVB and UVA testing and labeling.

In the **Federal Register** of June 8, 2000 (65 FR 36319), FDA reopened the administrative record of the rulemaking for OTC sunscreen drug products to allow for specific comment on high SPF and UVA radiation testing and labeling. FDA also extended the effective date for the FM to December 31, 2002.

In the **Federal Register** of December 31, 2001 (66 FR 67485), FDA stayed the December 31, 2002, effective date of the FM for OTC sunscreen drug products in part 352 until we provided further notice in a future issue of the **Federal Register**. FDA took this action because we planned to amend part 352 to address formulation, labeling, and testing requirements for both UVB and UVA radiation protection. This document proposes such changes. This document also proposes an effective date related to publication of an amended FM (see section X of this document). The existing stay of the effective date for part 352 remains in effect at this time.

In the **Federal Register** of June 20, 2002 (67 FR 41821), FDA published a technical amendment to change the names of four sunscreen active ingredients in § 352.10 of the monograph to be consistent with name changes that appeared in USP 24. The new names, which are simpler and more convenient, are meradimate for menthyl anthranilate, octinoxate for octyl methoxycinnamate, octisalate for octyl salicylate, and ensulizole for phenylbenzimidazole sulfonic acid. Because the names became official on March 1, 2001, manufacturers could begin using them at any time after that date.

In the **Federal Register** of June 4, 2003 (68 FR 33362), FDA issued a final rule

establishing conditions under which OTC skin protectant products are generally recognized as safe and effective and not misbranded. This final rule lifted the stay of 21 CFR part 352 to amend the final monograph for OTC sunscreen drug products to include sunscreen-skin protectant combination drug products. This final rule concluded by placing a stay on both part 352 and on § 347.20(d). The proposed rule that is the subject of this document provides UVA testing and labeling that is necessary on sunscreen and sunscreen-skin protectant combination drug products. This proposed rule, therefore, proposes that the stays of both part 352 and § 347.20(d) be lifted when this rule is finalized. These stays will be maintained until a final rule based on this proposed rule becomes effective.

In the **Federal Register** of September 3, 2004 (69 FR 53801), FDA delayed the implementation date for OTC sunscreen drug products subject to the final rule that established standardized format and content requirements for the labeling of OTC drug products (i.e., Drug Facts rule). FDA explained that we postponed the Drug Facts implementation date because we did not expect to complete the final amendment of the sunscreen monograph to include UVA testing and labeling by the Drug Facts implementation date of May 16, 2005 (64 FR 13254 at 13273 and 13274, March 17, 1999). Thus, FDA delayed the implementation date of the Drug Facts rule with respect to OTC sunscreen drug products until further notice to avoid issuing successive relabeling requirements for sunscreen drug products at two closely related time intervals, as required by the Drug Facts rule and the final amendment to the sunscreen monograph.

II. Summary of Major Changes to the FM

In response to the TFM and FM, FDA received substantial data and information regarding UVA and UVB active ingredients, claims, and testing procedures, as well as on other issues addressed in this document. FDA summarizes these issues and proposed changes to the FM in this section.

A. Ingredients

FDA proposes to add combinations of avobenzene with zinc oxide and avobenzene with ensulizole as permitted combinations of active sunscreen ingredients in the FM (see section III.C, comment 7 of this document).

B. UVB (SPF) Labeling

The FM allowed specific labeled SPF values up to, but not exceeding, 30. OTC sunscreen drug products with SPF values greater than 30 could be labeled with the collective term “30+.” In this amendment, FDA proposes to increase the specific labeled SPF value to 50 and revise the collective term to “50+.” FDA will consider higher specific labeled SPF values upon receipt of adequate, validated data (see section III.F, comment 15 of this document).

In addition, FDA proposes to revise the following FM labeling:

- The phrase “sun protection” to “sunburn protection” where used in §§ 352.3(b)(1), (b)(2), (b)(3), and (d) and 352.52(e)(1)(i), (e)(1)(ii), and (e)(1)(iii) (see section III.D, comment 10 of this document); and

- Section 352.50(a) to include the term “UVB” before the term “SPF” on the principal display panel (PDP), along with the product category designation (PCD) (see section III.E, comment 14 of this document).

FDA also proposes to revise the PCD SPF ranges in § 352.3(b)(1), (b)(2), and (b)(3) (proposed § 352.3(c)(1) through (c)(4)) to reflect the following:

- The current standard public health message concerning use of sunscreens,
- The proposed increase of the labeled SPF value to “50+,” and
- The proposed addition of the term “UVB” before the word “sunburn.”

Proposed § 352.3(c)(4) contains a new PCD of “highest UVB sunburn protection product” for products that provide an SPF value over 50. FDA further proposes to revise current § 352.3(b)(1) and (b)(2) to replace the current category descriptors of “minimal” and “moderate” with the terms “low” and “medium,” respectively. FDA considers the new terms to be simpler and uniform with the proposed UVB and UVA “Uses” statements. Proposed changes to PCDs and category descriptors also occur in proposed § 352.52(e)(1) (see section III.D, comment 13 and section III.G, comment 16 of this document). In addition, FDA proposes optional UVB radiation protection statements (see proposed § 352.52(e)(2) and (e)(3)).

C. UVA Labeling

FDA proposes new labeling to designate the level of UVA protection on the PDP of OTC sunscreen drug products. FDA proposes the use of symbols (“stars”) in conjunction with a descriptor (i.e., “low,” “medium,” “high,” or “highest”). FDA also proposes to add new § 352.50(b) specifying the required PDP labeling for

OTC sunscreen products tested in accordance with the proposed UVA testing procedures in §§ 352.71 and 352.72 (see section III.E, comment 14 and section III.N, comment 45 of this document).

D. Indications

The FM allowed the following two UVB indications in § 352.52(b)(1):

- “helps prevent sunburn”
- “higher SPF gives more sunburn protection”

In this amendment, FDA proposes to revise the first statement to read “low,” “medium,” “high,” or “highest” “UVB sunburn protection” in proposed § 352.52(b)(1)(i) through (b)(1)(iv). FDA is proposing to revise the additional indications in § 352.52(b)(2) to reflect the new PCD ranges in proposed § 352.3(c) (e.g., SPF of 2 to under 12 becomes SPF of 2 to under 15) and create the new PCD range over SPF 50. These proposed revisions are based upon the revised PCD categories in proposed § 352.3(c) (see section III.G, comment 16 of this document). FDA proposes that the second statement in current § 352.52(b)(1) (“higher SPF gives more sunburn protection”) no longer be required and proposes an additional indication regarding UVA protection (see proposed § 352.52(b)(2)(v)).

In proposed § 352.52(b)(2)(v), FDA includes a new indication for UVA protection that involves selection of the appropriate descriptor (“low,” “medium,” “high,” or “highest”) to describe the level of protection. In proposed § 352.52(b)(2)(vi), FDA includes a modified version of the sunburn “Uses” statement required by proposed § 352.52(b)(1)(i) through (b)(1)(iv) when the additional statement in proposed § 352.52(b)(2)(v) is used and bears the same category descriptor as the SPF value (e.g., medium UVA/UVB protection from sunburn) (see section III.G, comment 17 of this document).

E. Warnings

FDA is proposing to shorten the warning in § 352.52(c)(1)(ii) (proposed § 352.52(c)(3)) under the subheading “Stop use and ask a doctor if” from “[bullet] rash or irritation develops and lasts” to “[bullet] skin rash occurs.”

FDA proposes removing the optional “sun alert” product performance statement (current § 352.52(e)(2)) and requiring a revised “sun alert” statement in the “Warnings” section (proposed § 352.52(c)(1)). FDA proposes that this revised statement be required on all OTC sunscreen drug products except lip cosmetic-drug and lip protectant-sunscreen products subject to

§ 352.52(f), which are not required to include this statement under proposed § 352.52(f)(1)(v) and (f)(1)(vi) (see section III.G, comment 19 of this document). The statement in proposed § 352.52(c)(1) reads as follows: “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.” FDA proposes that the statement appear in bold type as the first statement in the “Warnings” section.

F. Directions

FDA proposes changes to the directions to reduce the likelihood that OTC sunscreen drug products are underapplied. Section 352.52(d)(1)(i) currently provides manufacturers the option to select one or more of the following terms: “liberally,” “generously,” “smoothly,” or “evenly.” FDA is proposing to allow the choice of one of two required terms (i.e., “liberally” or “generously”) and to include “evenly” as an additional optional term. FDA is proposing to eliminate the term “smoothly” because it is vague.

FDA also proposes to add a new direction “apply and reapply as directed to avoid lowering protection” (proposed § 352.52(d)(1)(ii)). Because new information demonstrates the importance of sunscreen reapplication, FDA also proposes to make the optional directions in paragraph (d)(2) a requirement. As a result of this change, FDA is proposing to remove the current language in paragraph (d)(3) because it is no longer necessary. Instead, FDA is proposing, in paragraph (d)(3), required information for products that do not satisfy the water resistant testing procedures in § 352.76. FDA is also proposing a required reapplication statement in § 352.52(d)(1)(ii). The reapplication information in current § 352.52(d)(2) appears in proposed § 352.52(d)(2) and (d)(3) of this document (see section III.H, comment 22 of this document).

G. UVB Testing

FDA is proposing to revise the SPF (UVB) testing procedure (see section III, paragraphs I through L of this document) and to move the SPF testing procedure currently in §§ 352.70 through 352.73 to proposed § 352.70. FDA proposes a padimate O/ oxybenzone sunscreen standard in § 352.70 that will be required for testing sunscreen products with SPF values over 15. Manufacturers may use either this padimate O/oxybenzone standard

or the homosalate standard to test products with SPF values of 2 to 15. FDA proposes a high pressure liquid chromatography (HPLC) method to replace the spectrophotometric method used to assay the homosalate and padimate O/oxybenzone standards.

FDA proposes the following modifications to the SPF testing procedure:

- Specifications for the solar simulator in § 352.71 (proposed § 352.70(b)),
- Instructions for the application of test materials and response criteria in § 352.72 (proposed § 352.70(c)), and
- Doses and determination of minimal erythema dose (MED) in § 352.73 (proposed § 352.70(d)).

FDA proposes to continue requiring a finger cot to be used in the application of sunscreen standard and test product as specified in § 352.72(e) (proposed § 352.70(c)(5)). However, FDA now proposes that the finger cot be pretreated. These two proposed UVB testing changes also apply to UVA in vivo testing.

H. UVA Testing

FDA proposes a combination of spectrophotometric (in vitro) and clinical (in vivo) UVA test procedures in proposed §§ 352.71 and 352.72, respectively. To assure UVA protection for “water resistant” and “very water resistant” sunscreen products, FDA proposes that the in vivo UVA test be conducted after the appropriate water immersion period for OTC sunscreen drug products making a UVA claim. Therefore, FDA proposes modification of § 352.76 to state that the water resistance claim applies to the SPF and, if appropriate, UVA values determined after the appropriate water immersion period as described in proposed § 352.70 and, if appropriate, proposed § 352.72.

III. FDA's Tentative Conclusions on the Comments

A. General Comments on OTC Sunscreen Drug Products

(Comment 1) Several comments asked that FDA provide more time to comply with requirements of the FM in order to avoid an adverse economic impact on the sun care industry and consumers. The comments described the seasonal dynamics of the sun care industry (i.e., products are sold in two marketing cycles over a period of 18 months) and stated that the industry would need more time to develop products that meet the FM requirements and allow for shipment of the previous year's returns. The comments mentioned times from 2

to 3 years after publication of the FM as appropriate or necessary for implementation. Several of these comments added that the date should be in the June/July time period because the shipping season is practically over at that time and manufacturing for the next season is just beginning.

FDA understands the seasonal nature of the sunscreen industry and the time required for product testing and relabeling. FDA is also aware that more than 1 year may be needed for implementation. FDA is proposing an 18- to 24-month implementation date and will try to have it coincide with the June/July time period (see section XI of this document).

(Comment 2) One comment requested that FDA and the Federal Trade Commission (FTC) take steps to make sure that sunscreen manufacturers provide information to the American public to help them understand and use the Ultraviolet Index (UVI) to determine their risk of sunburn.

The National Weather Service, the Environmental Protection Agency (EPA), and the Centers for Disease Control and Prevention (CDC) developed the UVI, which has been in use since 1995. This index is an indication of the amount of UV radiation reaching the surface of the earth as a function of ozone data, atmospheric pressure, temperature, and cloudiness and is generated for 58 cities around the United States.

Usage information required by the OTC sunscreen drug product monograph applies regardless of the UVI value. Therefore, FDA believes that UVI information need not be required in the monograph for the safe and effective use of these products and should not be included in the “Drug Facts” labeling. However, manufacturers who wish to do so may voluntarily include such information in their labeling outside the “Drug Facts” box.

(Comment 3) One comment requested that FDA make clear, through either the FM for skin protectant or sunscreen drug products, or both, that combination products containing sunscreen and skin protectant ingredients may be lawfully marketed.

Section 347.20(d) of the skin protectant FM (21 CFR 347.20(d)), which published in the **Federal Register** of June 4, 2003 (68 FR 33362), provides for combinations of sunscreen ingredients and specific skin protectant ingredients. The final rule for OTC skin protectant drug products also included an amendment to the sunscreen FM, adding new § 352.20(b), which allows combinations of sunscreen and skin protectant active ingredients. Thus, both

monographs now state the same conditions for lawfully marketing these combination products. The existing language in §§ 347.20(d) and 352.20(b) would include the two new combinations that FDA is proposing to add to the sunscreen monograph (see section II.A, comment 7 of this document).

B. Comments on Tanning and Tanning Preparations

(Comment 4) One comment requested that the effective date of § 740.19 (21 CFR 740.19) be extended to December 31, 2002, consistent with the delay of the effective date for § 310.545(a)(29) and (d)(31), part 352, and § 700.35 (65 FR 36319). The comment stated that singling out § 740.19 to become effective earlier might constitute an arbitrary and capricious decision by FDA.

The May 21, 1999, final rule set a 2-year effective date (May 21, 2001) for § 310.545(a)(29) and (d)(31), part 352, and § 700.35. In the **Federal Register** of June 8, 2000 (65 FR 36319), FDA extended the effective date for compliance with § 310.545(a)(29) and (d)(31), part 352, and § 700.35 until December 31, 2002, to provide time for completion of a more comprehensive UVA/UVB FM for OTC sunscreen drug products. On December 31, 2001, FDA then stayed the effective date of part 352 (but not § 310.545(a)(29) and (d)(31), and § 700.35) until further notice (66 FR 67485). FDA took this action because we are amending part 352 to address formulation, labeling, and testing requirements for both UVA and UVB radiation protection. The May 21, 1999, final rule also set a 1-year effective date (May 22, 2000) for new § 740.19, which addresses a warning statement for cosmetic suntanning preparations that do not contain a sunscreen active ingredient. These products are not subject to the monograph for OTC sunscreen drug products in part 352. FDA considered this warning to be sufficiently important for safety reasons when we issued the final rule (64 FR 27666 at 27669) to require a 12-month effective date as opposed to the 24-month effective date for the other sections of the rule. Further, FDA's primary reason for extending the effective date of those other sections to December 31, 2002, and then staying part 352 to address formulation, labeling, and testing requirements for both UVA and UVB protection, was to allow FDA to develop a comprehensive UVB/UVA final monograph. This reason does not apply to § 740.19. Accordingly, FDA did not extend the effective date for § 740.19, and § 740.19 is in effect at this time. FDA concludes that this

decision is not arbitrary and capricious, but is based on valid health concerns related to the products subject to the warning requirement in § 740.19.

(Comment 5) One comment requested that FDA and FTC take steps to ensure sunscreen manufacturers inform consumers that their natural skin pigmentation provides protection from sunlight. The comment stated that these adaptive individuals might not require a daily application of a sunscreen. Another comment submitted a copy of a patent for an electronic sensor device to measure solar radiation. The comment stated that the personal device could alert consumers to their level of UV exposure so they could either come out of the sun or apply a sunscreen to avoid sunburn and skin cancer.

FDA has no objection to sunscreen manufacturers informing consumers that their natural skin pigmentation provides protection from sunlight. However, FDA has no basis to require such information as part of the required labeling for OTC sunscreen drug products. Thus, manufacturers may include this information in labeling outside of the "Drug Facts" box, but are not required to include this information. FDA considers the comment regarding the UV measuring device to be outside the scope of this rulemaking, which evaluates the safety, effectiveness, and labeling of OTC drug products.

C. Comments on Specific Sunscreen Active Ingredients

(Comment 6) Several comments requested that dihydroxyacetone (DHA) be added to the monograph as a single active ingredient for UVA protection. The comments claimed that DHA alone provides an SPF of 2 to 4. One comment claimed that a 15 percent topical solution of DHA provided a photoprotective factor of 10 in the UVA region. Other comments contended that the brown color produced by DHA, resembling melanin, should potentiate the action of sunscreens. Another comment stated that DHA alone is not a sunscreen, but forms a sunscreen when combined with lawsone. The comment cited unpublished observations by two independent investigators that the melanoidins of DHA-induced skin pigment resemble melanin in that they absorb UVB strongly, with decreasing absorbance through the UVA region and into visible light. The comment added that, because DHA alters the structure of the skin surface, it is, by definition, a drug.

One comment provided information on the safety and UVA effectiveness of DHA alone (Ref. 1). Safety studies included the following:

- Oral and dermal toxicity studies,
- A chronic skin painting carcinogenicity study in mice,
- Comedogenicity tests in rabbits,
- Repeated insult patch test in humans, and
- Photoallergy tests.

Effectiveness studies consisted of published articles using either humans or photosensitized rats. Another comment discussed investigations with DHA on psoriasis patients sensitized with 8-methoxypsoralen (8-MOP).

FDA is not proposing to include DHA in the monograph as a single active ingredient in OTC sunscreen products. Although there were no product submissions to the Advisory Review Panel on Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products (the Panel) using DHA as a sunscreen ingredient, the Panel discussed available scientific evidence for DHA as a single sunscreen ingredient. The Panel concluded that DHA is not a sunscreen but a cosmetic; it is a sunscreen only when used with lawsone (43 FR 38206 at 38215 to 38216, August 25, 1978). Although one comment stated that DHA alters the structure of the skin, it did not provide data to support this claim. Thus, at this time, FDA agrees with the Panel that DHA is a cosmetic.

FDA acknowledges that DHA is the subject of an approved color additive petition and its safety as a color additive has been established. However, the submitted chronic (life-span) skin painting study in mice does not support the safe use of DHA as a sunscreen because no group of mice was included in the study to determine the possible photocarcinogenic effect of DHA. This effect needs to be studied because DHA is associated with carbonyl compounds known to react with pyrimidine bases in the presence of UV radiation, and it appears to be a potent inducer of thymine dimers, premutagenic deoxyribonucleic acid (DNA) lesions. Therefore, its safety, in terms of the type, extent, and location of photo-induced DNA damage, is of concern and should be determined. Whether DHA contributes or promotes UV carcinogenesis is not known.

The submitted studies on the effectiveness of DHA as a single UVA sunscreen ingredient add only qualitative information. Many of the studies utilized animal models; few included human subjects. One study involved only five subjects, three with erythropoietic protoporphyria and two with polymorphic light eruptions. Another study involved six subjects sensitized with 8-MOP. In both studies,

too few subjects were enrolled, and the study subjects were not representative of the average sunscreen user.

Well-controlled clinical trials with DHA alone are lacking. Although some investigations described by the comments suggest that DHA may help protect the normal skin of psoriasis patients, concerns remain about the usefulness of DHA products in the OTC market. For example, one comment stated that photoprotection provided by DHA depends upon the way the product polymerizes in the stratum corneum and that polymerization depends on the skin of each individual. Therefore, the photoprotection provided by DHA varies from person to person and has to be determined for each person by diffuse reflectance spectroscopy. Given these statements, it is not clear how appropriate OTC drug product labeling could be written to aid consumers in proper selection and use of a DHA sunscreen.

FDA concludes that current information is inadequate to include DHA in the monograph as a single sunscreen ingredient. None of the comments provided information to establish the appropriate number of consecutive product applications and the timing of these applications (how far apart or how soon before sun exposure) that are necessary to achieve the desired protection using products containing various concentrations of DHA. In two submitted studies, a preparation containing 3 percent DHA was applied six times prior to sun exposure and a preparation containing 15 percent DHA preparation was applied one time 24 hours prior to sun exposure, respectively (Ref. 1). The comments did not include any information on appropriate regimens for various skin types, which is necessary because the level of photoprotection provided by DHA is dependent on skin type. Therefore, based upon this lack of information, it is not clear how to state appropriate label directions for consumer use. FDA needs additional information from clinical studies to determine the effective concentration of DHA in sunscreen product formulations and the frequency and timing of product application.

(Comment 7) One comment submitted data to support the combination of avobenzene with ensulizole and avobenzene with zinc oxide (Ref. 2). The safety data included the following:

- A repeat insult patch test,
- A phototoxicity study, and
- A photoallergy study.

The effectiveness data involved a clinical study using the in vitro "critical wavelength" (CW) method and the in

vivo “protection factor A” (PFA) method to support the UVA radiation protection potential of the combination products. The PFA test data were from a double blind clinical study using five sunscreen formulations.

The safety studies demonstrated that the following combinations of active ingredients have a low potential for irritation, allergic sensitization, and phototoxicity:

- 3 percent or less avobenzone with 2 percent ensulizole
- 3 percent or less avobenzone with 5 percent zinc oxide

The data further suggested that the photoallergic potential of avobenzone is not augmented by its combination with either ensulizole or zinc oxide.

The clinical study using the PFA in vivo method demonstrated that the following combinations of active ingredients are significantly more effective than 1.5 percent ensulizole or 3 percent zinc oxide alone in protecting against UVA radiation:

- 3 percent avobenzone with 1.5 percent ensulizole
- 3 percent avobenzone with 4 percent zinc oxide

FDA’s detailed comments on the safety and effectiveness studies are on file in the Division of Dockets Management (Ref. 3).

FDA considers the data submitted by the comment sufficient to support the safety and effectiveness of avobenzone with ensulizole and avobenzone with zinc oxide when used in the concentrations established for each ingredient in § 352.10 of the sunscreen monograph. Accordingly, FDA is proposing to amend § 352.20(a)(2) by adding ensulizole and zinc oxide.

Marketing of products containing avobenzone with ensulizole and avobenzone with zinc oxide will not be permitted unless and until the following three actions occur:

1. The comment period specific to this proposal closes.
2. FDA has evaluated all comments on these combination products submitted in response to the proposal.
3. FDA publishes a **Federal Register** notice announcing our determination to permit the marketing of OTC sunscreen drug products containing these combinations.

D. General Comments on the Labeling of Sunscreen Drug Products

(Comment 8) One comment agreed that the labeling modifications allowed by the FM in § 352.52 for OTC sunscreen products marketed as a lipstick or labeled for use only on specific small areas of the face (e.g., lips, nose, ears, and/or around eyes) are

appropriate for these products. Based on the labeling in § 352.52, the comment proposed eight additional modifications for all other OTC sunscreen products regardless of package size:

1. Delete “Drug Facts” title because it is inappropriate and unnecessary for sunscreens.

2. Omit “Purpose” because it is repetitive of the statement of identity on the PDP and “Uses” information.

3. Revise “higher SPF gives more sunburn protection” in “Uses” to read “higher SPF products give more sun protection, but are not intended to extend the time spent in the sun,” and require this statement only on products with an SPF value over 30.

4. Omit “For external use only” warning because it is self-evident for sunscreen products.

5. Revise “When using this product [bullet] keep out of eyes. Rinse with water to remove” to read “Keep out of eyes.”

6. Revise “Stop use and ask a doctor if [bullet] rash or irritation develops and lasts” to read “Stop use if skin rash occurs.”

7. Omit barlines, hairlines, and box enclosure.

8. Allow the option to list inactive ingredients in a different location on the label or in labeling accompanying the product.

The comment stated that these modifications would allow reduced Drug Facts labeling for all OTC sunscreen drug products.

The comment contended that sunscreen products meet all of FDA’s criteria for reduced labeling (64 FR 13254 at 13270):

- Packaged in small amounts,
- High therapeutic index,
- Extremely low risk in actual consumer use situations,
- A favorable public health benefit,
- No specified dosage limitation, and
- Few specific warnings and no general warnings (e.g., pregnancy or overdose warnings).

The comment added that OTC sunscreen products are a unique category substantially different from most other types of OTC drug products because they are recommended for use on a daily basis to prevent serious disease. The comment concluded that FDA’s rationale for standardized labeling format and content requirements does not necessarily transfer to OTC sunscreen products and specifically not to drug-cosmetic products with a sunscreen.

When FDA created the standardized labeling format and content requirements (i.e., “Drug Facts” labeling) for OTC drug products, we

recognized that some product packages were too small to accommodate all of the required labeling. Therefore, under § 201.66(d)(10) (21 CFR 201.66(d)(10)), FDA allows labeling format modifications for all OTC drug products sold in small packages. In the final rule establishing “Drug Facts” labeling, FDA also stated that we may allow reduced labeling requirements beyond those specified under § 201.66(d)(10) for OTC drug products that meet the criteria listed in the preceding paragraph (see section III.D, comment 9 of this document).

In the final rule for OTC sunscreen drug products (64 FR 27666 at 27681 to 27682), FDA recognized that some OTC sunscreen drug products meet these criteria for reduced labeling. Specifically, FDA identified OTC sunscreen drug products that qualify for the small package specifications in § 201.66(d)(10) and are labeled for use only on specific small areas of the face as meeting the criteria for reduced labeling. Therefore, FDA allows content and format modifications for these products under § 352.52(f). FDA allows further modifications for lip products containing sunscreen because these products for small areas of the face are sold in even smaller packages than the other sunscreen products marketed under § 352.52(f) (68 FR 33362 at 33371; 64 FR 13254 at 13270). FDA believes that sunscreen products labeled for use only on small areas of the face, including lip products containing sunscreen, serve an important public health need and FDA does not want to discourage manufacturers from marketing these products (64 FR 13254 at 13270).

FDA does not find it appropriate to extend the labeling modifications for OTC sunscreen drug products marketed under § 352.52(f) to all OTC sunscreen drug products. FDA disagrees with the comment’s argument that all sunscreen products meet the criteria for reduced Drug Facts labeling (64 FR 13254 at 13270), because most sunscreen products are not sold in small packages. Therefore, because sunscreen products do not generally meet all of the criteria for reduced Drug Facts labeling, FDA is not proposing reduced labeling for all OTC sunscreen products.

FDA does not consider sunscreens as a unique category substantially different from other types of OTC drug products because they are recommended for use on a daily basis to prevent serious disease, as argued by the comment. Other OTC drug products are used on a daily basis, some to prevent serious disease and some for other reasons. For example, anticaries drug products are

used daily to prevent dental caries. Antiperspirant drug products can be used daily to reduce underarm wetness. FDA has concluded that these various products should generally be labeled using the standardized content and format in § 201.66. The standardized labeling allows consumers to more easily recognize that these products are, in fact, drug products and to more easily read and understand the labeling information.

The same principle applies when the product is a drug cosmetic product (e.g., sunscreen moisturizer or antiperspirant deodorant). Consumers need to be informed that the product has a drug effect, and the uniform Drug Facts labeling for all OTC drug and drug cosmetic products helps convey this message. FDA applied this rationale when it finalized the requirements in the final rule that established § 201.66.

FDA agrees that some OTC sunscreen drug products meet the criteria for reduced information for safe and effective use (64 FR 13254 at 13270, 64 FR 27666 at 27681 to 27682). However, FDA disagrees with most of the modifications proposed by the comment for all package sizes of OTC sunscreen products. FDA disagrees with deletion of the "Drug Facts" title and the "Purpose" information because many sunscreen products do not meet the parameters for reduced Drug Facts labeling.

FDA disagrees that the "Purpose" information is repetitive and, therefore, disagrees that it may be omitted where there is sufficient labeling space. The "Purpose" section is a standard part of Drug Facts labeling and is intended to inform consumers which ingredients are sunscreens in a product. This information is even more important when a sunscreen is marketed in a combination product. For example, in a sunscreen skin protectant drug product, the "Purpose" section informs consumers which ingredients are sunscreens and which are skin protectants.

FDA has revised the "Uses" section and deleted the statement "higher SPF gives more sunburn protection" (see section III.G, comment 16 of this document). FDA disagrees with omitting the "For external use only" warning for all OTC sunscreen drug products. FDA finds no basis to exclude all OTC sunscreen products from this requirement. Likewise, FDA finds no reason to omit the two standard subheadings that accompany the warning statements, as proposed by the comment. Further, FDA disagrees with the comment's suggestion to omit the statement "Rinse with water to

remove." This is useful information if a sunscreen product gets into the eyes. FDA agrees with part of the proposed shortened warning for OTC sunscreen drug products to "Stop use if skin rash occurs" in place of "Stop use and ask a doctor [bullet] if rash or irritation develops and lasts." Therefore, FDA is proposing to amend § 352.52(c)(1)(ii) (proposed § 352.52(c)(3)) to state: "Stop use and ask a doctor if [bullet] skin rash occurs."

FDA finds no reason to omit barlines, hairlines, or the box enclosure for all OTC sunscreen drug products regardless of package size. These labeling formats help consumers identify a product as a drug and help make labeling information easier to read and understand. Thus, they should be included when package size allows. The FM already allows horizontal barlines and hairlines and the box enclosure to be omitted if a small package meets the criteria in §§ 352.52(f) and 201.66(d)(10).

Finally, FDA has no basis to provide an option for sunscreen products to list inactive ingredients in labeling that accompanies the products. FDA interprets section 502(e)(1)(A)(iii) of the act (21 U.S.C. 352(e)(1)(A)(iii)) as requiring the inactive ingredients to be listed on the outside container of a retail package or on the immediate container if there is no outside container or wrapper (§ 201.66(c)). Because this information, by law, must appear either on the outside container or immediate container of the product, FDA does not find a basis for allowing an option to list the inactive ingredients in a different location, such as other labeling accompanying the product. In accordance with § 201.66(c)(8), the inactive ingredients must be listed on the product label in the "Drug Facts" box.

(Comment 9) Two comments supported extending the labeling in § 352.52(f) for products intended for use only on specific small areas of the face and sold in small packages to all OTC sunscreen products. The comments contended that all OTC sunscreen drug products meet most of FDA's criteria for products that require minimal information for safe and effective use (64 FR 13254 at 13270) (see section III.G, comment 8 of this document).

The first comment added that FDA should permit the labeling modifications in § 352.52(f) for the following products:

- Makeup products (as defined in 21 CFR 720.4(c)(7)) with sunscreen, and
- Lotions and moisturizers for the hands or face with sunscreen in

containers of 2 ounces (oz) or less (by weight or liquid measure). The comment added that most facial makeup products are typically packaged in small containers. The comment stated that to meet any of FDA's concerns that lotions and moisturizers sold in larger packages may be used over the entire body despite labeling that restricts use to the face or hands, FDA could limit the flexible labeling to containers of 2 oz or less. Furthermore, the comment added that containers of 2 oz or less could not feasibly include the full OTC drug labeling.

The second comment contended that the modified labeling in § 352.52(f) is particularly compelling for color cosmetic products for the face that contain sunscreens (i.e., "facial makeups with sunscreen"). The comment added that these products and OTC sunscreen drug products for use only on specific small areas of the face have the same overall safety profile, and, therefore, FDA should allow these products to be labeled similarly.

A third comment strongly disagreed with a specific labeling exemption for makeup with sunscreen and moisturizer products for use on the face and hands. The comment contended that an exemption would not be in the best interest of consumers. The comment also argued that consumer confusion and subsequent misuse of sunscreen products, particularly failure to apply adequate amounts of sunscreen or to reapply a product after certain activities, will occur if FDA permits reduced labeling for these products. The comment added that many consumers use face and hand cosmetic products with sunscreen as their primary and only source of UV radiation protection for those areas of the body. Moreover, consumers are more likely to use these products properly if they contain full sunscreen drug labeling. The comment concluded that makeup foundations, tints, blushes, rouges, and moisturizers that are intended to be used on a daily or frequent basis to protect against the adverse health and skin aging effects of acute and chronic sun exposure must be labeled as drugs similar to other OTC sunscreen products.

FDA is not proposing to extend the labeling modifications in § 352.52(f), which is specific for products used only on small areas of the face and sold in small packages, to all OTC sunscreen products. FDA has determined that most OTC sunscreen products should have full drug labeling information using the standardized content and format in § 201.66 to ensure the safe and effective use of these products. In establishing the labeling modifications in § 352.52(f),

FDA determined how the labeling information for sunscreen drug products, including drug cosmetic products, could best be presented on products with limited labeling space and still provide consumers with adequate information to use these products safely and effectively. Although any sunscreen products sold in small packages that meet the criteria in § 201.66(d)(10) are allowed the format exemptions under that section, FDA is also proposing content exemptions for sunscreen products marketed under § 352.52(f). FDA is proposing these exemptions under § 352.52(f) because sunscreen products labeled for use only on small areas of the face and sold in small packages are generally sold in packages substantially smaller than other sunscreen products, even those sunscreen products labeled for other uses that meet the criteria in § 201.66(d)(10).

FDA continues to believe that requiring full Drug Facts labeling on sunscreen products used only on specific small areas of the face and sold in small packages (i.e., § 352.52(f)) would discourage manufacturers from marketing some of these products for drug use. Many of these products, such as sunscreen-lip protectant products, are sold in extremely small packages that cannot accommodate the required labeling even with the format exemptions allowed under § 201.66(d)(10). As explained in a number of rulemakings (64 FR 27666 at 27681 to 27682; 68 FR 33362 at 33371; 64 FR 13254 at 13270), these products meet the criteria for additional reduced labeling. Removal of these products from the OTC market would have a negative impact on public health. FDA believes that the benefit of UV radiation protection provided by these products outweighs the need for manufacturers to include all sunscreen labeling information. In contrast, FDA believes manufacturers of sunscreen products that are not within the scope of § 352.52(f) will continue to market their products even though full Drug Facts labeling is required. Unlike sunscreen products that meet § 352.52(f), the package size of products that do not meet § 352.52(f) will accommodate full Drug Facts labeling.

Although FDA is not extending the labeling modifications in § 352.52(f) to all OTC sunscreen products, as requested by the first and second comments, we are allowing these labeling modifications for certain makeup with sunscreen products. Specifically, these labeling modifications would apply to makeup with sunscreen products that are labeled

for use only on specific small areas of the face and that meet the criteria in § 201.66(d)(10). However, FDA does not agree that these labeling modifications should apply to all makeup products identified in § 720.4(c) (21 CFR 720.4(c)) that contain sunscreen, because most are not sold in small packages and, therefore, do not meet all of the criteria for reduced labeling (64 FR 13254 at 13270). Thus, most of these products can accommodate full Drug Facts labeling, and FDA finds no reason to extend the labeling modifications in § 352.52(f) to all makeup with sunscreens products.

As explained in the previous paragraph, the labeling modifications in § 352.52(f) apply to makeup with sunscreen products labeled for use only on specific small areas of the face and sold in small packages. FDA also believes that any sunscreen products that are used only on specific small areas of the face and sold in small packages meet FDA's reduced labeling criteria regardless of whether they are drug or drug-cosmetic products. Therefore, FDA is proposing to amend the heading of § 352.52(f) to read as follows: "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."

In addition, FDA is proposing to extend the labeling exemptions, with some modifications, currently allowed for lipsticks in § 352.52(f)(1)(vi) to the following lip products with sunscreen, as defined in § 720.4(c):

- Lipsticks,
- Lip products to prolong wear of lipstick,
- Lip gloss, and
- Lip balm.

FDA has identified lip products to prolong wear of lipstick as "makeup fixatives" under § 720.4(c)(7)(viii). Lip gloss and lip balm fall under "other makeup preparations" in § 720.4(c)(7)(ix). As long as these lip products with sunscreen are used only on specific small areas of the face and are sold in small packages (i.e., meet the criteria in § 201.66(d)(10)), they would meet FDA's reduced labeling criteria. As discussed earlier in this comment, FDA believes not allowing Drug Facts labeling exemptions for these products would discourage manufacturers from marketing some of these products for drug use. In proposed § 352.52(f)(1)(vi), FDA is proposing to extend the labeling modifications for lipsticks to other lip cosmetic products containing sunscreen

and clarifying that the labeling modifications in § 352.52(f) apply to both sunscreen and makeup with sunscreen products. Furthermore, because lip products with sunscreen have substantially less labeling space than the nonlip products with sunscreen used only on specific small areas of the face and sold in small packages, proposed § 352.52(f)(1)(vi) allows more labeling exemptions for lip products with sunscreen than other products that are within the scope of § 352.52(f).

(Comment 10) Several comments recommended changing the acronym "SPF" from "sun protection factor" to "sunburn protection factor" because the latter definition is more descriptive of the use of OTC sunscreen drug products and avoids giving consumers the impression of solar invincibility and a false sense of security.

FDA agrees. In § 352.52(b) of the sunscreen FM, FDA included only indications for sunburn protection (e.g., "helps prevent sunburn") (64 FR 27666 at 27691). In this document, FDA is proposing to change the word "sun" to "sunburn" in § 352.3(b)(1), (b)(2), (b)(3), and (d) and § 352.52(e)(1)(i), (e)(1)(ii), and (e)(1)(iii).

Manufacturers can continue to use existing labeling until the compliance dates of a final rule based on this proposal. However, FDA encourages manufacturers to revise any labeling that states "sun protection" attributed to sunscreen active ingredient(s) to the new term "sunburn protection" as early as possible.

(Comment 11) Some comments questioned the constitutionality of the FM's labeling provisions. Specifically, the comments contended that the FM's prohibition on the labeling of SPF products over 30, its restrictions on skin aging claims, and its limitation of the indications for use for OTC sunscreen drug products all violate the first amendment to the U.S. Constitution. The comments asserted that these bans on allegedly truthful labeling in the FM go well beyond constitutionally permissible restrictions on commercial free speech.

One comment contended that FDA had failed to meet its burden to demonstrate that the claims at issue are misleading or that the restrictions on speech directly advance any substantial governmental purpose. In addition, the comment claimed that any interest FDA has asserted in restricting the speech at issue is served equally well, if not better, by regulations that do not restrict speech to the same extent as FDA's regulations.

FDA disagrees with the comments for the following reasons. OTC drug monographs establish conditions under which ingredients for certain OTC uses are generally recognized as safe and effective (GRASE) and are not misbranded. General recognition of safety and effectiveness in an OTC drug monograph means that experts qualified by scientific training and experience recognize the conditions as safe and effective for OTC marketing for the use recommended or suggested in the product's labeling. An OTC drug monograph establishes, among other things, specific indications that are appropriate for the safe and effective use of a drug. An OTC drug product with labeled indications different than those set forth in an applicable OTC drug monograph would not be considered GRASE.

OTC drug monographs allow manufacturers to market those products satisfying the monograph standard without requiring the specific approval of the product by means of a new drug application (NDA) under section 505 of the act. FDA has issued numerous OTC drug monographs for certain categories of OTC drug products. If an OTC drug product subject to a final monograph is labeled for indications that differ from those set forth in the monograph, then it would be a "new drug" under section 201(p) of the act. In order to be legally marketed and distributed in interstate commerce, the drug manufacturer would be required to obtain approval from FDA for that product, and those conditions varying from the monograph, in an NDA under section 505 of the act.

All OTC drug monographs place limits on the conditions that have been found acceptable for inclusion in the monograph by an administrative rulemaking process based on scientific data. Here, FDA set certain limits on the labeling of sunscreen drug products in the final rule, such as the prohibition on specific SPF values over 30, certain skin aging claims, and other indications for use. FDA is maintaining similar labeling restrictions in this proposed rule with respect to skin aging claims and other indications proposed by the comments. Also, as described elsewhere in this document, the revised "sun alert" in the "Warnings" section does not include any skin aging claims (see section III.G, comment 19 of this document). However, FDA is proposing to increase the SPF labeling limit from 30 to 50, based on additional data that was submitted subsequent to the issuance of the FM. FDA is also proposing that the term "SPF 50+" can be used, rather than the term "SPF 30+" allowed in the FM. This increase in the SPF labeling limit

addresses, in part, the comments' request that FDA allow specific labeled SPF values over 30.

Elsewhere in this document, FDA explains the reasons for the specific labeling proposals, such as the required SPF labeling, revised "sun alert" in the "Warnings" section of the Drug Facts box, and indications for use (see section III.F, comment 15 and section III.G, comments 16, 17, and 19 of this document). FDA also explains our denial of specific labeling claims suggested by the comments, including the prohibition on specific SPF values over a certain threshold (SPF 50), skin aging claims, and additional indications for use (see section III.F, comments 15 and 17 of this document). As noted earlier in this comment, any variation from these labeling conditions in the monograph, if finalized, would cause an OTC sunscreen drug product to be a new drug requiring an approved NDA before it could be legally marketed in the United States.

The labeling requirements in this proposed rule would not violate the first amendment. FDA's requirements for the disclosure of information in the labeling of OTC sunscreen drug products are constitutionally permissible because they are reasonably related to the Government's interest in promoting the health, safety, and welfare of consumers and because they are not an "unjustified or unduly burdensome" disclosure requirement that offends the first amendment (see *Zauderer v. Office of Disciplinary Counsel*, 471 U.S. 626, 651 (1985); see also *Ibanez v. Florida Dep't of Bus. and Prof'l Regulation*, 512 U.S. 136, 146 (1994)). The reasonable relationship between the required labeling disclosures proposed herein and the Government's interest is plain here.

The proposed labeling disclosures addressed by the comments, such as the SPF value, indications for use, and revised "sun alert," would contribute directly to the safe and effective use of OTC sunscreen drug products. The SPF value and indications for use are critical components of labeling that allow consumers to understand more clearly a sunscreen product's use in preventing sunburn and relative level of UVA/UVB protection. As explained elsewhere in this document, the revised "sun alert" we propose to require in the "Warnings" section would help consumers understand more clearly the role of sunscreens as part of a comprehensive sun protection program (see section III.F, comment 19 of this document). The greater consumer understanding resulting from all of these labeling conditions would

promote directly the proper use of sunscreens, which, in turn, would better ensure the protection of public health.

In addition, it would not be "unduly burdensome" to sunscreen manufacturers to require these labeling disclosures. Finally, it is important to note that a sunscreen manufacturer could pursue alternative labeling conditions for its product by filing an NDA with the appropriate evidence demonstrating the product's safety and effectiveness under the proposed conditions.

In any event, FDA believes that the labeling requirements outlined in this proposed rule would pass muster when analyzed under the four-part test for restrictions on commercial speech set forth by the Supreme Court in *Central Hudson Gas & Electric Corporation v. Public Service Commission*, 447 U.S. 557 (1980). Under the test, the first question is whether the commercial speech at issue is false, misleading, or concerns unlawful activity, because such speech is beyond the first amendment's protection and may be prohibited. If the speech is truthful, nonmisleading, and concerns lawful activity, the Government may nonetheless regulate it if the government interest asserted to justify the regulation is substantial, the regulation directly advances the asserted governmental interest, and the regulation is no more extensive than necessary to serve the government interest (Id. at 566). The Supreme Court has explained that the last element of the test is not a "least restrictive means" requirement but, rather, requires narrow tailoring (i.e., "a fit that is not necessarily perfect, but reasonable" between means and ends) (*Board of Trustees of the State Univ. of N.Y. v. Fox*, 109 S.Ct. 3028, 3032-35 (1989)). In subsequent decisions, the Court has also clarified that "misleading" in the first element of the test refers to speech that is inherently or actually misleading. Thus, if the speech to be regulated concerns lawful activity and is not inherently or actually misleading, the remainder of the test applies (see *In re R.M.J.*, 455 U.S. 191, 203 (1982)).

Based on the data currently available, FDA believes that the labeling statements proposed by the comments (i.e., specific SPF values above FDA's established threshold, skin aging claims, and certain other indications) would not be protected speech and may be prohibited under the first prong of the *Central Hudson* test. FDA has tentatively determined that these proposed labeling statements would be inherently misleading on OTC sunscreen products sold and, thus,

misbrand the products under section 502(a) and 201(n) of the act. Because FDA believes these labeling statements are inherently misleading, they would not be subject to protection under the first prong of the Central Hudson test.

With respect to the labeling limitations for SPF values, based on current data, FDA believes that the labeling of sunscreens with specific SPF values greater than 50 would be inherently misleading. As discussed elsewhere in this document, FDA is concerned with the accuracy and reproducibility of test results showing protection greater than SPF 50 due to the lack of adequate validation data (see section III.F, comment 15 of this document). FDA had the same concern with SPF values above 30 when we published the FM in 1999. At that time, FDA had only received data demonstrating that the SPF test produces accurate results for products with SPF values of 30 or less. Since publication of the FM, FDA has received additional SPF testing data for sunscreen products with SPF values between 30 and 50 (Ref. 13). However, FDA has not received any data for sunscreen products with SPF values greater than 50. The data submitted to FDA indicate that the SPF test is accurate and reproducible for sunscreen products with SPF values up to 50 (Ref. 13). However, these data cannot be extrapolated to SPF values above 50. Thus, FDA is proposing to allow specific labeled SPF values only up to 50.

Increasing variability in test results is likely with increasing SPF values. If there is large variability in test results, then the SPF value determined from the test is not accurate (i.e., an SPF 60 product may not actually be an SPF 60 product). The submitted data demonstrated that variability is not an issue for sunscreen products with SPF values up to 50. However, FDA is concerned that variability will become an issue for sunscreen products with SPF values over 50.

For those sunscreens with SPF values above 50, FDA is proposing that the labeling can denote such values by a "50+" designation. As discussed elsewhere in this document, FDA has sufficient assurance that a result over 50 from the required SPF test is, in fact, greater than 50 and can be labeled "50+" (see section III. F, comment 15 of this document). Thus, FDA believes that the term "50+" is truthful and nonmisleading on the label of OTC sunscreen drug products for which the SPF test in the monograph has indicated an SPF value greater than 50. However, without proper validation of specific

SPF values above 50, there is no assurance that the specific values themselves are in fact truthful and not misleading. Thus, labeling of specific values above SPF 50 without appropriate validation (which FDA currently lacks) would be inherently misleading. As noted elsewhere, FDA invited any interested parties to submit such validation data for consideration by FDA and possible inclusion of specific values above SPF 50 in the FM.

With respect to anti-aging, skin cancer, and sun damage claims proposed by the comments, as discussed elsewhere in this proposed rule, FDA is concerned that these statements would be false or misleading due to lack of sufficient data in support of these claims (see section III.F, comment 17 of this document). FDA has reviewed the submitted articles concerning UV-induced skin damage (i.e., premature aging and cancer) along with the articles obtained from a search of scientific literature (Refs. 26 through 34). As discussed elsewhere, although FDA has concluded that the studies support the conclusion that exposure to UV rays increase the risk of premature skin aging, the study data fails to show that sunscreen use alone helps prevent premature skin aging and skin cancer for several reasons (see section III. F., comment 17 of this document).

First, with respect to premature skin aging, the studies have not completely defined the action spectrum for the majority of UV radiation-induced effects on human skin. Second, the inability to identify the exact UVB and UVA wavelengths that induce each histological change in skin derives from the study designs. Without knowing which UVB and UVA wavelengths induce each histological change in the skin, FDA is unable to determine which wavelengths are most important to causing skin aging and cannot determine the action spectrum for aging. Third, the studies did not examine the chronic, long-term consequences of UV radiation exposure in human skin. Fourth, although the studies that examined the ability of sunscreens to protect against UV radiation-induced histological changes in the skin provide useful data, it is difficult for FDA to conclude that sunscreen use alone helps prevent skin aging based on these studies.

Likewise, FDA is not aware of data demonstrating that sunscreen use alone helps prevent skin cancer. Like skin aging, these are studies examining the effects of sunscreen drug products on short-term factors for skin cancer, such as sunburn and other cellular damage. However, it is difficult to extrapolate

these short-term adverse effects of UV radiation to a long-term, chronic effect such as skin cancer. In addition, like skin aging, the complete action spectrum for skin cancer is not known at this time.

For all these reasons, FDA has tentatively concluded that the available evidence fails to show that sunscreen use alone helps prevent skin cancer or premature skin aging. Thus, the anti-aging, skin cancer, and sun damage claims proposed by the comments would be false or misleading due to lack of sufficient data in support of these claims. For example, the statement proposed by one comment that sunscreen use "may help prevent sun-induced skin damage, such as premature skin aging" would be inherently misleading to consumers by suggesting that sunscreen use alone may help prevent premature skin aging. As explained in this response, the available data fail to show that sunscreen use alone helps prevent premature skin aging and skin cancer.

As described elsewhere, FDA is proposing a revised "sun alert" so that the labeling of OTC sunscreen drug products include the most accurate information, based on the available scientific evidence, concerning the relationship of sunscreen use to the prevention of sunburn, skin cancer, and premature skin aging caused by UV exposure (see section III.F, comment 19 of this document). The revised "sun alert" also includes a statement about limiting sun exposure and wearing protective clothing because FDA has tentatively determined that it is critical for consumers to understand the role of sunscreen use in a comprehensive sun protection program. As FDA has explained, the available evidence strongly suggests that consumers rely more heavily on sunscreens alone without taking other protective measures against sunlight, particularly when the labeling of products indicates the potential for greater protection (see section III.F, comment 19 of this document). By indicating the potential for greater protection than is supported by the available evidence, the proposed anti-aging, skin cancer, and other related claims would mislead consumers into relying more heavily on sunscreens alone. Such excessive reliance would undermine consumers' protection from the sun and, thus, FDA's public health mission.

FDA has also preliminarily determined that the proposed labeling statements would concern unlawful activity which are not protected speech under the first prong of the Central Hudson test.

FDA is proposing specific conditions in the monograph under which OTC sunscreen drug products would be GRASE. Elsewhere, FDA explains how the labeling statements proposed by the comments would not be appropriate monograph indications for these sunscreen products (see section III.G, comment 17 of this document). Thus, the proposed labeling statements outside the proposed indications of the final monograph, as FDA proposes to revise it, would promote a sunscreen drug product for use as an unapproved new drug, which is illegal. In addition, any variation in the statements in a "Warnings" section of a final monograph, such as the revised "sun alert" statement in this proposed rule, would be outside the monograph conditions and, thus, would promote the product as an unapproved new drug. The marketing and distribution in interstate commerce of an OTC sunscreen drug product with such labeling variations would be prohibited under sections 301(d) and 505(a) of the act. Speech promoting such an illegal activity may be restricted without violating the first amendment (*Central Hudson*, 447 U.S. at 563–564).

If a manufacturer could circumvent the requirements and restrictions imposed by a final monograph by including nonmonograph labeling statements, or excluding required monograph statements, based on its own assertions of the alleged appropriateness and truthfulness of the statements, then such activity would significantly undermine the monograph system and FDA's assurance that OTC drugs are safe and effective for their labeled conditions. FDA has assessed the labeling statements proposed by the comments and preliminarily determined that they are not justified by the available scientific evidence as GRASE conditions for the monograph. Instead, in order to legally market a sunscreen drug product with such labeling statements, an interested manufacturer would have to submit an NDA to FDA with the appropriate evidence to show the safety and effectiveness of the drug under the proposed nonmonograph labeling conditions. Requiring premarket FDA review and authorization of such nonmonograph drug claims ensures that such claims will be evaluated by a public health agency that has scientific and medical expertise so that only products that are safe and effective will be permitted to be sold for therapeutic purposes.

Although this preliminary-determination that the labeling statements at issue would be inherently misleading and would concern unlawful

activity would obviate the need for FDA to address the other three prongs of the *Central Hudson* test, we believe that the labeling requirements proposed in this document would satisfy each of the parts of this test. With respect to the second prong, FDA's interest in the required labeling disclosures and prohibitions addressed by the comments would contribute directly to the safe and effective use of these OTC sunscreen drug products, which is critical for the protection of public health. FDA's interest in protecting the public health has been previously upheld as a substantial government interest under *Central Hudson* (see *Pearson v. Shalala*, 164 F.3d 650, 656 (D.C. Cir. 1999) (citing *Rubin v. Coors Brewing Co.*, 514 U.S. 476, 484–485 (1995))).

The proposed labeling requirements would directly advance this interest, thereby satisfying the third prong of the *Central Hudson* test. By requiring labeling disclosure of the SPF value, the proposed revised "sun alert," and indications for use, FDA can better assure that consumers understand more clearly the use of sunscreens in preventing sunburn, their relative UVA/UVB protection, and their role as part of a comprehensive sun protection program. The greater consumer understanding resulting from all of these labeling conditions would promote directly the proper use of sunscreens, which, in turn, would better ensure the protection of the public health.

Likewise, this proposed rule's exclusion from the monograph of the labeling statements proposed by the comments also directly advances FDA's public health interest. FDA has preliminarily determined from the available evidence that these statements would not be appropriate conditions for OTC use under the monograph. Thus, the statements would directly undermine the protection of public health. In addition, it is important to note that the *Pearson* court, in assessing whether the specific dietary supplement regulations at issue directly advanced FDA's stated public health goals under the third prong of the *Central Hudson* test, explained that its findings under this prong did not apply to drugs, where "the potential harm is presumably much greater" than other products (*Pearson*, 164 F. 3d at 656, n 13).

Finally, under the fourth prong of the *Central Hudson* test, there are not numerous and obvious (*Cincinnati v. Discovery Network*, 507 U.S. 410, 418 n. 13 (1993)) alternatives to the required labeling statements or labeling prohibitions proposed herein.

Consumers are accustomed to using the label as their primary source of information about a drug product's contents and use. Neither a public education campaign, nor encouraging OTC drug product manufacturers to provide information, such as that in the proposed revised "sun alert," to consumers by other means, would ensure that people have the information they need about sunscreen products at the point of sale or use. Likewise, with respect to the alternative labeling statements proposed by the comments, FDA's proposed indications and revised "sun alert" present the relevant public health information to consumers in the clearest and most direct manner. Thus, FDA's proposed indications and prohibition of other labeling statements are not more extensive than necessary. In this way, the required labeling disclosures and prohibitions proposed in this document would meet the fourth prong of the test.

Furthermore, the proposed prohibition of claims in a final monograph does not prevent such claims from being approved in an NDA. As explained previously, a final monograph sets forth those conditions, including labeling, under which an OTC drug product would be considered GRASE and not misbranded. In issuing monographs, FDA considers whether the available scientific evidence demonstrates that OTC drug products within a therapeutic category are GRASE. A final monograph does not constitute an FDA decision regarding an NDA for an OTC drug proposing variations in these conditions. Thus, FDA's proposals in this document would not prohibit any interested manufacturer from filing an NDA, with the appropriate evidence, for any variations from the monograph labeling conditions. Because of this significant available option to manufacturers for proposing alternative labeling statements, FDA's proposed labeling requirements and prohibitions are not more extensive than necessary.

In conclusion, FDA believes it has complied with its burdens under the first amendment to support the labeling requirements of this proposed rule.

(Comment 12) One comment stated that voluntary professional labeling can be provided to physicians that will allow them to select or recommend sunscreen products for their patients' needs, based on more detailed information describing the quantity (protection factor) and the range of UV protection (e.g., UVB, UVA, or UVB/UVA protection). Another comment stated that FDA should not require professional labeling because complete

and accurate product labeling should be available to all consumers, not just to their health care providers.

FDA defines professional labeling in OTC drug monographs as labeling that is provided to health professionals but not to the general public (i.e., not directly to consumers) (for example, see § 331.80 (21 CFR 331.80)). In the final rule, FDA stated that it would consider professional labeling, such as protection against photosensitization reactions, if data were received (64 FR 22666 at 27674). FDA has not received any data to date. Therefore, FDA is not proposing any professional labeling in this document. FDA will consider professional labeling for OTC sunscreen drug products in the future if specific supportive data are provided.

(Comment 13) Some comments objected to the ranges of SPF values that define the product category designations (PCDs) in § 352.3(b). Stating that standard public health messages recommend use of a sunscreen with at least an SPF of 15, the comments contended that the “moderate” PCD (SPF values of 12 to under 30) may cause consumers to believe that SPF values of less than 15 provide adequate protection. One comment further stated that if the PCD range is from SPF 12 to 29, manufacturers will only produce the minimum SPF value as they can use less active ingredients and get the same PCD classification.

As discussed in the final rule (64 FR 27666 at 27681), the PCD ranges in § 352.3(b) and § 352.52(e) reflect a modified, simpler, combined version of the previously proposed five PCDs and the “Recommended Product Guide.” However, FDA agrees with the comments that the current standard public health message from public health organizations generally recommends use of a sunscreen with an SPF value of at least 15 (see section III.G, comment 19 of this document). We also agree that allowing SPF values below 15 in any but the lowest PCD range may appear to contradict this message. Therefore, FDA is proposing to modify the PCD SPF value range in proposed § 352.3(c)(1) from “2 to under 12” to “2 to under 15” and in proposed § 352.3(c)(2) from “12 to under 30” to “15 to under 30.” FDA is also proposing to replace the PCD terms “minimal” and “moderate” with the simpler terms “low” and “medium,” respectively, and to use these simpler terms for the UVA radiation protection categories (see section III.E, comment 14 of this document). These labeling changes will provide consumers with familiar and consistent terms describing both UVA and UVB radiation protection.

FDA disagrees with the comment contending that manufacturers will only produce the minimum SPF value in a given PCD range because they can use less active ingredients and get the same PCD classification. Section 352.50 of the current FM requires the SPF value to appear on a sunscreen product’s PDP. This proposed rule would not change that requirement. Thus, while the PCD provides additional information about the SPF value, consumers seeking higher SPF values can readily identify such products by the SPF value stated on a sunscreen product’s PDP.

E. Comments on the Labeling of Sunscreen Drug Products With UVA Protection

(Comment 14) Many comments discussed ways to categorize, phrase, and display UVA/UVB radiation protection on an OTC sunscreen drug product label. All of the comments stated that the SPF value should retain preeminence on the label’s PDP and be the consumers’ criteria for choosing an OTC sunscreen product. Some comments recommended that UVA radiation protection be stated on the PDP in descriptive words or simple phrases, rather than numbers or symbols, for the following reasons:

- Simplicity,
- Clarity,
- To avoid confusion with SPF, and
- To maximize consumer comprehension.

Some comments referenced consumer research, discussed in subsequent paragraphs, to support this recommendation (Refs. 4 and 5).

One comment suggested the following labeling statements:

- “Protects against UVA rays”
- “screens out UVA rays”
- “shields from UVA rays”
- “broad spectrum sunscreen”
- “UVA/UVB protection”
- “provides protection against both UVB and UVA rays”

other truthful and nonmisleading statements describing a quantification of the product’s UVA radiation protection. The comment stated that quantification of the UVA radiation protection should be allowed in labeling, but not required, so that consumers can have additional product performance information to help them select appropriate products.

Another comment stated that UVA radiation protection should be labeled only as grades of effectiveness (multiple levels) for the following reasons:

- UVA radiation irritation induces various skin reactions (e.g., erythema, pigment darkening, skin cancer, and photodermatitis), and
- Some action spectra of damages have not been determined.

This comment referred to The Japan Cosmetic Industry Association (JCIA) Measurement Standards for UVA Protection Efficacy (Ref. 6), which recommend labeling UVA protection as three grades: (1) PA+, (2) PA++, or (3) PA+++.

Several comments recommended two categories of UV protection labeling based on the ratio of UVA radiation protection factor to SPF value:

- “with UV protection” if ratio equals 0.20
- “with extra UV protection” if ratio equals 0.25

The proposed ratio is based on the UVA radiation protection factor as determined by the persistent pigment darkening (PPD) test method (see section III.N, comment 46 of this document). These comments stated that, because the ratio of damage from solar UVB radiation to that of solar UVA radiation is 80:20 over a day, a sunscreen must protect against an 80:20 ratio of UVB to UVA radiation. The comments also recommended that products labeled “with UV protection” or “with extra UV protection” exhibit absorbance of 360 nanometers (nm) and longer wavelengths.

Another comment suggested two categories to state overall UV radiation protection: “regular” and “broad spectrum.” The comment proposed that the ratio of a sunscreen product’s SPF value to its UVA protection factor be the single criterion for the “broad spectrum” designation, with the maximum ratio no greater than 4:1. For example, an SPF 16 product would need to provide a UVA protection factor of at least 4 to be designated “broad spectrum.”

One comment disagreed with the previous comment, stating that there is no supportable scientific basis for the relevance of the 4:1 ratio. The comment argued that the ratio inappropriately combines, in the same equation, SPF values obtained with a solar simulator and solar irradiance values at low sun angles.

Another comment suggested that sunscreen products with an SPF value of 2 or greater must have a UVA protection factor of at least 2 to be labeled “UVA/UVB” or “broad spectrum protection.” The comment stated that products with SPF values of at least 15 and UVA protection factors of at least 4 may be labeled “extra (or extended or enhanced) UVA protection.” The comment stated that these criteria are independent of test method and should apply to any of the proposed UVA radiation test methods.

Another comment proposed establishing PCDs based on the UVA

radiation protection value obtained by the PPD test method. The comment suggested four PCDs that would enable consumers to choose the desired levels of protection:

- “moderate”
- “high”
- “very high”
- “extra”

Another comment recommended three PCDs:

- “low UVA protection”
- “moderate UVA protection”
- “maximum UVA protection”

Another comment suggested using the five PCDs proposed in the TFM (58 FR 28194 at 28295) and added a UVA protection factor number for each PCD based on the immediate pigment darkening (IPD) test method.

Two comments recommended a four-star rating system to describe UVA radiation protection. The comments stated that this system, based on the ratio of UVA to UVB radiation absorbance, would provide a simple method for consumers to determine the protective nature of an OTC sunscreen drug product. The absorbance ratio would range from 0 for products exhibiting no protection against UVA radiation to 1 for products exhibiting equal absorption at all wavelengths throughout the UVA/UVB radiation spectrum. Using this ratio, products would be classified in one of the following five categories:

- 0 to < 0.2 = no UVA radiation protection claim
- 0.2 to < 0.4 = Moderate (★)
- 0.4 to < 0.6 = Good (★★)
- 0.6 to < 0.8 = Superior (★★★)
- 0.8 plus = Maximum (★★★★)

Another comment recommended a five point rating system using the “critical wavelength” (CW) (λ_c) test method. This system uses a scale analogous to the star rating system to assign products a “broad spectrum” rating as follows:

- $\lambda_c < 325 = “0”$
- $325 < \lambda_c < 335 = “1”$
- $335 < \lambda_c < 350 = “2”$
- $350 < \lambda_c < 370 = “3”$
- $370 < \lambda_c = “4”$

Several comments supported a single claim, such as “provides broad spectrum protection against UVB and UVA radiation,” based on determining a sunscreen pass/fail CW (λ_c). Comments that supported this “broad spectrum protection” claim stated that, in combination with SPF, it provides simple and accurate labeling that is easily understood by consumers. The comments referred to a research study that suggested this approach to UVA radiation protection labeling was superior for consumer comprehension

and ease of product selection (Ref. 7). Other comments provided consumer research data, discussed elsewhere in this comment, suggesting this approach was least preferred by consumers (Refs. 4 and 8).

One comment stated that UVA radiation protection claims should be allowed for sunscreen products with SPF values of 4 and higher. The comment added that, for products claiming to protect against UVA and UVB radiation, a minimum UVA protection factor of 2 should be required if the SPF value is less than or equal to 12.

Several comments stated that sunscreen drug products labeled as “full spectrum” or “broad spectrum” should protect consumers from substantially all of the harmful effects of the sun, including sunburn associated with UVA radiation. According to one comment, sunscreen drug products labeled “full spectrum” or “broad spectrum” that do not protect against nearly all UVB and UVA radiation wavelengths seriously risk misleading consumers into believing they are fully and completely protected from the dangers of the sun. One comment recommended using the claim “full spectrum” rather than “broad spectrum” to describe products that attenuate more than 90 percent of UVA radiation and are at least SPF 15. The comment suggested no UVA radiation protection claims be allowed if the product is below SPF 15.

In support of their proposed UVA labeling, a number of comments provided results from consumer research studies that assessed consumer labeling preferences for stating UVA radiation protection. One comment described a 1996 survey (Ref. 4) in which 275 subjects compared two labeling systems:

- 3-level descriptive (“light,” “intermediate,” or “extended” “UVA protection”) and
- Grapho/numerical (a bar graph indicating a level, 0, 4, 8, or 12, with the corresponding number appearing alongside the graph).

The comment stated that the survey data suggested that, while equally able to understand both types of labels, the panelists preferred the grapho/numerical system over the descriptive system.

Another comment described two consumer research studies, conducted in 1994 and 1995 (Ref. 9), in which 235 subjects compared three potential UVA radiation labeling options:

- Numerical (2, 3, or 5),
- Symbolic (4 stars with 1, 2, 3, or 4 stars filled), and

- 3-level descriptive (labeled blank if no UVA radiation protection provided or labeled “UVA and UVB Protection” or “UVB Plus Extended UVA Protection,” depending on the level of UVA radiation protection provided). The studies included focus group discussions and indepth interviews. The comment stated that the data suggested that a numeric designation for UVA radiation protection (in addition to the SPF value) created confusion for consumers and that symbols (i.e., stars) misled consumers into giving equal or greater importance to the UVA radiation rating compared to the SPF value. The comment concluded that a descriptive approach better conveyed to consumers the added benefit of UVA protection without detracting from the SPF value.

Another comment described two consumer research studies conducted in 1999 (Ref. 7) in which 2,238 consumers assessed three sunscreen product labeling systems:

- A pass/fail descriptive (labeled blank if no UVA protection provided (i.e., fails) or labeled “Broad Spectrum UVA and UVB Protection” if UVA radiation protection provided (i.e., passes)),
- A 3-level descriptive (labeled blank if no UVA radiation protection provided or labeled “UVA and UVB Protection” or “UVB Plus Extended UVA Protection,” depending on the level of UVA radiation protection provided), and

- A 3-level grapho/numerical (a bar graph indicating a level, 4, 8, or 12, with the corresponding number appearing alongside the graph). The comment stated that the data suggested the pass/fail descriptor, “broad spectrum,” was significantly superior to the other labels and recommended that FDA use this labeling to designate UVA radiation protection.

Another comment described a consumer research study conducted in 2000 (Ref. 8) at 20 urban and suburban shopping malls in which 1,921 subjects ranked four labeling systems:

- 4-level numerical,
- 4-level symbolic,
- 4-level descriptive, and
- Pass/fail descriptive (“with/without broad spectrum UVA/UVB protection”). The numerical labeling system was shown as Arabic numerals “1, 2, 3, 4” with the number “2” highlighted. The descriptor labeling system was shown as the words “Minimum, Moderate, High, Maximum” with the word “Moderate” highlighted. The symbolic labeling system was shown as a picture of four stars with two stars highlighted.

The comment concluded that the subjects had a significant preference for a labeling system based on descriptive words or numbers because of clarity, specificity, and ease of comprehension. Subjects least preferred the pass/fail system because they found it unclear, nonspecific, and lacking sufficient information to compare sunscreen products. This study also revealed that the numerical labeling system was one of the top two choices because numbers were "clearer, more specific, and easier to understand." Age, gender, and educational or ethnic background were reported as not affecting the study results.

In the TFM for OTC sunscreen drug products (58 FR 28194 at 28233), FDA proposed to allow claims relating to "broad spectrum protection" or "UVA radiation protection" for OTC sunscreen products that meet the following two criteria:

1. Contain sunscreen active ingredients with absorption spectra extending to 360 nm or above, and
2. Demonstrate meaningful UVA radiation protection using appropriate testing procedures to be developed.

In the FM for OTC sunscreen drug products (64 FR 27666 at 27672), FDA stated that UVA radiation labeling of OTC sunscreen drug products could continue in accordance with the TFM and its amendments until addressed in a future issue of the **Federal Register**. Elsewhere in this document, FDA is proposing test methods for determining the UVA radiation protection potential of an OTC sunscreen drug product (see section III.N, comment 46).

FDA believes that the existing data do not clearly define the relationship between UVA radiation and skin damage. The principal reason for not better understanding this relationship is that the action spectra for specific types of UVA radiation-induced skin damage (i.e., which wavelengths of UVA cause which types of skin damage) have not been established. However, most scientific data demonstrate that UVA radiation is harmful to the skin. Thus, until these action spectra are known, FDA believes that more protection against UVA radiation damage is better for consumers' health. Therefore, FDA believes it is important, as with the SPF value, to designate UVA radiation protection in a straightforward manner that consumers clearly understand.

FDA proposes that the UVA radiation protection of an OTC sunscreen drug product determined from these UVA test methods be designated on the PDP using a combination of category descriptors (i.e., "low," "medium," "high," or "highest") and stars (i.e.,

symbols) similar to those described by some of the comments. The category descriptors and stars will designate relative levels of UVA radiation protection as measured by the UVA radiation test methods. The level of UVA radiation protection identified on the label reflects the following:

- A numerical "UVA protection factor" (from the clinical test), and
 - A numerical ratio of UVA I (340 to 400 nm) radiation absorption to UVB/UVA (290 to 400 nm) radiation absorption (from the in vitro test).
- The test that indicates the lowest level of UVA radiation protection determines the level identified on the label. For example, if the clinical test indicates "low" protection and the in vitro test indicates "medium" protection for a product, the product is labeled as providing "low" UVA radiation protection. This system comprises four categories of UVA radiation protection as described in table 1 of this document.

TABLE 1.—OVERALL UVA PROTECTION OF A SUNSCREEN DRUG PRODUCT

| Star category | Category descriptor |
|---------------|---------------------|
| ☆☆☆☆ | Low |
| ★★★★ | Medium |
| ★★★★☆ | High |
| ★★★★★ | Highest |

Some of the comments argued that the UVB radiation protection labeling is more important than UVA radiation protection and should be emphasized in the labeling over UVA radiation protection. FDA disagrees with the comments and proposes that the UVA radiation protection designation appear on the PDP along with the SPF value in an equally prominent manner that does not conflict with the SPF value. Because action spectra for UV-induced skin damage have not been clearly defined, FDA is unable to specify labeling for OTC sunscreen drug products that indicates what ranges of UV radiation are most harmful to consumers. In other words, FDA cannot conclude whether UVB or UVA radiation is more harmful to humans based on the scientific data collected to date. Therefore, FDA considers both UVB and UVA radiation protection equally important at this time because scientific data demonstrates that both have harmful effects on the skin.

So that consumers consider UVB and UVA radiation protection equally in selecting an OTC sunscreen drug product, FDA is proposing a number of labeling requirements. Under this proposal, the font size of the stars and

category descriptors for UVA radiation protection must be the same size as the SPF value and its descriptors. All four stars must appear and be preceded by the term "UVA" and followed by the appropriate category descriptor (e.g., UVA ★★☆☆ High). All star borders and the color inside a solid star must be the same while the color of "empty" stars must be lighter and distinctively different than solid stars. The color inside a solid star must be distinctively different than the background color. The stars must be filled in starting with the first star on the left and must appear in a straight horizontal line.

As requested by some comments, an OTC sunscreen drug product that does not provide the minimum UVA protection, as determined by the proposed UVA test methods, may only display an SPF value on the PDP. An OTC sunscreen drug product is not required to provide UVA protection and may bear only a sunburn (UVB/SPF) protection claim. However, FDA is proposing that a sunscreen product that does not provide at least a "low" level of UVA protection include the following statement on the PDP: "no UVA protection." This statement must be the same font size as the SPF value and its descriptor. FDA is not proposing four empty stars because we are concerned that consumers may confuse products providing no UVA protection (i.e., four empty stars) with those providing the highest UVA protection (i.e., four filled stars).

In developing this UVA radiation protection labeling, FDA has particularly considered the label comprehension studies (Refs. 4, 7, 8, and 9). These studies used multiple methodologies and report a diverse range of preferences for each labeling system:

- Category descriptors,
- Graphics,
- Symbols,
- Numerics, and
- "Pass/fail" descriptors.

The diverse results and varying methodology make it difficult to identify a clear preference for one labeling system. However, the studies indicate an overall preference for category descriptors.

In agreement with the studies, FDA is proposing category descriptors to indicate the relative level of UVA radiation protection. As discussed in preceding paragraphs, FDA believes consumers should consider UVB and UVA radiation protection equally when selecting an OTC sunscreen drug product. For this reason, FDA is proposing that stars be used with category descriptors. FDA believes that

the category descriptor and star labeling for UVA radiation protection will give it equal prominence with UVB radiation protection (i.e., category descriptor and SPF) on the PDP.

FDA is not proposing grapho/numeric labeling because we are concerned that consumers may be confused by a second number on the PDP (i.e., in addition to the SPF value). FDA is also not proposing any of the simple two-category designations suggested by the comments:

- With/without UVA protection,
- With UVA protection/with extra UVA protection, or

• Regular/broad spectrum protection. FDA agrees with one of the comments, which argued that these types of statements are misleading. FDA does not consider this labeling as providing consumers with enough information about the magnitude of UVA protection offered by an OTC sunscreen product. However, FDA does not object to the use of the following four statements for OTC sunscreen drug products that satisfy the requirements of proposed § 352.73 for a labeled UVA protection value:

- “broad spectrum sunscreen”,
- “provides [select one of the following: ‘UVB and UVA,’ or ‘broad spectrum’] protection”,
- “protects from UVB and UVA [select one of the following: ‘rays’ or ‘radiation’]”, and
- [select one of the following: “absorbs” or “protects”] “within the UVA spectrum”.

These statements may appear elsewhere in product labeling outside the “Drug Facts” box or enclosure but not intermixed with the information required on the PDP under § 352.50. FDA agrees with some comments that these statements, by themselves, may be misleading by implying that a sunscreen protects against nearly all UVB and UVA radiation. However, FDA does not believe these optional statements will be misleading in the context of the entire label, because the relative level of UVB and UVA protection must be stated on

sunscreen product labels (alongside these more general statements).

Although none of the studies combined labeling systems as proposed in this document, FDA believes the studies support use of category descriptors and symbols together. One study suggested that symbols may imply importance over SPF values (Ref. 9). However, FDA believes consumers will not place greater importance on UVA protection because we are proposing a required statement to inform consumers about the importance of both UVB and UVA protection. We are proposing to require one of the following statements on the PDP of all OTC sunscreen drug products:

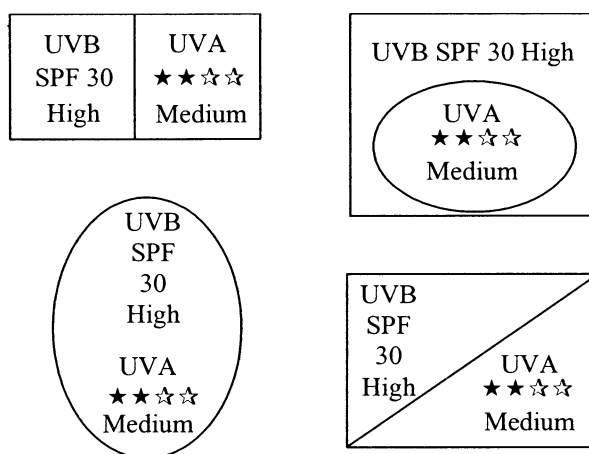
- “UV rays from the sun are made of UVB and UVA. It is important to protect against both UVB & UVA rays.”
 - “UV rays from the sun are made of UVB and UVA. It is important to protect against both UVB & UVA rays to prevent sunburn and other skin damage.”
- FDA believes that the use of one of these statements, along with the proposed UVB and UVA radiation protection labeling, including the format requirements described in preceding paragraphs, will lead consumers to view UVB and UVA radiation protection as equally important.

In addition, this statement will educate consumers about UVA radiation, which will be a new term and concept to many consumers. The proposed statement should help consumers better understand the new UVB and UVA labeling when it is initially introduced to the OTC market. Thus, FDA believes that the consumer label comprehension studies, along with the proposed educational statement about UVB and UVA radiation, support the stars and descriptor UVA radiation protection labeling proposed in this document. Moreover, a similar “star rating system” for UVA radiation protection (i.e., the Boots Star System) has been used to label sunscreen products throughout Europe for over 10 years.

To prevent consumer confusion about UV radiation protection, FDA is proposing changes to UVB radiation protection labeling (i.e., the SPF value). SPF values indicate how effective a sunscreen product is in protecting against sunburn. By displaying the relative level of sunburn protection on the sunscreen drug product PDP in terms of an SPF value, consumers can choose their desired level of UVB radiation protection. To further improve consumers’ understanding of the sunburn protection level provided by a certain sunscreen product, FDA is proposing to require descriptive terms of relative sunburn protection (i.e., “low,” “medium,” “high,” and “highest”) to accompany the SPF value on the PDP. FDA is further proposing that the SPF value must be preceded by the term “UVB” to further differentiate the SPF value from the UVA symbol/descriptor on the PDP. FDA believes that numerical labeling for UVB protection, symbolic labeling for UVA protection, and the same descriptive labeling for UVB and UVA protection will allow consumers to easily understand and choose from relative levels of UVB and UVA radiation protection.

FDA is aware that consumers have used and become accustomed to choosing OTC sunscreen drug products based on the SPF value for many years. Likewise, FDA believes that, over a period of time, consumers will similarly become accustomed to the proposed labeling using symbols and descriptors to designate relative UVA radiation protection. Furthermore, FDA believes consumer familiarity with similar star rating systems (e.g., movies, hotels, and restaurants) used for many years in the United States provide a basis for consumers’ understanding of this proposed labeling for OTC sunscreen drug products.

FDA is providing a number of examples of how the UVA/UVB protection designations could appear on the PDP.



FDA believes that, as with SPF values, identifying the relative level of UVA radiation protection provides the most useful information for consumers. Consumers who desire more protection from the sun will be able to identify products with higher UVB (SPF) and UVA radiation protection. FDA agrees with the comments that a product must provide at least some minimum level of UVA radiation protection (as with SPF values) to be labeled as providing UVA radiation protection. Therefore, FDA is proposing minimum criteria for the lowest UVA category in its proposed test procedures (see section III.N, comment 46 of this document).

F. Comments on the Labeling of Sunscreen Drug Products With High SPF Values

(Comment 15) Several comments objected to FDA limiting specific labeled SPF values “up to but not above 30.” The comments stated that data and information supplied to FDA since publication of the sunscreen FM demonstrate that SPF values over 30 can be safely tested with accuracy. The comments also argued that removing the limit will not lead to consumers spending more time in the sun when using high SPF sunscreens in comparison to low SPF sunscreens. To address that point, one comment proposed labeling to help reduce potential consumer misuse of sunscreens with SPF values over 30: “higher SPF products give more sun protection, but are not intended to extend the time spent in the sun.” Another comment noted that the SPF value, in addition to proper sunscreen application and reapplication, is only part of a comprehensive sun protection program.

Other comments explained the need for high SPF sunscreen products. The comments contended that consumers and physicians are familiar with and

want the many currently marketed sunscreens that are labeled as “SPF 45, SPF 50, etc.” Thus, the comments argued that U.S. consumers will be at a disadvantage within the international community, because products providing SPF values over 30 are available in other countries. In addition, the comments stated that many prominent medical authorities maintain the need for high SPF sunscreens for individuals at “high risk” based on medical and/or occupational concerns and individuals who desire increased protection from photoaging and lengthy/intensive sun exposure situations. The comments argued that the need for high SPF sunscreens is supported by findings that UV exposures in several cities are considerably higher than previously recognized and because high SPF products can reduce cumulative UV exposure. The comments stated that consumer desire for high SPF products is demonstrated by sales data showing that products with an SPF value of 45 are one of the fastest growing segments of the total sunscreen market.

The remaining comments discussed the consequences of limiting the specific labeled SPF value. For example, one comment noted that if manufacturers cannot state the SPF level above 30, they will no longer have an incentive to fund research for better sunscreens. In addition, manufacturers may reformulate products to reduce active ingredients and, thus, reduce the level of UV protection. A comment argued that another adverse consequence results from most consumers failing to achieve the labeled SPF value because they do not apply enough sunscreen and/or reapply it too infrequently. Because high SPF products can help make up for such improper use, limiting the specific labeled SPF value to 30 has a negative impact on UV protection.

A foreign industry organization suggested an upper limit for labeled SPF values of 50+ and provided three reasons:

- Unreasonably high SPF values will lead consumers to expect “too much effectiveness” from sunscreen products.
- Higher concentrations of sunscreen active ingredients are not “in the interest of safety.”
- Higher SPF values will invite excessive, meaningless competition in the industry.

The comment explained that competition would be meaningless because the amount of UV protection provided by products with SPF values above 50 is not significantly greater than products with an SPF of 50.

Another comment from a sunscreen manufacturer agreed with FDA’s concern about the possibility of increasing variability when testing high SPF sunscreens. The comment suggested a modified “binomial” test method and labeling requirements for SPF values over 20 that would allow for high SPF products.

Another comment submitted a published survey of 208 sunbathers on Miami’s South Beach during July 2001 with the goal of measuring UV radiation exposure and probable injury (Ref. 10). The “worst case” scenario identified by the survey was based on sunbathers with Type I skin (persons most sensitive to sunlight who burn easily and never tan) exposed to UV radiation near the longest day and highest sun angle of the year at the “southern-most major beach” in the United States. The survey was a followup to one conducted in 1993 with 62 sunbathers and evaluated by FDA in the FM (64 FR 27666 at 27674). The 2001 survey determined MEDs absorbed by the following three steps:

1. Measuring incident UV radiation (using three dosimeters),
2. Multiplying by an adjusting factor for skin type (using a 30 percent

increase in sensitivity between skin types), and

3. Dividing by the SPF worn by the sunbather.

The survey suggests that sunbathers with Type I skin might receive a cumulative dose of 49.5 MEDs with 8 hours of exposure. The comment concluded that, while SPF values up to, and including, 50 are warranted, values over 50 are unwarranted in any condition for sunburn protection.

Two comments submitted testing data for sunscreens with SPF values between 30 and 50 using the test method in the FM. The comments concluded that the test method was valid for these high SPF values. In addition, one comment indicated that a very water resistant test for an SPF 45 to 50 sunscreen would take nearly 4.5 hours using the skin types of subjects in the SPF testing procedures in the FM (i.e., skin types I, II, and III) (Ref. 13). The comment concluded that it is beyond the practical endurance capabilities of many people in the test to spend more than 5 to 6 hours in front of a UV radiation lamp and that fatigue can lead to errors in test results. The comment also noted that the potential for intra and interlaboratory variability in test results increases as sunscreen SPF values increase.

FDA concluded in the FM (64 FR 27666 at 27675) that test methods supported specific SPF label values up to 30. FDA invited interested persons to submit data in support of high SPF test methods and to consider proposed methods for communicating the level of protection in labeling. Data and information on high SPF testing and labeling were submitted to FDA at, and following, public meetings on July 22, 1999, and October 26, 1999, and after reopening of the administrative record (65 FR 36319) (see section III.I, comment 24 of this document) (Refs. 11 and 12).

FDA continues to be aware that many OTC sunscreen products with specific labeled SPF values over 30 are currently marketed, both nationally and internationally, and are increasingly used by consumers and recommended by health professionals (64 FR 27666 at 27675). FDA agrees that these products should be available for those sun-sensitive consumers who require such products based upon personal knowledge, planned sun exposure, geographical location, or advice of a health professional. FDA previously noted the lack of any known safety problems for sunscreen products with SPF values greater than 30 (64 FR 27666 at 27675). The comment that argued higher concentrations of sunscreen

active ingredients are not “in the interest of safety” did not supply any new data to support its contention. FDA will continue to monitor adverse drug experience reports for sunscreen drug products reported to its Medwatch program and in the medical literature.

As noted by one comment, some researchers have raised the concern that sunscreen use may lead to increased sun exposure. The “compensation hypothesis” states that consumers who use high SPF sunscreens spend more time in the sun and/or use less protective clothing. The only double blind, randomized trial that addressed this issue showed a significant increase in sun exposure time when comparing use of SPF 30 to SPF 10 (Ref. 14). In addition, two retrospective survey studies showed that sun exposure time is longer when using sunscreen compared to not using sunscreen (Refs. 15 and 16). Other studies cited by the comment to support the premise that the “compensation hypothesis” is incorrect and either did not provide data about the length of sun exposure or the study method did not allow for data interpretation (Refs. 17 through 20). Based on all of this data, FDA believes that some consumers may increase total UV exposure through over-reliance on sunscreens. The apparent divergent results on the validity of the “compensation hypothesis” between studies may indicate that sun protection behaviors vary greatly for each person. More specifically, there is a spectrum of attitudes about the sun, from those individuals who seek dark suntans to those who seek to avoid the sun and consequent UV skin damage (Ref. 21). Such evidence underscores the need for adequate labeling so consumers can make informed decisions regarding their use of OTC sunscreen drug products.

FDA agrees that the SPF value is one factor in a comprehensive sun protection program. However, the SPF is only a measure of protection from erythema (i.e., UVB radiation-induced sunburn) and does not measure protection from other UV skin damage, such as that induced by UVA radiation. While increased short wavelength UVA radiation protection generally increases with increasing SPF values, studies using in vivo or in vitro UVA radiation testing methods demonstrate that sunscreen products with the same SPF values can have markedly different levels of UVA protection, especially for long wavelength UVA radiation (Refs. 22 and 23). These studies also indicate that a specific high SPF product can provide much less UVA radiation protection than a product with a much lower SPF value. Elsewhere in this

document, FDA is proposing UVA radiation testing methods and labeling that will categorize the relative levels of protection provided by the SPF and UVA values of the sunscreen product (see section III.E, comment 14 and section III.N, comment 45 of this document), allowing consumers to compare products and choose the levels of UVB and UVA radiation protection desired.

An SPF 30 sunscreen product may provide adequate sunburn protection for many consumers. However, FDA believes that appropriately tested and labeled high SPF value sunscreen products should be available for consumers who desire or need high levels of UV protection, in particular, those who burn easily. Such products would do the following:

- Help compensate for inadequate application and/or reapplication,
- Provide additional sunburn protection during intense UV radiation conditions,
- Help reduce cumulative UV radiation exposure (when used in conjunction with other measures to reduce overall sun exposure), and
- Generally provide consumers incremental increases in sunburn protection.

FDA agrees that SPF values should be supported by scientific evidence. In the FM, FDA limited the specific labeled SPF value to 30. At that time, FDA had only received data demonstrating that the SPF test produces accurate results for products with SPF values of 30 or less. Since publication of the FM, FDA has received additional SPF testing data for sunscreen products with SPF values between 30 and 50 (Ref. 13). However, FDA has not received any data for sunscreen products with SPF values greater than 50. The data submitted to FDA indicate that the SPF test is accurate and reproducible for sunscreen products with SPF values up to 50 (Ref. 13). However, these data cannot be extrapolated to SPF values above 50. Thus, FDA proposes to allow specific labeled SPF values up to 50.

FDA agrees with the sunscreen manufacturer that increasing variability in test results is likely with increasing SPF values. If there is large variability in test results, then the SPF value determined from the test is not accurate (i.e., an SPF 50 product may not actually be an SPF 50 product). The submitted data demonstrate that variability is not an issue for sunscreen products with SPF values up to 50. However, FDA is concerned that variability will become an issue for sunscreen products with SPF values over 50.

FDA recognizes that future data may demonstrate that variability may not be a problem for sunscreen products with SPF values over 50. Therefore, FDA will consider specific SPF values greater than 50 upon receipt of data demonstrating that accurate and reproducible results can be obtained from the SPF test for sunscreen products with SPF values over 50. Generally, such data should include results from multiple laboratories using the same sunscreen formulations and using the SPF test proposed in this document, along with a statistical analysis of the overall results. In addition, FDA believes that the modified "binomial" test method submitted by one comment has merit for high SPF sunscreens and is requesting others' views on this method during the comment period for this rulemaking (see section III.I, comment 24 of this document).

In the FM (64 FR 27666 at 27675), FDA disagreed with the comment that manufacturers would have no incentive to fund research for better sunscreens and may reformulate to less protective products if there is an upper limit to specific labeled SPF values. Although FDA would not want to decrease research incentive, FDA is more concerned about valid scientific data demonstrating the ability of multiple laboratories to accurately and reproducibly determine SPF values. However, FDA does not believe it is necessary to arbitrarily limit specific labeled SPF values. To the contrary, both in the FM and in this proposal, FDA has specifically stated that high SPF sunscreens should be available for those individuals desiring such products. The maximum allowable specific labeled SPF value, both in the FM and in this proposal, is based upon the review of data and information submitted to FDA. FDA purposely did not limit labeled SPF values at 30 in the FM. Instead, FDA used the value of "30+," pending the receipt of adequate data to support any higher specific label values.

Similarly, in this document, FDA is proposing the collective value "50+." FDA has sufficient assurance that a result over 50 from the required SPF test is, in fact, greater than 50 and can be labeled "50+." Thus, FDA believes that the term "SPF 50+" is truthful and nonmisleading on the label of OTC sunscreen drug products for which the SPF test in the monograph has indicated an SPF value greater than 50. FDA believes that allowing manufacturers to label sunscreens as "SPF 50+" may encourage further research in human skin photobiology and the development of safe and effective sunscreen drug

products with specific SPF values over 50. As explained earlier in this comment, FDA is not proposing that the specific value over 50 be stated in the labeling because there is no data, at this time, demonstrating the accuracy and reproducibility of the specific value over 50. Based upon the proposed labeling, improvements to SPF testing methods, and specific high SPF test data, FDA is proposing to modify the labeled SPF values in current § 352.50(a)(1) and (a)(2) by changing the SPF values from "30" to "50."

G. Comments on Indications for Sunscreen Drug Products

(Comment 16) One comment requested that the "Uses" statement, "higher SPF gives more sunburn protection," be omitted except for products with an SPF over 30. This and other comments suggested that FDA's labeling concerns regarding high SPF sunscreens could be alleviated if the following statement was required on sunscreens over SPF 30: "Higher SPF products give more sun protection, but are not intended to extend the time spent in the sun."

FDA is proposing to revise the sunscreen FM "Uses" statement "helps prevent sunburn" and delete the "Uses" statement "higher SPF gives more sunburn protection" in current § 352.52(b). The first indication, "helps prevent sunburn," is being revised to one of the following, which would be required on all sunscreens:

- "low UVB sunburn protection"
- "medium UVB sunburn protection"
- "high UVB sunburn protection"
- "highest UVB sunburn protection"

The relative level of sunburn protection is determined from the SPF value:

- low = SPF 2 to under 15
- medium = SPF 15 to under 30
- high = SPF 30 to 50
- highest = SPF over 50

Thus, relative descriptors (low, medium, high, and highest) describe SPF values, which are relative and not absolute levels of sunburn protection intended to help consumers determine differences in sunburn protection offered by different sunscreen products (see section III.I, comment 23 of this document).

FDA considers it important that consumers be made aware of the relative level of sunburn protection provided by a product in addition to its indication for sunburn protection. Individuals may select a low, medium, high, or highest sunburn protection product to meet their specific needs. The descriptor "UVB" is included to describe the predominant rays that are screened. The phrase "helps prevent" is being deleted

because it is duplicative and no longer necessary. This phrase would only lengthen the "Uses" statement. Furthermore, consumers will now be able to equate a product's UVB radiation protection rating (i.e., SPF value) directly to the relative level of sunburn protection.

The second indication "higher SPF gives more sunburn protection" is no longer needed because the relative level of sunburn protection is provided in the new "Uses" statements. In addition, without clarification, the statement may encourage consumers to spend more time in the sun. Clarification is necessary because, as discussed in comment 19 of this document, surveys reveal that consumers spend more time in the sun with increasingly higher SPF sunscreen products (Refs. 14, 15, and 16). Therefore, FDA is not allowing this statement in the "Uses" section.

However, under proposed § 352.52(e)(2), FDA is proposing the following optional statement under "Other information" or anywhere outside of the "Drug Facts" box or enclosure: "higher SPF products give more sun protection, but are not intended to extend the time spent in the sun." The phrase "but are not intended to extend the time spent in the sun" is additional information not included in the FM indication. FDA believes this revised indication statement will discourage consumers from spending more time in the sun when using a higher SPF product.

FDA is proposing additional revisions in "Uses" in § 352.52(b)(1) to include UVA claims and other information (see section III.G, comments 17 and 18 of this document). The proposed revisions will help consumers to more fully understand the uses and expected results for individual sunscreen products. These changes are necessary because the PDP for a sunscreen product will now include two performance ratings (see section III.E, comment 14 of this document):

- The well-accepted SPF value and new descriptor rating for UVB radiation protection, and

- A new star/descriptor rating for UVA radiation protection.

Consequently, FDA considers it important that the "Uses" statements in the "Drug Facts" box accurately reflect product claims related to specific indications, UVA and UVB radiation, and the level of anticipated protection (low, medium, high, or highest) determined by the UVA and UVB product ratings. As with the introduction of SPF labeling years ago, it will take the combined efforts of government, manufacturers, consumer organizations, and the health care

community to educate consumers to fully understand these labeling initiatives to enhance their safe and effective use of sunscreen products.

(Comment 17) One comment stated that FDA's "sun alert" statement in the FM recognized that sun-induced skin damage can contribute to photoaging and increase the risk of skin cancer. This statement reads: "Sun alert: Limiting sun exposure, wearing protective clothing, and using sunscreens may reduce the risks of skin aging, skin cancer, and other harmful effects of the sun." The comment urged FDA to allow other truthful use statements, such as the following:

- "helps protect against skin damage caused by the sun"
- "helps protect against skin aging caused by the sun"
- "regular use helps protect against certain forms of skin cancer caused by the sun"
- "helps protect against fine lines and wrinkles caused by the sun"
- "helps protect against pigmentary changes due to sun exposure"

Another comment urged FDA to include the first three use statements suggested by the first comment, as well as "helps protect against the harmful effects of the sun" and "helps protect against (select one: 'casual,' 'incidental,' 'intermittent,' or 'daily') sun exposure." The comment contended that, when used effectively as part of a sun protection program, sunscreens may prevent very serious disease conditions.

Another comment provided citations from the medical literature to support its contention that claims of sunscreens preventing skin cancer induction may be false, deceptive, misleading, and unsubstantiated. The comment mentioned an article by Garland (Ref. 25) that states the following: "No epidemiological studies were identified that showed a protective effect of use of chemical sunscreen on risk of melanoma or other cutaneous malignancies in humans." The comment also mentioned an article by Gasparro (Ref. 24) that states the following: "Although some have promoted daily use (of sunscreen) for the prevention of premature aging of the skin and the prevention of skin cancer, actual data are lacking to support these recommendations."

FDA has reviewed the submitted articles concerning UV-induced skin damage (i.e., premature aging and cancer) along with articles obtained from a search of the scientific literature (Refs. 26 through 34). Many of the articles involved preclinical data, which can be difficult to extrapolate to consumer (human) actual use

conditions. FDA believes that the articles with clinical data provide more meaningful results, as they can be easily extrapolated to consumer actual use conditions. Therefore, FDA is focusing discussion in this document on the clinical studies. In agreement with Garland (Ref. 25) and Gasparro (Ref. 24), FDA does not believe, as a whole, that the studies demonstrate that sunscreens alone help prevent skin aging or skin cancer.

Some of the clinical studies examined the role of UVB and UVA radiation in producing histological changes indicative of skin aging due to the sun. Lowe et al. demonstrated that high doses of UVA radiation (320 to 400 nm) increased melanization of human skin more than lower doses of UVA or solar simulating UV radiation at 290 to 400 nm (Ref. 26). Seite et al. demonstrated that melanization of human skin increased with exposure to UVB/UVA radiation at 290 to 400 nm (Ref. 32) and UVA radiation at 330 to 440 nm (Ref. 27). Seite et al. also showed that human skin hydration decreased after chronic exposure to UV radiation at the wavelengths studied.

Five studies revealed stratum corneum thickening produced by both UVB and UVA radiation (Refs. 26 through 29 and 32). Stratum granulosum thickening was transiently induced after 6 weeks of exposure to UV radiation (UVB/UVA) at 290 to 400 nm (Ref. 32). The same effects were seen with solar simulated radiation and high and low doses of UVA radiation after 12 weeks of exposure (Ref. 26). Viable epidermal thickening was seen after 6 weeks of exposure to UV radiation at 290 to 400 nm in one study (Ref. 32) and after 9 days of exposure to UVA radiation at 335 to 345 nm in another study (Ref. 31).

Inflammation and lysozyme deposition along the dermal elastic fibers were increased more in human skin exposed to UVA than UVB radiation (Refs. 26, 28, 29, and 31). Sunburn cell appearance, a typical response to UVB radiation, was also found to be present after exposure to different UVA radiation regimens in two studies (Refs. 28 and 31) but not found in a third study (Ref. 27). Thus, FDA concludes that these studies demonstrated that both UVB and UVA radiation induce histological changes associated with skin aging.

Four of these studies focused on the histological changes within the skin induced by UVB and UVA radiation and explored the ability of sunscreens to protect human skin against these changes (Refs. 29, 30, 32, and 33). The first study suggested that an SPF 29

sunscreen prevented the development of solar elastosis, a condition in which skin loses its elasticity after chronic exposure to the sun (Ref. 33). However, these method and data analyses raise questions about the validity of the reported conclusion:

- Discrepancies were noted concerning demographic characteristics of subjects, sunscreen application, and compliance rates.

- Skin biopsy data at all three time points in the study were available from only 10 of the 35 subjects.

- The only statistically significant difference between the sunscreen and placebo treatment groups was achieved in a computerized evaluation of solar elastosis at baseline and 24 months.

The second study demonstrated significant contribution of a sunscreen in preventing UV radiation-induced skin damage (Ref. 32). The use of sunscreens with absorption spectra covering the 290 to 400 nm range prevented all of the effects of chronic exposure (6 weeks) to UV radiation evaluated in the study. The third study showed a photoprotective effect of an SPF 15 sunscreen product from damage induced by short term exposure to UVB radiation (Ref. 30). The fourth study showed that a UVB only sunscreen did not provide protection against chronic exposure to UVA radiation (Ref. 29).

The studies provide evidence that both UVB and UVA radiation induce histological changes in the skin consistent with skin aging. Thus, the studies support the conclusion that exposure to UV rays increases the risk of premature skin aging. However, the study data fails to show that sunscreen use alone helps prevent premature skin aging for several reasons. First, the studies have not completely defined the action spectrum for the majority of UV radiation-induced effects on human skin. While studies demonstrate that a given histological change, such as thickening of the stratum corneum, is induced by certain wavelengths within the UVB and UVA region, studies have not examined the ability of the remaining UVB and UVA regions outside of these wavelengths to induce the same change. For example, studies may have shown that 290 nm to 310 nm and 360 nm to 400 nm radiation induce stratum corneum thickening, but it is not known whether 311 nm to 359 nm radiation induces the same histological change.

Second, the inability to identify the exact UVB and UVA wavelengths that induce each histological change in the skin derives from the study designs. Each study differed in the following parameters:

- UV radiation wavelengths,
 - UV exposure regimens,
 - Sunscreen doses,
 - Sunscreen application techniques,
- and
- Endpoints.

Therefore, FDA cannot combine all of the data from these studies to define a complete action spectrum for each histological change in the skin. Furthermore, the action spectrum for each histological change would need to be combined to define a single action spectrum for skin aging, which is a cumulation of these histological changes. Without knowing which UVB and UVA wavelengths induce each histological change in the skin, FDA is unable to determine which wavelengths are most important in causing skin aging and cannot determine the action spectrum for aging.

Third, the studies did not examine the chronic, long-term consequences of UV radiation exposure in human skin. Thus, it is not possible for FDA to extrapolate the data to longer time points at which the short-term histological changes may cumulate to produce visible signs of skin aging.

Fourth, although the studies that examined the ability of sunscreens to protect against UV radiation-induced histological changes in the skin provide useful data, it is difficult for FDA to conclude that sunscreens alone help prevent skin aging based on these studies. The number of participants in each study was relatively small, with only 10 to 35 subjects per study. Different sunscreen formulations, with differing absorption spectra, were used in each study. As explained previously, these studies do not identify exactly which UVB and UVA wavelengths contribute the most to skin aging (i.e., the studies do not define the skin aging action spectrum). For all of these reasons, the studies do not prove that sunscreens alone help prevent premature skin aging.

Likewise, FDA is not aware of data demonstrating that sunscreens alone help prevent skin cancer. It has been known for many years that UV radiation increases the risk of skin cancer. It has also been known for many years that a higher incidence of sunburn earlier in life corresponds to a higher incidence of skin cancer later in life. However, FDA is not aware of any studies demonstrating that the use of sunscreens alone decreases the risk of skin cancer. Like skin aging, there are studies examining the effects of sunscreens on short-term factors for skin cancer, such as sunburn and other cellular damage. However, it is difficult to extrapolate these short-term adverse

effects of UV radiation to a long-term, chronic effect such as skin cancer. In addition, like skin aging, the complete action spectrum for skin cancer is not known at this time.

Unlike skin cancer and premature skin aging, FDA has evidence that sunscreens alone help prevent sunburn. The SPF test measures the effectiveness of sunscreens with sunburn (erythema) as the endpoint. Thus, the impact of sunscreens on sunburn can be measured directly. In contrast, it is difficult to measure directly the impact of sunscreens on skin cancer or premature skin aging because these are long-term, cumulative adverse effects of UV exposure.

Thus, for all of the reasons discussed in this comment, FDA concludes that the available evidence fails to show that sunscreens alone help prevent skin cancer or premature skin aging. Based on this conclusion, FDA is not proposing the indication statements proposed by the first and second comments, because these claims are for protection from premature skin aging, skin cancer, and related factors (e.g., “helps protect against skin aging caused by the sun”). FDA also is not proposing claims that sunscreens protect against “casual, incidental, intermittent, or daily” sun exposure, as proposed by the second comment, because the studies do not support these claims. Furthermore, FDA considers these terms as lacking sufficient meaning to be useful to consumers.

As described elsewhere in this document (see section III.G, comment 19), FDA is proposing to require a revised “sun alert” statement in the form of a new warning. The new warning statement is based on FDA’s review of the available evidence concerning UV exposure and skin cancer, premature skin aging, and other skin damage. The new warning statement clarifies that UV exposure from the sun increases the risk of skin cancer, premature skin aging, and other skin damage. In addition, the new warning statement specifies that consumers should use complementary sun protection measures along with sunscreen (i.e., limit sun exposure and wear protective clothing). FDA has concluded from the available evidence that it is important to adopt a complete sun protection program (sunscreen, sun avoidance, and protective clothing) to decrease UV exposure. In fact, the second comment argued for new indication statements by considering the sunscreen use as part of such a sun protection program (i.e., in conjunction with limiting time in sun and wearing protective clothing). Thus, the second

comment, along with the third comment, seemed to agree with FDA’s conclusions in this proposed rule concerning the need for consumers to use sunscreens in conjunction with other sun protection measures.

In addition, the reference in the new warning statement to sunscreen use combined with limiting sun exposure and wearing protective clothing is consistent with recommendations by other public health organizations. For example, the World Health Organization’s International Agency for Research on Cancer (IARC) (Ref. 21) makes the following assessments and recommendations:

- There is inadequate evidence in humans for a cancer preventative effect of sunscreens against basal cell or malignant melanoma cancers.
 - There is only limited evidence for a preventive effect of sunscreens against squamous cell cancer.
 - Sunscreens should not be the first choice for skin cancer prevention or used as the sole agent for protection against UV radiation.
- Likewise, the CDC recommends that sunscreens be used as a complementary measure in an overall sun protection program (Ref. 35).

FDA believes that additional information from controlled clinical studies is needed to better understand the role of sunscreens in preventing premature skin aging and skin cancer. Studies examining premature skin aging (using solar radiation or simulated solar radiation) are needed to determine the following in humans:

- Measurable skin properties such as elasticity, collagen/elastin ratios and properties, wrinkling, pigmentation changes and visual grades, leading to accepted quantitative definitions of chronological and sun-induced skin aging;
 - The relationship between sunlight exposure and skin aging, stratified by skin type;
 - An action spectrum for photoaging of skin;
 - A dose response for UV radiation-induced skin aging;
 - Quantitative estimates of realistic “worst case,” long-term exposures to sunlight in relevant UVA and UVB radiation spectral ranges (i.e., the level of UVB and UVA protection needed); and
 - How UV radiation-induced processes that occur at a given wavelength affect UV radiation-induced processes that occur at other wavelengths.
- Similar information is needed for skin cancer, except that studies should examine the different types of skin

cancer, rather than examining different skin properties. In addition, IARC has provided recommendations for research on skin cancer prevention and sunscreens. These recommendations can also be used as a guide in designing studies to examine the role of sunscreens in preventing premature skin aging due to the sun (Ref. 21). FDA encourages interested parties to submit study protocols to FDA for review to ensure that studies are as informative as possible. FDA also invites comments by interested parties on the feasibility and validity of surrogate endpoints for studies to determine whether the use of sunscreens alone help prevent skin cancer, premature skin aging, or other skin damage.

(Comment 18) As discussed in section III.E of this document, FDA received several comments discussing ways to categorize, phrase, and display UVA/UVB radiation protection on an OTC sunscreen drug product label. In the amendment to include avobenzone in the monograph (61 FR 48645 at 48655), FDA proposed the following indications for UVB and UVA radiation protection by sunscreen drug products containing avobenzone:

1. "Broad spectrum sunscreen";
2. "Provides" (select one of the following: "UVB and UVA," or "broad spectrum") "protection";
3. "Protects from UVB and UVA" (select one of the following: "Rays" or "radiation");
4. (Select one of the following: "Absorbs," "Protects," "Screens," or "Shields") "throughout the UVA spectrum"; and

5. "Provides protection from the UVA rays that may contribute to skin damage and premature aging of the skin". Likewise, in the amendment to include zinc oxide in the monograph (63 FR 56584 at 56588), FDA proposed similar labeling for UVA and UVB radiation protection for products containing zinc oxide (substituting the word "within" for the word "throughout" in the fourth statement). FDA did not include these indications in the FM but has allowed their use until the UVA portion of the monograph is established.

FDA has reconsidered these UVA protection indications. FDA is proposing to allow all of them except the fifth statement. In proposed § 352.52(e), the first four statements are optional statements allowed for products that demonstrate UVA protection according to the proposed testing (see section III.N, comment 45 of this document). The statements can only be included in labeling outside of the "Drug Facts" box. Within the "Drug Facts" box, FDA is proposing one of the

following UVA indication statements, depending on the level of UVA protection provided by a product:

- "low UVA protection"
- "medium UVA protection"
- "high UVA protection"
- "highest UVA protection"

The level of protection (i.e., low, medium, high, or highest) is determined from the UVA rating obtained from product testing (see section III.N, comment 45 of this document). Manufacturers who wish to combine the "Uses" statements about UVA protection and UVB sunburn protection may do so if the descriptors (i.e., levels of protection) are the same. For example, if the levels of UVA and UVB protection are medium, the "Use" may read: "medium UVA/UVB sunburn protection".

FDA is not including the fifth indication because FDA does not consider "skin aging" or "skin damage" claims adequately supported at this time. As discussed elsewhere in this document (see section III.G, comment 19), FDA is proposing a statement in the "Drug Facts" box that informs consumers that sunscreens may reduce the risks of skin aging, skin cancer, and other harmful effects from the sun when used in a regular program that relies upon limiting sun exposure and wearing protective clothing. Therefore, FDA believes the fifth indication statement would mislead consumers by not discussing sun exposure and protective clothing.

(Comment 19) As discussed in section III.G of this document, FDA received several comments concerning the "sun" alert statement. In § 352.52(e)(2) of the FM, FDA included the optional statement: "Sun alert: Limiting sun exposure, wearing protective clothing, and using sunscreens may reduce the risks of skin aging, skin cancer, and other harmful effects of the sun." This statement's emphasis of the need for a comprehensive sun protection program (64 FR 27666 at 27679) was based on the findings of numerous groups, including the following:

- The American Academy of Dermatology (AAD),
- The CDC,
- The Australian Government; and
- The New Zealand Government.

These groups have recommended that sunscreens be considered an adjunct to other UV protection strategies, such as avoiding the sun near midday, seeking shade, and wearing protective clothing and hats.

The FM provided that the "sun alert" appear under the heading "Other information" or anywhere outside of the "Drug Facts" box or enclosure. At that

time, FDA encouraged manufacturers to voluntarily include this statement in labeling, make it available at the point of purchase, and/or make it available through consumer education programs.

FDA is now proposing a revised "sun alert" statement be required in the "Warnings" section of the "Drug Facts" box. FDA is proposing the statement to read as follows: "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. FDA is proposing that the statement appear in bold type as the first statement in the "Warnings" section. FDA believes the statement is most appropriate in the "Warnings" section because it warns consumers that effective protection from the sun does not involve only the application of sunscreens, as many consumers believe. In addition, it warns consumers that UV radiation not only increases the risk of sunburn but also increases the risk of skin cancer and premature skin aging, which many consumers may not know. FDA believes the new warning will encourage consumers to use sunscreen, limit time in the sun, and wear protective clothing to reduce UV exposure. Because of the importance of warning statements and the need for consumers to receive a uniform message concerning such warnings, no variations in wording are allowed under § 330.1(c)(2).

FDA acknowledges that the new warning statement differs from the wording of the voluntary "sun alert" in the FM. These differences are based on FDA's assessment of the additional evidence available since publication of the FM in 1999. As explained in comment 17 of this document, FDA does not believe that the available data support a claim concerning the use of sunscreen and a reduction in the risk of premature skin aging and skin cancer. The revised wording of the statement more accurately reflects the scientific conclusions that can be drawn from this evidence.

FDA is proposing the warning because we continue to be concerned about adequate consumer understanding of a sun protection program that includes sun avoidance and wearing protective clothes along with sunscreen use. This proposed rule provides for even higher SPF values and a new rating system for UVA protection. Consumers may believe that sunscreens with higher SPF values (especially with UVA protection) provide complete UV radiation protection. Subsequently, consumers may prolong sun exposure

because they think higher SPF values equate to longer times in the sun without burning. FDA is aware of a double-blind, randomized clinical study that showed a significant increase in sun exposure time of persons using high SPF sunscreens compared to persons using low SPF sunscreens (Ref. 14). In addition, two questionnaire-based surveys showed that sun exposure time is prolonged for persons using sunscreens compared to persons not using sunscreens (Refs. 15 and 16). By educating consumers about a sun protection program, we believe requiring this new proposed warning will decrease the likelihood of consumers spending more time in the sun when using a sunscreen.

The new proposed warning also informs consumers that use of sunscreens alone is not the sole measure of protection from UV exposure, even with the use of high SPF products that provide UVA protection. Although it is well established that sunscreens protect against UV radiation, the following factors affect the level of protection provided by a sunscreen for each individual:

- Variations between individuals,
- UV radiation absorption,
- Ability of sunscreens to adhere to and be absorbed by the skin,
- Exposure conditions, and
- Conditions of use (e.g., inadequate application amount or reapplication frequency).

Therefore, FDA agrees with the numerous groups that promote sunscreen use as part of a total sun protection program.

FDA reviewed the relationship between sunscreen use and skin cancer incidence in the scientific literature and did not find confirmatory evidence that sunscreens alone protect against the development of skin cancer. The incidence of skin cancer continues to rise in the United States. The incidence of the most serious form of skin cancer, malignant melanoma, grew 6.1 percent per year during the 1970s (Refs. 14 and 36). The rate is still rising an average 2.8 percent annually, with a rate of 14.3 percent per 100,000 persons in 1997. Melanoma is one of the top 10 cancers, by incidence, for persons with white skin. The American Cancer Society (ACS) estimated the following statistics concerning skin cancer in 2007 (Ref. 37):

- More than 1 million new cases of curable basal cell and squamous cell carcinomas would be detected,
- Approximately 59,940 new cases of malignant melanoma would be diagnosed, and

- An estimated 8,110 persons would die from melanoma and 2,000 persons would die from other skin cancers.

Skin cancer affects roughly the same number of people as all other cancers combined. In view of the continuing increase in the incidence of all types of skin cancer and the lack of data demonstrating that sunscreens alone prevent skin cancer, FDA considers the new warning important for the protection of the public health.

FDA is proposing that the new warning be required on all OTC sunscreen drug products except lip cosmetic-drug and lip protectant-sunscreen products subject to § 352.52(f). FDA continues to believe that all sunscreen products should have labeling to ensure that consumers are adequately protected against overexposure to UV radiation (64 FR 27666 at 27673). Thus, sunscreen products labeled for use only on specific small areas of the face and sold in small packages (i.e., sunscreen products subject to § 352.52(f)) must include the new warning. The only sunscreen products not required to include the new warning are those lip cosmetic-drug and lip protectant-sunscreen products subject to § 352.52(f), as proposed in § 352.52(f)(1)(ii). FDA is making this proposal because lip cosmetic and lip protectant products are often sold in packages that are substantially smaller than those of other products that fall under § 352.52(f). FDA believes requiring the new warning on lip cosmetic-sunscreen and lip protectant-sunscreen products may discourage manufacturers from marketing these products because it requires a significant amount of labeling space.

FDA has limited labeling requirements as much as possible for sunscreen products subject to § 352.52(f). However, FDA believes consumers are at great risk for UV-induced skin damage, including cancer, on the face. Therefore, consumers who purchase products specifically for use on the face need to be informed about the information contained in the new warning. Although these products are marketed in small package sizes, FDA has determined that the products' labeling needs to include this important information in order to protect consumers.

(Comment 20) One comment stated that consumers who use color cosmetics or facial moisturizers with sunscreens make the informed decision to purchase them as an additional benefit to their cosmetic use. The comment contended that a significant number of people with dark skin types, who do not burn easily,

purchase sunscreens to provide protection from the sun damage that is not immediately recognizable. For these reasons, the comment requested claims such as the following:

- “helps protect against casual or incidental or intermittent daily sun exposure”
- “helps protect against the harmful effects of the sun”

Another comment acknowledged that facial makeups with sunscreen provide protection from sunburn, but that is not the primary reason why consumers use these products. The comment contended that requiring the “sunburn” indication would be inappropriate and misleading labeling for most facial makeups with sunscreen. The comment, instead, requested a claim such as “protects against the harmful rays of the sun.”

FDA notes that the second comment acknowledged that facial makeups with sunscreen provide protection from sunburn. Not every consumer who uses color cosmetics or facial makeups with sunscreen meets the following criteria:

- Has a dark skin type, or
- Uses these products solely to provide protection from sun damage that is not immediately recognizable.

As noted in section III.D, comment 9 of this document, many consumers use facial products with sunscreen as their primary and only source of sunscreen protection for that area of the body. As discussed in section III.G, comment 16 of this document, sunscreen products will be required to bear a claim of low, medium, high, or highest UVB sunburn protection. FDA does not consider it inappropriate or misleading for color cosmetic or facial makeup products containing sunscreens to have this sunburn protection claim of low, medium, high, or highest.

Sunscreen products that provide UVA radiation protection may also bear a claim about the level of protection. In addition, all OTC sunscreen products, except lip cosmetic-drug and lip protectant-sunscreen products subject to § 352.52(f), will be required to bear the revised “sun alert” statement, which is now included in the “Warnings” section of the “Drug Facts” box. FDA considers the information in this new “Warnings” statement much more beneficial to consumers than the statements proposed by the comments. FDA rejected the terms “casual, incidental, and intermittent,” as explained in section III.G, comment 17 of this document.

H. Comments on Directions for Sunscreen Drug Products

(Comment 21) Several comments requested alternative directions for makeup with sunscreen products. One comment requested “apply smoothly or evenly before sun exposure and/or as needed.” The comment added that “before sun exposure” may not always be appropriate as these makeup products are not exclusively or even primarily used for protection against sun exposure. A second comment requested “apply smoothly or evenly before sun exposure and reapply as needed.” A third comment did not suggest any specific language, but requested flexibility to recognize the product’s primary use as a makeup, while providing adequate information about the sunscreen component. This comment added that the direction to consult a doctor for children under 6 months of age was clearly unnecessary for facial makeup with sunscreen because these products cannot reasonably be expected to be used on children that age.

FDA agrees that flexibility is appropriate for the directions for makeup with sunscreen products. Elsewhere in this document, FDA is proposing to allow labeling modifications for makeup with sunscreen products used only on specific small areas of the face and sold in small packages (see section III.D, comment 9 of this document). Those modifications include modified directions for cosmetic lip products containing sunscreen that are within the scope of proposed § 352.52(f). FDA is not extending the proposed modifications to all makeup with sunscreen products. Makeup with sunscreen products not labeled only for specific small areas of the face may be applied to a large area of the face or other areas of the body. As explained later in this comment, FDA would have concerns with the modifications being applied to these products.

Whether intentional or not, makeup with sunscreen products may be the primary sunscreen for many consumers. A recent study examined sunscreen use patterns (Ref. 48). Participants were instructed to apply sunscreen every day. Of those who used sunscreen infrequently, the majority spent some time outdoors with 11 percent spending the majority of their time outdoors. These same participants explained that they did not believe sunscreen was necessary because of their planned activities. The authors cited this finding in advocating educating consumers on the need for sunscreen for frequent

incidental sun exposure in addition to intentional sun exposure, such as sunbathing.

For these reasons, FDA considers it important that consumers using makeup with sunscreen products not labeled for use only on specific small areas of the face recognize that these products are sunscreens and use them appropriately to maximize UV protection. Therefore, FDA is not proposing modified directions for these makeup with sunscreen products.

(Comment 22) One comment requested that FDA require sunscreen manufacturers to provide accurate and appropriate instructions about how much sunscreen should be applied to the body. The comment also suggested that a warning about the dangers of sunburn from applying suboptimal amounts be included in sunscreen product labeling. A second comment stated that it was not aware of any study indicating that consumers use adequate amounts of sunscreen. The comment supplied data and other information concerning the dependency of the SPF value on the total quantity of sunscreen applied (Ref. 49).

Section 352.52(d)(1) currently provides manufacturers the option to select one or more of the following application terms for a sunscreen product: “liberally, generously, smoothly, or evenly.” Manufacturers may also include optional directions that state “[bullet] reapply as needed or after towel drying, swimming, or (select one of the following: ‘sweating’ or ‘perspiring’).” In the final rule, FDA had concluded that the directions in § 352.52(d)(1) to apply “liberally” or “generously” convey the appropriate message to ensure that consumers adequately apply the sunscreen (64 FR 27666 at 27679).

Several studies suggest that, in practice, consumers may apply amounts of sunscreen below the density of 2 milligrams/square centimeter (mg/cm^2), which is the amount of product required for the SPF determination in § 352.72(e) (proposed § 352.71(e)). These data suggest that consumers may apply as little as 0.5 to 1.0 mg/cm^2 (Refs. 50 through 54). One comment reported that, to achieve the rated protection over the whole body, a typical adult with a surface area of 1.73 square meters (m^2) would need to apply 35 milliliters (mL) of sunscreen, roughly one-third of a 4 oz bottle per application (Ref. 55). Studies indicate that SPF values determined at an application rate of 1 mg/cm^2 are approximately 50 percent of those determined at 2 mg/cm^2 , and when applied at 0.65 mg/cm^2 , the SPF values are 20 to 30 percent of those determined

at 2 mg/cm^2 (Refs. 49, 50, and 51). Gasparro notes that statements such as “apply liberally and frequently” are too vague to be informative (Ref. 24).

FDA is concerned that, in practice, consumers may be getting less protection than the labeled SPF value and believes that further information should be included in the labeling for sunscreen drug products to reduce the likelihood of underapplication. FDA believes that this information is better communicated as revised product directions rather than a warning. FDA is, therefore, proposing to revise § 352.52(d)(1). The directions will continue to state that OTC sunscreen drug products should be applied “liberally” or “generously” because it would be cumbersome to specify quantitative amounts for all possible body areas and the various uses on the label. However, FDA is proposing to make optional the directions in § 352.52(d)(1)(i) to apply “evenly.” FDA believes that this term, if used alone, may not convey the appropriate message to ensure that consumers apply sufficient sunscreen. In addition, FDA is proposing to remove the term “smoothly” from § 352.52(d)(1)(i) because FDA considers that term to be vague and it may have different meanings to different consumers. FDA also believes this term is more likely to result in product underapplication.

In addition to labeling directing consumers to apply sufficient amounts of sunscreen, FDA is also proposing to revise the labeling requirements concerning reapplication of the sunscreen product. In § 352.52(d) of the FM, the general reapplication statement “and as needed” was the only required information. FDA made specific reapplication directions in § 352.52(d)(2) of the FM optional in an effort to equalize requirements between sunscreens with and without water resistant claims (64 FR 27666 at 27681). FDA now believes that more detailed reapplication directions must be included on all OTC sunscreen products, because sunscreens may be underapplied as suggested by the comments.

FDA came to this conclusion after reviewing studies concerning sunscreen reapplication as well as recommendations of public health organizations. Wright, et al. suggests that inadvertent sunburn may be due to the failure to use and reapply sunscreen appropriately (Ref. 56). Study subjects who reapplied sunscreen every 1 to 2 hours and after swimming did not report sunburn. Rigel et al. reported that, even under intense solar conditions, those reapplying an SPF 15

sunscreen every 2 hours or sooner were five times less likely to sunburn compared to those who reapplied every 2.5 or more hours (Ref. 57). The AAD (Refs. 38, 58, and 59), the ACS (Ref. 60), and the EPA (Ref. 40) recommend reapplying sunscreens every 2 hours or sooner and also recommend application to all exposed areas of the body (Refs. 60, 61, and 62).

Because the frequency of application appears to be critical for proper protection, FDA is proposing to add the statement "apply and reapply as directed to avoid lowering protection." In addition, FDA is proposing to further revise the directions in § 352.52(d) to include the following reapplication statement: "reapply at least every 2 hours." Likewise, for those products making a water resistant claim, FDA is proposing to include the number of minutes (i.e., 40 or 80) that the product maintains its water resistance before the "swimming/sweating" term. FDA believes these additional proposed directions will alert consumers about the hazards of using insufficient amounts of sunscreen product and encourage reapplication after the appropriate time. FDA considers these specific, informative reapplication statements, instead of "and as needed," to be necessary on all OTC sunscreen products. FDA is also proposing the optional direction "apply to all skin exposed to the sun." FDA is proposing that this direction be optional because we believe most consumers know to apply sunscreen to all exposed skin. However, if a sunscreen product can accommodate this direction, it will serve to remind consumers that all exposed skin is susceptible to UV damage. These proposed directions, as a whole, should serve to better protect consumers, particularly those who tend to underapply sunscreen, from overexposure to the sun.

Accordingly, FDA is proposing to change § 352.52(d) to read as follows:

(d) *Directions.* * * *

(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 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']".

As discussed in the FM (64 FR 27666 at 27679), manufacturers who have data to support different reapplication directions based on specific substantiation information may submit the information for approval of those directions via an NDA deviation as provided in § 330.11 (21 CFR 330.11).

I. General Comments on SPF Testing Procedure

(Comment 23) One comment suggested that the SPF test incorporate an amount of product that more closely reflects the amount applied by consumers. More specifically, the comment requested that FDA replace the 2 mg/cm² required in § 352.72(e) (proposed § 352.70(c)(5)) to a value between 0.5 and 1.0 mg/cm². The comment argued that the protection afforded during actual usage may be only one-quarter to one-half the labeled SPF value (see section III.H, comment 22 of this document). The comment also suggested that SPF could be stated using descriptive terms, such as "light," "moderate," or "heavy" protection, instead of a numerical value.

FDA is not proposing the suggested change in test method at this time. This issue was discussed in detail in the TFM (58 FR 28194 at 28264 to 28266). The majority of comments advocated continuing the use of an application density of 2 mg/cm². The current comment did not provide data demonstrating the suitability of a smaller test amount. FDA is concerned that a uniform distribution of sunscreen over the test area might be difficult using a smaller amount of sunscreen. Further, the standard application density used worldwide in the SPF test is 2 mg/cm² (Ref. 63).

FDA agrees that SPF values do not reflect exact levels of sunburn protection that consumers receive under actual use conditions. The required SPF test is a clinical test conducted with strict control over factors such as product application density. However, under actual use conditions, these factors are not controlled and vary greatly. The actual level of sunburn

protection under consumer use conditions is affected by a number of factors. Some of the key factors are

- Application density,
- Reapplication frequency,
- Skin type (e.g., burns easily versus never burns),

• Time of day during sun exposure, and

- Geographical location during sun exposure.

Thus, SPF values reflect relative and not absolute levels of sunburn protection.

Although SPF values do not convey actual levels of sunburn protection, when comparing multiple sunscreen products, SPF values enable consumers to determine which products provide the most sunburn protection. For example, FDA believes most consumers would correctly identify an SPF 20 product as providing more sunburn protection than an SPF 10 product.

Thus, lowering the sunscreen application density would not be necessary to more accurately reflect the degree of relative sunburn protection.

FDA agrees that, in addition to bringing SPF values closer to representing absolute levels of protection, lowering the sunscreen application density might also reduce some of the inaccuracies and limitations encountered when testing high SPF sunscreen products. Thus, FDA invites interested parties to submit data supporting a smaller application density for SPF testing of all sunscreen dosage forms in accordance with § 352.77.

However, developing a single global method and labeling would require a coordinated effort between the regulatory agencies in many countries around the world. Because FDA does not have data to validate the SPF test using a lowering sunscreen density, FDA is proposing directions that we believe will encourage consumers to apply greater densities of sunscreen (i.e., closer to 2 mg/cm²) (see section III.H, comment 22 of this document).

FDA does not find that there are sufficient benefits for using descriptors instead of numerical values for SPF on the PDP. Consumers are familiar with numerical SPF values from over 20 years of usage. As described in section III.G, comment 16 of this document, FDA believes that the use of descriptors in combination with numerical values on the PDP may be beneficial to consumer understanding of the level of sunburn protection provided by a product. Thus, as explained in comment 16, FDA is proposing to include a descriptive term of relative sunburn protection (i.e., low, medium, high, or highest) with the proposed sunburn protection statement in the "Uses"

section and on the PDP. The intent of this dual descriptive and numerical sunburn protection measure is to allow consumers to more easily differentiate the level of sunburn protection provided by different sunscreen products. In addition, this proposed labeling for sunburn protection is similar to the proposed UVA protection labeling (see section III.G, comment 14 of this document).

FDA is also aware of sunscreen drug products marketed in dosage forms that may not be addressed by current SPF testing procedures. The SPF testing procedure described in § 352.72 (proposed § 352.70) references oils, lotions, creams, gels, butters, pastes, and ointments. FDA invites interested parties to submit SPF testing modifications for new dosage forms (e.g., mousses, foams, and towelettes) in accordance with § 352.77.

(Comment 24) One comment recommended a pass/fail (binomial) test to determine SPF values (Ref. 49). The test would demonstrate that subjects have no reaction to a quantity of UV energy equivalent to an expected SPF value (for products passing the test). For example, subjects being tested with a product with an expected SPF value of 30 would be dosed only at the SPF 30 level, and the product would either pass or fail. A product passing this test would actually have an SPF value of 30 or over, whereas a product failing this test would have an SPF value below 30. The comment argued that while 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/cm² 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 erythema-effective dose transmitted by the sunscreen exceeds 1 MED, where 1 MED equals 0.02 erythema-effective Joules (J)/cm². 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 erythema-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 JCLIA 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

and

- Ease of preparation with a reasonable degree of accuracy.

These data are also needed for the JClA 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/cm²) 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 erythema 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 erythema effectiveness by successive wavebands. The erythema effectiveness of each waveband is expressed as a percentage of the total erythema effectiveness from 250 nm to 400 nm, or

as the Percentage Relative Cumulative Erythema 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 erythema action spectrum to obtain the erythema effectiveness of the source. The spectral erythema 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 erythema effectiveness for each spectral waveband, and the total erythema effectiveness is calculated up to 400 nm. Finally, the %RCEE is calculated at the reference waveband as the percentage ratio of the cumulative erythema 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 erythema wavelengths (i.e., up to 400 nm) when standardizing solar simulator output. As argued by the comment, the erythema 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 erythema 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/m²) 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/m². 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/m² 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 cm², an appropriate input aperture would be 0.25 cm². 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 $J/m^2\text{-eff}$ (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 than 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 erythema threshold of the skin, or MED(US). The comment argued that SPF decreases with increasing erythema 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 cm² test subsite area in § 352.72(d)(2). One comment proposed the minimum test subsite area be decreased to 0.5 cm². Two comments suggested that the test subsite area be defined by minimum diameters of 0.8 cm (circular area of 0.5 cm²) and 0.15 cm (circular area of 0.017 cm²), respectively.

The comment supporting the 0.5 cm² 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 cm². FDA cannot determine the suitability of a 0.5 cm² test subsite area compared to a 1 cm² 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 cm² 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 cm² 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 erythema 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/cm². 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/m²). 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,
- Skin² 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 JClA 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 vitro 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 erythema 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 pigmentation 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/cm²) 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:

UVA area under curve per unit wavelength

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):

$$PID (J/m^2\text{-eff}) = SPF * 1 \text{ MED} * 2/3,$$

where 1 MED = 200 J/m²-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/cm² multiplied by a factor of 2/3. The comment stated that 2 J/cm² 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 "erythema effective dose." The erythema effective dose of a solar simulator can be 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/m²-eff) for an MED in a Skin Type II individual is 200 J/m²-eff (Ref. 93). Thus, FDA is proposing to use the following formula to determine the required pre-irradiation dose:

$$\text{PID (J/m}^2\text{-eff)} = \text{SPF} * 1 \text{ MED} * 2/3$$

where 1 MED = 200 J/m²-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 (*Glatetter 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).

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

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.

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 coincide 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.
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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.
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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.
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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.
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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)(i) 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:

(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*

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

§ 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:

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

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 |

COMPOSITION OF THE PADIMATE O/ OXYBENZONE STANDARD SUNSCREEN—Continued

| Ingredients | Percent by weight |
|--------------------|-------------------|
| Oxybenzone | 3.00 |
| Propylparaben | 0.10 |
| Part B | |
| Purified water USP | 71.60 |
| Sorbitol solution | 5.00 |

COMPOSITION OF THE PADIMATE O/
OXYBENZONE STANDARD SUN-
SCREEN—Continued

| Ingredients | Percent by weight |
|----------------------------------|-------------------|
| 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)

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

¹ weight in grams

² DF is a dilution factor calculated as in paragraph (a)(2)(ii)(G) of this section.

(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/m²) 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 erythral 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 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.

(c) *General testing procedures—(1) Medical history.* Obtain a medical history from each subject with emphasis on the effects of sunlight on his/her skin. Determine that each subject is in good general health with skin type I, II, or III (as described in this paragraph). *Skin Type and Sunburn and Tanning History (Based on first 30 to 45 minutes of sun exposure after a winter season of no sun exposure).*

I: Always burns easily; never tans (sensitive).
 II: Always burns easily; tans minimally (sensitive).
 III: Burns moderately; tans gradually (light brown) (normal).

IV: Burns minimally; always tans well (moderate brown) (normal).
 V: Rarely burns; tans profusely (dark brown) (insensitive).
 VI: Never burns; deeply pigmented (insensitive).

Determine that the subject is not taking topical or systemic medication that is known to alter responses to ultraviolet radiation and that the subject has no history of sensitivities to topical products and/or abnormal responses to sunlight, such as a phototoxic or photoallergic response.

(2) *Physical examination.* Conduct a physical examination to determine the presence of sunburn, suntan, scars, active dermal lesions, and uneven skin tones on the areas of the back to be tested. A suitable source of low power UVA, such as a Woods lamp, is helpful in this process. If any of these conditions are present, the subject is not qualified to participate in the study. The presence of nevi, blemishes, or moles will be acceptable if in the physician's judgment they will neither compromise the study, nor jeopardize subject safety. Subjects with dysplastic nevi should not be enrolled. Excess hair on the back is acceptable if the hair is clipped. Shaving is unacceptable because it may remove a significant portion of the stratum corneum and temporarily increase skin permeability to ultraviolet radiation.

(3) *Informed consent.* Obtain legally effective written informed consent from all subjects.

(4) *Test site delineation—(i) Test site.* A test site is the location on the back for determining the subject's initial and final minimal erythema dose (MED) for unprotected skin and for determining SPF values after application of the sunscreen standard and the test sunscreen product(s). There typically are 4 to 6 test sites for each subject. Test sites should be located on the back between the beltline and the shoulder blades (scapulae) and lateral to the midline. Each test site shall be a minimum of 50 square centimeters, e.g., 5 x 10 centimeters. Outline the test sites to which the sunscreen standard and the test sunscreen product(s) will be applied with indelible ink. If the subject is to receive the doses of ultraviolet radiation in an upright (seated) position, draw the lines on the skin with the subject upright (seated). If the subject is to receive the doses of ultraviolet radiation while prone, draw the lines with the subject prone.

(ii) *Test subsite.* Test subsites are the locations to which ultraviolet radiation is administered within a test site. At least 5 test subsites will receive UV doses within each test site. Test subsites

will be at least 1 square centimeter (cm²) in area and will be separated from each other by at least 1 cm. Mark the location of each test subsite with indelible ink.

(5) *Application of test materials.* Apply the test sunscreen product and the standard sunscreen at 2 milligrams per square centimeter (mg/cm²) to their respective test sites to establish standard films. Test sites will be randomly located on the back in a blinded manner. 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/cm².

(6) *Waiting period.* Before exposing the test site areas after applying a product, wait at least 15 minutes.

(7) *Number of subjects—(i) For products with an expected SPF 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.

(8) *Response criteria.* In order that the person who evaluates the MED responses is not biased, he/she must not be the same person who applied the sunscreen drug product to the test site or administered the doses of UV radiation. After UV radiation exposure from the solar simulator is completed, all immediate responses shall be recorded. These may include an immediate darkening or tanning, typically grayish or purplish in color, which fades in 30 to 60 minutes; an immediate reddening at the subsite, due to heating of the skin, which fades rapidly; and an immediate generalized heat response, spreading beyond the subsite, which fades in 30 to 60 minutes. After the immediate responses are noted, each subject shall shield the exposed area from further UV radiation until the MED response is evaluated. Determine the MED 16 to 24 hours after exposure. Evaluate the erythema

responses of each test site using either tungsten or warm white fluorescent lighting that provides 450 to 550 lux of illumination at the test site. For the evaluation, the test subject should be in the same position used when the test site was irradiated. For each test site, determine the smallest UV dose that produced redness reaching the borders of the test subsite. The MED is the quantity of erythema-effective energy required to produce the first perceptible, redness reaction with clearly defined borders at 16 to 24 hours post-exposure. To determine the MED, there must be at least one subsite that received a smaller UV dose and does not produce redness as well as a subsite(s) with somewhat

more intense redness. For subsites showing an erythema response, the maximal exposure should be no more than twice the total energy of the minimal exposure.

(9) *Rejection of test data.* Reject test data if the exposure series fails to elicit an MED response on either the treated or unprotected skin sites; or all subsites within a test site show more intense responses than the threshold erythema response; or the responses are inconsistent with the series of UV doses administered; or the subject was noncompliant, e.g., the subject withdraws from the test due to illness or work conflicts or does not shield the

exposed testing sites from further UV radiation until the MED is read.

(d) *Determination of SPF—(1) Determination of erythema action spectrum.* (i) Use the following erythema action spectrum as weighting factors to calculate the erythema-effective exposure produced by a solar simulator:

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

$$V_i(\lambda) = 10^{0.094 * (298 - \lambda)} \quad (298 < \lambda < 328 \text{ nanometers})$$

$$V_i(\lambda) = 10^{0.015 * (140 - \lambda)} \quad (328 < \lambda < 400 \text{ nanometers})$$

(ii) Integrate the erythemally-effective spectral irradiance over wavelength and time to calculate the erythema-effective UV dose delivered by a solar simulator as follows:

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

where: E = Erythema-Effective Dose (Effective Joules per square meter (J/m²-eff))
 V_i = Weighting Factor (Erythema Action Spectrum)
 I = Spectral Irradiance (Watts per square meter per nanometer)
 t_{exp} = exposure time (seconds)

(iii) The erythema action spectrum may be determined using a handheld radiometer with a response weighted to match the spectrum in "CIE S 007/E Erythema Reference Action Spectrum and Standard Erythema Dose," dated 1998, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from CIE Central Bureau, Kegelgasse 27, A-1030, Vienna, Austria, or may be examined at the Center for Drug Evaluation and Research, 10903 New Hampshire Ave., Bldg. 22, Silver Spring, MD, or at the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC. It is advisable to measure the solar simulator output before and after each phototest or, at a minimum, at the beginning and end of each test day. This radiometer should be calibrated using side by side comparison with the spectroradiometer (using the weighting factors determined according to paragraph (d)(1)(i) of this section) at the time of the semiannual spectroradiometric measurement of the solar simulator.

(2) *Determination of MED of unprotected skin.* Administer a series of five UV radiation doses expressed as J/m²-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. Use the series of five exposures to the unprotected test site to determine the initial unprotected MED.

Select the doses that are a geometric series represented by (1.25ⁿ), wherein each exposure dose is 25 percent greater than the previous exposure dose to maintain the same relative uncertainty (expressed as a constant percentage), independent of the subject's sensitivity to UV radiation. Usually, the UV radiation for determining the initial unprotected MED is administered the day prior to applying the sunscreen product and standard sunscreen, and the responses then are evaluated immediately prior to applying the sunscreen product and sunscreen standard. Determine the final unprotected MED on the same day that UV radiation is administered to the sunscreen-protected test sites. Use the final unprotected MED (MED(US)) in calculating SPF.

(3) *Determination of individual SPF values.* Administer a series of five UV radiation doses expressed as J/m²-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 than 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. The MED is the smallest erythemally-effective UV dose required to produce mild redness within the subsite border at 16 to 24 hours post-exposure. Calculate the SPF value of each sunscreen product and sunscreen standard using the MED of sunscreen-protected skin (MED(PS)) and the final unprotected skin MED (MED(US)) as follows:

$$SPF = \frac{MED(PS) (J/m^2\text{-eff})}{MED(US) (J/m^2\text{-eff})}$$

(4) *Determination of the test product SPF and PCD.* Use data from at least 20 test subjects with n representing the number of subjects used. First, compute the SPF value for each subject as stated in paragraphs (d)(2) and (d)(3) of this section. Second, compute the mean SPF value, \bar{x} , and the standard deviation, s, for these subjects. Third, obtain the upper 5-percent point from Student's t distribution table with n-1 degrees of freedom. Denote this value by t. Fourth, compute ts/√n. Denote this quantity by A (i.e., A = ts/√n). Fifth, calculate the SPF value to be used in labeling as

follows: The label SPF equals the largest whole number less than $\bar{x} - A$. Sixth and last, the sunscreen product is classified into a PCD as follows: If $50 + A < \bar{x}$, the PCD is Highest; if $30 + A \leq \bar{x} \leq 50 + A$, the PCD is High; if $15 + A \leq \bar{x} < 30 + A$, the PCD is Medium; if $2 + A \leq \bar{x} < 15 + A$, the PCD is Low; if $\bar{x} < 2 + A$, the product shall not be labeled as an OTC sunscreen drug product and may not display an SPF value.

§ 352.71 UVA in vitro testing procedure.

(a) *Light source for transmittance/absorbance measurements.* The light source should satisfy the requirements for solar simulators described in § 352.70(b).

(b) *Substrate.* Use optical-grade quartz plate suitable for substrate spectrophotometry that has been roughened on one side.

(c) *Sample holder.* The sample holder should hold the substrate in a horizontal position to avoid flowing of the sunscreen drug product from one edge of the substrate to the other. It should be mounted as close as possible to the input optics of the spectroradiometer to maximize capture of forward scattered radiation. The sample holder should be a thin, flat plate with a suitable aperture through which UV radiation can pass. The substrate will be placed on the upper surface of the sample holder.

(d) *Spectroradiometer input optics.* Unless the spectroradiometer is equipped with an integrating sphere, an ultraviolet radiation diffuser should be placed between the sample and the input optics of the spectroradiometer. The diffuser will be constructed from any UV radiation transparent material (e.g., Teflon® or quartz). The diffuser ensures that the radiation received by the spectroradiometer is not collimated. The spectroradiometer input slits

should be set to provide a bandwidth that is less than or equal to 5 nanometers.

(e) *Sunscreen drug product application to substrate.* The accuracy of the test depends upon the application of a precisely controlled amount of sunscreen product with a uniform distribution over the application area of the substrate. The product is applied at 2 milligrams per square centimeter to the substrate. To achieve uniform distribution over the substrate, the sunscreen product should be applied in a series of small dots over the application area of the substrate and then spread evenly using a gloved finger. A very light spreading action for a short period of time (approximately 10 seconds) should be used when distributing the product to ensure complete coverage without excessive buildup of product in the troughs of the substrate.

(f) *Pre-irradiation to account for differences in photostability.* To account for potentially varying degrees of photostability between sunscreen drug products, irradiate the sunscreen product on the substrate with a dose of UV radiation equal to the SPF of the sunscreen product multiplied by 200 J/m²-eff multiplied by 2/3. A UV radiation dose of 200 J/m²-eff is equivalent to one minimal erythema dose (MED). The UV dose to be delivered is determined by multiplying the light source spectral irradiance action spectrum for erythema in "CIE S 007/E Erythema Reference Action Spectrum and Standard Erythema Dose," at each wavelength, integrating over wavelength, and multiplying the integral by the exposure time. "CIE S 007/E Erythema Reference Action Spectrum and Standard Erythema Dose," dated 1998, is incorporated by

reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from CIE Central Bureau, Kegelgasse 27, A-1030, Vienna, Austria, or may be examined at the Center for Drug Evaluation and Research, 10903 New Hampshire Ave., Bldg. 22, Silver Spring, MD 20993, or at the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC.

(g) *Calculation of the spectral transmittance at each wavelength interval.* The dynamic range of the measurement system and the intensity of the light source should be sufficiently high that signals measured at all UV wavelengths (290 to 400 nanometers) through a highly absorbing sunscreen product are above the noise level of the measurement system. Spectral irradiance will be measured at 5 nanometer intervals, from 290 to 400 nanometers. At least 12 measurements of spectral irradiance transmitted through the substrate without sunscreen drug product present will be obtained from different locations on the substrate surface $C(\lambda)_1, C(\lambda)_2, C(\lambda)_3, \dots, C(\lambda)_{12}$. In addition, a minimum of 12 measurements of spectral irradiance transmitted through the substrate with the sunscreen drug product present will be similarly obtained after pre-irradiation of the sunscreen drug product $P(\lambda)_1, P(\lambda)_2, P(\lambda)_3, \dots, P(\lambda)_{12}$. The mean transmittance for wavelength λ , $\overline{T(\lambda)}$, is the ratio of the mean of the $C(\lambda)$ values to the mean of the $P(\lambda)$ values, as follows:

$$\overline{T(\lambda)} = \frac{\sum_1^n P(\lambda) / n}{\sum_1^n C(\lambda) / n}$$

The standard deviation, s , associated with the spectral transmittance is evaluated using Taylor's approximation, as follows:

$$s = \sqrt{\left[\frac{P(\lambda) * s(C(\lambda))}{(C(\lambda))^2} \right]^2 + \left[\frac{(sP(\lambda))}{C(\lambda)} \right]^2}$$

where $\overline{C(\lambda)}$ = mean of the measurements of C at wavelength λ .

$\overline{P(\lambda)}$ = mean of the measurements of P at wavelength λ .

$s(C(\lambda))$ = standard deviation of the measurements of C at wavelength λ .

$s(P(\lambda))$ = standard deviation of the measurements of P at wavelength λ .

$s(C(\lambda))$ is calculated as follows:

$$s(C(\lambda)) = \sqrt{\frac{\sum_1^n (C(\lambda) - \overline{C(\lambda)})^2}{(n - 1)}}$$

$s(P(\lambda))$ is calculated as follows:

$$s(P(\lambda)) = \sqrt{\frac{\sum_1^n (P(\lambda) - \overline{P(\lambda)})^2}{(n - 1)}}$$

This calculation gives 23 spectral transmittance values with associated standard deviations, one for each 5 nanometer wavelength increment from

290 to 400 nanometers. The standard deviation values will provide an indication of the uniformity of sunscreen drug product spreading during application to the substrate. The coefficient of variation, which is the standard deviation divided by the mean, and expressed as a percentage, should be less than 10 percent.

(h) *Calculation of the UVA I/UV ratio.* (1) Spectral transmittance values, $T(\lambda)$, are converted into absorbance values, $A(\lambda)$, by taking the negative logarithm of

the spectral transmittance value as follows:

$$A(\lambda) = -\log T(\lambda)$$

The calculation yields 23 monochromatic absorbance values in 5 nanometer increments from 290 to 400 nanometers.

(2) The index of UVA I protection is calculated as the area (per unit wavelength) under the UVA I portions of a plot of wavelength versus A(λ), divided by the area (per unit wavelength) under the total curve, as follows:

$$\text{UVA I/UV ratio} = \frac{\text{UVA I area per unit wavelength}}{\text{UV area per unit wavelength}}$$

UVA I area per unit λ is given as:

$$\int_{340}^{400} A(\lambda) d(\lambda) B(\lambda) / \int_{340}^{400} d(\lambda)$$

UV area per unit λ is given as:

$$\int_{290}^{400} A(\lambda) d(\lambda) B(\lambda) / \int_{290}^{400} d(\lambda)$$

where: A(λ) = effective absorbance given as -log T(λ)

d(λ) = wavelength interval between measurements

B(λ) = any biological action spectrum factor

Because no appropriate biological action spectrum for UVA radiation damage has been universally accepted, no action spectrum is specified. The value of B(λ) is, therefore, equal to 1.0 for all wavelengths.

(3) The integrals in the formulae in paragraphs (h)(1) and (h)(2) of this section are evaluated using Simpson's Rule for irregular areas, which states: Area = h/3 x [Y₀ + Y_{2m} + 4(Y₁ + Y₃ . . . + Y_{2m-1}) + 2(Y₂ + Y₄ + . . . Y_{2m-2})]

In this equation, Y₀, Y₁, Y₂, . . . Y_{2m} are the lengths of 2m parallel lines drawn vertically to divide the area under the curve of a graph into 2m-1 segments of equal width, h. In practice, the values of Y₀, Y₁, Y₂, . . . Y_{2m} are the A(λ) values determined and h is the wavelength interval at which the spectral transmittance is determined (i.e., 5 nanometers).

(4) UVA I area per unit wavelength (aUVA I/λ) is calculated as follows:

$$aUVA I/\lambda = 5/3 \times [A_{340} + A_{400} + 4(A_{345} + \dots + A_{395}) + 2(A_{350} + A_{360} + A_{370} + \dots + A_{390})]/60$$

UV area per unit wavelength (aUV/λ) is calculated as follows:

$$aUV/\lambda = 5/3 \times [A_{290} + A_{400} + 4(A_{295} + A_{305} + A_{315} + \dots + A_{395}) + 2(A_{300} + A_{310} + \dots + A_{390})]/110$$

UVA I/UV ratio is calculated as follows:

$$\text{UVA I/UV ratio} = \frac{aUVA I/\lambda}{aUV/\lambda}$$

(i) *Category determination of the UVA I/UV ratio.* Perform at least 5 separate determinations of the UVA I/UV ratio, from which the mean can be calculated. Using the mean, the sunscreen drug product is classified by in vitro UVA I/UV ratio as follows:

| UVA I/UV Ratio | Category |
|-------------------|----------|
| 0.20 to 0.39 | Low |
| 0.40 to 0.69 | Medium |
| 0.70 to 0.95 | High |
| greater than 0.95 | Highest |

§ 352.72 UVA in vivo testing procedure.

(a) *Standard sunscreen.* A standard sunscreen shall be tested concomitantly in the procedure for determining the UVA protection factor (UVA-PF) value by means of persistent pigment darkening to ensure the uniform evaluation of sunscreen drug products. The standard sunscreen shall be a preparation containing 7 percent padimate O and 3 percent oxybenzone as specified in § 352.70(a)(3). For the test to be valid, the measured mean UVA-PF value of the standard preparation shall be 3.2 with a standard deviation less than or equal to 0.5.

(b) *Light source.* The light source used for determining the UVA-PF value of a sunscreen drug product shall provide a continuous emission spectrum in the range of 320 to 400 nanometers. The ratio of UVA I (340 to 400 nanometers) to UVA II (320 to 340 nanometers) in the final beam shall be close to that of sunlight, i.e., emitted UVA II shall be 8 to 20 percent of the total UVA radiation. Optical radiation from 250 to 320 nanometers shall be less than 0.1 percent of the optical radiation between 320 to 400 nanometers. Exclude visible and infrared light to avoid the darkening effects of visible light and the effect of heat. Perform monitoring and maintenance of the light source as specified in § 352.70(b)(3).

(c) *General testing procedures—(1) Medical history.* Obtain a medical history from each subject with emphasis on the effects of sunlight on his/her skin. Determine that each subject is in good general health and has skin type II or III (as described in this paragraph). *Skin Type and Sunburn and Tanning History (Based on first 30 to 45 minutes of sun exposure after a winter season of no sun exposure).*

I: Always burns easily; never tans (sensitive).

II: Always burns easily; tans minimally (sensitive).

III: Burns moderately; tans gradually (light brown) (normal).

IV: Burns minimally; always tans well (moderate brown) (normal).

V: Rarely burns; tans profusely (dark brown) (insensitive).

VI: Never burns; deeply pigmented (insensitive).

Determine that the subject is not taking topical or systemic medication that is known to alter responses to ultraviolet radiation and that the subject has no history of sensitivities to topical products and/or abnormal responses to sunlight, such as a phototoxic or photoallergic response.

(2) *Physical examination.* The physical examination shall be conducted as specified in § 352.70(c)(1).

(3) *Informed consent.* Obtain legally effective written informed consent from all subjects.

(4) *Test site delineation—(i) Test site.* A test site is the location on the back for determining the subject's initial and final minimal pigmentation dose (MPD) for unprotected skin and for determining UVA-PF values after application of the sunscreen standard and the test sunscreen product(s). There typically are 4 to 6 test sites for each subject. Test sites should be located on the back between the beltline and the shoulder blades (scapulae) and lateral to the midline. Each test site shall be a minimum of 50 square centimeters (cm²) (i.e., 5 x 10 centimeters). Outline the test sites to which the sunscreen standard and the test sunscreen product(s) will be applied with indelible ink. If the subject is to receive the doses of ultraviolet radiation in an upright (seated) position, draw the lines on the skin with the subject upright (seated). If the subject is to receive the doses of ultraviolet radiation while prone, draw the lines with the subject prone.

(ii) *Test subsite.* Test subsites are the locations to which ultraviolet radiation is administered within a test site. At least 5 test subsites will receive UV doses within each test site. Test subsites will be at least 1 cm² in area and will be separated from each other by at least 1 cm. Mark the location of each test subsite with indelible ink.

(5) *Application of test materials.* Apply the test sunscreen product and the standard sunscreen as specified in § 352.70(c)(5).

(6) *Waiting period.* Before exposing the test site areas after applying a product, wait at least 15 minutes.

(7) *Number of subjects.* A test panel shall consist of 20 to 25 subjects with at least 20 subject who produce valid data for analysis. Data is valid unless rejected in accordance with § 352.70(c)(9). If more than 5 subjects are rejected based on § 352.70(c)(9), the panel is disqualified, and a new panel must be created.

(8) *Response criteria.* In order that the person who evaluates the MPD responses is not biased, he/she must not be the same person who applied the sunscreen drug product to the test site or administered the doses of UV radiation. After UV radiation exposure from the solar simulator is completed, all immediate responses shall be recorded. These may include an immediate darkening or tanning, typically grayish or purplish in color, which fades in 30 to 60 minutes; an immediate reddening at the subsite, due to heating of the skin, which fades rapidly; and an immediate generalized heat response, spreading beyond the subsite, which fades in 30 to 60 minutes. After the immediate responses are noted, each subject shall shield the exposed area from further UV radiation until the MPD response is evaluated. Determine the MPD 3 to 24 hours after exposure. Evaluate the pigmentation responses of each test site using either tungsten or warm white fluorescent lighting that provides 450 to 550 lux of illumination at the test site. For the evaluation, the test subject should be in the same position used when the test site was irradiated. For each test site, determine the smallest UV dose that produced mild pigmentation reaching the borders of the test subsite. The MPD is the smallest UV dose required to produce the first perceptible pigment darkening at 3 to 24 hours post-exposure. To determine the MPD, there must be at least one subsite that received a smaller UV dose and does not produce pigmentation as well as a subsite(s) with somewhat more intense pigmentation. For subsites showing pigmentation, the maximal exposure should be no more than twice the total energy of the minimal exposure.

(9) *Rejection of test data.* Reject test data if the exposure series fails to elicit an MPD response on either the treated or unprotected skin sites, or all subsites within a test site show more intense responses than the threshold pigmentation response, or the responses are inconsistent with the series of UV doses administered, or the subject was noncompliant, e.g., the subject withdraws from the test due to illness or work conflicts or does not shield the exposed testing sites from further UV radiation until the MPD is read.

(d) *Determination of UVA-PF values*—(1) *Determination of MPD of unprotected skin.* Administer a series of five UV radiation doses expressed as Joules per square meter to the subsites within each test site on a subject using the light source described in paragraph (b) of this section. Use the series of five exposures to the unprotected test site to

determine the initial unprotected MPD. Select the doses that are a geometric series represented by (1.25^n) , wherein each exposure dose is 25 percent greater than the previous exposure dose to maintain the same relative uncertainty (expressed as a constant percentage), independent of the subject's sensitivity to UV radiation. Usually, the UV radiation for determining the initial unprotected MPD is administered the day prior to applying the sunscreen product and standard sunscreen, and the responses are then evaluated immediately prior to applying the sunscreen product and sunscreen standard. Determine the final unprotected MPD on the same day that UV radiation is administered to the sunscreen-protected test sites. Use the final unprotected MPD (MPD(US)) in calculating UVA-PF.

(2) *Determination of individual UVA-PF values.* Administer a series of five UV radiation doses expressed as Joules per square meter to the subsites within each test site on a subject using the light source described in paragraph (b) of this section. The five UV doses will be a geometric series as described in paragraph (d)(1) of this section, where the middle exposure represents the expected UVA-PF. Use exposures that are the product of the initial unprotected MPD times 0.64X, 0.80X, 1.00X, 1.25X, and 1.56X, where X equals the expected UVA-PF of the test product. The MPD is the smallest UV dose required to produce pigmentation at 3 to 24 hours post-exposure. Calculate the UVA-PF value of each sunscreen product and sunscreen standard using MPD of sunscreen-protected skin (MPD(PS)) and the final unprotected MPD (MPD(US)) as follows:

$$UVA-PF = \frac{MPD(PS) (J/m^2)}{MPD(US) (J/m^2)}$$

(3) *Determination of test product UVA-PF and UVA product category designation (PCD).* Use data from at least 20 test subjects with n representing the number of subjects used. First, compute the UVA-PF value for each subject as stated in paragraph (d)(2) of this section. Second, compute the mean UVA-PF value, \bar{x} , and the standard deviation, s, for these subjects. Third, obtain the upper 5-percent point from Student's t distribution table with n-1 degrees of freedom. Denote this value by t. Fourth, compute ts/\sqrt{n} . Denote this quantity by A (i.e., $A = ts/\sqrt{n}$). Fifth, calculate the UVA-PF value to be used in labeling as follows: The label UVA-PF equals the largest whole number less than $\bar{x} - A$. Sixth and last, the drug product is classified into a PCD as

follows: If $12 + A \leq x$, the PCD is Highest; if $8 + A \leq x < 12 + A$, the PCD is High; if $4 + A < x < 8 + A$, the PCD is Medium; if $2 + A \leq x < 4 + A$, the PCD is Low; if $x < 2 + A$, the product shall not display a UVA-PF value.

§ 352.73 Determination of the labeled UVA protection value.

Test the sunscreen product in accordance with §§ 352.71 and 352.72. The UVA category on the principal display panel (PDP) of the tested sunscreen product, as specified in § 352.50, shall be the lower of either the UVA I/UV ratio category determined in § 352.71(j) or the UVA-PF product category designation (PCD) determined in § 352.72(d)(3). If the product does not attain at least a "low" category rating for both the UVA-PF and the UVA I/UV ratio, the product shall not display a UVA claim. State the final combined category rating (i.e., the lower of either the UVA I/UV ratio or UVA-PF PCD categories) on the PDP of the product along with the corresponding number of stars for that combined category rating as follows:

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

11. Section 352.76 is amended by revising the introductory paragraph and paragraphs (a) introductory text, (a)(6), (b) introductory text, and (b)(10) to read as follows:

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

The general testing procedures in § 352.70(c) shall be used as part of the following tests, except where modified in this section. An indoor fresh water pool, whirlpool, and/or jacuzzi maintained at 23 to 32 °C shall be used in these testing procedures. Fresh water is clean drinking water that meets the standards in 40 CFR part 141. The pool and air temperature and the relative humidity shall be recorded.

(a) *Procedure for testing the water resistance of a sunscreen product.* For sunscreen products making the claim of "water resistant," the label SPF and, if appropriate, UVA values shall be the label SPF and UVA values determined after 40 minutes of water immersion using the following procedure for the water resistance test:

(6) Begin light source exposure to test site areas as described in § 352.70(b) and, if appropriate, § 352.72(b).

(b) *Procedure for testing a very water resistant sunscreen product.* For

sunscreen products making the claim of “very water resistant,” the label SPF and, if appropriate, UVA values shall be the label SPF and UVA values determined after 80 minutes of water

immersion using the following procedure for the water resistance test:

* * * * *

(10) Begin light source exposure to test site areas as described in § 352.70(b) and, if appropriate, § 352.72(b).

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Jeffrey Shuren,

Assistant Commissioner for Policy.

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