Federal Register

Wednesday
May 12, 1993

Part III

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 352 et al.
Sunscreen Drug Products for Over-the-Counter Human Use; Tentative Final Monograph; Proposed Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 352, 700, and 740

[Docket No. 78N–0038]

RIN 0905–AA06

Sunscreen Drug Products for Over-the-Counter Human Use; Tentative Final Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) sunscreen drug products are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products, public comments on an advance notice of proposed rulemaking that was based on those recommendations, public comments submitted in response to a notice of public meeting to discuss appropriate testing procedures for OTC sunscreen drug products, presentations made at the public meeting, and public comments submitted in response to the meeting. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by November 8, 1993. New data by May 12, 1994. Comments on the new data by July 12, 1994. Written comments on the agency's economic impact determination by November 8, 1993.

ADDRESSES: Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD–810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–295–8000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of August 25, 1978 (43 FR 38206), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC sunscreen drug products, together with the recommendations of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products (Topical Analgesic Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by November 24, 1978. In a notice published in the **Federal Register** of December 1, 1978 (43 FR 56249), FDA extended the period for comments to December 15, 1978, to allow more time for the collection and assessment of data to provide for more meaningful comments on the advance notice of proposed rulemaking. Reply comments in response to comments filed in the initial comment period could be submitted by December 26, 1978.

In a notice published in the **Federal Register** of March 21, 1980 (45 FR 18403), the agency advised that it had reopened the administrative record for OTC sunscreen drug products to allow for consideration of data and information that had been filed in the Dockets Management Branch after the date the administrative record previously had officially closed. The agency concluded that any new data and information filed prior to March 21, 1980, should be available to the agency in developing a proposed regulation in the form of a tentative final monograph.

In a notice of public meeting and reopening of the administrative record published in the **Federal Register** of September 4, 1987 (52 FR 33598), the agency announced that a public meeting would be held to discuss recommendations of the Topical Analgesic Panel regarding final product testing and related claims of OTC sunscreen drug products. The meeting was held on January 26, 1988, and minutes of the meeting are on public display in the Dockets Management Branch (Ref. 1). Interested persons were given until April 26, 1988, to submit comments in response to the meeting. In a notice published in the **Federal Register** of May 4, 1988 (53 FR 15853), FDA extended the period for submission of comments on the testing procedures and related claims for OTC sunscreen drug products to May 26, 1988, to allow full opportunity for informed comments on the testing procedures.

The agency has received four petitions and one comment requesting that it reopen the administrative record for sunscreen drug products to admit several OTC sunscreen ingredients that have been marketed in Europe but not in the United States. Although no decision has been reached regarding these petitions, they are discussed in this tentative final monograph. All data and information on other subjects that have been submitted to the agency while the rulemaking was closed will be considered after the tentative final monograph is published.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (address above), after deletion of a small amount of trade secret information. Data and information received after the administrative record was reopened have also been put on display in the Dockets Management Branch.

In response to the advance notice of proposed rulemaking, 27 manufacturers, 2 manufacturers' associations, 31 consumers, 6 universities, 1 health care professional, and 1 health care professional society submitted comments. Two manufacturers, one manufacturer's association, and one university submitted reply comments. In response to the notice of public meeting and the public meeting, 13 manufacturers, 2 manufacturers' associations, 1 foreign manufacturer's association, 1 foreign professional association, 2 universities, 1 foreign government, 2 testing laboratories, 1 health care research institute, and 5 health care professionals submitted comments. Copies of the comments received are on public display in the Dockets Management Branch.

The advance notice of proposed rulemaking, which was published in the **Federal Register** on August 25, 1978 (43 FR 38206), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the present document is designated in the OTC drug review regulations as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule) to establish part 352 (21 CFR part 352), FDA states for the first time its position on the establishment of a monograph for OTC sunscreen drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC sunscreen drug products.

This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC sunscreen drug products as modified on the basis of the comments

received and the agency's independent evaluation of the Panel's report. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them.

The OTC drug procedural regulations (21 CFR 330.10) now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA will no longer use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but will use instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the **Federal Register**. On or after that date, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. Further, any OTC drug product subject to this monograph that is repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In the advance notice of proposed rulemaking for OTC sunscreen drug products (43 FR 38206), the agency suggested that the conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the **Federal Register** and that the conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of whether further testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products may have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and if further reformulation is required, there could be a further delay in having a new product available for manufacture.

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss, but also interfere with consumers' access to these drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the **Federal Register**. The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and reformulate their products and have them in compliance in the marketplace.

If the agency determines that any labeling for a condition included in the final monograph should be implemented sooner than the 12-month effective date, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notice published in the **Federal Register** of December 12, 1972 (37 FR 26156) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch (address above).

Reference

(1) Comment No. TR1, Docket No. 78N0038, Dockets Management Branch.

I. Introduction

In section 201(g) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(g)(1)), a "drug" is defined as (A) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them, (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals, (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals, and (D) articles intended for use as a component of any articles specified in (A), (B), or (C) above. Sunscreen products are marketed with various intended uses, such as (1) beach products for occasional use to protect consumers from extreme sunlight conditions, (2) tanning products to aid consumers in acquiring a tan, and (3) non-beach products for daily use to protect consumers from chronic exposure to sunlight (e.g., make-up preparations and lipsticks). Although these intended uses are different, the agency considers each one a drug use.

Beach products are considered drugs because they prevent sunburn, protect the skin against harm from the sun, and prevent skin damage through overexposure to the sun. In addition, consumers equate these products with mitigating harmful effects of the sun. For these reasons, sunscreen beach products are drugs under section 201(g)(1)(B). Such products are also drugs under section 201(g)(1)(C) because they affect the body's physiological response to solar radiation (i.e., they lessen the erythema reaction). Tanning products that contain sunscreens are drugs because they prevent a sunburn (section 201(g)(1)(B)) and affect melanogenesis (section 201(g)(1)(C)). Non-beach sunscreen products are drugs because they prevent lip or skin damage (section 201(g)(1)(B)) as well as freckling and uneven skin coloration (section 201(g)(1)(C)). The drug/cosmetic distinction of products containing sunscreens is discussed further in comment 27.

Throughout this tentative final monograph, the agency makes extensive use of acronyms. For the reader's convenience, the agency is including in one easily accessible place a chart containing the most commonly used acronyms in this document.

Acronym	Definition
AAD	American Academy of Dermatology.
CIE	Commission International De L'Eclairage.
CTFA	Cosmetic, Toiletry and Fragrance Association.
DIN	Deutsches Institut fuer Normung.
IR	Infrared.
MED	Minimal Erythema Dose.
MED(PS)	Minimal Erythema Dose on Protected Skin.
MED(US)	Minimal Erythema Dose on Unprotected Skin.
NDA	New Drug Application.
NDMA	Nonprescription Drug Manufacturers Association.
PCD	Product Category Designation.
SPF	Sun Protection Factor.
U.S.P.	United States Pharmacopeia.
UV	Ultraviolet.
UVA	Ultraviolet A.
UVB	Ultraviolet B.
UVC	Ultraviolet C.

II. The Agency's Tentative Conclusions on the Comments

A. General Comments on Sunscreen Drug Products

1. One comment urged the agency to recognize explicitly the legal status of the monographs issued under the OTC drug review as being interpretive, as distinguished from substantive, regulations. The comment incorporated by reference previous comments dated March 4, 1972 on the proposed procedural regulations governing the OTC drug review and comments dated June 4, 1973 on the proposed antacid monograph.

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products, published in the **Federal Register** of May 11, 1972 (37 FR 9464 at 9471 to 9472) and in paragraph 3 of the preamble to the tentative final monograph for OTC antacid drug products, published in the **Federal Register** of November 12, 1973 (38 FR 31260). FDA reaffirms the conclusions stated in those documents. Court decisions have confirmed the agency's authority to issue substantive regulations by rulemaking. (See, e.g., *National Nutritional Foods Association* v. *Weinberger,* 512 F.2d 688, 696–98 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers* v. *FDA,* 487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd.,* 637 F.2d 887 (2d Cir. 1981).)

2. One comment recommended that the term "ultraviolet light" should be replaced throughout the Panel's report by the term "ultraviolet radiation." The comment stated that light is the part of the electromagnetic spectrum that can be seen by the eye, and because UV radiation is by definition invisible, the use of the word "light" is inappropriate.

The agency agrees with the comment that the use of the term "ultraviolet light" is inappropriate. Because the term "light" refers to the waveband detectable by the human eye (i.e., visible light of approximately 400 to 760 nanometers (nm)), the term "ultraviolet radiation" is preferred when speaking of the wavelength region of approximately 100 to 400 nm (Refs. 1 and 2). Therefore, the agency is using the term "ultraviolet radiation" throughout this tentative final monograph. The agency is also using the following terminology for 3 wavelength ranges in the UV radiation portion of the spectrum: UVA for the range from 320 to 400 nm, UVB for the range from 290 to 320 nm, and UVC for the range from 200 to 290 nm.

References

(1) Magnus, I. A., "An Introduction to the Basic Physics of Electromagnetic Radiation," *in* "Dermatological Photobiology," Blackwell Scientific Publications, London, p. 5, 1976.

(2) "Dermatology in General Medicine," 3d Ed., edited by T. B. Fitzpatrick, et al., McGraw-Hill Book Company, New York, p. 1443, 1987.

3. Referring to the Panel's discussion of the types of solar radiation (43 FR 38206 at 38209), one comment stated that the reference cited for the statement that the solar spectrum at the earth's surface consists of wavelengths between 295 and 1,800 nm is not authoritative. The comment stated that Bener (Ref. 1), Johnson (Ref. 2), and Schulze and Grafe (Ref. 3) should be credited for that statement.

Referring to the Panel's discussion at 43 FR 38214, the comment stated that reference 2 had been incorrectly quoted. The comment provided the correct reference as "Pathak, M. A., et al., 'Sunlight and Melanin Pigmentation,' in 'Photochemical and Photobiological Reviews,' Vol. I, edited by K. C. Smith, Plenum Press, New York, pp. 211–239, 1976" (Ref. 4).

The agency agrees with the comment and is including the above information in the administrative record for this rulemaking.

References

(1) Bener, P., "Spectral Intensity of Natural Ultraviolet Radiation and its Dependence on Various Parameters," *in* "The Biologic Effects of Ultraviolet Radiation (with Emphasis on the Skin)," edited by F. Urbach, Pergamon Press, London, pp. 351–358, 1969.

(2) Johnson, F. S., "The Solar Constant," *Journal of Meteorology,* 11:431–439, 1954.

(3) Schulze, R., and K. Grafe, "Consideration of Sky Ultraviolet Radiation in the Measurement of Solar Ultraviolet Radiation," *in* "The Biologic Effects of Ultraviolet Radiation," edited by F. Urbach, Pergamon Press, London, pp. 359–372, 1969.

(4) Pathak, M. A., et al., "Sunlight and Melanin Pigmentation," *in* "Photochemical and Photobiological Reviews," Vol. I, edited by K. C. Smith, Plenum Press, New York, pp. 211–239, 1976.

4. One comment recommended that a general discussion on the radiation in "artificial sunlight" or "natural sunlight" should be added to the Panel's discussion of the types of solar radiation (43 FR 38206 at 38209). The comment stated that, in addition to UV radiation, visible sunlight and IR light play an important role in solar radiation. (The comment apparently is referring to the fact that an artificial light source ("artificial sunlight") emits mainly UV radiation, whereas the sun's spectrum ("natural sunlight") includes UV radiation and also visible light and IR radiation.)

The Panel's discussion focused on the UV radiation emitted by an artificial light source ("artificial sunlight") and by the sun. Although agreeing with the comment's observation that visible and IR radiations are also important components of natural sunlight, the agency believes that these radiations (400 nm and beyond) are not within the scope of the OTC drug review of sunscreens. It is the UV portion (290 to 400 nm) of the sun's spectrum ("natural sunlight") that reaches the earth's surface and the UV radiation from artificial light sources ("artificial sunlight") that can produce skin erythema, melanogenesis, and cancer (Ref. 1) (43 FR 38206 at 38210 and 38211). The majority of OTC sunscreen ingredients primarily protect the skin from UVB radiation (290 to 320 nm) (43 FR 38219 to 38253). Therefore, the Panel did not discuss solar radiation of longer wavelengths, i.e., visible and IR radiations. Accordingly, the agency does not believe that it is necessary to add a discussion of the visible and IR radiation present in "natural sunlight" in this tentative final monograph.

References

(1) Parrish, J. A., H. A. D. White, and M. A. Pathak, "Photomedicine," *in* "Dermatology in General Medicine," 2d Ed., edited by T. P. Fitzpatrick, et al., McGraw-Hill Book Company, New York, pp. 942–994, 1979.

5. One comment asserted that the Panel's statement, "The sun's rays

associated with diseases are related to the light sensitivity range from 290 to 800 nm," at 43 FR 38206 at 38209 is inconsistent with statements made at 43 FR 38210 to 38212 about the harmful effects of sunlight on the skin. The comment stated that the Panel's discussion on disease resulting from exposure to the sun's rays referred only to effects caused by rays in the range of 290 to 400 nm. Therefore, according to the comment, it was inappropriate to generalize and refer to the effects of solar radiation from 290 to 800 nm.

The Panel's reference to solar radiation in the range of 290 to 800 nm was background information to identify the range of wavelengths associated with diseases related to light sensitivity, i.e., photosensitivity reactions (Ref. 1). The Panel's discussion of photosensitization appears at 43 FR 38219. The Panel's discussion at 43 FR 38210 to 38212 describes in detail the more serious and common harmful effects, i.e., skin cancer and premature skin aging, that may be induced by the UV radiation from the sun. It was not intended to be a discussion of all light sensitivity diseases. Therefore, the agency finds no inconsistency in the statements referred to by the comment.

Reference

(1) Kesten, B. M., and M. Slatkin, "Diseases Related to Light Sensitivity," *Archives of Dermatology and Syphilology*, 67:284–301, 1953.

6. Referring to the Panel's statement that "UV-C is not effective in stimulating pigmentation (tanning)" (43 FR 38206 at 38209 and 38210), one comment contended that this statement is incorrect and should have read "UV-C is much less effective in producing pigmentation than UV-B."

The agency has reviewed the scientific literature regarding the types of solar radiation involved in tanning and agrees with the Panel's statement. As the Panel pointed out, UVC radiation from sunlight does not reach the earth's surface (43 FR 38209). Tanning involves two distinct photobiological processes: immediate tanning and delayed tanning (Refs. 1 and 2). Immediate tanning can be induced by UVA radiation (320 to 400 nm) and visible light (400 to 700 nm). It is an immediate darkening reaction that occurs 1 to 2 hours after exposure to sunlight. It does not involve melanogenesis but is due to the darkening of preformed pigment in the skin. Delayed tanning is a process that occurs 48 to 72 hours after exposure to UVB radiation (290 to 320 nm) and involves the synthesis of new melanin pigment. The agency is unaware of any data showing that solar UVC radiation (200 to 290 nm) stimulates pigmentation through either of the two tanning processes.

References

(1) Jimbow, K., M. A. Pathak, G. Szabo, and T. B. Fitzpatrick, "Ultrastructural Changes in Human Melanocytes after Ultraviolet Radiation," *in* "Sunlight and Man," edited by M. A. Pathak, et al., University of Tokyo Press, Tokyo, pp. 195–215, 1974.

(2) Pathak, M. A., and K. Stratton, "Effects of Ultraviolet and Visible Radiation and the Production of Free Radicals in Skin," *in* "The Biological Effects of Ultraviolet Radiation (with emphasis on the skin)," edited by F. Urbach, Pergamon Press, London, pp. 207–222, 1969.

7. One comment argued that the Panel's statement that the maximum UVB effect is reached at 296.7 nm (43 FR 38206 at 38209) is incorrect and that the maximum effectiveness of the UVB erythema action spectrum is between 292 and 295 nm.

For many years, 296.7 or 297 nm was accepted as the most erythemogenic UVB wavelength in the standard erythema curve. At the time the Panel conducted its review, various sources reported different wavelengths of UVB radiation as producing the maximum erythemogenic skin response: 296 nm (Ref. 1), 296.7 nm (Ref. 2), and 297 nm (Ref. 3). However, other sources have reported slightly lower wavelengths as producing this response. For example, the results of a study on the maximum erythemogenic response of the skin of the abdomen using a high pressure xenon arc grating monochromator showed 292 nm as the most erythemogenic UVB wavelength (Ref. 4). Another investigation of the effect of UVB radiation on the skin on the back of the trunk utilizing a high intensity prism grating monochromator resulted in values of 292.5 and 294 nm for the maximum erythemogenic response (Refs. 5 and 6). Such discrepancies may be the result of improvements in the integrity of monochromatic light sources that have caused the erythema action spectrum to be reassessed. Furthermore, because the area of the body exposed to the radiation and the method for assessing the erythemogenic response may vary from laboratory to laboratory, slight differences in values may be reported for the most erythemogenic UVB wavelength. The agency invites the submission of more recent data and comment on a proposed action spectrum appropriate for sunscreen drug product testing. (See comment 84.)

References

(1) Berger, D. S., "The Theory of Sunscreens and Suntanning," *in* "The Chemistry and Manufacture of Cosmetics," 2d Ed., Vol. III, edited by M. G. de Navarre, Continental Press, Orlando, FL, pp. 159–172, 1975.

(2) Schulze, R., "Effectiveness of UV Absorbers and Commercially Available Sunscreens (Wirksamkeit von UV-Absorbern und Handelsueblicher Sonnenschutzmittel," *Journal of the Society of Cosmetic Chemists*," 14:544–565, 1963.

(3) Hausser, K. W., and W. Vahle, "Sunburn and Suntanning," *in* "The Biologic Effects of Ultraviolet Radiation," edited by F. Urbach, Pergamon Press, Oxford, United Kingdom, 1969, pp. 3–21.

(4) Freeman, R. G., et al., "Relative Energy Requirements for an Erythemal Response of Skin to Monochromatic Wavelengths of Ultraviolet Present in the Solar Spectrum," *Journal of Investigative Dermatology*, 47:586–592, 1966.

(5) Cripps, D. J., and C. A. Ramsay, "Ultraviolet Action Spectrum with a Prism-Grating Monochromator," *British Journal of Dermatology*, 82:584–592, 1970.

(6) Cripps, D. J., "Instrumentation and Action Spectra in Light-associated Diseases," *Journal of Investigative Dermatology*, 77:20–31, 1981.

8. One comment disagreed with the Panel's statement, "At 307.4 nm the maximal amount of energy to cause sunburn is delivered by the sun to the skin" (43 FR 38206 at 38209). The comment noted that the integration of the action spectrum for erythema and the emission spectrum for UVB in the summer at noon in Davos, Switzerland, shows the peak of the effectiveness spectrum to lie in the vicinity of 305 to 308 nm. Therefore, the comment contended that "the maximal amount of sunburn causing energy" is not delivered at 307.4 nm, but rather that the "maximal effectiveness" of noon sunlight UV radiation is located near 306 nm rather than 295 nm.

The agency has reviewed the study by Schulze (Ref. 1), which the Panel cited as the basis for its statement that the maximal amount of energy to cause sunburn is delivered at 307.4 nm. The agency agrees with the comment that the statement is incorrect. Schulze combined data from a 1935 study by the CIE, which determined the relative erythema efficiency of various wavelengths of UV radiation, with data from a study by Bener conducted in Davos, Switzerland, which determined the irradiation intensity of sunlight (see Table 1 and Fig. 2 in Ref. 1). Schulze combined the data from the two studies to obtain an efficiency curve for global radiation, i.e., the relative erythema efficiency of various wavelengths of UV radiation multiplied by the intensity of the irradiation of those wavelengths. This produced an efficiency curve for natural sunlight with a peak at 307.4 nm. Because 307.4 nm is the peak of the curve resulting from the combination of

the erythema action spectrum (CIE values) and the solar spectrum, the value actually represents an erythema effectiveness maximum. (See comment 84 for a discussion of the erythema effectiveness spectrum.) Therefore, the Panel's statement should have read, "The maximal effectiveness of ultraviolet radiation from noon sunlight occurs at about 307 nm."

Reference

(1) Schulze, R., "Effectiveness of UV Absorbers and Commercially Available Sunscreens (Wirksamkeit von UV-Absorbern und Handelsublicher Sonnenschutzmittel)," *Journal of the Society of Cosmetic Chemists*, 14:544–565, 1963.

9. Three comments disagreed with the Panel's statement that the erythema reaction is maximal in intensity at 6 to 20 hours after exposure to UVB radiation (43 FR 38206 at 38209). Two of the comments stated that the postexposure time for the maximum intensity of the erythema reaction to UVB radiation is 12 to 24 hours, and the third comment reported it as 18 to 24 hours. One comment added that if postexposure redness is maximum in 6 to 8 hours, the radiation source contained significant UVC radiation (wavelengths less than "280 nm"), and provided a reference for this statement (Ref. 1). One of the comments also disagreed with the Panel's statement that the erythema reaction to UVA radiation is maximal in intensity about 72 hours after exposure (43 FR 38209). The comment maintained that the erythema reaction to UVA radiation is maximal in intensity at 12 to 24 hours following exposure and is only maximum at 72 hours when photosensitizing agents such as methoxypsoralen (8–MOP) are applied topically or given orally.

The information on solar energy provided by the Panel at 43 FR 38209 was intended as background information and is not included in the tentative final monograph. Because UVC radiation from the sun is strongly absorbed by the earth's ozone layer and, thus, largely prevented from reaching the earth's surface (Ref. 2), the agency believes that it is not necessary to consider UVC radiation in the tentative final monograph on OTC sunscreen drug products.

The Panel recommended postexposure time limits of 16 to 24 hours for the evaluation of an erythema reaction to UV radiation under the testing procedures described in §§ 352.42(h), 352.43, and 352.46. Although the comments differed on the lower time limit for the occurrence of the maximum intensity of an erythema reaction following UVB radiation exposure, there appears to be general agreement on 24 hours as the upper time limit. Investigators assessing the effects of UVA and UVB radiations generally use 24 hours postexposure as the time period to determine the skin's erythema reaction to these radiations. The agency believes that the disagreement concerning the lower postexposure time limit for the maximum intensity of the erythemogenic response is a result of differences in methodology between laboratories, i.e., differences in light source, skin-types, area and location of skin exposed, and variations in the judgment of the maximum response.

Moreover, the agency believes that immediate pigmentation may interfere with an investigator's perception of the MED if the evaluation is done at 16 hours' postexposure. The agency believes that sunscreen testing results will be more accurate if the MED is determined at 22 to 24 hours post irradiation rather than 16 to 24 hours post irradiation. Therefore, the agency is proposing those time frames in §§ 352.72(h) and 352.73 of this tentative final monograph. (See comment 95.)

References

(1) Pathak, M.A., and J.H. Epstein, "Normal and Abnormal Reactions of Man to Light," *in* "Dermatology in General Medicine," edited by T.B. Fitzpatrick, et al., McGraw Hill Book Company, New York, pp. 977–1036, 1971.

(2) Pathak, M.A., T.B. Fitzpatrick, and J.A. Parrish, "Topical and Systemic Approaches to Protection of Human Skin Against Harmful Effects of Solar Radiation," *in* "The Science of Photomedicine," edited by J.D. Regan and J.A. Parrish, Plenum Press, New York, pp. 441–473, 1982.

10. Referring to the Panel's statement that "approximately 20 to 50 millijoules per centimeter squared (mJ/cm²) of UVB energy is required to produce one MED * * *" (43 FR 38206 at 38209), one comment stated that this number is approximately correct, provided it is specified that all the UVB energy has been converted by means of an action spectrum to the effectiveness of UV radiation of a wavelength of approximately 297 nm. The comment added that the statement is untrue if it is integrated energy from 290 to 320 nm.

The agency agrees with the comment. In its report, the Panel stated the approximate amount of energy required for each of the bands of the UV spectrum (UVA, UVB, and UVC) to induce one MED. This statement illustrated the relative amounts of energy required for each of these bands to produce one MED. The agency notes that the determination of an MED is highly variable. The MED varies among individuals and for different sites of the body, mainly, because of varying degrees of pigmentation and thickness of the stratum corneum layer of the skin (Ref. 1). Other variables affecting MED measurements are the wavelengths and irradiance of the optical source, the distance of the test subject from the source, the size of the exposed test area, the angle of incidence of the radiation on the test area, heat, humidity, wind, previous light exposure, definition of the end point, and the time the response is read (Ref. 1). In a study where these variables were controlled and the MED of one individual measured for UVB and UVA radiations, the amount of energy of UVB radiation required to cause 1 MED was 19 mJ/cm² (Ref. 2). The agency notes that this value correlates reasonably well with the range cited by the Panel (43 FR 38206 at 38209).

The agency agrees that UV energy should be converted to erythema effective radiation before determining MEDs. The agency discusses the use of an appropriate action spectrum for the OTC sunscreen testing procedures in comment 84.

References

(1) Parrish, J.A., H.A.D. White, and M.A. Pathak, "Photomedicine," *in* "Dermatology in General Medicine," 2d ed., edited by T.B. Fitzpatrick, et al., McGraw-Hill Book Company, New York, pp. 952 and 953, 1979.

(2) Ying, C.Y., J.A. Parrish, and M.A. Pathak, "Additive Erythemogenic Effects of Middle (280–320 nm) and Long (320–400 nm) Wave Ultraviolet Light," *Journal of Investigative Dermatology*, 63:273–278, 1974.

11. Two comments disagreed with the Panel's statement "In the long run, suntanning is not good for the skin," (43 FR 38206 at 38209). One comment felt that the term "suntanning" is not accurate in this context and that the term "prolonged sunbathing" would be preferred. The other comment stated that the term "suntanning" is erroneous and anecdotal and that the resulting tan is protective against subsequent actinic damage. This comment stated that the terms "prolonged sunbathing" or "excessive sun exposure" should have been used.

The Panel felt that overexposure to sunlight damages the skin and can lead to various skin lesions, and that the cumulative exposure to sunlight from childhood into adulthood can lead to skin cancer (43 FR 38209). When the Panel stated that "suntanning is not good for the skin," it was expressing a general opinion on the cumulative effects of exposure to sunlight. The use of the term "suntanning," as opposed to "excessive sun exposure" or "prolonged sunbathing," was the Panel's choice of words. The use of any of these terms

would be acceptable; however, changing the Panel's statement would not affect the substance of the Panel's report or the tentative final monograph. Therefore, the agency sees no basis for revising the Panel's statement.

12. One comment stated that the investigators (Refs. 1 and 2) who were cited in the Panel's discussion of the types of solar radiation (43 FR 38206 at 38210) did not evaluate the energy requirements for the induction of an erythema reaction by UVA, UVB, or UVC radiation. The comment stated that the Panel should have referred to investigators who reported the energy required to produce the MED reaction (i.e., UVA radiation requires about 20 to 50 J/cm², UVB radiation requires approximately 20 to 50 mJ/cm², and UVC radiation requires about 5 to 20 mJ/cm²) (43 FR 38209 to 38210). The comment argued that a literature citation of this important information is essential.

The agency is not aware of the specific source used by the Panel for the data on energy requirements for the induction of an erythema reaction as a result of UVA, UVB, or UVC radiation. The agency notes, however, that the figures used at 43 FR 38209 are comparable to those appearing generally in the literature (Refs. 3 and 4).

References

(1) Kesten, B.M., and M. Slatkin, "Diseases Related to Light Sensitivity," *A. M.A. Archives of Dermatology and Syphilology*, 67:284–301, 1953.

(2) Schulze, R., "Effectiveness of UV Absorbers and Commercially Available Sunscreens (Wirksamkeit von UV-Absorbern und Handelsublicher Sonnenschutzmittel)," *Journal of the Society of Cosmetic Chemists*, 14:544–565, 1963.

(3) Cripps, D.J., and C.A. Ramsay, "Ultraviolet Action Spectrum with a Prism-Grating Monochromator," *British Journal of Dermatology*, 82:584–592, 1970.

(4) Freeman, R.G., et al., "Relative Energy Requirements for an Erythemal Response of Skin to Monochromatic Wave Lengths of Ultraviolet Present in the Solar Spectrum," *The Journal of Investigative Dermatology*, 47:586–592, 1966.

13. Referring to the Panel's discussion of factors affecting the amount of sunlight exposure (43 FR 38206 at 38210), one comment stated that the UV energy of sunlight is greatest between 10 a.m. and 2 p.m. at all times of the year, rather than (just) in midsummer as stated by the Panel. The comment added that while the amount of radiation received varies with the seasons, relative intensity does not. The comment said that, in the Panel's discussion of morning and late afternoon sun angle, the phrase "reducing the ultraviolet radiation component of sunlight by as much as 75 percent" is an appropriate statement, rather than the phrase "reducing the sunlight's intensity by 75 percent."

The agency agrees with the comment. On any day of the year, the intensity of the UV energy of sunlight is greatest between 10 a.m. and 2 p.m. (Ref. 1); the intensity of the UV sunburning component of sunlight is reduced 75 percent when the sun is at an angle of about 45 degrees (e.g., in the late afternoon) (Ref. 2). The amount or intensity of UVB radiation received at the earth's surface is reduced in proportion to the angle of incidence of the radiation. At lower angles of incidence UVB radiation is attenuated by a longer passage through the ozone layer, which absorbs UVB radiation.

References

(1) Kreps, S.I., "Sun Burn Protection and Sun Tan Preparations," *American Perfumer and Cosmetics*, 78:73–77, 1963.

(2) Fitzpatrick, T.B., M.A. Pathak, and J.A. Parrish, "Protection of the Human Skin Against the Effects of the Sunburn Ultraviolet (290–320 nm)," *in* "Sunlight and Man," edited by M.A. Pathak et al., University of Tokyo Press, Tokyo, pp. 751–765, 1974.

14. One comment contended that the table "Guide for Fair-Skinned People" (43 FR 38206 at 38210) is confusing. The comment stated that it is not apparent why 4 times the MED should produce a painful sunburn in New Jersey, but 5 times the MED should do so in Florida, or why 8 times the MED should produce a blistering sunburn in New Jersey and 12 times the MED should do so in Florida. The comment argued that these data are incompatible with each other and should be verified with the authors (Ref. 1).

The agency has determined that the cited reference (Ref. 1) in the Panel's report is not the source of the information that appears in the "Guide for Fair-Skinned People" (43 FR 38210). Further, the agency is not aware of the source of this information. Because the information in the "Guide" has no bearing on the content of the tentative final monograph, it will not be discussed further.

Reference

(1) Fitzpatrick, T.B., M.A. Pathak, and J.A. Parrish, "Protection of the Human Skin Against the Effects of the Sunburn Ultraviolet (290–320 nm)," *in* "Sunlight and Man," edited by M.A. Pathak, et al., University of Tokyo Press, pp. 751–765, 1974.

15. Referring to the Panel's discussion of the harmful effects of sunlight on the skin (43 FR 38206 at 38210), one comment stated that "light is only one of the parameters inducing skin cancer." The comment added that "other environmental parameters are responsible for a less resistant cell, e.g., nutrition, lack of exercise, alcohol, drugs, smoking."

The agency recognizes that UV radiation is not the only parameter believed to be responsible for inducing skin cancer. However, parameters such as those named by the comment are unrelated to the use of OTC sunscreen drug products and are beyond the scope of this rulemaking.

16. One comment stated that the word "would" appearing at 43 FR 38206 at 38210, third column, line 6 should be replaced by "could," and that at 43 FR 38211, second column, line 23, the words "lower wavelength limit of cancer-producing radiation" should be replaced by "upper wavelength limit."

The word "would" referred to by the comment is part of a quote by Cleary (Ref. 1). The agency has reviewed this reference and found that it is correctly quoted. Therefore, the comment's suggested change would be incorrect.

The words at 43 FR 38211 referring to the wavelength limits of cancer-producing radiation were cited by the Panel as being supported by Blum (Ref. 2). The agency has reviewed this reference and agrees with the comment that the words "lower wavelength limit" are incorrect; however, the agency believes that the sentence in the Panel's report could have been clearer if it had stated "* * * because the wavelengths that cause cancer of the skin of experimental animals are those 320 nm and shorter, i.e., the same spectral range that produces sunburn in human skin * * *." This wording would be more consistent with the statement made by Blum.

References

(1) Cleary, D. M., "Is There Too Much Sunshine in Your Life?," The Sunday Bulletin/Discoverer, Philadelphia, pp. 12–16, May 15, 1977.

(2) Blum, H. F., "Carcinogenesis by UV Light," Princeton University Press, Princeton, NJ, pp. 285–305, 1959.

17. Referring to the Panel's definition of "sunscreen sunburn preventive agent" (43 FR 38206 at 38213), one comment recommended that the Panel make a statement that "the sunscreen may remove the sunburning rays, but it may or may not transmit long-wavelength ultraviolet radiation of 320–400 nm." The comment mentioned that PABA may absorb radiation from 290 to 320 nm but will transmit radiation greater than 320 nm, whereas a benzophenone derivative may absorb UV radiation from 290 to 380 nm.

In discussing the types of solar radiation, the Panel noted that

"sunburn" radiation has a wavelength in the 290 to 320 nm region and not the 320 to 400 nm region (43 FR 38209). Therefore, the Panel defined a sunscreen sunburn preventive agent as an active ingredient that absorbs 95 percent or more of the light in the UV range at wavelengths from 290 to 320 nm and thereby removes the sunburning rays (43 FR 38213). The Panel did not include this definition for a "sunscreen sunburn preventive agent" in its recommended monograph, but included a definition for a "sunscreen active ingredient" (in § 352.3(b)) as follows: "An active ingredient that absorbs at least 85 percent of the light in the UV range at wavelengths from 290 to 320 nanometers, but transmits UV light at wavelengths longer than 320 nanometers. Such agents permit tanning in the average individual and also permit some reddening (erythema) without pain." This definition contains part of the statement requested by the comment concerning the transmittance of the longer wavelengths of UV radiation, i.e., "transmits UV light at wavelengths longer than 320 nm." However, the definition would not apply to ingredients which absorb UV radiation longer than 320 nm, e.g., dioxybenzone, a benzophenone derivative. Therefore, the agency is replacing the word "transmits" with the phrase "may or may not transmit" in the definition and is including the revised definition in § 352.3(c) of this tentative final monograph. The definition will be applicable to sunscreen active ingredients that absorb and transmit UV radiation in the 320 to 400 nm range. The agency is also proposing to replace the term "UV light" with "UV radiation." (See comment 2.) Regarding the last sentence in the Panel's recommended definition, the agency does not believe that this sentence is necessary to define a sunscreen active ingredient. Therefore, the last sentence in the Panel's recommended definition is not being retained. The proposed definition in § 352.3(c) for a sunscreen active ingredient now reads as follows: "An active ingredient that absorbs at least 85 percent of the radiation in the UV range at wavelengths from 290 to 320 nanometers, but may or may not transmit radiation at wavelengths longer than 320 nanometers."

18. Referring to the Panel's definitions of a sunscreen sunburn preventive agent and a sunscreen suntanning agent (43 FR 38206 at 38213), one comment suggested that these definitions should mention "the measuring conditions because of the correlation between layer thickness and transmission."

The Panel realized that its definitions are based on the UV-absorbing properties of a single active ingredient of a sunscreen product, not on how the ingredient might perform in a final formulation or in combination with other active ingredients (48 FR 38213). Therefore, the Panel included final formulation testing, with specific measuring conditions, in its recommended monograph. The Panel, however, did not include definitions of a sunscreen sunburn preventive agent or a sunscreen suntanning agent in its recommended monograph. The agency also does not propose to include definitions in the tentative final monograph. Thus, it is not necessary to revise the Panel's definitions.

19. One comment noted that the Panel stated that sunscreen active ingredients may be combined with other active ingredients such as skin protectants (43 FR 38206 at 38217). The comment added that the Panel did not define the term "skin protectant" and asked the meaning of the term.

The term "skin protectant" was defined in proposed § 347.3(a) of the tentative final monograph for OTC skin protectant drug products, published in the **Federal Register** of February 15, 1983 (48 FR 6832), as follows: "A drug which protects injured or exposed skin or mucous membrane surface from harmful or annoying stimuli." A final definition will appear in the final monograph for OTC skin protectant drug products in a future issue of the **Federal Register**.

20. Referring to the Panel's general discussion on sunscreens (43 FR 38206 at 38218), one comment questioned the source of the Panel's description of an ideal sunscreen vehicle. The comment stated that every person has his or her own ideas about an ideal vehicle, depending on skin constitution and the environment, and added that a certain content of emollients is important, especially in a dry climate and in water.

The Panel described the characteristics of an ideal sunscreen vehicle at 43 FR 38218 as follows: "An ideal sunscreen vehicle would be stable, neutral, nongreasy, nondegreasing, nonirritant, nondehydrating, nondrying, odorless, efficient on all kinds of human skin, hold at least 50 percent water, be easily compounded of known chemicals, and have infinite stability during storage." The Panel pointed out that there is no ideal vehicle and that the vehicles in common use represent a compromise of advantages against disadvantages. Vehicles for topical delivery of active ingredients are complex mixtures of substances involved in physical and chemical interactions with the outer layer of human skin. The effects of abrasion, sweating, and washing on the physical and chemical properties of the active ingredients often depend upon the vehicle.

The agency believes that the Panel based its description of an ideal sunscreen vehicle on the experience of its members with various dermatological preparations and on information found in standard references, textbooks, and the scientific literature concerning the anatomy and physiology of the skin (43 FR 38217). The Panel did not make any recommendations concerning sunscreen vehicles for inclusion in the monograph. However, it did state in its definition of SPF value in § 352.3(d) that this determination is to be made on the "final formulation of the sunscreen product," which includes the vehicle. Also, the water resistant tests proposed by the Panel in § 352.46 are to be conducted with the final-formulated sunscreen product. (The agency is not proposing the Panel's recommended sweat resistance test. See comment 100.)

The agency acknowledges that there are different ideas about what constitutes an ideal vehicle for a sunscreen drug product. The Panel's general discussion of an ideal vehicle provides useful guidance to manufacturers of these products.

21. Referring to the Panel's general discussion on sunscreens (43 FR 38206 at 38219), one comment stated that the Panel's definition of the term phototoxicity is inaccurate and incomplete. The comment recommended careful rewording and revision of the definition. The comment argued that (1) Phototoxicity is a dose-related response ("usually an exaggerated sunburn reaction of all individuals to adequate simultaneous exposure to a photoreactive chemical and radiation of appropriate wavelengths"), (2) the exposure of skin to radiation alone may not produce any reaction in skin or may produce a minimal reaction which is not pathologic, (3) the topical application of the product or the chemical ingredient of the product may not produce any reaction, (4) in phototoxic reactions, simultaneous exposure of the skin to the chemical and the radiation of appropriate wavelength will result in an abnormal pathologic reaction manifested by erythema, edema, and even a blistering response, (5) the fluorescence property of a molecule has nothing to do with phototoxicity because there are hundreds of molecules that are fluorescent and yet are not photosensitizing, and (6) skin

photosensitization can occur when the absorbed energy by the chemical leads to the formation of either free radicals, singlet oxygen, covalent conjugation with DNA, ribonucleic acid, and protein, or damage of the cell membrane and lysosomes.

The Panel's report was not intended to be an in-depth discussion of phototoxicity. Rather, the Panel defined phototoxicity as it relates to the general discussion of sunscreens and the effects of exposure to sunlight. The agency is not including a definition of phototoxicity in this tentative final monograph. However, the agency discusses its position on sunscreen protection from phototoxic and photoallergic reactions in comment 33.

22. One comment recommended that FDA "advertise" the most effective sunscreen products and the recommended percentage of the ingredients in sunscreen preparations.

The agency is proposing in this tentative final monograph explicit and detailed labeling that manufacturers may use for all Category I sunscreen drug products. This includes SPF values, which are required in sunscreen labeling as a guide as to how a product will act on a consumer's skin, and five optional labeling claims (under "Product Category Designation") that are related to the SPF values of sunscreen ingredients (e.g., minimal (SPF 2 to under 4), moderate (SPF 4 to under 8), high (SPF 8 to under 12), very high (SPF 12 to under 20), and ultra high (SPF 20 to 30)). (See comment 45 for a discussion of new terminology for PCD's.) In addition, the monograph will provide the effective dosage limits (on a percentage basis) for each Category I sunscreen ingredient. (See comment 37.)

After publication of the final monograph, all sunscreen drug products marketed OTC will have to comply with the standards of safety and effectiveness established by the agency and be labeled accordingly. This labeling will enable consumers to select the product that is appropriate for their use.

23. One comment suggested that the agency formulate specific guidelines for providing safe, effective sunscreen lotions, creams, and gels for use on children. The comment stated that the AAD and the Skin Cancer Foundation are committed to educating parents on the importance of protecting their children against the potential harmful effects of solar radiation. The comment contended that, although the skin of children is more sensitive to the effects of sunlight than is the skin of adults, specific sunscreens for children have not been marketed. Also, specific guidelines for evaluating the safety and effectiveness of sunscreens for children are not available. However, the comment also stated that children are more sensitive to contact irritation reactions and delayed hypersensitivity reactions to chemicals that may be present in a sunscreen product. The comment added that recently some manufacturers are claiming effectiveness of their product for children's skin, but that tests performed to support such a claim were unsatisfactory.

A second comment disagreed with the comment above regarding the need for special guidelines on SPF values of sunscreens designed especially for children. This comment stated that, as with all sunscreen products, appropriate safety and effectiveness testing should be conducted prior to marketing. This comment cited the transcript of the January 26, 1988 FDA meeting on OTC sunscreen drug products at page 37 (Ref. 1) where one participant contended that "* * * there is a great need for high SPF sunscreens in children. They are the ones who get the most sunlight." In addition, the participant stated that "* * * two-thirds of all the radiation you are going to get is before age 15 or 20 and it is there that the greatest protection has to be given."

The Topical Analgesic Panel discussed "adult skin" and "infant skin" in its report on OTC external analgesic drug products, published in the **Federal Register** of December 4, 1979 (44 FR 69768 at 69773), and in its report on OTC sunscreen drug products (43 FR 38206 at 38217). The Panel was concerned with possible differences in percutaneous absorption between infant skin and adult skin. The Panel thoroughly discussed the absorptive characteristics of infant and adult skin and defined adult human skin to be that of individuals older than 6 months of age. The Panel stated that the skin of infants under 6 months may have different absorptive characteristics. In order to provide an added margin of safety, the Panel stated that sunscreen ingredients which it reviewed are not to be used on children under the age of 6 months (44 FR 69773). The Panel considered this margin of safety important because biologic systems which metabolize and excrete drugs absorbed through the skin may not be fully developed in children under the age of 6 months (43 FR 38217). The Panel recommended, and the agency agrees, that only sunscreen drug products providing a minimum SPF value of 4 should be used on children between 6 months and 2 years of age. All sunscreen products, regardless of their SPF value, may be used on children 2 years of age and older. The agency is proposing to include these requirements in the directions for use. (See comments 61 and 66.)

In addition, the agency notes that the first comment did not submit data to support its contention that the skin of children is more sensitive than is the skin of adults to sunlight, contact dermatitis, or delayed sensitivity reactions; nor did the comment submit results to substantiate its claim that "tests performed * * * were unsatisfactory."

The agency agrees that the use of sunscreens with high SPF values may be advantageous to adults and children. (See comment 46.) The agency believes, however, that the need for special guidelines for the use of sunscreen drug products designed especially for children, as suggested by the first comment, has not been established.

Reference

(1) Transcript of meeting between the public and FDA to discuss appropriate testing procedures for OTC sunscreen drug products, January 26, 1988, Rockville, MD, page 37, comment no. TR, Docket No. 78N–0038, Dockets Management Branch.

B. Comments on Drug/Cosmetic Status of Sunscreen Drug Products

24. Four comments maintained cosmetic companies were not afforded the opportunity to participate in the sunscreen products rulemaking process because they were not given adequate notice. One comment stated that the fact that a cosmetic trade association and certain cosmetic manufacturers participated in these proceedings does not alter this reasoning because many cosmetic companies also sell drug products. Two comments emphasized that although a notice was published in the **Federal Register** of December 12, 1972 (37 FR 26456), this notice gave no indication that FDA might attempt to reclassify, as drugs, articles historically regulated as cosmetics or otherwise to establish any requirements for cosmetics. The comments stated that (1) The notice invited submissions with respect to "sunburn prevention and treatment drug products" and (2) that there was no indication that manufacturers of cosmetic products containing sunscreens might be subject to the same compositional or labeling requirements as sunburn prevention products. The comments added that there were factors that could have led the cosmetic industry, including manufacturers of suntan products, to conclude that there was no need to submit data and information to the Topical Analgesic Panel concerning

products traditionally regarded solely as cosmetics. These factors included FDA's statement in the **Federal Register** of May 11, 1972 (37 FR 9473) in the procedural regulations governing the OTC drug review that it would not review products for which only cosmetic claims were made, FDA's Trade Correspondence (Ref. 1), and FDA's cosmetic product regulations. The comments stated that if FDA intends to regulate cosmetic products under the OTC drug regulations, the current proposal should be withdrawn and the Panel reconvened to consider submissions from cosmetic manufacturers, pursuant to a new and sufficient notice and request for information.

The agency does not agree with the comments. Both the public and the cosmetic industry have had and will continue to have the opportunity to participate fully in the process for developing the sunscreen monograph. The agency regularly published notices in the **Federal Register** announcing the dates of the Topical Analgesic Panel's meetings. A part of each meeting was open to the public, and minutes of the meetings were available to the public. One of the industry liaison members on the Panel was nominated by the CTFA, the principal cosmetic industry trade association. Thus, adequate notice was provided for all parties, including cosmetic manufacturers, to present their positions to the Panel during its deliberations. Interested persons had a similar opportunity to comment and submit information to the agency following publication of the Panel's report. Furthermore, in the **Federal Register** of September 4, 1987 (57 FR 33598), the agency announced that a public meeting to discuss sunscreen testing procedures would be held on January 26, 1988, and that the administrative record for sunscreen drug products would be reopened until April 2, 1988. Several cosmetic companies and the CTFA participated in that meeting and submitted written comments to the agency. Finally, the present tentative final monograph is a proposed regulation. Once again, all interested parties have an opportunity to participate and to make their views known before a final regulation (monograph) is issued.

The agency emphasizes that this rulemaking for OTC sunscreen products applies only to drug products that contain sunscreen ingredients, display labeling that identifies those active ingredients as sunscreens, or display labeling claims that allude to the sun-blocking or sun-protection properties of those active ingredients. The distinction between sunscreen-containing products that are drugs and those that are cosmetics is discussed in comment 27.

Reference

(1) "FD & C Act Trade Correspondence," United States Department of Agriculture, Food and Drug Administration, TC-61, February 15, 1940.

25. Several comments stated that many cosmetics are currently "represented" as aids in acquiring an even tan or as useful in screening the sun, but are not "represented" for the treatment or prevention of sunburn. The comments maintained that the proposed monograph should be clarified to eliminate ambiguity and to exclude cosmetic products (e.g., moisturizers, make-up, and lipsticks) more explicitly by revising the monograph to state that cosmetics are excluded. The comments stated that the proposed rule can have no application to cosmetic products as they are defined in the Federal Food, Drug, and Cosmetic Act (the act), and that the mandate of the OTC drug review is to evaluate the safety and effectiveness of acknowledged drugs, not to provide a means for the reclassification of products. Consequently, some comments suggested that proposed § 352.1 "Scope" be amended by: (1) Changing the term "sunscreen product" to read "drug represented for use in prevention of sunburn" and (2) adding at the end of § 352.1 the sentence "This part does not apply to an article represented for use as a sunscreen or containing an ingredient with sunscreen properties if the article is intended for use solely as a cosmetic as defined in section 201(i) of the act, 21 U.S.C. 321(i)." One comment suggested rewording § 352.1 to read "An Over-the-Counter sunscreen drug product in a form suitable for topical administration * * *." This comment also suggested adding the following to the end of § 352.1: "a product otherwise a cosmetic shall not be considered a 'drug' because it contains a sunscreen agent and such fact is recognized in product labeling or promotion as 'contains sunscreen.'"

Conversely, one comment contended that the word "sunscreen" in § 352.1 should be clearly defined to include all products that consumers consider within the meaning of the term suntan lotion, i.e., any product sold for use on the skin in connection with sunbathing, swimming, or other outdoor activity.

The agency agrees with the comments that stated that the monograph for OTC sunscreen products applies only to drugs. However, the agency has tentatively concluded that any product containing sunscreen active ingredients and displaying sunscreen labeling claims is a drug even if the product is not labeled for the prevention or treatment of sunburn (see comment 27). In order to clarify that the scope of this monograph extends only to drug products, and to be consistent with the format of monographs for other OTC drug product categories, the word "drug" is being added to § 352.1 to read: "An over-the-counter sunscreen drug product in a form suitable for topical administration * * *." Because this section, as revised, clearly applies only to drug products, the agency believes that it would be redundant to add a sentence to the end of § 352.1 emphasizing that the proposed rule does not apply to cosmetics.

The agency disagrees with the comments that products which are primarily designed to be used as cosmetics but which contain a sunscreen active ingredient are outside the scope of the monograph. However, the agency recognizes that products such as lipsticks and make-up preparations containing sunscreen active ingredients and displaying sunscreen labeling claims may require separate consideration. Accordingly, the agency is proposing appropriate labeling for such products. (See comments 27 and 52.)

The agency does not agree with the comment that suggested that the word "sunscreen" should be defined as pertaining to all products sold for use on the skin in connection with sunbathing, swimming, or other outdoor activity. The agency recognizes that many OTC products sold for use on the skin in connection with sunbathing, swimming, or other outdoor activity contain no sunscreen active ingredients, provide no sunscreening protection, and do not have drug labeling. In addition, as discussed in comment 27, some products such as shampoos, hair conditioners, or nail polishes may contain a sunscreen and bear only cosmetic labeling. These products are cosmetics and, therefore, are not within the scope of this monograph.

The agency believes that the revised "Scope" language being proposed in § 352.1 of this tentative final monograph will adequately define the coverage of this class of drugs.

26. Four comments suggested revising the statement of identity in § 352.50(a) to read "sunburn prevention product" (instead of "sunscreen") in order to distinguish between sunscreen-containing products that make a specific "representation" regarding usefulness in the prevention of sunburn (i.e., sunscreen drug products) and sunscreen-containing products that refer

to suntanning or to screening or blocking the sun (i.e., sunscreen cosmetic products). The comments recommended using the term "sunburn prevention product" throughout the monograph instead of the term "sunscreen" to describe the regulated class of drug products. Another comment suggested that the term "sun prevention product" be used in the monograph in lieu of "sunscreen."

One of the comments stated that FDA should adopt a statement of identity for cosmetic products containing a sunscreen ingredient intended for everyday nonbeach use that is different from the statement adopted for beach products containing a sunscreen ingredient. The comment suggested "skin shield," "UV light block," "UV light filter," or any other such similar statement. The comment recommended that this statement of identity appear on the label of an everyday use, nonbeach cosmetic product along with any other statement of identity required for such a product in 21 CFR 701.11 (e.g., "Brand X Facial Cream and (or with) Skin Shield").

The comment also suggested that FDA define products for which this new statement of identity would be applicable as "Drug products containing one of the active ingredients set forth in § 352.10 and bearing labeling limited to the chronic exposure representations in § 352.50(b)(1)(iv) or (b)(1)(v), and not represented for use in the prevention or treatment of sunburn." The comment maintained that "adoption of such a definition is a necessary recognition of the distinctive nature of everyday use, nonbeach beauty products that contain a sunscreen ingredient and are represented as useful in the prevention of skin cancer and/or premature aging of the skin, but are not represented for the prevention or treatment of sunburn."

The agency does not agree with the comments that the statement of identity in § 352.50(a) of this tentative final monograph should be changed to read "sunburn prevention product" or "sun prevention product" instead of "sunscreen," or that these terms should replace "sunscreen" throughout the monograph. The agency believes that the term "sunscreen" appropriately identifies a product that reduces the amount of harmful UV radiation from sunlight impinging on the skin. Sunscreen active ingredients absorb specific segments of the UV spectrum, or they reflect or scatter UV radiation and thereby prevent it from reaching the skin. Sunscreens only extend the amount of time necessary for the sun to produce a sunburn. To classify these products as "sunburn prevention products" or "sun prevention products" would mislead the consumer; these products only moderate the erythemal reaction of the exposed skin, and the possibility of sunburn still remains. The agency tentatively concludes that the term "sunscreen" appropriately describes the principal intended action of these drug products, and that this term is well understood by consumers. Therefore, in this tentative final monograph, the agency is proposing that the labeling of the product identifies the product as a "sunscreen."

The agency does not believe that separate statements of identity or separate definitions are necessary to distinguish "nonbeach" products that contain sunscreens but are not indicated for the prevention or treatment of sunburn from "beach" products containing sunscreens. The agency is aware that some products, such as lipsticks and make-ups, contain sunscreen active ingredients and display Category I sunscreen labeling claims other than for the prevention or treatment of sunburn. These products are primarily intended for use as cosmetics. Nevertheless, these products are also drugs and cannot be regarded solely as cosmetics because the sunscreen added to the product is intended to provide protection from the sun. Some of the labeling recommended by the Panel for sunscreen drug products may not be appropriate for these products. Therefore, the agency is proposing alternative labeling, including specific warnings and directions, for products such as lipsticks and make-ups. (See comments 27 and 52.) The agency believes that these regulations will adequately distinguish between "beach" and "nonbeach" sunscreen-containing drug products.

27. Several cosmetic manufacturers and a cosmetic trade association submitted comments stating that certain cosmetic products are not subject to regulation under an OTC drug monograph. Such products include makeups, lipsticks, and suntanning preparations containing a sunscreen ingredient and displaying labeling that refers to the sun-shielding or sun-blocking properties of the product, but not claiming to prevent sunburn. The comments maintained that when an ingredient can be used for either drug or cosmetic purposes, its status as a drug or a cosmetic, or both, is determined by the representations made by the manufacturer or distributor in the labeling or advertising for the product. Many comments emphasized that mere inclusion of an ingredient in a product does not cause the product to become a drug if the finished product is intended for use only as a cosmetic. To support their contentions, some of the comments cited the definitions of "drug" and "cosmetic" in sections 201(g) and (i) of the act (21 U.S.C. 321(g) and (i)) and prior case law. The comments also maintained that, according to an "FDA FD & C Act Trade Correspondence of 1940 (TC–61)" (Ref. 1), a product containing a sunscreen ingredient and represented as an aid to acquiring an even tan (but not for the prevention or treatment of sunburn) is a cosmetic and not a drug. Some comments added that FDA regulations in 21 CFR 720.4(c), which establish cosmetic product categories, include "suntan and sunscreen preparations."

Several comments stated that the mere use of the term "sunscreen" or of a truthful reference to blocking the rays of the sun or protection against the sun does not cause a product to be a drug. These comments asserted that only a product explicitly offered for use in preventing sunburn or other diseases may be categorized as a drug. The comments maintained that many products such as lipsticks, make-up preparations, and suntanning lotions that contain sunscreens have traditionally been regulated as cosmetics. The comments added that consumers use such products to avoid freckling, redness, or uneven coloration resulting from exposure to the sun. According to the comments, such uses are cosmetic. Many comments implied that if a reference to sunscreen ingredients and sunscreen properties in the labeling of a cosmetic would cause the product to be a drug, then cosmetic manufacturers would exclude sunscreen active ingredients from their products. The comments added that FDA should encourage the use of sunscreen ingredients in cosmetic skin products because of the favorable impact of the use of such products on the incidence of skin cancer and premature aging of the skin.

One comment stated that the inclusion of sunscreens can be rationalized as contributing to tanning rather than preventing sunburn. The comment added that sunscreens allow the consumer to stay in the sun longer, which is necessary for a deep, long-lasting tan; consumers can use these products to plan a tan and to increase the time in the sun. According to the comment, consumers can thereby obtain an even tan and one that does not readily fade.

The Panel was charged with evaluating the safety, effectiveness, and labeling of OTC active ingredients intended to prevent injury from exposure to the sun. It concluded that

overexposure to the sun results in various kinds of skin damage including sunburn, premature aging of the skin, and skin cancer (43 FR 38206 at 38211). The Panel stated that the use of sunscreens may mitigate the harmful effects of UV radiation from the sun on the exposed skin of susceptible individuals. The Panel recognized that many suntanning products had been traditionally regarded by FDA as cosmetics. However, the Panel believed that "regardless of the claims, products intended to be used for the prevention of sunburn or any other such similar condition should be regarded as drugs" (43 FR 38209). As discussed below, the agency concurs with this view.

After evaluating the active ingredients in the products submitted for review, the Panel stated:

(T)hese preparations reduce by varying amounts the solar radiation absorbed by the skin and thereby affect the physiological response and extent of the erythema reaction (redness) produced. Indeed, these products affect the structure and function of the body by screening, reflecting, or scattering the harmful, burning rays of the sun. This is a desirable alteration to a normal physiological response to solar radiation for individuals with sensitive and extra sensitive skin (43 FR 38209).

The Panel classified products intended to be used for preventing sunburn and similar conditions as drugs regardless of claims that were made for the products.

In a 1940 advisory opinion referred to as Trade Correspondence (TC)–61 (Ref. 1), the agency stated its policy regarding the drug/cosmetic status of sunburn and suntan preparations. TC–61 holds that a product promoted for prevention of damage from the sun is a drug, and a product that is promoted solely for the purpose of acquiring an even tan can be considered a cosmetic. Overexposure to the sun was not generally perceived to be harmful in 1940, and most of the products currently on the market were not available then. Since 1940, however, there has been a significant body of information developed on the harmful effects of the sun on human health and a significant change has occurred in consumer perception of the purpose of suntanning products. Today, consumers expect protection from a product that is promoted for suntanning. A letter from FDA to industry counsel, dated June 17, 1976 (Ref. 2), stated that the agency had changed the position set out in TC–61. FDA's present policy, as expressed in the 1976 letter, is that a product containing a sunscreen ingredient, even when labeled solely as a tanning aid, is both intended and understood to be a sunburn preventive. Such a product, therefore, is a drug under the act.

Sunscreen active ingredients affect the structure and function of the body by screening, reflecting, or scattering the harmful, burning rays of the sun, thereby altering the normal physiological response to solar radiation. Use of these ingredients helps to prevent diseases such as sunburn and may help to reduce the chance of skin lesions and skin cancer. When used in a suntan product, sunscreen active ingredients may help to obtain a tan by permitting the user to remain in the sun for a longer time without burning. Their primary intended use, however, is as a drug: to screen out UV radiation during the extended time of exposure so as to prevent skin damage through overexposure. Further, the agency believes that consumers expect protection from a tanning product that contains a sunscreen, irrespective of the claims for which the product is promoted.

The agency finds that TC–61 is out of date with current scientific knowledge and is no longer applicable. The agency intends to revoke TC–61 in accordance with 21 CFR 10.85(g). A notice of revocation and the final monograph for OTC sunscreen drug products will be published concurrently.

When an ingredient can be used for either drug or cosmetic purposes, its regulatory status as a drug or cosmetic, or both, is determined by objective evidence of the distributor's intent. As suggested by the comments, this includes, but is not limited to, the representations made by the manufacturer or distributor in the labeling or promotion of the product. The agency believes that the inclusion of a sunscreen active ingredient in a product that is intended or promoted to protect the consumer's skin from the harmful effects of the sun brings the product within the statutory definition of a "drug." A "drug" is defined in the act as an article "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" or "intended to affect the structure or any function of the body." (21 U.S.C. 321(g)). It is, of course, settled law that in determining whether an article is a drug, FDA is not bound by the manufacturer's subjective claims, but can find actual therapeutic intent on the basis of objective evidence. *National Nutritional Foods Association* v. *Matthews,* 557 F.2d 325 (2d Cir. 1977). Such intent may be derived from labeling, promotional material, advertising, and any other relevant source. *Id.* Such "relevant source" can be the consumer's intent in using the product. *Action on Smoking and Health* v. *Harris,* 655 F.2d 236 (D.C. Cir. 1980).

Also, when consumers see on the label of a product the term "sunscreen" or similar terms that could be interpreted as claiming that the product functions as a sunscreen, such as "sun shield" or "UVA/UVB filter," they quite rightly expect the product to protect them in some way from the harmful effects of the sun, irrespective of other labeling statements. The agency believes that consumers equate the term "sunscreen" or similar terms with the mitigation of the harmful effects of the sun, such as sunburn, premature aging of the skin (or skin aging due to the sun), and skin cancer.

Accordingly, the agency tentatively concludes, and is proposing in this tentative final monograph, that the use of the term "sunscreen" or a similar term on the label of a product causes that product to be a drug, except for specific nontherapeutic uses as discussed below. Likewise, similar claims, such as "shields from the sun," "blocks out the rays of the sun," "protects from the sun," "protects against UV rays," "prevents freckling," "prevents redness," or "prevents uneven coloration" are drug claims. Such claims imply that exposure to the sun is harmful, and that blocking it will provide benefits. These claims also imply that the product affects a physiological function of the body. The agency also considers that the use of the term "SPF" or the use of any SPF value in the labeling of a product as a basis for the product to be considered a drug. An SPF value provides assurance that the product will protect the skin from sun damage and, thus, will help to prevent disease and will affect the structure and function of the body.

The agency agrees with one of the comments that the inclusion of sunscreen ingredients in some cosmetic skin products is of benefit to the consumer. However, long-term use of products containing ineffective (or less then fully effective) sunscreen ingredients could result in a consumer being exposed to more UV radiation than the consumer would expect. Such use could have serious effects (e.g., increase the chance of skin lesions and skin cancer). The agency believes that all products containing a sunscreen active ingredient and claiming to protect the consumer from the sun or to enhance the consumer's ability to obtain an effect from sun exposure (i.e., a tan) must be regulated as drugs in order to ensure the effectiveness of the sunscreen ingredient. Therefore, FDA tentatively concludes that, except for a few select exceptions discussed below,

all products that contain sunscreen active ingredients and bear labeling identifying these active ingredients as sunscreens are drugs. Likewise, sunscreen containing-products that bear claims alluding to the sun-blocking or sun-shielding properties of the products or claims promoting a product's ability to help the consumer stay in the sun longer without harmful effects are drugs. Such products may also be regulated, but not solely, as cosmetics. Regarding the statement made by some comments that FDA regulations in 21 CFR 720.4(c) include suntan and sunscreen preparations, in the Federal Register of January 28, 1992 (57 FR 3128 at 3129), the agency revised § 720(c)(13) to delete sunscreen preparations.

Regarding one comment's statement that sunscreens may be added to a product to contribute to the tanning process and not to prevent sunburn, the agency agrees that sunscreens may indirectly aid the tanning process by allowing a person to remain in the sun for a longer period of time without burning. However, the agency believes that tanning products that contain sunscreens are drugs because the inclusion of a sunscreen in a tanning product implies that the product will protect against harm from the sun while the user is tanning. For a further discussion of tanning products and claims, see comments 29 and 58.

The agency is aware that there are many skin products such as lipsticks and make-up preparations on the market that contain sunscreens, and whose primary intended use is as a cosmetic. Nevertheless, under this tentative final monograph, such products are also drugs if they contain any of the following anywhere in their labeling or promotional material:

(1) The terms "sunscreen" (or a similar term as discussed above) or "SPF,"

(2) An SPF value, or

(3) Any other claims referring to the therapeutic attributes of sunscreen ingredients.

The agency acknowledges that a product may contain a sunscreen ingredient and be a cosmetic and not a drug. For example, a sunscreen ingredient may be included in a cosmetic product without making it a drug if: (1) It is a color additive (e. g., titanium dioxide in a lipstick), (2) it is used to protect the color of the product (e.g., sulisobenzone in a cologne, or (3) it is not intended to function as a drug, and no claims are made about the ingredient. In these cases, the term sunscreen is not used, no SPF value is given, and the sunscreen ingredient is only mentioned in the product's labeling by its cosmetic name in the ingredient list in accordance with agency regulations in § 701.3. There are several specific conditions described below where additional information about the sunscreen may be provided.

In order to provide guidance regarding appropriate labeling for cosmetic products containing sunscreen ingredients, the agency is providing in this document some examples of labeling that would cause a product to be a drug. Any labeling on a cosmetic product that implies that the product has a therapeutic benefit or affects the structure or function of the body is unacceptable. The agency tentatively concludes that the following labeling is unacceptable for cosmetic products that contain a sunscreen:

(1) The word "sunscreen" or similar terms anywhere in the labeling (except for the specific instances described below)
(2) "shields from the sun"
(3) "blocks out the rays of the sun"
(4) "protects from the sun"
(5) "prevent or protect against freckling"
(6) "prevent or protect against wrinkling"
(7) "prevent or protect against redness or uneven coloration of the skin"
(8) "protects against UVA/UVB"
(9) "shields the skin against specific factors that accelerate the signs of skin aging"
(10) "helps to acquire an even tan"
(11) "permits tanning"
(12) "protects against premature aging, skin aging, skin lesions, and skin cancer" with or without stating "due to the sun") in the labeling of the product.

Such labeling would cause sunscreen-containing products to be considered drugs as well as cosmetics under the act.

As discussed in comment 52, the agency does not believe that all of the labeling recommendations made by the Panel are applicable to drug/cosmetic products that contain sunscreens. Therefore, the agency is proposing specific directions and other labeling appropriate for this type of product.

As stated above, in most situations, the use of the word "sunscreen" or similar terms in the labeling of a product would cause the product to be considered a drug. The agency recognizes, however, that there are a few situations in which the term "sunscreen" could be used in the labeling of a strictly cosmetic product for which there is no therapeutic use. For example, a sunscreen ingredient may be included in a product to protect hair from sun damage (e.g., padimate O in a hair conditioner or hair spray). Also, a sunscreen ingredient may be used in a nail polish to protect the color of the polish after application on the fingernails. If there are other instances where the nontherapeutic use of a sunscreen should be included in the labeling of the product, manufacturers should inform the agency in comments to this notice.

In the example cited above, the sunscreen ingredient is not being used to protect the skin from sunburn or other adverse effects of the sun; therefore, it would be misleading to represent anywhere in the product's labeling that the sunscreen has any therapeutic purpose. However, the labeling could state that the product contains a sunscreen to inform consumers why the product would protect the hair. For example, the labeling might state "contains a sunscreen to protect the hair from the damaging effects of sunning." It would be misleading to consumers to only use the term "contains a sunscreen" in such labeling without clarifying the purpose of the ingredient. Without such qualification, consumers might believe the product offered skin protection. Therefore, the product would be misbranded under section 201(n) and 602(a) of the act (21 U.S.C. 321(n) and 362(a)).

The agency is proposing to amend 21 CFR part 700 in subpart B, *Requirements for Specific Cosmetic Products,* by adding new § 700.35, as follows:

(a) A product that includes a sunscreen active ingredient and the term "sunscreen" in its labeling or in any other way represents or suggests that it is intended to prevent, cure, treat, or mitigate disease or to affect a structure or function of the body comes within the definition of a drug in § 201(g)(1) of the Federal Food, Drug, and Cosmetic Act. Sunscreen active ingredients affect the structure or function of the body by screening, reflecting, or scattering the harmful, burning rays of the sun, thereby altering the normal physiological response to solar radiation. These ingredients also help to prevent diseases such as sunburn and reduce the chance of premature skin aging or skin cancer due to the sun. Moreover, when consumers see the term "sunscreen" on the label of a product, they expect the product to protect them in some way from the harmful effects of the sun, irrespective of other labeling statements. Consequently, the use of the term "sunscreen" in a product's labeling normally makes that product a drug. However, sunscreen ingredients may also be used in some cosmetic products

for nontherapeutic uses. In order to avoid consumer misunderstanding, if a cosmetic product uses the term "sunscreen" anywhere in its labeling, the term "sunscreen" must be qualified by describing the cosmetic benefit provided by the sunscreen. For example: "This product contains a sunscreen that assists in protecting the hair from damage by the sun."

(b) Any information describing the purpose of the sunscreen in the product shall appear in direct conjunction with the term "sunscreen."

The final monograph will cover only the drug use of the active ingredients listed therein. The concentration ranges, limitations, warnings, and directions established for these ingredients in the monograph will not apply to the use of the same ingredients in products intended solely for use as cosmetics. Those products intended for both drug and cosmetic use will be required to conform to the requirements of the final monograph. However, such products, in addition to bearing the indications allowed for sunscreen drug products, may also be labeled for cosmetic use, in conformity with section 602 of the act (21 U.S.C. 362) and the provisions of 21 CFR parts 701 and 740.

In accordance with the revised labeling requirements for OTC drug products, it is the agency's view that cosmetic claims may not appear within the boxed area designated "APPROVED USES." As discussed in the final rule on the agency's "exclusivity policy" (51 FR 16258 at 16264 (paragraph 14)), cosmetic terminology is not reviewed and approved by FDA in the OTC drug monographs and therefore could not be placed in the box. Cosmetic claims may appear elsewhere in the labeling, should manufacturers choose the labeling alternative provided in § 330.1(c)(2)(i) or (c)(2)(iii) for labeling drug/cosmetic products. Although the agency does not specifically prohibit commingled drug and cosmetic labeling in other than the indications section, such claims should be appropriately described so that consumers will more readily be able to differentiate the drug aspects from the cosmetic aspects of such labeling. If commingled drug and cosmetic labeling claims are confusing or misleading, the product's labeling could be misleading within the meaning of the act and misbranded under sections 502(a) and 602(a) of the act (21 U.S.C. 352(a) and 362(a)).

References

(1) "FD & C Act Trade Correspondence," United States Department of Agriculture, Food and Drug Administration, TC-61, February 15, 1940.

(2) Letter from S. Fine, FDA, to R. Kingham, Covington and Burling, dated June 17, 1976, OTC Vol. 06ATFM, Docket No. 78N-0038, Dockets Management Branch.

28. Three comments, referring to the cosmetic portion of the labeling of a drug/cosmetic product, argued that the limitations set by the Panel for ingredients for drug use do not establish an inference with respect to the use of the same ingredient as a cosmetic. For example, § 352.10 of the Panel's proposed monograph (43 FR 38206 at 38264) restricts red petrolatum to use at a level of 30 percent or more in a sunscreen drug product, yet that same ingredient may be used properly at any safe level in a cosmetic. The comments also asserted that the warnings in proposed § 352.50(c) (43 FR 38268) do not establish any need for warnings on cosmetic products. Citing the Comptroller General's "Report to the Congress" concerning cosmetics, HRD-78-139, August 8, 1978, page 132, the comments added that FDA has recognized that a warning required for a particular ingredient in a drug product may not be appropriate when that ingredient is used in a cosmetic product. The comments maintained that FDA may not prohibit truthful and nonmisleading labeling concerning cosmetic aspects of a cosmetic that is also a drug, and that such labeling is subject to regulation by FDA under its cosmetic authority, not under its drug authority.

The agency agrees that this monograph applies only to sunscreen products that fall within the statutory definition of "drugs." In order to make it clear that the scope of the monograph extends only to drug products, the agency is proposing that the word "drug" be added to § 352.1 ("Scope"), to read "An over-the-counter sunscreen drug product * * *." (See comment 25.)

29. Stating that tanning is in the cosmetic area, one comment opposed any requirement that a cosmetic suntan product contain a sunscreen agent at any concentration level. Conversely, a number of comments contended that allowing "tanning" products to be marketed without sunscreens is misleading because consumers would believe that they have protection against sunburn when in fact they do not. The comments maintained that such products would actually promote sunburn and its subsequent, serious side effects. The comments asserted that allowing a tanning claim for products without sun protective factors would be contrary to the best interest of the public. Expressing concern that products making "tanning only" claims would be exempt from the proposed OTC sunscreen standards, one comment contended that these regulations are designed to provide protection from the acute effects of UV radiation in the 290 to 320 nm range (UVB), and that tanning is a direct response to that radiation. The comment stated that for products to influence tanning, they can either accelerate, diminish, or have no effect on UVB radiation. The comment argued that "tanning only" products should either diminish the amount of "UV-B flux" or should be labeled "sunburn, then tan." The comment contended that the term "tanning only" should not be allowed if those products allow normal or accelerated sunburn.

One comment was opposed to the sale of "tanning" products, but felt that the government cannot restrict the sale of such products. The comment, therefore, suggested that tanning products be required to carry warning labels. Another comment acknowledged that tanning products do not make a claim for sunburn protection, but suggested that, because of the consumer's perception that such products will reduce the risk of sunburn, all tanning products should contain a sunscreen agent with a minimum SPF value of 4.

Another comment urged that any product that claims to promote or permit tanning be required to contain a sunscreen and have a minimum SPF value of 2 or be deemed adulterated and/or misbranded. The comment argued that suntanning products without a minimum SPF value of 2 are dangerous and pose serious health hazards. The comment stated that the agency banned the use of chlorofluorocarbon propellants because chlorofluorocarbons cause a decrease in the ozone layer which can result in an increase in UV radiation to the earth and increased skin damage. The comment contended that, from a public health viewpoint, a requirement of a minimum SPF value of 2 for suntanning products is as necessary to protect the skin as the ban of chlorofluorocarbon propellants. The comment cited research indicating that the use of certain suntanning products without sunscreens may increase the amount of UV radiation penetrating the skin by as much as 10 percent (Ref. 1). The comment added that the health hazards attributable to long-term overexposure to the sun have been proven conclusively, and that it is less than responsible to market products that promote tanning but afford no protection from overexposure to UV radiation. The comment further contended that a sunscreen-containing product with an SPF value of 2 will

afford 50 percent more protection from long-term and short-term harm induced by overexposure to the sun than products without sunscreens.

The comment claimed that a survey that it conducted (Ref. 2) involving 903 consumers (age 35 and under) who purchase products for use in the sun demonstrated that 92 percent felt that protection from sunburning, as well as tanning, are expected attributes of a tanning product whether or not the label claims protection. From the results of the survey, the comment concluded that consumers believe and expect that a product that promotes or permits tanning will also provide protection from sunburn and other harmful effects of the sun.

Although the comment felt that the Panel recognized that suntanning products should contain a sunscreen with a minimum SPF value of 2, the comment did not agree that suntanning products need to be regulated as drugs. The comment recommended an addition to the cosmetic regulations in 21 CFR part 700 that would define suntanning cosmetic products as articles making suntanning claims and formulated with a minimum SPF value of 2. The comment cited the following examples as precedent for such a regulation: (1) The banning of hexachlorophene in cosmetics except as a preservative at levels not higher than 0.1 percent, (2) the banning of halogenated salicylanilides in cosmetics, and (3) the defining of the term "egg" as a name in cosmetic products containing not less than 2 percent egg. The comment contended that failure to enact such a regulation will force manufacturers of sunscreen products to market more tanning products without sunscreens in order to compete with products making only tanning claims. The comment stated further that this action would increase consumer use of tanning only products (without sunscreens) and increase the number of consumers placed in danger from overexposure to the sun. The comment concluded that, if the agency does not promulgate the comment's recommended cosmetic regulation, suntanning products should be included within the scope of the proposed rule for OTC sunscreen drug products.

The agency recognizes that tanning products have traditionally been used for cosmetic purposes to help an individual acquire a tan. These products are of two basic types: those that contain sunscreen ingredients and those that do not. Suntanning products that contain sunscreen ingredients are designed to minimize the burning effects of the sun. They permit the user to stay in the sun longer without receiving a painful sunburn and still acquire the desired tan. Tanning products without sunscreen ingredients are designed primarily to condition the skin while sunbathing to acquire a tan. Although the agency does not believe that all suntanning products should be required to contain a sunscreen ingredient, it believes that all suntanning products should be labeled so that the consumer can use them safely.

The agency believes that, as the data cited in the comments suggest, there has been a change in consumer perception regarding the purpose of suntanning products, and that the consumer expects a certain amount of protection from the sun from a product that is marketed for suntanning. The agency has tentatively determined that any tanning product that contains a sunscreen ingredient should be regulated as a drug product regardless of its claims because the inclusion of a sunscreen ingredient in a tanning product implies that the product will protect against harm from the sun while the user is tanning. Moreover, these products have a drug effect by reducing by varying amounts the UV radiation absorbed by the skin and affecting the physiological response and extent of the erythema reaction produced. Therefore, any tanning product that contains a sunscreen ingredient must comply with the monograph for OTC sunscreen drug products and must provide a minimal SPF of 2. A suntanning product that does not contain a sunscreen may be considered a cosmetic.

The agency is aware that some tanning products containing no sunscreen ingredient are labeled with SPF 0 and SPF 1. The use of SPF values in the labeling of a tanning product may lead the consumer to assume that the product contains a sunscreen ingredient when, in fact, it does not. Such labeling, especially SPF 1, could cause consumers to expect the product to provide some protection against the adverse effects of the sun. The agency considers such labeling on a tanning product that contains no sunscreen ingredient to be false and misleading and causes the product to be misbranded under section 602 of the act (21 U.S.C. 362).

In addition, because suntanning products are marketed specifically for use in the sun or at commercial tanning facilities, the agency is concerned about the health hazards associated with using such products if they do not contain sunscreen ingredients. The agency believes that in the absence of labeling statements that inform the consumer of the amount of protection that can reasonably be expected from the use of these products, such products could be potentially dangerous. The agency tentatively finds that the majority of consumers expect sunburn protection from suntanning products, whether the product contains a sunscreen ingredient or not. Because of the serious consequences of overexposure to the sun, the agency believes that it is important for the consumer to know whether a suntanning product contains a sunscreen ingredient or not. Failure to contain such information would constitute a failure to reveal facts material in light of the representations that are made (e.g., "suntanning") and with respect to the consequences that may result from the use of the article. Therefore, in conjunction with this tentative final monograph, the agency is proposing, under 21 U.S.C. 321(n), 362(a), and 371(a), to amend the cosmetic regulations in 21 CFR Part 700 by adding § 740.19 as follows:

"*Suntanning preparations.* The labeling of suntanning preparations that do not contain a sunscreen ingredient must display the following warning: 'Warning—This product does not contain a sunscreen and does not protect against sunburn.'"

References

(1) White, H., et al., "Enhancement of Transmission of Optical Radiation Through Human Epidermis by Topical Applications," 1978, OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

(2) Comment No. C00046, Docket No. 78N–0038, Dockets Management Branch.

C. Comments on Specific Sunscreen Active Ingredients

30. One comment recommended the use or creation of simpler names for many of the sunscreen active ingredients because simpler names would be more easily recognized by the public. Maintaining that sunscreens with simpler names have a marketing advantage over other sunscreen ingredients with more complex names, the comment contended that the variety of sunscreens available to the public will tend to become limited if some sunscreen ingredients have very complex names. The comment added that the variety of sunscreens available is very important to consumers with specific allergies or sensitivities. Stating that section 508 of the act (21 U.S.C. 358) clearly authorizes the assigning of simple names, the comment suggested establishing simple names for all approved ingredients by using CTFA names or abbreviations where available and by creating simple names using CTFA guidelines for the remaining compounds. The comment claimed that

the following names are unduly complex: diethanolamine p-methoxycinnamate, ethyl 4-[bis(hydroxypropyl)] aminobenzoate; 2-ethylhexyl 2-cyano-3,3-diphenylacrylate; and ethylhexyl p-methoxycinnamate. The comment added that the CTFA name PABA for aminobenzoic acid is very widely recognized, and that elimination of this name would confuse many consumers. The comment argued that use of the name aminobenzoic acid for chemical accuracy seems ludicrous when proprietary names such as Padimate A are allowed.

Another comment urged that the name PABA or p-aminobenzoic acid be used rather than the chemical name aminobenzoic acid recommended by the Topical Analgesic Panel at 43 FR 38206 at 38219. The comment stated that the name PABA designates the para position of the amino group to the carboxyl group, that the U.S.P. uses the name PABA, and that other pharmacopeias list the ingredient as a para derivative. The comment contended that this designation distinguishes the para-derivative from the ortho- and meta-amino derivatives of benzoic acid, which is a desirable distinction because the ortho derivative is potentially a photosensitizing agent.

Under section 502(e) of the act (21 U.S.C. 352(e)), any drug, including any sunscreen drug product, is deemed misbranded unless its label bears, to the exclusion of any other nonproprietary name, the established name of the active ingredient, if the active ingredient has an established name. Agency regulations in 21 CFR 299.4(b) relating to official names and established names for drugs provide that the established name of an active ingredient is defined as (1) an official name designated pursuant to section 508 of the act (21 U.S.C. 358); (2) if no such official name has been designated for the active ingredient and the active ingredient is a chemical entity that is recognized in an official compendium, then the established name of the active ingredient will be the name recognized in such compendium; and (3) if neither paragraphs (1) or (2) applies, then the common or usual name for the active ingredient will be the established name.

In the **Federal Register** of September 25, 1984 (49 FR 37575), the agency revoked the existing list of official names of drugs designated by the agency in § 299.20 (21 CFR 299.20) and stated that the agency will not routinely designate official names under section 508 of the act. As stated in paragraph (e) of § 299.4 (21 CFR 299.4(e)), the established name of an active ingredient under section 502(e) of the act will ordinarily be either the compendial name of the active ingredient or, if there is no compendial name, the common and usual name of the active ingredient. Interested persons are advised, in the absence of the designation of an official name, to rely on the nonproprietary name listed in the publication entitled *USAN and the USP Dictionary of Drug Names* (Ref. 1) as the established name for any drug.

As the Panel pointed out, aminobenzoic acid has been the official name for this compound since the publication of the National Formulary XII in 1965 (43 FR 38206 at 38219). Prior to that, the official name was PABA (p-aminobenzoic acid). The Panel noted that this obsolete designation occasionally appears in the published literature (43 FR 38219). Aminobenzoic acid is the name used in U.S.P. XXI for para-aminobenzoic acid (Ref. 2). Therefore, aminobenzoic acid is the established name used by FDA for this ingredient and is the name that must appear in the labeling of sunscreen drug products. The agency does not believe that it is necessary to distinguish the para-derivative from the ortho- and meta-amino derivatives of benzoic acid because, as the Panel pointed out, the ortho and meta isomers have little, if any, use in human therapeutics (43 FR 38219), and these isomers are neither included in this tentative final monograph nor in the U.S.P. Therefore, in § 352.10(a) of this tentative final monograph, the agency is using the name "aminobenzoic acid."

Although padimate A is an established name (Ref. 3), it does not appear in this tentative final monograph because FDA has determined that there are insufficient data to support the safety of this ingredient. The agency is reclassifying padimate A in Category III. (See comment 35.)

Regarding 2-ethylhexyl 2-cyano-3,3-diphenylacrylate, one of the examples of long and confusing ingredient names given by the first comment, the agency notes that the established name for this ingredient is octocrylene (Ref. 4). Therefore, in § 352.10(k) of this tentative final monograph, the agency is proposing the name "octocrylene" in place of the name "2-ethylhexyl 2-cyano-3,3-diphenylacrylate" used by the Topical Analgesic Panel.

The following sunscreen active ingredients listed in § 352.10 of the Panel's recommended monograph do not currently have names established in official compendia or in *USAN and the U.S.P. Dictionary of Drug Names*: (1) Diethanolamine p-methoxycinnamate, (2) ethyl 4[bis(hydroxypropyl)] aminobenzoate, (3) ethylhexyl p-methoxycinnamate, (4) 2-ethylhexyl salicylate, (5) glyceryl aminobenzoate, (6) lawsone with dihydroxyacetone, (7) menthyl anthranilate, (8) 2-phenylbenzimidazole-5-sulfonic acid, and (9) red petrolatum. Several of these ingredients have names that have been used for many years in cosmetic labeling (Ref. 5). The agency believes that these names can be accepted as the common and usual names for these ingredients unless names are established in official compendia or in *USAN and the U.S.P. Dictionary of Drug Names*. Therefore, in this tentative final monograph, the agency is proposing, for these ingredients, that the following names should be accepted as the common or usual names: (1) Diethanolamine methoxycinnamate for diethanolamine p-methoxycinnamate, (2) octyl methoxycinnamate for ethylhexyl p-methoxycinnamate, (3) octyl salicylate for 2-ethylhexyl salicylate, (4) lawsone with dihydroxyacetone, as proposed by the Panel, (5) menthyl anthranilate, as proposed by the Panel, (6) phenyl benzimidazole sulfonic acid for 2-phenylbenzimidazole-5-sulfonic acid, and (7) red petrolatum, as proposed by the Panel.

The names used in cosmetic labeling for ethyl 4[bis(hydroxypropyl)] aminobenzoate and glyceryl aminobenzoate are ethyl dihydroxypropyl PABA and glyceryl PABA, respectively (Ref. 5). As explained above in the discussion of aminobenzoic acid, the use of PABA as part of established names for sunscreen ingredients is obsolete. In correspondence with USAN (Ref. 6), the agency requested USAN names for ethyl 4-[bis(hydroxypropyl)] aminobenzoate and glyceryl aminobenzoate. USAN provided USAN Council Members two names for each ingredient and asked them to select the preferable names (Ref. 7). For ethyl 4-[bis(hydroxypropyl)] aminobenzoate, USAN suggested either ethyl dihydroxypropyl aminobenzoate or roxadimate. For the other ingredient, USAN suggested either glyceryl aminobenzoate or lisadimate. Currently no final decision has been made regarding USAN names for these two ingredients. Therefore, in this tentative final monograph, the agency is using the names recommended by the Panel. When USAN designates new names for these ingredients, the agency will include these new names in the monograph for OTC sunscreen drug products.

References

(1) "USAN and the USP Dictionary of Drug Names," United States Pharmacopeial Convention, Inc., Rockville, MD, 1989.
(2) "United States Pharmacopeia XXI-National Formulary XVI," United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 63, 1989.
(3) "USAN and the USP Dictionary of Drug Names," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 419, 1989.
(4) "USAN and the USP Dictionary of Drug Names," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 494, 1989.
(5) "CTFA Cosmetic Ingredient Handbook, First Edition," The Cosmetic, Toiletry and Fragrance Association, Inc., Washington, pp. 86–87, 1988.
(6) Letter from C. S. Kumkumian, FDA, to D. O. Shiffman, USAN, dated May 25, 1989, OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.
(7) Letters from S. V. Fuerst, USAN, to USAN Council Members, dated August 16, 1989, OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

31. One comment contended that the Panel did not use the appropriate terminology in expressing the UV absorbance values for cinoxate (43 FR 38206 at 38222). The comment stated that absorbance values should be expressed in optical density units or as extinction coefficients, not as a percentage as done by the Panel.

In its discussion of the effectiveness of cinoxate, the Panel made the following statement: "The UV absorbance of cinoxate at 1 percent concentration in isopropyl myristate is less than 10 percent at 270 and 338 nm, but total between 280 to 320 nm with the maximum at 310 nm." (43 FR 38222). The agency has reviewed the data (Ref. 1) and agrees with the comment that the appropriate terminology for expressing absorbance values was not used in this statement. The agency also notes that the maximum wavelength of 310 nm was incorrectly reported; based on the data, the wavelength for maximum absorption should have been 308 nm. In addition, the cited data do not demonstrate total absorbance between 280 and 320 nm; they only demonstrate that the absorbance is nearly total. Therefore, the agency concludes that the relevant data can be summarized with the following statement: "The UV absorbance of cinoxate at 1 percent concentration in isopropyl myristate is nearly total between 280 to 320 nm with the maximum absorbance at 308 nm."

Reference

(1) OTC Vol. 060002.

32. One comment submitted data in support of the safety and effectiveness of 5-(3,3-dimethyl-2-norbornylidene)-3-penten-2-one and requested that it be reclassified from Category III to Category I as an OTC sunscreen drug product ingredient. The data included one effectiveness study and several safety studies, i.e., skin irritation, phototoxicity, photosensitization, acute oral toxicity, and eye irritation tests (Ref. 1).

"Bornelone" is currently the official title for this ingredient in the *USAN and the USP Dictionary of Drug Names* (Ref. 2). The Panel found bornelone safe in the dosage range used as a sunscreen ingredient (43 FR 38257). The agency concurs with the Panel's evaluation and also finds that the additional safety data submitted by the comment further support the Panel's recommendation. The agency has reviewed the efficacy study submitted by the comment and determined that the data are inadequate to support the reclassification of bornelone from Category III to Category I. The test protocol used was deficient because it failed to specify the experimental conditions, i.e., the emittance specifications of the light source, the film thickness of the test material (amount applied per skin area), the distance between the light source and the exposure surface, and the skin types of the test subjects. In addition, the study lacked a control standard sunscreen to validate the experimental data. As a result, the data are insufficient to establish the effectiveness of bornelone as an OTC sunscreen drug ingredient. Based on the data reviewed, the agency is proposing to classify bornelone in Category III for effectiveness as a sunscreen ingredient. The agency's detailed comments and evaluation of the data are on file in the Dockets Management Branch (Ref. 3).

References

(1) Comment No. C00066, Docket No. 78N–0038, Dockets Management Branch.
(2) "USAN and the USP Dictionary of Drug Names," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 82, 1989.
(3) Letter from W. E. Gilbertson, FDA, to E. R. Yuhas, Dragoco, Inc., coded LET016, Docket No. 78N–0038, Dockets Management Branch.

33. One comment questioned the effectiveness of lawsone with dihydroxyacetone against UVA radiation (320 to 400 nm), especially when photoprotection against a photosensitization reaction induced by UVA radiation plus orally administered drugs such as declomycin or psoralen is investigated. The comment stated that the Panel should have investigated photoprotection against drug-induced photosensitivity reactions, which are usually caused by UVA radiation. The comment contended that the Panel should not have approved a claim of photoprotection against UVA radiation until the product is tested and the data are submitted for evaluation and approval. The comment stated that, although people with Skin Types I and II can normally tolerate up to 30 to 40 J/cm² of UVA radiation, if such a person has ingested or applied a photosensitizing agent, he or she may not tolerate 3 to 5 J/cm² of UVA radiation. Contending that in such situations only careful testing can demonstrate whether a product protects against UVA, the comment concluded that a testing procedure for a claim of UVA photoprotection should be included in the Panel's recommendations.

In its discussion of Category I sunscreen ingredients (43 FR 38206 at 38235), the Panel referred to a report (Ref. 1) that the use of lawsone with dihydroxyacetone is effective against both UVB radiation (290–320 nm) and UVA radiation (320–400 nm). In evaluating the effectiveness of Category I sunscreens, the Panel determined whether the individual sunscreen ingredients absorbed UV radiation in the UVB band, the range between 290 and 320 nm (43 FR 38218). This spectrum is most likely to cause sunburn in normal individuals (43 FR 38209). The Panel did not evaluate sunscreen ingredients for protection against photosensitization reactions, which are normally induced by radiation in the UVA band (i.e., 320–400 nm) (Ref. 2). Accordingly, the Panel did not include in § 352.50(b) a claim of photoprotection against UVA radiation for lawsone with dihydroxyacetone or for any other Category I sunscreen drug product. However, as stated in comment 53, the agency believes that claims related to UVA protection are important information for consumers because UVA radiation has been shown to be harmful to the skin in that it contributes to both acute and chronic skin damage. Therefore, the agency is proposing in this tentative final monograph that a product may, in certain circumstances, include UVA protection claims in its labeling. The ingredient(s) used in such products must have an absorption spectrum that extends to 360 nm or above in the UVA range, and the product must demonstrate UVA protection using appropriate testing procedures that the agency is proposing be developed and included in the monograph for OTC sunscreen drug products. (See comments 53 and 73.) Therefore, the combination of lawsone with dihydroxyacetone could display

UVA protection claims if it fulfills the above requirements.

The agency acknowledges that some Category I sunscreen ingredients may protect the user from drug-induced photosensitization reactions caused by UVA radiation (43 FR 38206 at 38235, 38239, 38249, and 38250). However, the agency is aware that numerous chemicals, including ingredients in soaps and perfumes as well as therapeutic drugs, can induce photosensitivity reactions in a person exposed to UVA radiation (Refs. 2 and 3). Furthermore, depending upon the absorption spectrum of the photosensitizing compound, the photosensitivity reaction may be elicited by different wavelengths (Ref. 3). If a sunscreen ingredient does not protect against the appropriate wavelength for a specific ingredient, it will not protect against a photosensitivity reaction to that ingredient. Many variables are involved in the relationship between the photosensitizing chemicals, the UV radiation, and the host, and the consumer is often unaware of these relationships (Ref. 3). Factors related to the chemical include the route of administration, ability to penetrate the skin, formulation, interaction with skin, metabolism and elimination, absorption spectrum, and quantum yield of the parent chemical and its metabolites. The radiation variables include the spectral irradiance of the source, dose and rate of delivery, number and frequency of exposures, the timing of the radiation relative to the presence of the chemical, and optics of the skin. Host factors include thickness and hydration of stratum corneum, melanization of the epidermis, integrity of the skin, and immune status (Ref. 3). Even when a patient reports a skin eruption to a physician, the etiologic role of sunlight may not be immediately apparent to the physician. Therefore, the agency concludes that claims for protection against drug-induced photosensitization reactions induced by UVA radiation should only be made in professional labeling; such information should not be included in labeling directed to the general public. The Panel did not include professional labeling in its proposed monograph, and at present the agency does not have adequate data for developing such labeling in this tentative final monograph. The agency invites comment on this matter and will consider professional labeling for claims of protection against photosensitization reactions in the final monograph for OTC sunscreen drug products, if adequate data are submitted in response to the tentative final monograph. (See comment 69.)

References

(1) "Proposed Physicians Only Professional Literature," draft of unpublished study in OTC Vol. 060069.

(2) Fitzpatrick, et al., "Sunlight and Man," edited by M.A. Pathak et al., University of Tokyo Press, Tokyo, pp. 8–11, 1974.

(3) Parrish, J.A., H.A.D. White, and M.A. Pathak, "Photomedicine," *in* "Dermatology in General Medicine," 2d Ed., edited by T.B. Fitzpatrick, et al., McGraw Hill Book Company, New York, pp. 952, 966, 969, and 977–978, 1979.

34. One comment requested that 3-(4-methylbenzylidene)-camphor be included in the monograph as a Category I sunscreen. The comment stated that it had submitted data (Ref. 1) on this ingredient to the Panel, and, at its fourteenth meeting, the Panel had classified the ingredient in Category III based on a lack of in vivo data to demonstrate effectiveness in man or animals (Ref. 2). The manufacturer submitted additional data that included controlled studies in seventy subjects performed in three independent investigations (Ref. 3). Based on these data, the Panel reclassified 3-(4-methylbenzylidene)-camphor 0.1 to 2.5 percent to Category I at its twenty-first meeting (Ref. 4). The comment explained that it assumed from the minutes of that meeting (Ref. 4) that this classification was settled. The comment stated it was surprised when the advance notice of proposed rulemaking stated that the ingredient 3-(4-methylbenzylidene)-camphor was not generally recognized as safe and effective for OTC use, based on a lack of clinical and marketing data, and the ingredient was classified in Category II (43 FR 38206 at 38255).

The comment stated that 3-(4-methylbenzylidene)-camphor had been marketed in the United States and throughout the world under the trade name Eusolex 6300 since December 1973. The manufacturer also indicated that approximately 350,000 units of an OTC sunscreen product containing 3 percent Eusolex 6300 were sold at retail in the United States during 1974 to 1978 (Ref. 5). The comment provided letters from distributors and manufacturers of OTC sunscreen drug products who used 3-(4-methylbenzylidene)-camphor as a sunfilter in their products. One manufacturer stated that some sunscreen drug products containing 3-(4-methylbenzylidene)-camphor were distributed in Europe as well as marketed in North America under different trademarks.

The comment contended that general recognition of the safety of a product could, in fact, be based in part or in whole upon foreign experience, and that the relevance of foreign experience would depend not upon geography alone, but upon a scientific and medical determination. The comment cited the case of *FMALI Herb, Inc.* v. *Heckler*, 715 F.2d 1385 (9th Cir. 1983) as support for its argument.

The comment subsequently provided additional marketing history information for 3-(4-methylbenzylidene)-camphor (Ref. 6). However, the manufacturer was unable to provide documentation to substantiate the dates of the labeling presented at the meeting. Therefore, the agency concluded that no decision could be made until the manufacturer was able to document the marketing history of 3-(4-methylbenzylidene)-camphor. To date, no new data or information has been submitted to support the reclassification of 3-(4-methylbenzylidene)-camphor from Category II to Category I.

Three similar petitions have requested the agency to reopen the administrative record for this rulemaking to include additional ingredients. One petition (Ref. 7) requests that the agency include the ingredient ethoxylated ethyl-4-aminobenzoate (PEG–25 PABA) as Category I in the monograph for OTC sunscreen drug products. The petition contends that the extensive marketing experience of ethoxylated ethyl-4-aminobenzoate in Europe as an OTC sunscreen ingredient since the early 1950's and the available data supporting the safety and effectiveness of this ingredient satisfy the statutory and regulatory criteria for inclusion of this ingredient in the OTC drug review.

The second petition (Ref. 8) requests that the agency include the ingredient isoamyl-p-methoxycinnamate in Category I. The petition states that isoamyl-p-methoxycinnamate has been marketed in Europe since 1976 and is not a new drug because there is general recognition among experts that the drug is safe and effective for its intended use. The petition contends that the available data for this ingredient conform to the standards for safety and effectiveness set forth in the agency's review of OTC sunscreens.

The third petition (Ref. 9) requests that the agency include the ingredient avobenzone (Parsol 1789), a UVA absorber, in Category I. The petition states that since avobenzone was introduced in 1981, it has been continuously used throughout the world, including Europe, Africa, Asia, Australia, South America, and Canada. The petition noted, however, that the United States is the only country in

which avobenzone is not freely available for use in sunscreen formulations. The petition mentioned that avobenzone is available in the United States in one product, "Photoplex," approved under an NDA. The petition mentioned that avobenzone is the only available sunscreen ingredient that affords broad spectrum UVA protection and that including avobenzone in the monograph for OTC sunscreen drug products would provide United States consumers with broader access to an important UVA sunscreen that is currently available to other consumers around the world.

The agency is currently considering these petitions, but has not yet reached a decision concerning the use of foreign marketing data as the sole basis to support the inclusion of an ingredient in the OTC drug review. The agency's decisions on these petitions will have an impact on any decisions it makes concerning whether 3-(4-methylbenzylidene)-camphor can be included in the OTC drug review unless documentation of the marketing of this ingredient in the United States prior to December 4, 1975 is provided.

The agency has determined that it would not be in the public interest to unduly delay publication of the tentative final monograph for OTC sunscreen drug products while this matter is being resolved. Therefore, at this time the agency is deferring a decision concerning whether any of these ingredients should be considered for inclusion in the OTC sunscreen monograph. A decision will be announced in a future issue of the **Federal Register**.

References

(1) OTC Volumes 060086 and 060090.

(2) Summary Minutes of the 14th Meeting of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Treatment and Prevention Products, October 22–23, 1974, OTC Vol. 060181.

(3) OTC Vol. 060115.

(4) Summary Minutes of the 21st Meeting of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Treatment and Prevention Products, September 30 and October 1, 1975, OTC Vol. 060181.

(5) Comment No. SUP5, Docket No. 78N–0038, Dockets Management Branch.

(6) Memorandum of Meeting between FDA and E. Merck Industries, Inc., Rona Pearl, and Covington and Burling, coded MM1, Docket No. 78N–0038, Dockets Management Branch.

(7) Comment No. CP2, Docket No. 78N–0038, Dockets Management Branch.

(8) Comment No. CP3, Docket No. 78N–0038, Dockets Management Branch.

(9) Comment No. CP4, Docket No. 78N–0038, Dockets Management Branch.

35. Two comments contended that padimate A is phototoxic and is inappropriate for use as a Category I sunscreen ingredient. One comment cited a study by Kaidbey and Kligman (Ref. 1) as evidence that padimate A is phototoxic to humans. The comment strongly urged that padimate A be removed from the list of safe and effective sunscreen active ingredients. The other comment noted that the Panel was apparently unaware, at the time of its deliberations, of subsequently published reports by Kaidbey and Kligman (Ref. 1) and by Emmett, Taphorn, and Kominsky (Ref. 2) which document the phototoxic properties of padimate A. The comment stated that these reports should be fully considered by the Commissioner prior to final categorization of this sunscreen ingredient as safe for use in drug products. The comment concluded it is inappropriate to permit any active ingredient that has been demonstrated to be phototoxic to be used in products intended for use in direct sunlight.

Stating that padimate A is safe at concentrations up to 3 percent, another comment contended that it is an irritant, especially on the face, at the maximum 5-percent concentration recommended by the Panel. Remarking that 5 percent padimate A can be an irritant to 70 percent of users who swim in chlorinated pools, the comment stated that several published studies (not identified in the comment) indicate that 5 percent padimate A causes burning, itching, and contact and photocontact irritation reactions. The comment claimed that many manufacturers have reduced the concentration or discontinued the use of padimate A because of its irritating effect. Noting that the Panel determined that padimate A is a dose-related irritant, the comment stated that a safe concentration needed to be resolved.

A reply comment stated that studies done in its own laboratories, as well as a review of the raw data for the study conducted by Kaidbey and Kligman (Ref. 1) and discussion of that study with the authors, supported its belief that padimate A is not a phototoxic agent in the concentrations in which it is used in sunscreen products. A second reply comment referred to the submitted reports (Refs. 1 and 2) and stated that the ingredient referred to in the Emmett, Taphorn, and Kominsky study is not padimate A, but a mixture of the para and ortho isomers of amyl dimethylaminobenzoate containing a substantial quantity of the ortho isomer. The reply comment explained that padimate A is the para isomer, while the ortho isomer is phototoxic and is not used in sunscreen products. The reply comment submitted a report on a padimate A phototoxicity test on mice and swine by Forbes (Ref. 3) and contended that the test results refute the claim that padimate A is a phototoxic material. The comment added that 12 years of marketing over 250 million packages also support the evidence against phototoxicity.

The Panel classified 1 to 5 percent padimate A in Category I as a sunscreen ingredient. The agency has reviewed the literature submitted by the comments and believes that there is sufficient evidence that padimate A at a 5-percent concentration is a weak phototoxic agent. Further studies are necessary to determine the drug's phototoxic potential at lesser concentrations.

Kaidbey and Kligman (Ref. 1) tested various sunscreen agents to determine their potential for provoking phototoxicity. The test agents included aminobenzoic acid and its esters (glyceryl aminobenzoate, padimate A, padimate O) obtained from a commercial source, and the purified isomeric forms of amyl dimethylaminobenzoate (amyl ortho-dimethylaminobenzoate and amyl paradimethylaminobenzoate (padimate A)). A 5-percent solution of each sunscreen dissolved in 95 percent ethanol was used. Additionally, proprietary sunscreens containing sulisobenzone, aminobenzoic acid, and esters of aminobenzoic acid (identified above) were tested. The number of subjects varied between 8 and 17 per test agent. Each preparation was applied to the subjects' backs and covered with patches of nonwoven cotton cloth. Six hours later the sites were uncovered and irradiated with UVA and visible light. Responses were evaluated 24 hours later.

In the tests comparing aminobenzoic acid and its esters, only sites treated with padimate A (5 percent) exhibited phototoxicity after exposure to 30 J/cm^2 of UVA radiation over a period of 14 minutes; 12 out of 17 subjects experienced reactions. In the tests comparing ortho and para isomers of amyl dimethylaminobenzoate, in which subjects were exposed to 15 J/cm^2 of UVA radiation over a period of 7 minutes, the ortho isomer was a far more potent photosensitizer with 10 out of 10 positive responders; the para isomer (padimate A) produced 2 out of 10 positive responders. In the tests comparing proprietary sunscreens containing sulisobenzone, aminobenzoic acid, and esters of aminobenzoic acid, in which subjects were exposed to 30 J/cm^2 of UVA radiation over a period of 14 minutes,

only products containing padimate A exhibited a phototoxic reaction. In this test, 4 out of 9 subjects responded positively to one product containing padimate A alone; 9 out of 13 subjects responded positively to another product containing padimate A alone; and 6 out of 10 subjects responded positively to a product containing a combination of aminobenzoic acid and padimate A. Products containing aminobenzoic acid alone, padimate O alone, glyceryl aminobenzoic acid alone, and sulisobenzone alone did not cause a positive response.

The solar simulator used in the study by Kaidbey and Kligman (Ref. 1) did not emit a spectrum with the same proportions of UVA, visible, and infrared radiation as present in natural sunlight. The wavelength range of most importance when considering the question of phototoxicity is the UVA range. The UVA radiation emitted by the light source used in these studies is sufficiently comparable to natural UVA to make the use of this source valid. The amount of UVA used was approximately 30 J/cm^2, which is a very large amount, equal to several hours of UVA from sunlight on a sunny summer day in the northeastern U.S., and approaches the MED for UVA in some light-skinned individuals (43 FR 38206 at 38209). This dose, however, did not elicit erythema in the sites used as controls or in the sites to which other sunscreen agents had been applied.

In the Kaidbey and Kligman study (Ref. 1), the test materials were applied and occluded for 6 hours prior to radiation exposure. Occlusion enhances penetration and would tend to maximize the responsiveness to the applied agent. In practice, sunscreen products are rarely occluded; therefore, the phototoxicity resulting from occlusive test methods may be more severe than that obtained during normal use patterns. However, the Kaidbey and Kligman study shows that it is possible to elicit human cutaneous phototoxicity with 5 percent padimate A at UVA doses that may be encountered by individuals during prolonged, intense sunlight exposure. Therefore, the agency believes that this study does indicate that 5 percent padimate A is a phototoxic agent, although a weak one.

The Emmett, Taphorn, and Kominsky study (Ref. 2) used mixed para and ortho isomers of amyl dimethylaminobenzoate, as stated by the second reply comment. However, the investigators also tested the phototoxicity of the amyl paradimethylaminobenzoate isomer, which is known as padimate A. In this study, an in vitro test of padimate A using Ehrlich ascites cells showed phototoxicity. In the human photopatch testing, patches containing the test agents were applied to the skin of four normal subjects (i.e., subjects free of photosensitivity) for 24 hours. Subsequently, the subjects were exposed to clear noonday sunlight for 30 minutes. The reactions observed 24 hours later showed that the mixed ortho and para isomers of amyl dimethylaminobenzoate resulted in a phototoxic response (marked erythema and/or erythema with edema) in three of four subjects, and one subject experienced mild erythema in reaction to the purified amyl dimethylaminobenzoate. The authors concluded that the phototoxic reaction on human skin with pure amyl para-dimethylaminobenzoate was less marked than with the mixed isomer preparations, suggesting that ortho isomers may be the most important phototoxic agents.

The testing of mice and swine by Forbes (Ref. 3) showed that padimate A was not phototoxic to those animals. However, the agency does not believe that the Forbes study demonstrates that padimate A is not a phototoxic agent at concentrations and light exposures that may be encountered by humans using padimate A in the concentrations recommended by the Panel. From the information submitted, it is not possible to determine what concentrations of the active ingredients were applied to the mice and swine used in these experiments. The dose of UVA radiation used (36×10^3 J/M^2=3.6 J/cm^2) is much less than that used in the Kaidbey and Kligman study (Ref. 1). Also, it is not easy to quantitatively relate dose/response from animal models to human skin, except in a general sense.

The weight of these studies suggests that padimate A is phototoxic in humans at concentrations in the 5-percent range if sufficient UVA exposure occurs, particularly if the test is maximized by occlusive techniques. However, lesser concentrations and/or lesser UVA exposures may not produce sufficient damage to be appreciable at a clinical threshold. There is no evidence to indicate that phototoxicity is truly absent at any specific concentration, because an increased UVA dose may be able to elicit such reactions. For example, if 5 percent padimate A and a 5– to 10–J/cm^2 UVA dose produces no visible reaction, but 5 percent padimate A and a 30–J/cm^2 UVA dose produces visible phototoxicity, will 3 percent padimate A and a 40–J/cm^2 UVA dose be phototoxic? Although these higher doses of UVA approach the minimal erythemal dose for UVA in some individuals, one can conceive of circumstances in which individuals could encounter such levels from natural sunlight (e.g., lifeguards, equatorial vacationers, etc.).

From the information available, the agency cannot determine a "safe" level of padimate A. The agency believes the available evidence shows that 5 percent padimate A is a weak phototoxic agent. Large but obtainable doses of UVA in human subjects are required in order to elicit clinically-evident effects from padimate A, particularly if maximization factors are present (such as occlusion, multiple applications during sunbathing, or hydration of skin after bathing but before application). The agency is not aware of any padimate A phototoxicity studies more recent than the 1978 Kaidbey and Kligman study (Refs. 1 and 4). Furthermore, the agency has been informed that manufacturers in the U.S. no longer use padimate A in sunscreen drug products and that the ingredient has been banned from use by the European Economic Community (Ref. 5).

Therefore, in this tentative final monograph, the agency is classifying padimate A at 5 percent and higher concentrations in Category II and in concentrations less than 5 percent in Category III. Further studies are required to determine the phototoxic potential of padimate A at less than 5 percent concentrations. Human studies should be designed to test these lower concentrations, using maximization as well as "normal use" procedures. The Kaidbey and Kligman study (Ref. 1) can be used as a suitable model of a maximization study. Reproducibly negative tests done with a statistically sufficient number of light-skinned individuals would tend to indicate levels of padimate A that would be "safe," as defined by a lack of clinically observable toxicity. The agency's detailed comments on the data are on file in the Dockets Management Branch (Ref. 6).

References

(1) Kaidbey, K.H., and A.M. Kligman, "Phototoxicity to a Sunscreen Ingredient, Padimate A," *Archives of Dermatology*, 114:547–549, 1978.

(2) Emmett, E.A., B.R. Taphorn, and J.R. Kominsky, "Phototoxicity Occurring During the Manufacture of Ultraviolet-Cured Ink," *Archives of Dermatology*, 113:770–775, 1977.

(3) Forbes, P.D., "Phototoxicity Test," unpublished report in C00058, Docket No. 78N–0038, Dockets Management Branch.

(4) Memorandum of telephone conversation between J. Rippere, FDA, and K. Kaidbey, Ivy Laboratories, dated May 6, 1988, OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

(5) Memorandum of telephone conversation between J. Rippere, FDA, and M. Gardner, The Cosmetic, Toiletry and Fragrance Association, dated March 3, 1989, OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

(6) Letters from W.E. Gilbertson, FDA, to J.M. Clayton, Plough, Inc.; Howard Iserman, Van Dyk & Company, Inc.; and A.M. Kligman and K.H. Kaidbey, University of Pennsylvania, coded LET026, LET027, and LET028, respectively, Docket No. 78N–0038, Dockets Management Branch.

36. One comment noted that zinc oxide had been present in earlier lists of sunscreen ingredients, but was not included in the final list of active sunscreen ingredients recommended by the Panel in § 352.10. Stating that zinc oxide ointments and creams have a long history of use as a sunblock, as well as a skin protectant, the comment requested that the original data on the drug be reviewed and that zinc oxide be listed as a sunscreen active ingredient in the monograph.

FDA listed zinc oxide as an active sunscreen ingredient in its request for data on OTC topical analgesic drug products, which included antirheumatic, otic, burn, sunburn prevention and treatment drug products (37 FR 26456). Zinc oxide was a labeled ingredient in marketed products submitted for review to the Panel (Refs. 1 through 4). The Panel that reviewed these drug products evaluated both sunscreen and skin protectant drug products. After reviewing the submitted data, the Panel classified zinc oxide at concentrations of 1 to 25 percent as a Category I skin protectant (43 FR 34628 at 34648). Although zinc oxide was a labeled ingredient in a marketed sunscreen product (Ref. 3), the Panel classified zinc oxide as an inactive ingredient in the advance notice of proposed rulemaking for OTC sunscreen drug products (43 FR 38206 at 38208).

The comment did not present any data or information to support the use of zinc oxide as a sunblock, i.e., sunscreen opaque sunblock ingredient. The agency has reviewed the data in a study by Luckiesh et al. (Ref. 5), which had been submitted to the Panel (Ref. 3), in which zinc oxide was used alone and in combination with phenyl salicylate, another sunscreen ingredient. The study was designed to measure the ability of zinc oxide at concentration levels from 15 to 33.3 percent, as well as other ingredients, to absorb UV radiation over a broad range of wavelengths. Zinc oxide (33.3 percent) was the only test preparation that was studied as a single ingredient.

All subjects in the study developed skin erythema after 15 seconds of exposure to a lamp that was a source of UV radiation intensity equivalent to sixty times the most intense sunlight measured in Cleveland, Ohio over a 4-year period. One minute exposure to the lamp was determined to be equivalent to 1 hour of exposure to that sunlight. The subjects were then treated on the upper arm with a thin coating of the various sunscreen test preparations. A thin coating was defined as one which was rubbed out quite well, corresponding to the thinnest coating which is likely to be applied on the skin. The sunscreen properties of zinc oxide at 33.3 percent in white petrolatum were tested in only one subject. Although the test product demonstrated sunscreen properties, results from one subject alone are insufficient to support effectiveness of this ingredient as a sunblock.

Using a thin-film spectrophotometric method, Luckiesh et al. (Ref. 5) recorded the UV radiation transmitted by the test ingredients at wavelengths from 296.7 to 365 nm. The study revealed that with a 0.03 millimeter (mm) thickness coat of 33.3 percent zinc oxide in combination with 10 percent phenyl salicylate in white petrolatum there was zero transmission of UV energy at various wavelengths between 296.7 and 313 nm, and 0.8 and 3 percent transmission at 334.2 and 365 nm, respectively. When the concentration of zinc oxide was reduced to 15 percent in a combination product with 10 percent phenyl salicylate, the UV energy transmission of the 0.03 mm coat was then 0.02, 0.04, 0.1, 6, and 44 percent at 296.7, 302.2, 313, 334.2, and 365 nm, respectively. When the coat of this test preparation was increased to 0.06 mm there was zero transmission of UV energy at the four lower wavelengths (296.7 to 334.2 nm) and 0.3 percent at 365 nm. With a 0.03 mm coat of a 33.3 percent zinc oxide in white petrolatum test preparation, there was 2.2, 3.0, 5, 7.8, and 8.5 percent transmission of UV energy at wavelengths 296.7, 302.2, 313, 334.2, and 365 nm, respectively. When the coat of zinc oxide was increased to 0.06mm, the UV energy transmission was reduced to 0.18, 0.3, 0.75, 2.2, and 2.4 percent at the respective wavelengths. The investigators concluded from this study that "Undoubtedly, zinc oxide is not to be ignored as an ultraviolet light filter," and "zinc oxide is of definite value in preventing sunburn."

The agency recognizes that the range of UV radiation absorbance reported in this limited study is similar to the UV radiation range reported for other sunscreen products reviewed by the Panel. The agency is aware that for many years zinc oxide has been used by consumers as a sunblock (Refs. 6 through 10). However, the agency concludes that the data submitted on zinc oxide to this rulemaking are insufficient to support its effectiveness as a Category I sunscreen as a sunblock because the effectiveness data for this ingredient when used alone are limited to one subject. Studies to demonstrate the effectiveness of zinc oxide as a Category I sunscreen should follow the requirements of the testing procedures in Subpart D of this tentative final monograph.

Therefore, because the available data are insufficient to demonstrate the effectiveness of zinc oxide as a sunscreen active ingredient, the agency is proposing to classify zinc oxide in Category III.

References

(1) OTC Vol. 060007.
(2) OTC Vol. 060137.
(3) OTC Vol. 060154.
(4) OTC Vol. 060001.
(5) Luckiesh, M., et al., "Protective Skin Coatings for the Prevention of Sunburn," *Journal of the American Medical Association*, 130:1–6, 1946.
(6) Harber, L. C., "Photosensitivity and Sunburn," *in* "Current Therapy," edited by H. F. Conn, W. B. Saunders Co., Philadelphia and London, pp. 571–572, 1968.
(7) Wilkinson, D. S., "Treatment," *in* "Textbook of Dermatology," edited by A. Rook, D. S. Wilkinson, and F. J. G. Ebling, F. A. Davis Co., Philadelphia, pp. 1810 and 1820, 1968.
(8) Arndt, K. A., "Manual of Dermatologic Therapeutics with Essentials of Diagnosis," Little, Brown, and Co., Boston, p. 329, 1978.
(9) "Drug Evaluations," 6th Ed., American Medical Association, Chicago, pp. 1025–1026, 1986.
(10) Lysne, J. M., "Prevention and Treatment of Sunburn," insert from *Drug Store News*, (4) 1956, OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

D. Comments on Dosages for Sunscreen Drug Products

37. One comment contended that the minimum dosage requirement for sunscreen active ingredients in § 352.10 is unnecessary and should be deleted. The comment proposed that a manufacturer be permitted to use an ingredient at any lower concentration which provides an SPF of at least 2. The comment provided an example where a manufacturer may wish to combine two or more active sunscreen ingredients in a formulation that would provide an acceptable SPF value of 2, but would be unable to do so because using the minimum allowable concentrations of the active ingredients would result in a preparation with an SPF value greater than 2. The comment added that such

a restriction would be arbitrary and not in the best interest of the consumer.

A second comment also questioned the necessity of the lower dosage limits because all sunscreen products must be tested for effectiveness. The comment pointed out that the recommended lower dosage limits would not allow 1 percent aminobenzoic acid preparations even though the products may show an SPF value well above the minimal requirement (Ref. 1). The comment concluded that if the product is effective, then the dosage is not low.

Another comment recommended that the concentration range for aminobenzoic acid in the Panel's monograph be changed from a range of 5 to 15 percent to a range of 2 to 15 percent or that the lower limit be eliminated. The comment asserted that although the Panel stated that 2 percent aminobenzoic acid has been found to be an effective sunscreen (43 FR 38206 at 38221), it set the minimum concentration of aminobenzoic acid at 5 percent for any sunscreen product. The comment stated that the effectiveness of aminobenzoic acid as a sunscreen is dependent on the vehicle used and not just on the concentration of the active ingredient. As an example, the comment stated that aminobenzoic acid is less effective in certain creams or oils even if the product contains 20 percent aminobenzoic acid. The comment added that the range of concentrations given in § 352.10 of the Panel's monograph does not ensure effectiveness, but that determination of SPF values for individual products will ensure effectiveness.

A reply comment supported the position that the effectiveness of sunscreen products, not the amount of sunscreen in the products, is the standard by which performance efficacy is measured. The comment recommended that the minimum dosage requirement be deleted because it will not affect product safety or efficacy.

Two comments, submitted in response to the public meeting held on January 26, 1988, to discuss appropriate sunscreen testing methods, also requested that no minimum dosages be required for sunscreen ingredients. These comments urged FDA in determining effectiveness to rely solely on the product's performance as established by appropriate SPF testing. One comment stated that the requirement to meet a minimum dosage level can have an impact on formula flexibility and safety and is not scientifically sound because a specific product's performance is dependent upon the formulation rather than simply on the amount of active ingredient. Stating that the SPF value is a better and more accurate measure of the effectiveness of a sunscreen drug product, the comment recommended that §§ 352.10 and 352.20 be amended to eliminate the lower dosage range for each of the listed active sunscreen ingredients.

The Panel recommended minimum concentrations for all Category I sunscreen ingredients based on effectiveness data submitted for its review. The agency, however, agrees with the comments that a sunscreen active ingredient's performance is not totally dependent upon the concentration of the active ingredient in the product. Because the formulation of a sunscreen drug product influences the effectiveness of the active ingredient in the product, the Panel recommended final product testing of each formulation to determine the SPF and to assure proper use (43 FR 38206 at 38213). The agency is aware that the presence of a required minimum amount of a sunscreen ingredient in a drug product does not guarantee effectiveness; final product testing can ensure effectiveness. Therefore, the agency agrees with the comments that the effectiveness requirements, i.e., the determination of an SPF value for a sunscreen product, make the use of minimum concentration requirements unnecessary for single ingredient products.

However, the agency is concerned that each ingredient in a sunscreen combination product contributes to the overall effectiveness of the product. To require no minimum contribution at all could allow the use of amounts so small as to be misleading and deceptive to the consumer and could permit the inclusion of ingredients solely for promotional purposes. In addition, this could result in the consumer's exposure to an additional ingredient or ingredients with minimal additional benefit being provided. The agency believes that a minimum amount of each sunscreen ingredient should be present in a combination sunscreen product. The agency has looked for similar situations in other OTC drug monographs and notes that OTC antacid ingredients have no minimum dose stated for the individual ingredients in the final monograph. (See 21 CFR 331.11.) One or more antacid active ingredients may be combined within any maximum daily dosage limit established provided each ingredient is included at a level that contributes at least 25 percent of the total acid neutralizing capacity of the product. The antacid monograph also provides a test for determining the percent contribution of an antacid ingredient in the combination product. (See 21 CFR 331.21.) The agency believes that sunscreen manufacturers who wish to market a combination sunscreen product should be required to determine that each ingredient in the sunscreen combination contributes in some way to the effectiveness of the product, e.g., that the combination of ingredients produces a higher SPF value than any of the ingredients alone used at monograph concentrations in a single ingredient product or that the combination product protects against a wider range of UV radiation than any of the ingredients alone. Such a requirement is consistent with Part 3 of the agency's "General Guidelines for OTC Combination Products," which states: "Category I active ingredients from the same therapeutic category that have the same mechanism of action * * * may be combined in selected circumstances * * * if the combination meets the OTC combination policy in all respects, the combination offers some advantage over the active ingredients used alone, and the combination is, on a benefit-risk basis, equal to or better than each of the active ingredients used alone at its therapeutic dose" (Ref. 2).

Because the agency agrees with the deletion of the minimum strength requirements for sunscreen ingredients, only maximum concentrations for individual active ingredients are being proposed in § 352.10. However, because of its concern that each ingredient in a combination drug product contributes to the overall effectiveness of the product, the agency concludes that a method must be developed that demonstrates the contribution of each ingredient in a combination sunscreen product before the minimum doses for sunscreen ingredients in combination can be deleted from the monograph. At this time, the agency is unaware of any existing method for determining the contribution of each sunscreen ingredient in a combination sunscreen product. Therefore, although the agency is not including minimum doses for individual sunscreens in proposed § 352.10, it is including minimum doses for sunscreens used in combination with one another in § 352.20(d). The agency invites manufacturers and sunscreen testing laboratories to comment on this matter and to propose an appropriate test method for determining the contribution of each sunscreen ingredient in a combination sunscreen product.

References

(1) Willis, I., and A.M. Kligman, "Aminobenzoic Acid and Its Esters: The

Quest for More Effective Sunscreens," *Archives of Dermatology*, 102:405–417, 1970.

(2) Food and Drug Administration, "General Guidelines for OTC Combination Products," September 1978, Docket No. 78D–0322, Dockets Management Branch.

38. One comment stated that the dosage limits for sunscreen active ingredients in the Panel's recommended monograph do not provide protection from ineffective products. The comment explained that the vehicle can have a tremendous effect on product efficacy and that some of the approved sunscreens are used primarily in combinations because they are not sufficiently effective when used alone in the currently recommended lower dosage.

The agency concludes that the lower dosage limits recommended by the Panel for sunscreen active ingredients are effective when properly formulated in a product that provides an SPF of at least 2. As the Panel pointed out, the effectiveness of all Category I sunscreens has been demonstrated by appropriate studies. The UV absorbance of the individual sunscreen between 290 and 320 nm was established and, in most instances, data were available from studies on human subjects treated either with artificial sunlight or with natural sunlight (43 FR 38206 at 38218).

The agency agrees that the vehicle can have a significant effect on the product's effectiveness. However, the influence of the vehicle on the effectiveness of a sunscreen drug product is accounted for in the SPF testing procedure because the test is done on the final formulation of a sunscreen product. As provided in § 352.10, a final sunscreen drug product must have an SPF value of not less than 2. Any product that can demonstrate that it meets the labeled SPF value is considered to be effective.

E. General Comments on Labeling for Sunscreen Drug Products

39. One comment contended that FDA does not have the authority to legislate the exact wording of OTC labeling claims. The comment objected to the agency limiting the labeling claims to the exact terminology of the monograph and rejecting all other terminology, regardless of accuracy. The comment requested that more flexibility in labeling be permitted by adding to the approved indications a statement as follows: "* * * or similar indication statements which are in keeping with the Panel's report."

In the **Federal Register** of May 1, 1986 (51 FR 16258), the agency published a final rule changing its labeling policy for stating the indications for use of OTC drug products. Under 21 CFR 330.1(c)(2), the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either (1) the specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "APPROVED USES"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "APPROVED USES"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "APPROVED USES," plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All other OTC drug labeling required by a monograph or other regulation (e.g., statement of identity, warnings, and other regulations (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under the OTC drug monograph or other regulation where exact language has been established and identified by quotation marks, e.g., 21 CFR 201.63 or 330.1(g). The proposed rule in this document is subject to the labeling provisions in § 330.1(c)(2); the wording in § 352.52 is consistent with these regulations.

40. A number of comments requested that the labeling of sunscreen products contain more information for using these products. The requests included the following: information on the effectiveness of sunscreens when used for different skin types, or on different parts of the body, or with moisturizers, makeup, or cola drinks, or when used in water, chlorine, or sea spray; more information concerning safe and effective use; labeling which would permit consumers to choose a sunscreen product appropriate for their skin sensitivity; and labeling products with the names and percentage composition of ingredients.

The Panel considered some of the above factors in making its labeling recommendations, e.g., use in water and skin type. The Panel recommended labeling concerning a sunscreen's resistance to its removal by water, i.e., sweat resistance, water resistance, and waterproof properties (43 FR 38206 at 38268). The Panel also recommended that the labeling contain a guide that relates skin types and product category designations to the type of sunscreen product needed for protection (43 FR 38269). The agency agrees that the labeling for sunscreen products should contain such information to aid consumers in choosing the most suitable sunscreen for their needs. Therefore, the agency is proposing these labeling recommendations. The Panel did not discuss the impact of all the factors mentioned by the comments that may interfere with a sunscreen's effectiveness; factors such as beverages ingested, sea spray, and chlorine were among those not considered. The agency is only proposing those factors in the Panel's recommended labeling that directly relate to the safe and effective use of sunscreen drug products. The agency recognizes that information about other factors may be useful in product selection. However, the agency does not believe that it is practical or necessary to include all of these possible factors in the monograph. Statements and terms outside the scope of the monograph may be included elsewhere in the labeling, provided they are not false or misleading. Such statements or terms will be evaluated by the agency on a product-by-product basis, under the provision of section 502 of the act (21 U.S.C. 352) relating to labeling that is false or misleading. Even though it is truthful and not misleading, any statement or term that is outside the scope of the monograph may not appear in any portion of the labeling required by the monograph and may not detract from such required information.

Other OTC advisory review panels have recommended, as did the Topical Analgesic Panel, that manufacturers list all inactive ingredients in the labeling of OTC drug products. However, the act does not require the identification of all inactive ingredients in the labeling of OTC drug products.

The act specifies the requirements for ingredient labeling of OTC drug products. Section 502(e) of the act (21 U.S.C. 352(e)) requires that all active ingredients and certain other ingredients, whether included as active or inactive, be disclosed in the labeling. The act also limits the requirement for stating quantity of ingredients in OTC drug products to those specifically mentioned in section 502(e). Although the act does not provide for full labeling of ingredients, as requested by the comment, the SPF value of a sunscreen drug product does provide a quantification of the protection afforded by the active ingredient(s).

Although the act does not require the disclosure of all inactive ingredients in the labeling of OTC drug products, the agency agrees with the Panel that listing of inactive ingredients in OTC drug product labeling would be in the public interest. Consumers with known allergies or intolerances to certain ingredients would then be able to

identify substances that they may wish to avoid.

The NDMA (formerly "The Proprietary Association"), the trade association that represents approximately 85 OTC drug manufacturers who reportedly market between 90 and 95 percent of the volume of all OTC drug products sold in the United States, has announced that its member companies would voluntarily begin to list inactive ingredients in the labeling of OTC drug products under guidelines established by the Association (Ref. 1). Under another voluntary program begun in 1974, the member companies of NDMA have been including the quantities of active ingredients on OTC drug labels. The agency commends these voluntary efforts and urges all other OTC drug manufacturers to voluntarily label their products in accordance with NDMA's guidelines.

Reference

(1) "Voluntary Codes and Guidelines of the OTC Medicines Industry," Nonprescription Drug Manufacturers Association, Washington, DC, pp. 18 and 19, copy included in OTC Vol. 06ATFM, Docket No. 78N-0038, Dockets Management Branch.

41. One comment contended that a package insert is essential for OTC sunscreen drug products. The comment stated that because uncontrolled exposure to the sun leads to premature aging of the skin and skin cancer, all sunscreen drug products should have "danger signs" about solar radiation and artificial UV light sources, instructions for regular use of sunscreens, and guidelines to create public awareness about the ways to prevent the effects of the sun's damaging rays. The comment felt that substantial information about solar radiation and UV radiation should be provided to consumers and that precautions such as the following should be included in a package insert for sunscreen drug products: "apply sunscreens uniformly and liberally before every sun exposure," "reapply after swimming or perspiration," "wear * * * lightly [tightly] woven clothing," "protect the eyes with ultraviolet opaque sun goggles," "beware of reflective surfaces (sand, snow, water, etc.)", "use sunscreens even on cloudy or hazy days," "avoid tanning parlors." The comment added that OTC drugs such as aspirin, antihistamines, nasal decongestants, and antifungal agents have package inserts. A second comment opposed the requirement of a package insert because it would single out sunscreens as the only OTC drugs requiring this extraordinary labeling.

The agency agrees that educating the public about the dangers of excessive sun or UV radiation exposure is important. However, a number of the items that the comment suggested for inclusion in a package insert, while useful, go beyond the necessary information required for the safe and effective use of these drug products. Examples include the statements about wearing certain types of clothing and avoiding tanning parlors. After evaluating the comment's other suggestions for information to be contained in a package insert, the agency believes that the labeling proposed in this tentative final monograph addresses many of these items and it is not necessary specifically to require a package insert for these products. One example is the "alert" statement being proposed in this document, which states: "SUN ALERT: The sun causes skin damage. Regular use of sunscreens over the years may reduce the chance of skin damage, some types of skin cancer, and other harmful effects due to the sun." (See comment 56.) A statement similar to this currently appears in the labeling of many marketed sunscreen drug products. In addition, the directions for use being proposed in this tentative final monograph advise the consumer to apply the sunscreen liberally, generously, smoothly, or evenly before exposure to the sun and after swimming, excessive sweating, or towel drying. (See comment 66.)

The agency encourages manufacturers to provide consumers useful information and does not oppose the inclusion of a package insert containing additional information. As noted in comment 40, other statements may be included in labeling provided they are not false or misleading.

Although package inserts are not essential for OTC sunscreen drug products, there may be cases where it is necessary for the manufacturer to use a package insert or other mechanism to provide the required monograph labeling for an OTC drug product. For example, when an OTC drug product is packaged in a container that is too small to contain the required labeling, it should be enclosed in a carton or be accompanied by a package insert that provides the labeling required by the monograph. This type of packaging is likely to be necessary for sunscreen drug products marketed specifically for application to the lips or nose.

42. One comment stated that the labeling requirements for sunscreen drug products do not include provisions for small packages, and that alternatives should be developed because all of the required statements will not fit on small packages. A reply comment added that sunscreen-containing products are often marketed in sizes too small to accommodate the full product performance statement (recommended by the Panel in § 352.50(e)) on the principal display panel. This comment objected to the Panel's requirement that product performance statements be placed on the principal display panel, arguing that these statements are quite long and that it is repetitious to require them in addition to the indications in § 352.50(b). The reply comment suggested that the information on the principal display panel be limited to the product's PCD and SPF designations, e.g., "extra protection-SPF 6," with the remainder of the performance statement permitted to appear elsewhere in labeling.

The agency has reviewed the Panel's recommended labeling and, wherever possible, has revised and clarified the labeling so that only essential information is required. The product performance statements proposed in this tentative final monograph (§ 352.52(e)) cover the following four areas: (1) a statement of the PCD, e.g., "Minimal Sun Protection Product," (2) a statement of the product's resistance to removal by sweat or water, e.g., "sweat resistant," (3) a compilation of skin types and recommended PCD's, e.g., "Rarely burns; tans profusely * * * Minimal," and (4) a statement for sunscreens that contain an opaque sunscreen, i.e., "Sunblock." The agency concludes that the labeling information in § 352.52 (e)(1), (e)(2), (e)(3), and (e)(5) is useful but not essential; therefore, the agency is proposing that this information be optional and may be used in labeling if a manufacturer wishes. The information in § 352.52(e)(4) is essential and must be displayed on a sunscreen drug product, but it does not need to be on the principal display panel of the product. The indications in § 352.52(b)(1) include a series of statements concerning sunburn and protection from the harmful effects of the sun. The manufacturer must use any one or more of these indications in the labeling of sunscreen drug products. The indications in § 352.52(b)(2) are "Additional Indications" that are optional statements which may be used on a sunscreen drug product in addition to any of the statements in § 352.52(b)(1).

The agency does not consider the proposed product performance statements in § 352.52(e) to be repetitions of the required indications in § 352.52 (b)(1) and (b)(2). The proposed

indications in § 352.52 (b)(1) and (b)(2) provide the consumer with a variety of indications. The product performance statements in § 352.52(e) include information on the product's water resistance capability and a compilation of skin types and PCD's; the indications do not include similar information.

The Panel concluded that informative labeling should be provided to consumers to aid in the selection of the most appropriate sunscreen product. The Panel recommended that such labeling be placed on the principal display panel of a product where it is most likely to be read. The agency is proposing labeling for the principal display panel of sunscreen drug products in § 352.50 of this tentative final monograph that includes SPF values and water resistance information. PCD information is not required to be placed on the principal display panel. (See comments 45 and 51.)

The labeling provisions in part 201 (e.g., §§ 201.10(i), 201.15, 201.60, 201.61, and 201.62) address various requirements for labeling drugs including drugs packaged in containers too small to accommodate a label with sufficient space to bear all the information required for compliance with various regulations. In those instances where an OTC sunscreen drug product is packaged in a container that is too small or otherwise unable to include all of the required labeling, the product can be enclosed in a carton or be accompanied by a package insert that contains the information complying with the monograph. Manufacturers are also encouraged to print a statement on the product container label, carton, or package insert suggesting that the consumer retain the carton or package insert for complete information about the use of the product when all the required labeling does not appear on the product container label. However, the principal display panel must contain certain information, e.g., statement of identity (§ 201.61) and SPF and water resistance information (proposed § 352.50).

The NDMA has recently promulgated guidelines for industry to consider when examining product labels for readability and legibility (Ref. 1). These guidelines are designed to assist manufacturers in making the labels of OTC drug products as legible as possible. The agency commends this voluntary effort and urges all OTC drug manufacturers to examine their product labels for legibility.

Reference

(1) "Label Readability Guidelines," The Nonprescription Drug Manufacturers Association, Washington, copy included in OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

43. Two comments objected to the Panel's list of skin types (43 FR 38206 at 38213) and to the recommended labeling of sunscreen products according to these skin types. Another comment requested that the Roman numeral designation for skin types be replaced by Arabic numbers. One of the comments suggested that the numbering of skin types should relate directly to the numbered grades of sunscreen protection, i.e., the most sensitive skin, Type I, requiring the "number 1" or highest protection sunscreen and that the skin type list should be shortened so that the information could be presented in large print on the sunscreen label. The comment also felt that skin type VI ("Never burns; deeply pigmented (insensitive)") is unnecessary and offered the following list for sunscreen labeling:

"I for those who burn easily and never tan. Grades 1–2 sunscreen."

"II for those who burn easily and tan minimally. Use grades 3–4."

"III for those who burn when first exposed and tan gradually. Use grades 5–6. etc. for the rest."

Stating that the SPF is more useful for the research and development of sunscreen products than for the labeling of sunscreen products, another comment argued that the consumer would be confused when confronted with a choice of five protection levels and five skin types on a sunscreen label. The comment suggested that skin types be classified in relation to a standardized sunscreen formulation (e.g., the formulation given at 43 FR 38259) as follows:

Very Sensitive Skin—Skin that needs more protection than that provided by the standardized sunscreen formula.

Moderately Pigmented—Skin burns moderately during the first exposures to sun (before skin becomes tan); after tan, skin doesn't burn unless exposed to very intense sun.

Insensitive Skin—Rarely or never burns.

In this suggested system, the protection afforded by each sunscreen product would also be in reference to the standard formulation, e.g., a product offering twice the protection of the standard formulation would be labeled 2X standard. The comment felt that this approach would provide the consumer with a better method for choosing a sunscreen as well as a measure of a sunscreen product's bioequivalence to a well-studied standard formulation.

The agency notes that the Roman numeral designation of skin types found objectionable by some comments is not included in the Panel's recommendations for sunscreen labeling. These skin type designations were only included in the Panel's report (43 FR 38206 at 38213) for completeness of information as part of a table which relates skin types to recommended sunscreen products. The Roman numeral skin type designations are also found in the selection of test subjects under the general testing procedures (43 FR 38265). The Panel did recommend that information on skin types and PCD statements be included in sunscreen labeling as a guide to the consumer (43 FR 38214). The agency agrees with the Panel that such information aids the consumer in choosing an appropriate product. However, in this tentative final monograph, the agency is proposing that PCD labeling be optional, and therefore, PCD labeling might not be included in the labeling of all products. (See comment 44.) The agency is proposing that an SPF value be displayed on the principal display panel of all sunscreen drug products. (See comment 45.) The agency has determined that the product guide recommended by the Panel would be more useful in aiding consumers to choose an appropriate product if the guide included SPF ranges rather than PCD categories. Furthermore, the agency is proposing to replace the Panel's recommended word "never" in "always burns easily; never tans" with the word "rarely" because "never" is an absolute term, and such an absolute condition is unlikely to be fulfilled. In addition, the agency is adjusting the proposed SPF ranges to more accurately reflect the protection potential of currently marketed sunscreen drug products and the amount of protection needed by the various skin types.

The agency believes that the information in the product guide should be presented in a manner that catches consumers' attention and allows them to quickly ascertain which type of product is appropriate for their skin types. Therefore, the agency is proposing in § 352.52(e)(4) that the following recommended Sunscreen Product Guide appear in the labeling of all sunscreen drug products:

RECOMMENDED SUNSCREEN PRODUCT GUIDE

Sunburn and tanning history	Recommended sun protection product
Always burns easily; rarely tans.	SPF 20 to 30.
Always burns easily; tans minimally.	SPF 12 to under 20.

RECOMMENDED SUNSCREEN PRODUCT GUIDE—Continued

Sunburn and tanning history	Recommended sun protection product
Burns moderately; tans gradually.	SPF 8 to under 12.
Burns minimally; always tans well.	SPF 4 to under 8.
Rarely burns; tans profusely.	SPF 2 to under 4.

The agency points out that the sunburn and tanning history of skin type VI ("Never burns; deeply pigmented (insensitive)") is not included in the proposed guide. The Panel stated that no sunscreen use was indicated for this skin type (43 FR 38206 at 23213); thus it did not include skin type VI in its Recommended Sunscreen Product Guide (43 FR 38269). The agency requests comment on whether such information should be added to the guide.

The alternative statements offered by one comment as shorter than the Panel's recommended statements actually contain more words, e.g., "For those who burn easily and never tan" to replace "Always burns easily; never tans." In addition, in this comment's alternative statements, the PCD statements (maximal, ultra, etc.) are replaced with undefined numerical grades of sunscreen protection level. The alternative statements offered by another comment only included three skin types that would be defined according to a standardized sunscreen formulation. The agency believes that the consumer requires information on more than three skin types and that the proposed suggested compilation of five skin types based on sunburn and tanning history and five SPF ranges offers more thorough and more useful information than the alternatives suggested by the comments.

Furthermore, since 1980, the labeling of most sunscreen products in the United States has voluntarily included SPF values and sometimes has also included PCD statements. (For a discussion of SPF values and PCD statements, see comment 44.) For over a decade, consumers have used and become accustomed to choosing sunscreen products based on this system. The agency believes that consumers are familiar with choosing sunscreen products according this system and that it would be confusing and unnecessary to introduce an entirely new system for grading protection as suggested by the comments without additional justification. In addition to required SPF values and optional PCD statements proposed in this tentative final monograph for OTC sunscreen drug product labeling, the agency believes that the required Recommended Sunscreen Product Guide, which relates skin type to the amount of protection needed (i.e., SPF value), will provide consumers with the necessary information from which to choose the sunscreen product best suited for their skin type.

F. Comments on SPF and PCD Labeling for Sunscreen Drug Products

44. In response to the Panel's report, numerous comments "fully supported" the proposed SPF numerical rating system in sunscreen product labeling, indicating that such information will be most helpful to consumers, especially those with fair and sensitive skin. One comment emphasized the necessity for a numerical rating system of no less than 4 categories of protection if the proposed plan of 6 to 15 ratings was unacceptable. Several comments believed that a numerical rating system should be correlated with both efficacy and skin types. Two comments stated that there are too many number categories for the sun protection factor. Another comment suggested alternative labeling based on a numerical rating or a comparison of sunscreen products by reference to a FDA standard sunscreen formula, adding that this approach recognizes the validity of the agency's emphasis on bioequivalence. The comment maintained that the SPF values are more related to research than to practical approaches for labeling. Two comments suggested that, to avoid confusion by the consumer, SPF values should be included in the labeling on sunscreen products and one comment provided the following examples:

"I—Always burns easily, never tans. Use sunscreens grade 8–14."

"II—Always burns easily, tans minimally. Use grades 6–7."

"III—Burns moderately, tans gradually. Use grades 4–5 * * * etc."

Two comments opposed the system recommended by the Panel because they believed it was confusing and unnecessary. One comment felt that there is no need for a double scale to exist, i.e., a numerical rating system with SPF values and a classification system, composed of PCD statements.

In response to the notice of public meeting to discuss appropriate testing procedures for OTC sunscreen drug products, published in the **Federal Register** of September 4, 1987 (52 FR 33598), several comments discussed the relative merits of using PCD's and/or SPF values in the labeling of sunscreen drug products. Many of the comments supported the use of the PCD on the label, either alone or in addition to the SPF number. One comment maintained that use of the PCD in the labeling of sunscreen products is more useful to the consumer than the SPF, which the comment contended is information used by less than 10 percent of the consumers. Acknowledging that the PCD's are not as widely recognized by consumers as is the SPF numbering system, another comment maintained that PCD's are, nevertheless, useful for standardizing product claims and SPF values and should be retained. One comment contended that numerical SPF values are more meaningful to the consumer than PCD's, but supported retaining the PCD as an optional label statement because these "descriptives" are currently used on some products and have been for many years.

Another comment maintained that the agency should continue to permit the use of both SPF values and PCD's in the labeling of sunscreen drug products because each has meaning and usefulness to both consumer and industry. The comment recognized the need to ensure that sunscreen products are classified into some type of category system that is meaningful to the consumer and that adequately protects the public health. However, the comment argued that SPF values help best to accomplish these goals because they are used (1) to compare the effectiveness of existing products, (2) to monitor product performance over time, and (3) during product development to distinguish the best available formulation. The comment added that SPF values have been in use for 10 years, and the consumer has become accustomed to using these values when selecting products. The comment mentioned data from a consumer survey (Ref. 1) that shows that SPF values are a major factor in a consumer's selection of a sunscreen product. The comment asserted that a review of educational literature published by organizations such as The Skin Cancer Foundation, American Institute for Cancer Research, American Cancer Society, and others indicates that the SPF is discussed more often than the PCD.

One comment maintained that the PCD labeling serves no useful purpose and may be confusing and misleading. In place of the PCD's, the comment recommended that manufacturers continue to use SPF values to provide the sun protection value of a sunscreen formulation. The comment maintained that this would be the simplest and most straightforward manner of

describing a product so that consumers can choose the product appropriate for their needs by comparing the protection offered by one product with another. Stating that consumers are aware of SPF values and base their purchase decisions on these factors, another comment maintained that consumers are largely unaware of PCD's, that PCD's are redundant and less informative than SPF values, and that nothing would be lost by dropping them. Two other comments proposed eliminating the PCD's because they serve no useful purpose and may be misleading and confusing. One comment maintained that manufacturers should continue to use SPF values as the sole means of disclosing the sun protection value of a product. The comment stated that sunscreen testing procedures provide an accurate and reproducible measure of the erythema protection performance of the products tested and that the consumer is familiar with the SPF as a measure of the relative protection offered by various products. The comment added that the consumer has been exposed to the SPF concept for 10 years or more and is well acquainted with the degrees of protection provided by products with different SPF values. Maintaining that the terms (e.g., "ultra," "maximal," and "extra") applied to the different PCD's have no intrinsic meaning that would allow the consumer to make an educated comparison between products, the comment recommended that SPF values alone be used to convey the sun protection performance of a sunscreen product. The comment felt that consumers were sufficiently well-educated regarding SPF values of sunscreens so that PCD's are redundant.

The agency agrees with many comments that the SPF provides consumers with important information. The SPF value is based on a numerical index designed to tell consumers how much protection from the sun a product will provide. The SPF value is defined as the ratio of the amount of energy required to produce a MED or minimal sunburn through a film of a sunscreen drug product to the amount of energy required to produce the same MED without any treatment (43 FR 38206 at 38213). The SPF values are correlated to the efficacy of the sunscreen product and thus are helpful to consumers in identifying the proper product for their needs. This information is especially important to consumers with fair or sensitive skin. The Panel's recommended SPF system contains an SPF scale with values of 2 to 15, i.e., products providing a minimal amount of protection to products providing the maximum amount of protection. The agency has further determined for the reasons more fully described below that an SPF scale with values up to and including SPF 30 is appropriate. (See comments 46 and 47.)

The agency believes that PCD's are useful for descriptive terms for standardizing the labeling of sunscreen drug products but should not be mandatory labeling. Although PCD labeling may provide useful information to the consumer, it is not necessary for the safe and/or effective use of the product provided an SPF value is included in the products labeling. A single PCD is established for each product after determining the product's SPF value. The five PCD statements being proposed by the agency in this tentative final monograph are as follows: Minimal (SPF 2 to under 4), moderate (SPF 4 to under 8), high (SPF 8 to under 12), very high (SPF 12 to under 20), and ultra high (SPF 20 to 30). (See comment 45.) The PCD and SPF of a sunscreen drug product determines which of the additional indications proposed by the agency in § 352.52(b)(2)(i) to (b)(2)(v) of this tentative final monograph are appropriate for use in the labeling of the product. For example, products whose SPF value (i.e., 8 to under 12) places them within the PCD of "high" may display the indication in § 352.52(b)(2)(iii)(F) "High protection against sunburn for blondes, redheads, and fair skinned people." Products whose SPF value (i.e., 2 to under 4) places them within a PCD of "minimal" may display the indication in § 352.52(b)(2)(i)(B) "Prolongs exposure time before sunburn occurs."

In § 352.52(e)(1) of this tentative final monograph, as with the additional optional indications, the agency is proposing that PCD labeling statements be optional (included by the manufacturer if desired), and not required as recommended by the Panel. This approach is consistent with the many comments that stated that PCD labeling is less important than SPF labeling.

The agency believes that the two comments opposed to the system of SPF values and PCD statements are examples of the misunderstanding by some consumers regarding what information will appear on the labeling of marketed sunscreen drug products. The Panel recommended that the labeling of all sunscreen drug products include a sunscreen drug product guide that lists five skin types and five PCD's with each PCD corresponding to the appropriate skin type (43 FR 38206 at 38268 and 38269). The agency is proposing to revise the Panel's recommended sunscreen drug product guide to include SPF ranges instead of PCD's. (See comment 43.) By using this sunscreen product guide, the consumer may select the proper sunscreen drug product, i.e., the product with the SPF value that conforms with the consumer's skin type and sunburn and suntanning history. Each sunscreen drug product must be labeled with an SPF value and may display an optional specific PCD claim if the manufacturer wishes to include such information in its product's labeling.

The PCD's and the SPF numerical rating system are designed to assist manufacturers and consumers in determining how effective a sunscreen drug product is in protecting a person from the sun's harmful rays and, thus, how effective the product will be in preventing sunburn or skin damage. However, safe use can only be achieved by also including in labeling a Recommended Sunscreen Product Guide so that consumers can select the most appropriate sunscreen drug product based on skin type (sensitivity) and the expected length of exposure time to direct sunlight. The agency concludes that sunscreen drug product labeling based on such a system will make it easier for consumers to select the proper sunscreen drug product. Accordingly, the agency is including the SPF rating system and the Recommended Sunscreen Product Guide in the required labeling for sunscreen drug products in proposed §§ 352.50 and 352.52(e)(4), respectively, and is proposing the PCD statements as optional labeling in § 352.52(e)(1).

Reference

(1) C00083, Docket No. 78N–0038, Dockets Management Branch.

45. In the notice of public meeting to discuss appropriate testing procedures for OTC sunscreen drug products (52 FR 33598 at 33602), the agency noted that the Panel's recommended PCD's may not adequately accommodate sunscreen drug products with high SPF values of 25 or 30. The agency requested comment on how the PCD's might be modified to include higher SPF values.

Several comments supported retaining the five PCD's that were recommended by the Panel. One comment suggested that products with SPF values of 15 or higher should continue to be designated as "ultra." One comment recommended that for those products that have SPF values over 15, the monograph should be changed to read "15 and above" for the "ultra" PCD.

One comment suggested that the ultra category should be comprised of sunscreens with SPF values between 15 and 30+. The comment maintained that retaining the currently proposed designations has a significant benefit in that current products would not need to be relabeled with the category designation and consumer reeducation would not be necessary. It added that the PCD's as currently proposed do encompass all SPF ranges without the necessity for a change. One comment suggested the addition of an SPF 25+ value to the ultra protection category.

Several comments suggested revisions to the PCD's that were recommended by the Panel. One comment maintained that the system found in Australian Standard AS2604 is readily understood by consumers, precludes ambiguity, and is compatible with SPF labeling in excess of 15. It recommended the following categories: (1) Minimal (SPF 2 to less than 4); (2) Moderate (SPF 4 to less than 8); (3) High (SPF 8 to less than 15); and (4) Maximum (SPF 15 and over). Another comment suggested revised wording for the PCD's as follows: (1) low (SPF 2 to under 4); (2) medium (SPF 4 to under 6); (3) high (SPF 6 to under 9); (4) very high (SPF 9 to under 15); and (5) maximal (SPF 15 and above). The comment maintained that this revised wording would be more comprehensible to the consumer than the descriptive terms recommended by the Panel. A third comment stated that PCD's should be divided as follows: (1) minimal (SPF 2 to under 5); (2) moderate (SPF 5 to under 10); (3) extra (SPF 10 to under 15); (4) maximal (SPF 15 to under 25); and (5) ultra (SPF 25 and above).

Noting that the suggested category designations in the September 4, 1987 notice (52 FR 33602) had deleted the SPF 15 category, one comment strongly recommended that the SPF 15 category be retained. The comment cited a survey of pediatricians and dermatologists (Ref. 1) that indicates that they usually recommend SPF 15 sunscreens to their patients. The comment favored retaining the current PCD ranges to maintain continuity, suggested two additional categories, and suggested revising the SPF 15 or greater category to accommodate currently marketed products as follows: for the PCD comprising SPF 15 to under 25, the labeled SPF should be 15; for the PCD comprising SPF 25 to under 30, the labeled SPF should be 25; and for the PCD comprising SPF values of 30 or greater, the labeled SPF should be 30+. However, the comment did not provide any names to be used for its additional PCD's.

One comment recommended that the following classes be used to designate categories rather than the Panel's recommended PCD's: (1) Class 1 (SPF 15 and more); (2) Class 2 (SPF below 15 to SPF 8); (3) Class 3 (SPF 8 to 6); (4) Class 4 (SPF 6 to 4); and (5) Class 5 (SPF below 4). The comment further suggested that each class could be given a specific name which may represent the sensitivity of the skin (e.g., Class 1 would be for very sensitive skin and/or extreme solar conditions; Class 2 would be for sensitive skin and/or moderate solar conditions; Class 3 would be for low sensitive or tanned skin; Class 4 would be for low sensitive or unsensitive skin; and Class 5 would be for minimal sun protection). Adding that Classes 3, 4, and 5 only protect in mild solar intensity, the comment further defined extreme solar conditions as those corresponding to 15 to 25 MED per day for sensitive skin, moderate solar conditions as those equal to about 10 MED per day for sensitive skin, and low solar conditions as those corresponding to about 5 MED per day for sensitive skin.

Some comments argued that the PCD descriptive terms recommended by the Panel (i.e., "minimal," "moderate," "extra," "maximal," and "ultra") are confusing, misleading, and ambiguous, and should not be included in the labeling of sunscreen drug products. Two comments contended that, by definition, the word "maximal" should be the highest rating category, but it falls in the middle of the Panel's recommended SPF range. The comments added that consumers have been educated to purchase products based upon SPF values. Another comment stated that the Panel's report permits a product with an "ultra" PCD to characterize itself as providing the "most protection against sunburn," the "greatest protection against sunburn," or the "highest degree of sunburn protection." The comment stated that these claims are potentially confusing because the product may provide less total sunscreen protection than a higher SPF product or a product with more UVA protection. The comment added that consumers cannot distinguish the true value or degree of protection suggested by these terms because it is not clear whether a "maximal" sunscreen provides greater or less protection than either an "extra" or "ultra" protection product. Another comment maintained that "maximal" and "ultra" each imply the most possible.

One comment maintained that labeling with SPF numbers using the fixed values set forth in the PCD labeling recommended by the Panel in its proposed monograph is appropriate. Another comment favored the restriction of labeled SPF values to the lowest value of the PCD range. The comment felt that allowing the actual intermediate SPF values within a category to be displayed on the principal display panel becomes a marketing ploy that would unnecessarily confuse the consumer. Stating that it is unlikely that meaningful differences in protection exist between products with SPF 9 and 11, for example, the comment stated that labeling the products as such would be misleading and that labeling both products with SPF 8 would be a more appropriate and conservative approach. A third comment recommended that for all PCD's, either the actual SPF value, as determined by testing, or the lowest SPF number in the PCD would be appropriate for label claims. The comment added that a cap should be set at SPF 30 and any tested value higher than 30 should be expressed on the label only as 30+. One comment maintained that the PCD's recommended by the Panel are not adequate to allow consumers to evaluate sunscreen drug products for effectiveness. Stating that consumers have a good basic knowledge of the SPF system, the comment suggested that actual SPF ratings, in whole number increments, should be allowed on all sunscreens so that accurate comparisons can be made. Another comment maintained that the consumer relies more on the actual SPF of a product than the PCD. The comment stated that providing the actual SPF on the label along with the appropriate PCD is in the best interest of the consumer.

The agency believes that the Panel's recommended PCD's should be revised slightly in order to better accommodate SPF values above 15. The agency believes that a modification of the PCD ranges will ensure that the protective qualities of a sunscreen drug product will be more accurately described. For example, the Panel recommended that SPF 15 sunscreens should be allowed to display the claim "Affords the most protection against sunburn." As stated in comment 46, the agency believes that SPF values above 15 are justified in part because an SPF 15 sunscreen drug product may not provide "the most protection against sunburn" for some fair-skinned persons or under certain circumstances. In the 12 years since the Panel's report on OTC sunscreen drug products was published, advances in technology have produced dramatic improvements in the effectiveness of

sunscreen preparations. Such products have become integral features in public health statements. The National Institutes of Health (NIH) Consensus Development Conference Statement and the AAD both recommend the use of sunscreens with SPF ratings of 15 or higher (Refs. 2 and 3). The Panel recommended that products providing an SPF value of 8 to under 15 could state "Affords maximal protection against sunburn" and that products providing an SPF value of 15 or greater could state "Affords the most protection against sunburn." Because the agency is proposing a revised SPF system in this tentative final monograph, it is also proposing to revise the PCD ranges and to use several different descriptive terms in place of those recommended by the Panel.

Regarding the terms used for PCD categories, the agency agrees with the comments and believes that some of the comparative terms recommended by the Panel (i.e., such as "+," "extra," "maximal," and "ultra") to identify PCD's are confusing and may be misleading to the consumer. It should be noted that the Panel was proposing a new labeling concept, and at the time of its deliberations, such terms were not commonly found in the labeling of sunscreen products. The agency agrees that it is especially difficult to distinguish between the term "maximal" and "ultra" because both would seem to indicate that the sunscreen drug product offers the most protection possible. The agency believes that the terms "minimal" and "moderate" recommended by the Panel are clear and that these terms properly indicate the performance that consumers may expect from a sunscreen drug product in these SPF ranges. The agency is, therefore, proposing that the terms "minimal," and "moderate" be retained. However, the agency proposes that the higher PCD's be identified as "high," "very high," and "ultra high." These terms should assist consumers in making a more informed comparison between sunscreen drug products. The agency invites specific comment on this issue. As mentioned above, the agency does not consider these terms as essential as SPF values and is proposing that the PCD labeling recommended by the Panel in § 352.50(e) of its monograph, as revised above, be optional. (See comment 44.)

In § 352.50(e) of its recommended monograph, the Panel proposed that sunscreen drug products be categorized into PCD's according to their tested SPF and that these products use the lowest SPF value in the applicable PCD as their labeled SPF number. For example, if a product's test SPF value were 14, the product was categorized into the maximal PCD (i.e., SPF 8 to under 15) and used SPF 8 in its labeling. The agency now believes that the product may display instead its tested SPF value up to SPF 30. (In this tentative final monograph, the agency is proposing that SPF values up to and including SPF 30 are justified. See comments 46 and 47.) A water resistant or very water resistant product must display both its static SPF value (up to SPF 30) and its SPF value that has been determined after the appropriate water immersion test. (See comment 51.) Such labeling will more accurately inform the consumer of the protection offered by a sunscreen drug product, especially for those products in the higher PCD categories, such as "very high", where SPF values may range from SPF 12 to under 20, or "ultra high", where SPF values range from 20 to 30.

Although PCD statements are proposed as optional in this tentative final monograph, the agency believes that SPF values need to be displayed on the principal display panel of OTC sunscreen drug products. Therefore, the agency is proposing a new § 352.50 entitled "Principal display panel of all sunscreen drug products" to include labeling that is required to appear on the principal display panel of all OTC sunscreen drug products as follows: *"For products that do not satisfy the water resistant or very water resistant sunscreen test procedures in § 352.76.* 'SPF (insert tested SPF value of the product up to 30).'" (For labeling required for the principal display panel of OTC sunscreen drug products that satisfy the water resistant and very water resistant testing procedures in § 352.76, see comment 51.)

Because of the addition of this new labeling section, the agency is proposing to renumber the Panel's recommended § 352.50 "Labeling of sunscreen products" as § 352.52.

In addition, in this tentative final monograph the agency is revising the Panel's recommended PCD labeling in § 352.50(e) and including it in § 352.52(e), as follows:

"(1) *For products containing any ingredient identified in § 352.10, the following PCD labeling claims may be used: (i) For products containing active ingredient(s) that provide an SPF value of 2 to under 4.* 'Minimal Sun Protection Product.'

(ii) *For products containing active ingredient(s) that provide an SPF value of 4 to under 8.* 'Moderate Sun Protection Product.'

(iii) *For products containing active ingredient(s) that provide an SPF value of 8 to under 12.* 'High Sun Protection Product.'

(iv) *For products containing active ingredient(s) that provide an SPF value of 12 to under 20.* 'Very High Sun Protection Product.'

(v) *For products containing active ingredient(s) that provide an SPF value of 20 to 30.* 'Ultra High Sun Protection Product.'"

References

(1) Comment No. C00083, Docket No. 78N–0038, Dockets Management Branch.

(2) "Sunlight, Ultraviolet Radiation, and the Skin," National Institutes of Health Consensus Development Conference Statement, Vol. 7, Number 8, May 8–10, 1989.

(3) "Cancer of the Skin," edited by the Task Force on Pamphlets, American Academy of Dermatology, Evanston, IL, 1986.

46. In the notice of public meeting to discuss sunscreen testing procedures (52 FR 33598 at 33599), the agency noted the proliferation of OTC sunscreen drug products that display SPF values greater than 15, which was the Panel's highest recommended classification. Stating that consideration should be given to modifying the Panel's recommended monograph to address these higher SPF values, the agency asked the following: "What benefit is provided to the consumer by sunscreen drug products claiming to have SPF values greatly in excess of 15 (i.e., 23 or even 30) if, as the Panel claims, SPF 15 offers the maximum possible protection?" (See 52 FR 33602.)

Most comments submitted in response to the public meeting maintained that sunscreen drug products with SPF values above 15 are beneficial and justified. One comment asserted that such products provide better protection against the deleterious effects of the sun than do sunscreen drug products with lower SPF values. Two comments noted that, at the time the Panel made its recommendations, SPF 15 was the highest value commercially available. Since that time, newer research and formulation techniques have made it possible to formulate sunscreen products with proven efficacy at SPF levels well above 15. One comment added that these newer products are more protective than those initially contemplated or reviewed by the Panel in the 1970's. Another comment remarked that because of advances in technology, the Panel's proposed labeling that "SPF 15 provides the highest degree of sunscreen protection" is now inaccurate and needs to be corrected.

Several comments pointed out that sunscreen drug products with an SPF of 15 will not offer maximal protection to

a person with extremely sensitive skin (i.e., an individual with Skin Type I who always burns and never tans) and noted that American consumers may be exposed to increased doses of sunlight when on vacation in sites like Hawaii, the Caribbean, and Mexico. One comment added that not only is the intensity of the sun greater in such areas, but persons on vacation in such places may stay out in the sun longer. Another comment stated that the potential for sunburn cannot be avoided completely by using a product with a lower SPF value and reapplying it frequently, and that products with SPF values higher than 15 provide an extra measure of protection for people who either do not want to be or who should not be exposed to the sun. One comment stated that although a product with an SPF of 15 provides significant protection from sunburn, the extra margin of protection afforded by a product with an SPF value in excess of 15 is useful to those sun-sensitive individuals desirous of all-day protection.

One comment stated that products with the higher SPF values screen out more of the sun's total UV radiation spectra responsible for both immediate burning and long-term damage such as photoaging and skin cancers. Another comment submitted several published scientific studies purporting to indicate the benefits of sunscreens in terms of skin cancer protection (Refs. 1 through 4), protection against photoaging (Refs. 5 and 6), and protection of the cutaneous immune functions (Ref. 7). Another comment added that the medical community has continued to stress the importance of adequate sun protection throughout one's lifetime to reduce the risk of skin cancer and premature aging of the skin, and that products with an SPF above 15 would better provide this protection.

One comment maintained that there is ample documentation to indicate that an SPF value of 15 is not adequate protection for a sizeable proportion of the United States' population (Refs. 8 through 11). Based on these data, the comment maintained that the average midsummer MED available per day range from 19 in Bismark, North Dakota, to 44 in El Paso, Texas, for skin Type II individuals. The comment pointed out that although these are sunrise to sunset measurements, 75 percent of the sunburning radiation dose is delivered between 9 a.m. to 3 p.m. During that time period individuals are most active outdoors, and there is a potential exposure in the 30–MED range. The comment also submitted 1980 Census Bureau data that indicate that 39.3 percent of the United States' population is of Celtic origin and would be classified into the lower skin type categories (i.e., Skin Types I or II) (Ref. 12). One comment stated that it had conducted an attitude and use survey in 1987 among 585 sunscreen consumers who were asked, "How important is an SPF of 15 or greater to you in a sunscreen?" The comment stated that 75 percent of the subjects responded positively by selecting either "extremely important" (48 percent) or "very important" (29 percent).

One comment maintained that the AAD and other scientific organizations recognize the need for high SPF products. The comment stated that the German sunscreen standard (DIN 607501) and the Australian standard (AS 2604) recognize that products need to be formulated to meet the needs of consumers with varying skin types. The comment added that, in addition to normal variations in skin type and susceptibility to sunburn, a substantial segment of the population appears to be sun sensitive (Ref. 13) and needs high SPF products to provide adequate protection.

One comment submitted the results of a nationwide random survey of 101 pediatricians and 99 dermatologists to determine their sunscreen recommendations to patients (Ref. 14). The survey found that 21 percent of pediatricians and 49 percent of dermatologists usually recommend products with SPF values higher than 15, and that 75 percent of dermatologists sometimes recommend products with SPF values higher than 15. Only 11 percent of pediatricians and 20 percent of dermatologists felt that sunscreens with SPF values higher than 15 were not medically necessary. The comment maintained that these results indicate that the majority of these medical specialists recognize that products with SPF values above 15 are valuable. Another comment submitted a study (Ref. 15) that investigated the risk reduction for nonmelanoma skin cancers associated with the childhood use of sunscreens. Using a mathematical model based on epidemiological data, the authors quantified the potential benefits of using an SPF 15 sunscreen and estimated that the regular use of such a sunscreen during the first 18 years of life reduced the lifetime incidence of nonmelanoma skin cancer by 78 percent.

Conversely, two comments were opposed to the availability of sunscreen drug products with SPF values higher than 15. One comment questioned the need for sunscreen drug products with high SPF values (i.e., 25 to 30) when people are not exposed to greater than 15 MED's in a day. The comment maintained that waterproof sunscreen drug products with an SPF of 15 are adequate for the average needs of all people. The comment felt that people with highly sun-sensitive skin are given a false sense of protection when the industry recommends sunscreen drug products with SPF values of 25 or 30, and this action endorses increased sunbathing. Such sun-sensitive persons are at greatest risk of developing acute and chronic skin changes and should not indulge in prolonged sunbathing or remain outdoors for long periods of time. The comment asserted that prolonged sunbathing should be discouraged and the regular use of sunscreen drug products should be encouraged in order to control the increasing trend of actinic keratoses, skin cancer, and the early onset of photoaging. Another comment submitted in response to the Panel's report contended that sunscreens with SPF values greater than 10 are not necessary because people with very sensitive skins with a "disposition to light disease" should use opaque sunscreens.

The agency agrees with the majority of comments that SPF values higher than 15 are justified. The agency notes that in the United States there are enormous variations both in skin type in the population and in the amount of UV radiation to which a person may be exposed, because of differences in geography. Many of the comments submitted to the agency cited varying average daily doses of UV radiation ranging from approximately 9 to 44 MED's depending upon location, altitude, and season. The agency believes that there are situations where consumers routinely are exposed to sufficient UV radiation may require sunscreen drug products with SPF values greater than 15.

Since the Panel's report on OTC sunscreen drug products was published, advances in technology have produced dramatic improvements in the effectiveness of sunscreen preparations. Several elements have contributed to these advances, e.g., development of solar simulators, more knowledge of the optical properties of the skin, greater skills in formulating sunscreen drug products, and greater awareness of the importance of the vehicle in such products (Ref. 16).

The agency believes that sunscreen preparations with SPF values above 15 are important from a public health standpoint. According to an NIH Consensus Development Conference Statement (Ref. 17), the average

American's exposure to UVB radiation has increased considerably over the past several decades due to changing lifestyles, i.e., more outdoor recreational activities, more emphasis on tanning, scantier clothing, and a population shift to the sunbelt. In addition, recent satellite measurements indicate a worldwide decrease in stratospheric ozone over the last decade. This reduction increases the amount of UV radiation that reaches the earth's surface. If the ozone layer continues to be depleted, human exposure to UV radiation will increase correspondingly.

There are serious risks involved with increased exposure to UV radiation. Sunscreen preparations with SPF values higher than 15 are necessary to provide fair-skinned individuals with maximum protection. A large proportion of the United States' population is of Celtic origin (Ref. 12). Such fair-skinned people burn very easily (i.e., in as little as 10 minutes (43 FR 38206 at 38210)) and are most susceptible to the adverse effects of sunlight, such as skin cancer and premature aging of the skin. Therefore, the agency believes that many people in the United States need more protection than that provided by an SPF 15 sunscreen. This need is especially important when people are being exposed to intense sunlight, such as that found in the southern portion of the United States and in many popular vacation areas where consumers normally receive even greater amounts of UV radiation. The NIH Consensus Development Conference Statement recommends the use of sunscreens with SPF ratings of 15 or higher (Ref. 17). It also recommends daily use of these products during appropriate times of the year and states that sunscreens should be applied before exposure, with frequent reapplications thereafter. The agency agrees that sunscreens should be applied frequently and is proposing such in the directions included in § 352.52(d) of this tentative final monograph. (See comment 66.) The AAD also recommends the use of sunscreens with SPF factors of *at least* 15 to protect against premature aging of the skin and skin cancer (Ref. 18).

The agency also believes that sunscreen drug products with SPF values above 15 may offer better protection to consumers who may not apply a sunscreen as liberally as they should or who do not always reapply a sunscreen as frequently as they should. For such consumers, a sunscreen with an SPF of 20 or 25 may offer an important extra margin of safety. The agency concludes that OTC sunscreen drug products with SPF values higher than 15 are beneficial to consumers and is proposing that the upper limit for SPF values be 30. (See discussion of proposed SPF 30 upper limit in comment 47.)

In regard to the one comment's concerns about individuals with a "disposition to light diseases," the agency has discussed such photosensitization reactions in comments 33 and 69.

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(12) "Statistical Abstracts of the U.S.: 1986," Comment No. C00083, Docket No. 78N–0038, Dockets Management Branch.

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47. Several comments discussed whether or not there should be an upper limit to SPF values. The Standards Association of Australia submitted a copy of its revised standard for sunscreen products (Ref. 1) and stated that it has deliberately restricted SPF factor claims to a maximum of "15+" to prevent the "inevitable number chasing" that is "now occurring in the USA." The comment stated that this restriction prevents products from being "loaded" with sunscreen ingredients for which chronic dermal toxicology data are often lacking.

Two comments believed that SPF values should be capped at 20. One comment stated that the most that it had measured with a Robertson-Berger meter in the tropics on Mauna Loa (19° North latitude, 12,000 feet elevation) was 27 MED's, on a flat surface, from sunrise to sunset. The comment maintained that because a human in the upright position receives at most 60 percent of the ambient UV radiation, a full day's dose would not exceed 16 MED's for a Skin Type I individual. The comment contended that sunscreen drug products with SPF values greater than 20 will only increase cost and make the possibility of irritation from multiple sunscreen ingredients and their photo-breakdown products more likely. Another comment maintained that unless one is at a high altitude (e.g., 15,000 to 20,000 feet), one is unlikely to receive UV radiation flux exceeding 15 MED on a clear, bright day. The comment asserted that an average person rarely stays out in the sun for more than 4.5 hours and thus would only receive a maximum dose of 10 to 12 MED. The comment urged the agency to adopt a maximum SPF value of 20, contending that it is not necessary to have "extra potent" sunscreens with SPF values of 25, 30, or 35 and to subject the consumer's skin to potentially toxic effects of high concentrations of chemicals.

Another comment stated that an upper limit of SPF "25+" should be established to ensure adequate sunscreen protection for highly sun-sensitive skin types without exposing consumers to unnecessarily high levels of sunscreen active ingredients. The comment expressed concern that many companies manufacturing sunscreen drug products have embarked upon an SPF "numbers game," leaving consumers with the impression that the higher the SPF number the better the product. The comment felt that such marketing strategies are not rational and expose consumers to excessive levels of sunscreen ingredients that may potentially cause more problems (e.g., invisible dermatitis) than are justified by the benefits. The comment added that placing the upper SPF limit at "25+" would provide industry with an opportunity to reasonably protect the consumer from UV radiation while restricting the current industry marketing movement toward very high SPF values, which needlessly confuse the user.

Several comments believed that SPF claims should be capped at 30. Stating that the trend toward higher SPF values has reached unjustifiable levels, one comment stated that the benefits derived from very high SPF values by the vast majority of consumers are negligible, and that many consumers think that they are getting much more protection than they actually are. Another comment suggested that products with SPF values greater than 30 cannot be justified on a risk/benefit basis because achieving SPF values higher than 30 requires unnecessary exposure to increased levels of sunscreening agents, while increasing overall protection by an insignificant degree. As an example, the comment noted that an SPF 30 sunscreen drug product blocks 96.7 percent of the incident UVB energy whereas an SPF 40 sunscreen drug product only increases this level of protection to 97.5 percent, and the amount of additional sunscreen ingredient "load" in the product to increase the SPF to 40 could realistically increase by up to 25 percent. The comment added that, in the extreme, an SPF 70 would block 98.6 percent of the UV energy versus 96.7 percent blocked by an SPF of 30. The comment maintained that such extra protection is not necessary and that sunscreen drug products with SPF values higher than 30 represent unnecessary and ill-advised exposure to increased sunscreen ingredients at a time when dermatologists and skin cancer groups are recommending that sunscreens be applied daily to minimize the adverse effects of the sun. The comment concluded that this additional unnecessary exposure to more sunscreen ingredients is ill advised.

One comment stated that a reasonable basis for selecting an SPF cap is the level of protection required for an average consumer who spends an entire day in the sun in a sub-tropical region of the United States such as Florida or Hawaii. The comment maintained that measurements of UV radiation taken in these areas have found that the average consumer can be exposed to as much as 20 MED's. The comment recommended an SPF cap of 30 because this is the maximum amount needed to protect the vast majority of consumers (including Skin Type I individuals) from sunburn under stress conditions of UV exposure.

One comment stated that proponents of high SPF values often cite as justification the needs of people with Skin Type I and people prone to skin cancer. The comment maintained that a sunscreen drug product with an SPF of 30 can adequately protect most of these individuals and added that it is not good public policy to expose most of the population to unnecessarily high levels of sunscreens to protect a very few. The comment contended that people can be misled into a false sense of security when told that a single application of a very high SPF product will protect them all day. In reality, the comment asserted these products are subject to washing or rubbing off, thus reducing their effective level of protection. The comment stated that the needs of special groups would be better served if they were encouraged to reapply their sunscreen products because two applications of an SPF 30 sunscreen drug product will provide more protection under real usage conditions than a single application of a higher SPF product. Another comment stated that individuals who are so sensitive as to need higher than SPF 30 protection should be encouraged to severely limit their sunlight exposure and to use a product with an SPF of 30 when they are necessarily exposed to sunlight. The comment concluded that SPF 30 should be sufficient for all-day sunburn protection for the vast majority of the population under maximum sun exposure conditions.

One comment argued there are data (Ref. 2) demonstrating that enough sunlight exists on many days during the summer months in various locations to permit exposure in excess of 25 MED's for the average Skin Type II and III individual. By extrapolation, the comment maintained that a Skin Type I individual could be exposed to approximately 30 MED's during this same time frame. The comment acknowledged that these calculations are based upon exposure of an individual lying in a quiet, prone position from sunup to sundown, and may be somewhat inflated. Nevertheless, the comment maintained that these data provide a convincing rationale for an SPF 30 sunscreen drug product that would permit even a Skin Type I to achieve all-day protection as well as allowing for an extra margin of protection to accommodate weather conditions that cannot be factored into SPF testing.

Several comments advocated that no upper limit be set on SPF values. One comment maintained that scientific information is not available to demonstrate a "no-effect" level of sun exposure, especially when considering the sun's contribution to photoaging and to the risk of skin cancer. The comment provided a pamphlet from the AAD (Ref. 3) to substantiate its position. The comment suggested that, in the absence of a demonstrable safety risk, it would be contrary to public policy and to consumers' best interest to preclude manufacturers from offering truthfully labeled sunscreen formulations with as much sun protection as is technologically feasible.

Citing an article by Urbach and Berger (Ref. 2) and stating that a person with average, untanned, Caucasian skin may receive 22 MED's of UV radiation in one day in El Paso, Texas, another comment supported an open-ended numbering system for SPF values, or as an alternative, an upper limit of not less than 40. The comment maintained that limiting the highest allowed SPF number would prevent those consumers who want and need a high level of protection from making valid comparisons among the highest SPF products available.

A comment from an institute that deals with systemic lupus erythematosus and discoid lupus research (diseases associated with photosensitivity) mentioned the need for a sunscreen drug product with an SPF value of up to 40. The comment maintained that the use of such sunscreen drug products would prevent the triggering of the onset of these diseases. The comment included abstracts of scientific publications that include information on the relationship between photosensitivity and lupus and that suggest that sunblocks may be essential for sensitive lupus patients (Ref. 4).

Although the agency has concluded that the available scientific data demonstrate that sunscreen drug products with SPF values above 15 are

reasonable and justified (see comment 46), it finds that SPF values above 30 are not necessary because the available data clearly indicate that a sunscreen drug product with an SPF of 30 assures adequate protection for the majority of consumers even under extreme conditions. As pointed out by one comment, an SPF 30 sunscreen drug product blocks 96.7 percent of the incident UVA energy, whereas an SPF 40 sunscreen drug product only increases this level to 97.5 percent. Further, data compiled by Berger and Urbach in 1982 (Ref. 2) demonstrated that approximately 25 MED's is the highest dose of UVB radiation that an individual with average Caucasian skin can expect to receive in Mauna Loa, Hawaii. In the southern states of the continental United States, an individual can be exposed to approximately 22 MED's in the hottest part of the summer. A sunscreen drug product with an SPF 30 provides all-day protection for all skin types. Such a product also provides an extra margin of protection that allows for the possibility that the product may be inadequately applied and accommodates weather conditions that cannot be factored into the SPF testing procedures that are done with artificial light sources.

Scientific evidence shows a point of diminishing returns at levels above SPF 30; any benefits that might be derived from using sunscreens with SPF values higher than 30 are negligible. The agency does not believe that an "open-ended" approach to SPF values is beneficial to consumers. The difference in protection provided by a sunscreen drug product with an SPF 40 or 50 compared to the protection offered by a product with an SPF 30 is so small as to be nonexistent, especially when one considers the biological variability inherent in an individual's response to the protective quality of sunscreen drug products. (See also discussion in comment 48.)

Regarding the use of high SPF sunscreen drug products to protect consumers with photosensitivity diseases, the agency notes that the exact etiology of these light-related diseases is not known. (See comment 69.) The fact that a sunscreen has a high SPF may not be as important to the consumer with a photosensitivity disease as the UV wavelengths that are absorbed or reflected by the sunscreen ingredient in the product. The agency does not believe that, apart from whatever ingredients may be in the formulation, an SPF 40 sunscreen drug product provides significant benefits that are not also provided by an SPF 30 sunscreen drug product. Unless such benefits can be shown, the agency believes that an SPF 30 sunscreen drug product provides adequate protection for a consumer with a photosensitivity disease provided that the appropriate wavelength is absorbed or reflected.

Based upon the above, the agency is proposing an upper limit of 30 for SPF values and is proposing to revise the Panel's recommended § 352.50(b) to reflect this maximum SPF value. (See comments 45 and 57.)

Several comments questioned the safety aspect of sunscreen drug products with extremely high SPF values (e.g., 25, 30, or higher). This issue is discussed in comment 48.

References

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(4) Comment No. C00094, Docket No. 78N–0038, Dockets Management Branch.

48. In response to the notice of public meeting to discuss appropriate testing methods for OTC sunscreen drug products (52 FR 33598), some comments expressed concern regarding the possible toxicity of OTC sunscreen drug products with high SPF values. Maintaining that there is no safety or toxicological data pertaining to "these new sunscreens with high SPF values that contain high concentrations of UV-absorbing and UV-reflecting chemicals," one comment expressed concern about the long-term effects of these preparations. The comment specifically mentioned that little is known about the long-term effects of the small concentration of lead in zinc oxide and titanium dioxide and stated that this may be especially harmful to children. Stating that the constant presence of chemicals on skin is potentially harmful, the comment questioned how many fair-skinned individuals might develop photoallergic reactions by using potent, high SPF sunscreen drug products. The comment suggested that the agency recommend certain test procedures in an animal model system to ensure the safety of high SPF sunscreen drug products when used on a long-term basis.

One comment stated that, at the January 26, 1988 public meeting, some of the discussion of possible safety issues relating to high SPF sunscreen drug products missed the point of the relevant benefit-risk analysis. The comment stated that, although products with SPF values greater than 15 utilize Category I ingredients within approved concentration ranges, the total sunscreen load tends to increase significantly. For example, in comparing similar lotion formulations, a sunscreen with an SPF of 15 may utilize 11.5 percent total sunscreen ingredients while a sunscreen with an SPF of 40 may require over 22 percent total sunscreen load. The comment stated that the consumer is therefore exposed to greater total levels of active ingredients. Conversely, the incremental difference in protection from UVB rays becomes increasingly smaller. For example, a sunscreen with an SPF of 15 screens 93 percent of UVB rays, a sunscreen with an SPF of 25 screens 96 percent of UVB rays, while a sunscreen with an SPF of 39 screens 97.44 percent of UVB rays. The comment stated that the obvious benefit-risk issue is whether the extremely modest increased protection from sunburn justifies the increased exposure to sunscreen ingredients that may cause skin irritation.

One comment pointed out that the level of sunscreen active ingredients allowed in a sunscreen drug product is now regulated by the advance notice of proposed rulemaking published in 1978 (43 FR 38206) and that all sunscreen drug products, even those with very high SPF values, are limited by these proposed rules. The comment maintained that advances in formulation technology have allowed manufacturers to develop products with relatively low levels of sunscreen active ingredients and still maintain high SPF values. The comment stated that responsible manufacturers test finished products to establish safety prior to marketing, in addition to adhering to the limits established in the proposed rules. The comment added that, although product safety is a very important consideration, limiting the SPF claim on sunscreen drug products will not have a substantial effect on the overall safety of these products.

The comment noted that three speakers at the public meeting suggested that skin irritation might result from use of sunscreen drug products with high SPF values. The comment cited the following three specific statements: (1) "the use of larger numbers and more sunscreen probably will only lead to trouble with photochemical reactions, * * * irritancy * * *;" (2) "[in work with] patients who experience either skin cancer or melanomine sore, [he] recommend[s] the use of 15 SPF and more, but at least 10 percent of [the subjects] have an irritation with this type of product;" and (3) "[he] recommended SPF–15 sunscreens and

* * * without sunlight exposure * * * [the subjects] had contact irritational reaction, no sensitization," (Ref. 1). The comment stated that no data were submitted to support these statements. The comment added that the patients to whom the last two statements applied had skin diseases and, thus, had compromised skin integrity. The comment maintained that, even if valid and documented scientific studies showed skin irritation in such subjects, there is no reason to believe that any significant irritation would result from the intended use of sunscreens by individuals with healthy skin.

The comment asserted that some of the reactions discussed at the public meeting were described as "some" irritation, "minor to some discomfort," "some burning sensation, a little bit of redness," and "discomfort, a little bit of redness" (Ref. 1). The comment contended that these reactions do not demonstrate a significant irritation problem with sunscreen drug products. The comment added that, in one case, the sunscreen preparations were European formulas, the active ingredients may not have been Category I ingredients, and the concentrations of the active ingredients in the products used were not provided (Ref. 1). The comment added that, as with any dermatological product, the irritation may have been caused by the inactive ingredients and not necessarily by the active sunscreen ingredients. The comment concluded that these speculative comments, by themselves, do not raise any significant safety concerns nor do they warrant any kind of additional warnings on OTC sunscreen drug products.

The comment stated that the Topical Analgesic Panel carefully evaluated the safety of the Category I ingredients included in the OTC drug review. The comment maintained that in the data base considered by the Panel no studies raised any serious concerns about skin irritation with these ingredients. The comment added that two commentators at the public meeting had said the following: (1) "We have not seen any problems in either human or animal safety testing," and (2) "in our experience with many, many customers and many cosmetic houses which use sunscreens, there is a negligible risk of exposure to the standard consumer, which actually is so small that it cannot be measured statistically" (Ref. 1). Maintaining that all drug products cause some type of adverse reaction in particular individuals, the comment added that the question is whether, when balanced against the benefit of the drug product, an adverse reaction is significant, taking into account the size of the affected population. The comment stated that sunscreen drug products provide not only protection against sunburn but also against development of skin cancer and other kinds of damage to the skin. The comment argued that these benefits greatly outweigh instances of minor, transitory skin reactions that may occur.

The comment stated that manufacturers report a low incidence of consumer complaints about significant skin irritation resulting from the use of OTC sunscreen drug products. The comment maintained that, if there were significant problems with skin irritation, industry and the agency would have heard of them. The comment added that the Panel's recommended monograph requires the label of a sunscreen drug product to display the following warning: "Discontinue use if signs of irritation or rash appear" (43 FR 38206 at 38268). The comment concluded that there are no valid data in the record that sunscreen drug products currently marketed in the United States pose a risk of significant skin irritation.

One comment submitted data purporting to demonstrate that sunscreen drug products with an SPF above 15 are no more irritating than products with an SPF below 15 (Ref. 2). A 21-day cumulative patch-test procedure was used to determine if there is a correlation between the SPF of a sunscreen and its irritation potential. Five pairs of sunscreens were tested, each pair (from a different manufacturer) consisting of a high and a low SPF product in identical or almost identical vehicles. The study demonstrated that the degree of irritation was sometimes slightly greater in the higher SPF product and sometimes slightly greater in the lower SPF product. The investigator concluded, therefore, that the SPF and the irritation potential have no correlation.

The agency has extensively reviewed the available data and does not believe that sunscreens with SPF values higher than 15 (up to SPF 30) pose any significant safety problems. None of the comments that expressed concern regarding the safety of high SPF products submitted any data or information to substantiate their concerns or to show that higher SPF sunscreen drug products pose a greater safety risk.

In § 352.20 of its recommended monograph, the Panel established no upper limit to the number of sunscreen active ingredients that a product may contain. In the absence of any data to the contrary, the agency agrees with the Panel that any number of sunscreen active ingredients may be combined in a product and is so proposing in § 352.20(a) of this tentative final monograph. Combining various sunscreen ingredients in a product can result in a product that provides protection against a wider spectrum of UV radiation than does a product containing a single sunscreen ingredient. Combinations of sunscreen ingredients, along with improved formulations, also result in products with higher SPF values and afford consumers more protection. However, because the agency requires that each ingredient in a product contribute to the effectiveness of the product, it is proposing in § 352.20(c) of this tentative final monograph that each ingredient in a combination sunscreen drug product should have a minimum concentration. (See comment 37.)

The agency agrees that advances in formulation technology have allowed manufacturers to develop products with relatively low levels of sunscreen active ingredients and still achieve high SPF values. The agency is aware of studies demonstrating the importance of the vehicle on the final performance of a sunscreen drug product. There is a lack of data showing a significant relationship between sunscreen ingredient concentration and the final SPF of a product. In one study (Ref. 3), designed to update performance data of a number of "high potency" sunscreens, the SPF and substantivity of several sunscreens were evaluated according to the testing procedures recommended by the Panel in its report on OTC sunscreen drug products (43 FR 38206 at 38267). The study demonstrated that formulation and vehicle design have a profound effect on SPF values. This was especially evident in the case of three sunscreens, each containing 8 percent padimate O (octyl dimethyl (PABA)) and 6 percent oxybenzone, that were found to have SPF values of 7.85, 15.85, and 18.43. Another sunscreen with a lower total concentration of the same active ingredients (i.e., 8 percent padimate O and 3 percent oxybenzone) had an SPF of 21.

The agency does not believe that increasing the concentration of active ingredients in a sunscreen drug product will necessarily make the product more irritating. The addition of another active ingredient to a drug product always has the potential to increase the risk of increased adverse effects. However, based on the study above (Ref. 3), there may not be any more of a problem in products with SPF values over 15 (up to SPF 30) than there is in products with

lower SPF values. The other study (Ref. 2) also supports this position.

The agency believes that the benefits derived from using a sunscreen drug product with an SPF value up to 30 outweigh any risk that may be present (see comment 46). As stated in comment 47, the agency believes that SPF values should be capped at 30, that any benefits that might be derived from using sunscreen drug products with SPF values higher than 30 are negligible, and that above SPF 30 the risk of added ingredients begins to outweigh the benefit of added protection.

The agency notes that many experts recommended the use of sunscreens with higher SPF values. As stated in comment 46, the NIH Consensus Development Conference Statement recommends the daily use of sunscreens with SPF ratings of 15 or higher (Ref. 4). Over the past several decades, the average consumer's exposure to UVB radiation has increased considerably due to changing lifestyles (e.g., more outdoor recreational activities, more emphasis on tanning, scantier clothing, and a population shift to the sunbelt. Along with increased exposure to UV radiation comes an increased occurrence of adverse effects from UV radiation. For example, the number of office visits for nonmelanoma skin cancer has increased more than 50 percent in the past decade while the overall increase in office visits has been only 11 percent. Therefore, it is imperative to consider ways to minimize the deleterious effects of UV radiation. Use of sunscreens with SPF values of 15 or higher will help to protect susceptible consumers from excessive exposure to UV radiation (Ref. 4).

The AAD also recommends the use of sunscreens with SPF factors of *at least* 15 to protect against premature aging of the skin and skin cancer (Ref. 5). Cancer of the skin occurs more frequently than any other form of cancer, with close to 400,000 new cases reported each year in the United States. As the human body's largest organ and chief protector against environmental onslaught, the skin is vulnerable to cancer-causing attacks. The principal cause is exposure to the UV rays of the sun. The majority of cancers develop on the unprotected parts of the face, neck, ears, forearms, and hands of persons constantly exposed to sunlight. For optimum protection against developing skin cancer, people should avoid constant exposure to the sun from infancy to adulthood. The use of sunscreens with SPF values of at least 15 are preferred for protection (Ref. 5). The agency agrees with these experts and believes that sunscreens with SPF values higher than 15 are beneficial to the consumer and are not safety hazards.

The agency agrees with one comment that stated that the warning recommended by the Panel in § 352.50(c)(1)(iii) protects consumers by informing them to discontinue using a sunscreen drug product if signs of irritation or a rash appears. The agency is proposing in this tentative final monograph to expand the Panel's recommended warning by adding a sentence that informs consumers to consult a doctor if the irritation or rash persists. (See comment 63.)

References

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(2) Comment No. C00096, Docket No. 78N–0038, Dockets Management Branch.

(3) Kaidbey, K. H., and A. M. Kligman, "An Appraisal of the Efficacy and Substantivity of the New High-Potency Sunscreens," *Journal of the American Academy of Dermatology*, 4:566–570, 1981.

(4) "Sunlight, Ultraviolet Radiation, and the Skin," National Institutes of Health Consensus Development Conference Statement, Vol. 7, Number 8, May 8–10, 1989.

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G. Comments on Water Resistant Labeling for Sunscreen Drug Products

49. Referring to recommended § 352.50 "Labeling of sunscreen products," one comment recommended allowing use of the word "perspiration" for "sweat" and the word "perspiring" for "sweating." The comment maintained that because the alternative words are synonymous and are well understood by consumers, they will not mislead or confuse consumers.

The agency concurs with the comment's recommendation and is proposing to allow manufacturers the option of using the words requested. In the labeling for the principal display panel in § 352.50(b) and (c), the "Directions" in § 352.52(d), and the "Statement on product performance" in § 352.52(e)(2), the agency is providing the option of using the terms "perspiration" and "perspiring" in place of the terms "sweat" and "sweating."

50. One comment stated that "water-resistance" is the strongest claim that should be permitted for any sunscreen drug product. The comment asserted that the use of "waterproof" sunscreens can result in occlusion of sweat ducts and hair follicles, contact dermatitis (contact and delayed hypersensitivity), and vesicular dermatitis secondary to the trapping of sweat at some point in the skin. The comment added that the closure of sweat pores can also cause miliaria crystallina and miliaria rubra (prickly heat).

Several comments maintained that consumers do not differentiate between the terms "water resistant", "waterproof," and "sweat resistant." One comment recommended reducing the number of "water-related" claims from three to one (i.e., "water resistant"). One comment stated that the Australian standard AS2604–1986 allows only the claim "water resistant" because it was felt that the claim "waterproof" is an absolute claim and would be construed by consumers that, once applied, the product need not be reapplied. This could be particularly dangerous given the possibility of removing the product while toweling off. The comment felt that the term "water resistant" indicated that some caution was still needed.

Another comment maintained that use of the terms "water resistant" and "waterproof" in sunscreen labeling is confusing and "potentially misleading" to consumers. The comment noted that an attitude and usage survey conducted in 1984 of 564 sunscreen users indicated that both of these terms seem to convey the same idea (i.e., that the product will not wash off during swimming). However, the comment stated that there was slight evidence suggesting that the term "waterproof" implies greater continued protection from the sun after being wet and that consumers preferred products that were labeled waterproof. The comment suggested that using only one term would benefit consumers. The comment asserted that because the waterproof methodology is the more stringent of the two, only products providing protection after the 80-minute water immersion tests should be allowed to make a claim and that claim should be "waterproof." The comment also suggested that the term "sweat resistant" is rarely used in labeling by any manufacturer and suggested that this term be deleted from the monograph. One comment stated that subjecting products to the more stringent standard of waterproof testing would provide a more conservative measure of the substantivity of the product and, therefore, provide the consumer with the most meaningful and accurate information on product performance.

In the Panel's recommended monograph, a "water resistant" sunscreen was described as one which

can withstand 40 minutes of water immersion (§ 352.46(a)); a "waterproof" sunscreen was described as one which can withstand 80 minutes of water immersion (§ 352.46(b)). The first comment did not submit any data or literature references demonstrating that any sunscreen products, including those described by the Panel as waterproof, occlude sweat ducts or hair follicles, or cause contact dermatitis, vesicular dermatitis, miliaria crystallina, or miliaria rubra. The Panel did not identify these conditions as occurring from the use of such products. The other comments also did not submit any data to substantiate their claims that consumers prefer the term "waterproof" or that consumers do not distinguish between "water resistant," "waterproof," or "sweat resistant." The agency therefore has no reason, based on safety concerns or consumer preference, to restrict sunscreen drug products to only "water resistant" or "waterproof" labeling claims.

The agency is concerned, nevertheless, that the term "waterproof," as used in the Panel's recommended monograph, may be confusing or misleading to consumers because of the manner in which consumers may consider this term. The term "waterproof" is defined as "impenetrable to or unaffected by water" (Ref. 1). The agency notes that the Commonwealth of Australia allows only the use of the term "water resistant" in its regulatory standards for sunscreen products (AS 2604–1986) (Ref. 2). According to the Australian Society of Cosmetic Chemists which assisted in the development of these standards, it was decided to recommend against allowing the term "waterproof" because it was an absolute claim whose meaning could be easily misconstrued by consumers (Ref. 3). The agency believes that the term "waterproof" could be interpreted by consumers to describe something that is completely resistant to water regardless of time of immersion, a meaning which is not consistent with the meaning of the term in the Panel's recommended monograph. Therefore, the agency is not proposing the labeling claim "waterproof," but is proposing instead the term "very water resistant." The term "water resistant" is defined as "resistant to wetting but not waterproof." (For a discussion of water resistant and very water resistant testing, see comment 103.)

Regarding the use of the term "sweat resistant," the agency is proposing in this tentative final monograph to permit the use of the terms "sweat resistant" or "resists removal by sweating" for a sunscreen drug product that qualifies for the claims of "water resistant" or "very water resistant." (See comment 100.)

References

(1) "The American Heritage Dictionary of the English Language," Houghton Mifflin Company, Boston, 1976, s.v. "water-resistant" and s.v. "waterproof."

(2) Comment No. C82, Docket No. 78N0038, Dockets Management Branch.

(3) Comment No. C88, Docket No. 78N0038, Dockets Management Branch.

51. In the notice of public meeting to discuss appropriate testing procedures for OTC sunscreen drug products (52 FR 33598), the agency stated that there may be situations in which use of the Panel's recommended criteria for a product to be labeled as "sweat resistant," "water resistant," or "waterproof" could lead to labeling that would be misleading to the consumer. For example, a product in the "moderate" PCD (SPF 4 to under 6) that maintained its PCD after 40 minutes of water immersion could be labeled "water resistant" whereas a product in the "ultra" PCD (SPF 15 or greater) that fell into the "maximal" PCD (SPF 8 to under 15) after the water immersion test could not. The agency was concerned that the Panel's recommended labeling would not reflect that the latter product would provide more sun protection after immersion than would the former. The agency suggested that a possible way of avoiding such a situation would be to label a product with a PCD established under the ordinary test conditions and with a PCD established under the "sweat resistant," "water resistant," or "waterproof" test conditions (52 FR 33598 at 33602).

Several comments were opposed to the idea of including two PCD's or two SPF values in the labeling of OTC sunscreen drug products. Most felt that such labeling would lead to consumer confusion. Stating that there is a history of consumer use of products with only one SPF on their label, one comment contended that providing the consumer with two numbers—one representing the SPF value before water immersion and the other after water immersion—would be confusing and would require a major re-education campaign to facilitate the public's understanding of the new labeling. Another comment stated that much effort has been made to educate the consumer to discern between waterproof and nonwaterproof products. The comment maintained that the labeling requirement for one SPF value recommended by the Panel is appropriate and represents a more conservative (and safer) approach to sunscreen products and consumer expectations. The comment suggested that not only should one SPF number be used on the principal display panel, but also that the description "waterproof," "water resistant," or "nonwaterproof" should be used in the label to qualify the conditions under which the SPF was tested. The comment believed that such labeling would eliminate the possible confusion of the conditions to which the claims applied. Another comment suggested that the agency require a manufacturer to label a sunscreen drug product with the most conservative SPF value that reflects a product's performance. For example, if a product has waterproof properties, then the product label should display a single SPF value determined under the immersion criteria.

One comment stated that using two sets of PCD's or SPF values on a label is inherently misleading and may cause confusion because the consumer may interpret the static SPF (i.e., the initial SPF of a product before water immersion testing) as applying to the waterproof or water resistant claim on the same label. One comment argued that dual labeling is a concession to those manufacturers unable to properly formulate a product with a comparable static or waterproof SPF value. The comment added that if a dual performance standard were imposed, manufacturers would be required to double the number of exposures to each test subject or, alternatively, double the number of test subjects that must be exposed to determine the static and water immersion SPF value.

One comment stated that there is no need to provide dual labeling of static and waterproof SPF values. The comment asserted that the label of a waterproof product only needs to display the waterproof SPF value (and not the static test value). Another comment stated that current labeling of sunscreen drug products makes it clear that the SPF value on the label is the SPF that is to be expected after water immersion. Another comment stated that if a manufacturer wants to make an SPF claim higher than the postimmersion SPF value of the product, the label should not contain "water related" claims. One comment recommended that the value of the SPF be tied to claims for sweat resistance, water resistance, or waterproofing. For example, if an SPF 15 sunscreen displays the claim "water resistant," then the SPF value on the label should reflect the SPF value after 40 minutes of water immersion. Similarly, a "waterproof" sunscreen should be labeled with the SPF obtained after 80 minutes of water immersion. This

would alleviate the need for water resistance claims to be tied to PCD's. It would also eliminate the possibility of an SPF 15 sunscreen decreasing to an SPF 8 after 40 minutes of water immersion and still being labeled as "water resistant."

Conversely, two comments agreed with the agency's proposal that sunscreen drug products should be labeled with both a static and a postimmersion SPF value. One comment stated that consumers would best be served by receiving complete information regarding the degree of protection that they can expect under various conditions, and dual labeling would allow consumers to make an informed purchase decision. The comment maintained that displaying only the waterproof SPF on waterproof sunscreen drug products is potentially misleading and confusing to consumers. The comment feared that a second SPF scale for waterproof products would be created, that it would be difficult for consumers to become aware of this scale, and that consumers would not be given enough information to compare sunscreen drug products on different scales. For example, consumers trying to choose between a static SPF 25 and a waterproof SPF 15 could easily choose the higher number even though its performance in water may be worse. The comment maintained that this result would be avoided by providing the option to list both static and waterproof SPF values for products that have also been tested for waterproofing. The comment added that this option would create consumer awareness of the two scales and would provide enough information for the consumer to make a rational product selection. Another comment proposed that when both static and waterproof SPF values are available for a product, both values should be permitted on the label if there is a difference in SPF levels of more than 5.

One comment stated that it did not believe that a dual labeling of static and waterproof SPF values is necessary. However, the comment maintained that, in special situations where a manufacturer wishes to label its product with both static and waterproof SPF values that are clear, truthful, and not misleading, it should be permitted to do so. The comment added that because such situations would be relatively uncommon, the dual labeling should be optional and not required. The comment supported the concept that truthful and nonmisleading optional labeling of dual static and waterproof SPF values should be allowed but should not be required. The comment added that an SPF value is deemed to be a static, nonwaterproof value unless the waterproof claim is affirmatively made.

The agency does not agree with the comments that dual SPF labeling of sunscreen drug products would be confusing to consumers. Although there is a history of consumer use of sunscreen products with only one SPF value in their labeling, the agency believes that displaying two SPF values on water resistant and very water resistant sunscreen drug products will help to avoid consumer confusion when trying to determine which sunscreen to purchase (e.g., whether a non-water resistant SPF 25 or a water resistant SPF 15 is a more appropriate product for use). Including both a static SPF value and a water resistant or very water resistant SPF value in the labeling of water resistant sunscreen drug products will provide consumers with more information and assist them in selecting the type of product that they desire when purchasing a sunscreen drug product. Because this information involves the SPF values of the product, the agency is proposing that it appear on the principal display panel of the labeling of the product. Furthermore, the agency does not agree with some of the comments that such labeling should be optional. If dual labeling were optional, it would be confusing to the consumer because some water resistant products might display two SPF values while other water resistant products would display only one SPF value.

One comment suggested that the description "waterproof," "water resistant," or "nonwaterproof" be used in the label to qualify the conditions under which the SPF was determined. In § 352.52(e) (2) and (3) of this tentative final monograph, the agency is proposing claims for sunscreen drug products that include "water resistant" for products that satisfy the water resistant testing procedures and "very water resistant" for products that satisfy the very water resistant testing procedures. In the absence of these claims, the agency does not believe that the consumer will expect the product to be water resistant or very water resistant. Regarding the use of the term "sweat resistant," the agency is proposing in this tentative final monograph to permit the use of the terms "sweat resistant" or "resists removal by sweating" for a sunscreen drug product that qualifies for the claims of "water resistant" or "very water resistant." (See comment 100.)

Regarding the comment that manufacturers would be required to double the number of exposures to each test subject or double the number of test subjects if dual SPF labeling were adopted, the agency notes that water resistant and very water resistant testing requires that two SPF values be determined. As the Panel recommended in its discussion of water immersion testing (43 FR 38206 at 38263) and the agency is proposing in § 352.76 of this tentative final monograph, a sunscreen drug product must retain the same PCD after the water immersion testing as it had before water immersion testing. (See comment 101.) Therefore, for all water immersion testing, either double the number of exposures or double the number of test subjects is necessary.

In this tentative final monograph, the agency is proposing the following labeling in § 352.50, *Principal display panel of all sunscreen drug products:*

"(b) *For products that satisfy the water resistant sunscreen product testing procedures in § 352.76.* (1) 'Water Resistant.'

(2) 'SPF=(insert SPF value before water resistant testing) before' (select one of the following: 'sweating' or 'perspiring') 'or going into the water. SPF=(insert SPF value resulting from water resistant testing) after 40 minutes of' (select one of the following: 'sweating' or 'perspiring') 'or activity in the water.'

(c) *For products that satisfy the very water resistant sunscreen product testing procedures in § 352.76.* (1) 'Very Water Resistant.'

(2) 'SPF=(insert SPF value before very water resistant testing) before' (select one of the following: 'sweating' or 'perspiring') 'or going into the water. SPF=(insert SPF value resulting from very water resistant testing) after 80 minutes of' (select one of the following: 'sweating' or 'perspiring') 'or activity in the water.'"

H. Comments on Labeling for Drug/Cosmetic Sunscreen Products Such as Lipsticks, Make-Up Preparations, and Lip Balms

52. Several comments suggested that certain specific types of products containing sunscreens should be exempted from some of the labeling recommended by the Panel for sunscreen drug products. One comment maintained that much of the labeling information required by the Panel's recommended monograph was developed for beach products that are used to acquire a suntan and to prevent painful sunburn. According to the comment, such labeling is "irrelevant, inappropriate, and misleading" for everyday use of nonbeach beauty products that contain a sunscreen but that are not represented for use in the prevention of sunburn.

One comment requested that everyday use, nonbeach beauty products be exempted from bearing the PCD required by the Panel in § 352.50(e) because "PCD labeling statements relate to the protection against sunburn afforded by a particular sunscreen-containing product * * * based on a Sun Protection Factor." Because nonbeach products are not represented for use in the prevention or treatment of sunburn, the comment maintained that the PCD declaration, which relates to the length of time one can intentionally be exposed to the sun without sunburning, is inappropriate. The comment stated that so long as a product containing a sunscreen ingredient is formulated to have an SPF of at least 2, the product provides an effective sunscreen and is permitted to bear claims against skin cancer and premature aging. The comment added that if declaration of the PCD is required for nonbeach products, its placement should not be required on the principal display panel.

One of the comments maintained that the general warnings recommended by the Panel in § 352.50(c)(1) are superfluous for everyday use, nonbeach products because an adult using these products would know the following: (1) That such products are for external use only and are not to be swallowed; (2) that one should avoid contact with the eyes; and (3) that one should discontinue use if signs of irritation or rash appear. One comment suggested that the specific warnings recommended by the Panel in § 352.50(c)(2)(i), "For sunscreen products providing an SPF value of 2 to under 4: Use on children under 2 years of age only with the advice of a physician," and § 352.50(c)(2)(ii), "For sunscreen products providing an SPF value of 4 or greater: Use on children under 6 months of age only with the advice of a physician," should not be required for nonbeach products. The comment asserted that the warnings appear to be designed to prompt parents to consult a pediatrician before intentionally exposing children to the sun for long periods of time. Therefore, the comment stated that these specific warnings have no relevance to everyday use, nonbeach products not labeled for the prevention of sunburn that would rarely, if ever, be used on a child under 2 years of age.

One comment stated that the directions recommended by the Panel in § 352.50(d) clearly relate exclusively to beach products. The comment suggested a simple, straightforward statement of directions, such as "Apply liberally," as sufficient for everyday use, nonbeach products.

One comment maintained that the Panel's recommended rules are designed for the labeling of sunscreen lotions, liquids, and creams that are used over large areas of the body for the prevention of sunburn. It emphasized that lip balms are formulated in a small solid stick form that is used primarily as a skin protectant on a limited, specific part of the body, and protection from the sun's rays is a significant but secondary purpose. Therefore, according to the comment, lip balms should be exempted from some of the labeling recommended by the Panel. Another comment asserted that the Panel did not take the lip balm dosage form into consideration. This comment stated that not only is it physically impossible to place all of the recommended labeling requirements on a lip balm tube, but also several of the labeling requirements are inappropriate for lip balm products.

Another comment requested that lip balms be exempted from the "Statement on Product Performance" requirements and the SPF numbering system. The comment cited the small surface area covered when lip balms are used and asserted that the SPF standards for skin protection would not apply to the lip balm's intended use on lip surfaces. The comment stated that an exemption could be based upon the designation of the product as a lip balm and/or a maximum quantity limitation such as 6 g of total ingredients or 100 milligrams (mg) of sunscreen ingredient.

Three comments suggested that the general warnings in § 352.50(c)(1) are not appropriate for lip balms. Specifically, one comment contended that the warning "For external use only, not to be swallowed" in § 352.50(c)(1)(i) is inappropriate and contradictory for lip balms. The comment asserted that people ingest minute quantities of the product under normal use conditions and that inclusion of the warning on the label would unnecessarily alarm and confuse consumers. A second comment stated that lip balms should be exempted from eye warning requirements because lip balms are not used close to the eyes. Another comment added that the warning "Avoid contact with the eyes" in § 352.50(c)(1)(ii) is unnecessary for a product that is intended for use exclusively on the lips and that is formulated in a solid dosage form that cannot be splashed into the eyes. The comment added that lip balms have been marketed for a number of years and, consequently, consumers are aware of their use and application. The comment maintained that because lip balms are applied to small areas and are formulated with the same type base that has been used for decades without a significant number of adverse reactions, the warning "Discontinue use if signs of irritation or rash appear" in § 352.50(c)(1)(iii) should not be required for lip balms.

Another comment maintained that the warnings required by § 352.50(c)(2)(i) and (c)(2)(ii) should not apply to lip balms. Stating that although it is unlikely that the need for using a lip balm on a child 6 months of age or younger would arise, if such a need did arise, the attention of a physician would not be necessary prior to prophylactic use on the child because of the nature of the tissue and the small area involved.

One comment stated that two ingredients, padimate O and oxybenzone, present in its lip balm product have been proven nontoxic at much higher levels than those used in its formulation, and the comment cited the Panel's report to support this statement (43 FR 38239 and 38244). The comment also submitted three additional toxicity studies (Ref. 1) on its lip balm product supporting its contention that the Panel's recommended labeling is unnecessary for this product. This comment suggested placing only essential information on the label because of the limited label area, and it submitted proposed labeling for its product.

Because lip balms are not designed for use on large skin areas when swimming or sunbathing around water, one comment requested that lip balms be exempted from the directions for use recommended by the Panel. Another comment suggested the following directions for use of lip balms: "Apply liberally as needed."

The agency has tentatively determined that sunscreen-containing products (e.g., sunscreen-containing make-up preparations, skin preparations, lip balms, and lipsticks) that are not specifically indicated for the prevention of sunburn, but which only bear indications for added protection against other harmful effects of the sun such as helping to prevent lip damage, skin damage, freckling or uneven coloration, are drugs under the act. These products may contain both cosmetic and drug labeling. (See comment 27.) However, the agency agrees with the comments that such products are not adequately addressed by the Panel's recommended monograph.

When the Panel reviewed sunscreen drug products, it found that these products were used mainly for sunburn protection. The products were, for the

most part, primarily intended for use under extreme conditions, such as a day at the beach. Since then, as more information has become available regarding the adverse effects of daily exposure to the sun, more and more daily use products have been formulated to contain sunscreens. (For a further discussion of the adverse effects of sunlight, see comments 46, 53 and 56.) Such products are primarily cosmetics to which sunscreens have been added to provide protection against UV radiation. The agency now tentatively concludes that these products are drugs because they contain sunscreens and bear drug claims.

The agency believes that some of the indications recommended by the Panel in § 352.50(b)(1) (e.g., "Sunscreen to help prevent sunburn," and "Screens out the sun's harsh and often harmful rays to prevent sunburn") were intended primarily for traditional sunscreen products. Given the range of products that now contain sunscreens, these indications are not appropriate for use on all of those products. Therefore, the agency is proposing to revise the Panel's recommended § 352.50(b)(1) by adding new indications to be used on the labeling of lipsticks, make-up preparations, lip balms, and other "nonbeach" products that contain sunscreen ingredients and is moving these indications out of § 352.50. The agency is placing these indications in § 352.52 as follows: § 352.52(b)(1)(v) (Select one of the following: "Filters" or "Screens") "out the" (select one of the following: "sun's rays," "sun's harsh rays," or "sun's harmful rays") "to help prevent" (select one or more of the following: "lip damage," "skin damage," "freckling," or "uneven coloration"),," and § 352.52(b)(1)(vi) (Select one of the following: "Protects from" or "Shields from") (select one of the following: "the harmful rays of the sun" or "the sun") "to help prevent" (select one or more of the following: "lip damage," "skin damage," "freckling," or "uneven coloration").

The agency agrees with the comments that the PCD labeling statements in § 352.50(e) of the Panel's recommended monograph are not appropriate or relevant to the use of "nonbeach" products such as make-up preparations, skin preparations, lipsticks, or lip balms that contain sunscreens. The agency is proposing that PCD statements for these products, as well as for other sunscreen products, be optional information that may be used in labeling if a manufacturer wishes. (See comment 44.)

The agency believes that sunscreen-containing drug products that are formulated as lip balms and lipsticks do not require the warning "For external use only, not to be swallowed" recommended in § 352.50(c)(1)(i) of the Panel's monograph. During normal use some of the product will invariably be swallowed; therefore, the above warning might be confusing to consumers. Only minuscule amounts of a sunscreen-containing lip balm or lipstick are likely to be swallowed, and the agency believes that these amounts pose no risk to the user. Consequently, the agency tentatively concludes that the warning is not necessary for the safe use of such products. Furthermore, in the tentative final monograph for OTC skin protectant drug products published in the **Federal Register** of February 15, 1983 (48 FR 6820 at 6829), the agency also concluded that lip balm drug products do not require the warning "For external use only" to assure safe use. Therefore, in this tentative final monograph, the agency is proposing to add § 352.52(c)(3), *"For products containing any ingredient identified in § 352.10 formulated as a lip balm or lipstick.* The warning in paragraph (c)(1)(i) of this section is not required."

The agency believes that any sunscreen-containing drug product that may be used near the eyes should be required to display the warning in § 352.52(c)(1)(ii) of this tentative final monograph, "Avoid contact with the eyes. If contact occurs, rinse eyes thoroughly with water." (See comment 62.) In addition to ocular irritancy problems, a product that is not formulated specifically for the eyes could cause problems because it is not sterile. Therefore, the product should not be placed in the eyes, and consumers should be warned against "contact with the eyes" in the labeling of any product that is intended for use near the eyes. The agency is aware that, although lipsticks are not intended for use near the eyes, there are sunscreen-containing lip balms that are indicated for use on "other sunsensitive areas of the face" such as the nose (Ref. 2). Such lip balms could be used near the eyes, as could other lip balms. Consequently, the agency is proposing to require that these products display the warning.

On the other hand, the agency believes that this warning is not necessary for OTC sunscreen drug products such as lipsticks that are not normally used near the eyes. Therefore, the agency tentatively concludes that lipsticks that contain sunscreen ingredients should not be required to display the warning "Avoid contact with the eyes. If contact occurs, rinse eyes thoroughly with water." The agency is proposing new § 352.52(c)(4) as follows: *"For products containing any ingredient identified in § 352.10 formulated as a lipstick.* The warning in paragraph (c)(1)(ii) of this section is not required."

The agency believes that the warning in § 352.50(c)(1)(iii) of the Panel's proposed monograph, "Discontinue use if signs of irritation or rash appear," is an appropriate warning for any product that contains a sunscreen ingredient. Any product intended for use on the skin may contain ingredients that cause irritation or allergic reactions in susceptible consumers. The appearance of irritation or a rash may be the result of a toxic or allergic reaction to an ingredient in a product; consumers should be adequately warned to discontinue use if such signs appear. The agency is also proposing to revise the Panel's recommended warning by adding the sentence "If irritation or rash persists, consult a doctor." (See comment 63.) Therefore, the agency is proposing the following warning in § 352.52(c)(1)(iii): "Discontinue use if signs of irritation or rash appear. If irritation or rash persists, consult a doctor." The agency is proposing to require this warning for all drug products that contain a sunscreen, irrespective of whether the product is intended for beach or nonbeach use.

The agency believes that the specific warnings proposed by the Panel in § 352.50(c)(2)(i) and (c)(2)(ii) that refer to the use of sunscreen ingredients in children are not relevant to the use of sunscreen-containing make-up products such as foundations or lipsticks that display sunscreen drug claims and that are normally used only in the adult female population. However, the agency concurs with the Panel's age limit recommendations for sunscreen-containing lip balms and skin preparations that display drug claims because such products are more likely to be used on children. The Panel found no convincing evidence that sunscreen ingredients are safe for use on children under the age of 6 months, or that sunscreen products with an SPF value of less than 4 provide reasonable protection for children between 6 months and 2 years of age. The agency has not been presented with any such evidence since the Panel completed its review. In order to be consistent with other recently published documents, the agency is deleting the Panel's recommended warnings in § 352.50(c)(2)(i) and (c)(2)(ii), as discussed below, and is including the content of the warnings in the proposed directions in § 352.52(d). (See comments 61 and 66.)

The agency agrees with the comments that the directions proposed by the

Panel are not relevant to the use of sunscreen-containing drug products, such as lip balms, make-up preparations, and skin preparations, which are not intended for beach use and do not claim to prevent sunburn. Given the similarity in products, the agency believes that the directions for skin protectants proposed in § 347.50(d) of the tentative final monograph for OTC skin protectant drug products (48 FR 6820 at 6833) are appropriate to the above dosage forms if the directions are revised to include age limitations relevant to the dosage forms. Therefore, the agency is proposing in § 352.52(d) the following directions for sunscreen-containing drug products such as lip balms, make-up preparations, skin preparations, and lipsticks:

(4) *For products containing any ingredient identified in § 352.10 labeled with only the indications in § 352.52(b)(1) (v) and/or (vi) and formulated as a make-up preparation or lipstick.* "Apply liberally as often as necessary."

(5) *For products containing any ingredient identified in § 352.10 labeled with only the indications in § 352.52(b)(1) (v) and/or (vi) and formulated as a lip balm or skin preparation.* "Adults and children 6 months of age and over: Apply liberally as often as necessary. Children under 2 years of age should use sunscreen products with a minimum SPF of 4. Children under 6 months of age: consult a doctor."

References

(1) Comment No. SUP004, Docket No. 78N–0038, Dockets Management Branch.

(2) OTC Vol. 060004

I. Comments on Indications for Sunscreen Drug Products

53. One comment stated that the primary emphasis of the Panel's report was on protection against UVB radiation but that the Panel should have addressed the question of photoprotection against UVA radiation (320 to 400 nm). The comment added that UVB radiation shorter than 310 nm contributes only 1.65 percent of the solar energy at the earth's surface. The comment maintained that although UVA radiation is less erythemogenic than UVB radiation, UVA radiation contributes to sunburn reactions when skin is exposed to the sun for prolonged periods (60 to 120 minutes). The comment stated that approximately 8 to 10 percent of the solar energy at the earth's surface is in the UVA range. The comment contended that these UVA wavelengths can stimulate the proliferation of melanocytes and the production of new melanin, are responsible for most of the phototoxic and photoallergic skin reactions, and can contribute to wrinkling and actinic elastosis. Stating that the Panel's report contained no recommendations for the evaluation of sunscreens that absorb radiation in the UVA range, the comment offered to assist in formulating such procedures.

In response to the notice of a public meeting to discuss OTC sunscreen testing procedures (52 FR 33598) and to the January 26, 1988 meeting, the agency received several comments regarding the use of sunscreens to protect individuals against UVA radiation. One comment stated that until recently sunscreens were formulated to protect individuals against UVB radiation (290 to 320 nm) and to allow the transmission of UVA radiation (320 to 400 nm) into the skin for stimulating melanogenesis (tanning reaction). The comment stated that recent evidence appearing in recognized journals of dermatology and photobiology indicates that UVA radiation is erythemogenic and carcinogenic and that it promotes photoaging. The comment added that the growing popularity of high-intensity UVA sources for "cosmetic tanning" has raised serious concerns among dermatologists regarding the potential hazards of UVA radiation to the skin, eyes, and immune system. The comment acknowledged that "a manufacturer must obtain an IND (Investigational New Drug) application to justify its claims" for new UVA absorbing compounds. However, the comment noted that if a company manufactures a sunscreen using the "existing 21 compounds which have been approved by the FDA," the manufacturer may market a UVA sunscreen without an "IND." The comment added that the Photobiology Task Force of the AAD is interested in recommending approaches to the evaluation of UVA absorbing sunscreens and is willing to submit such recommendations to the agency if so directed.

Another comment urged the agency to reopen the administrative record to include the "labeling, evaluation, etc." of "broad-spectrum" sunscreens and to develop a detailed system for adding new active ingredients to the monograph. A third comment stated that the issues of broad spectrum sunscreens are of increasing importance to consumers, but were not directly considered in the submissions to the Panel or in the Panel's recommended rule. These issues include UVA protection and the contribution of UVA radiation to premature aging, wrinkling, and skin cancer. The comment maintained that these issues represent a long-term, chronic health problem that should be addressed by the agency. A fourth comment requested that the agency publish a separate call for data to address sunscreens that provide UVA protection and to discuss methodologies and claims that can be made for these sunscreens.

Data and labeling regarding UVA protection were submitted to the Panel (Refs. 1 through 5), and the Panel discussed UVA radiation in its report (43 FR 38206 at 38209). Several of the 21 sunscreen active ingredients classified as Category I by the Panel have absorption spectra that extend into the UVA range. For example, dioxybenzone (260 to 380 nm) (Ref. 6), methyl anthranilate (290 to 360 nm) (Ref. 7), oxybenzone (270 to 350 nm) (43 FR 38239 and Ref. 6), sulisobenzone (270 to 360 nm) (Ref. 6), red petrolatum (260 to 380 nm) (Ref. 6), titanium dioxide (290–700 nm, UV scatter, complete block) (43 FR 38250 and Ref. 6), octyl methoxycinnamate (290 to 380 nm) (Ref. 6), and octocrylene (290 to 360 nm) (Ref. 6). Lawsone with dihydroxyacetone has been variously reported to absorb UV radiation between 290 and 400 nm (43 FR 38235) and between 290 and 340 nm (Ref. 6).

The Panel's recommended labeling claims for Category I sunscreen ingredients include claims for photoprotection against the harmful rays of the sun that cause sunburn and claims to help reduce the chance of cancer and premature aging of the skin due to the sun (43 FR 38267). However, at the time that the Panel evaluated these ingredients (1973 to 1977), UVA radiation was not commonly accepted as a significant factor in the development of these adverse effects (Refs. 8 and 9). The Panel did not differentiate between UVA and UVB radiation when discussing the adverse effects caused by the sun (43 FR 38209 through 38212). In fact, the Panel did not differentiate between UVA and UVB radiation in its labeling recommendations. For example, the Panel stated that sunscreens protect against "sunburn," the "sun's burning rays," or the "sun's harsh and often harmful rays." Since the Panel's report was published (1978), many reports have been published in the scientific literature indicating that UVA radiation, like UVB radiation, is harmful to the skin. (See comment 66.) Thus, the agency believes that consumers will benefit from labeling on OTC sunscreen drug products that clearly indicates if a

product provides protection against UVA radiation.

The agency is aware that UVA radiation contributes to both acute and chronic skin damage such as erythema, melanogenesis, carcinogenesis, drug-induced photosensitivity, photoaging, and morphological alterations of Langerhans cells (Ref. 6). Although UVB radiation is much more erythemogenic than UVA radiation, the large amount of UVA radiation present in the solar spectrum at the earth's surface results in a significant contribution to erythemogenesis. In fact, UVA radiation may contribute 15 percent of the erythemal effectiveness of the solar spectrum at noon. At other times of the day, because of the greater atmospheric attenuation of shorter wavelengths with increasing zenith angle, the contribution of longer wavelengths may be relatively greater (Ref. 10). It has also been reported that UVA radiation penetrates the skin more efficiently than UVB. Approximately 40 to 50 percent of UVA radiation is transmitted through Caucasian epidermis compared to 10 to 30 percent of UVB radiation (Refs. 11 and 12). UVA radiation penetrates more deeply into the dermis than does UVB radiation (Ref. 12). In addition, the agency is concerned that sunscreens with higher SPF values allow consumers to remain in the sun for long periods of time without burning, thus increasing UVA exposure. Accordingly, protection against UVA radiation is much more important than previously realized. The agency believes that protection against UVA radiation may be as important to consumers' well-being as protection against UVB radiation.

The agency wants to ensure that a sunscreen ingredient claiming to protect consumers against UVA radiation truly offers such protection. According to a 1989 NIH consensus development statement on sunlight, UV radiation, and the skin, recent evidence suggests that the longer UVA wavelengths (i.e., UVA I, 340 to 400 nm) are less damaging than shorter UVA wavelengths (i.e., UVA II, 320 to 340 nm), but further research is needed to confirm the distinction (Ref. 13). It has been reported that long wavelength UVA radiation induces connective tissue damage that is related to human photoaging (Ref. 14) and that wavelengths longer than 340 are effective in producing tumors (Ref. 15). Sunscreen ingredients whose spectra extend only into the lower UVA range (i.e., oxybenzone and possibly lawsone with dihydroxyacetone) may not absorb sufficient UVA radiation to provide an adequate level of protection against that radiation. Thus, UVA protection claims in the labeling of products containing such ingredients would be partially false and would be misleading. To ensure that sunscreen products displaying UVA protection claims offer significant UVA protection, the agency is proposing that a Category I OTC sunscreen ingredient must have an absorption spectrum extending to 360 nm or above in order to display UVA protection claims in its labeling. A product containing such an ingredient must also demonstrate meaningful UVA protection by satisfying the UVA testing method requirements that the agency is proposing be developed and included in this rulemaking. (For a discussion of this testing method, see comment 73.) The agency requests comments on these proposals.

The agency is proposing labeling that would apply if the ingredient meets certain criteria. These criteria are: (1) the ingredient has an absorption spectrum extending to 360 nm or above in the UVA range (e.g., dioxybenzone, lawsone with dihydroxyacetone, octocrylene, octyl methoxycinnamate, red petrolatum, sulisobenzone, and titanium dioxide), and (2) the product containing the ingredient demonstrates UVA protection using appropriate testing procedures that the agency is proposing be developed. The labeling for acceptable products would include the following: (Select one of the following: "Protects against," "Absorbs," "Screens out," or "Shields from") "UVA" (select one of the following: "Rays" or "radiation"). A product that contains ingredients that absorb and/or reflect both UVA and UVB radiation may also display the following labeling: "Broad spectrum sunscreen; provides protection against UVB and UVA radiation." As noted in comment 73, there is a lack of adequate information for FDA to propose a method for determining UVA protection. Accordingly, although these indications are discussed in this document for public comment, they are not currently included in the tentative final monograph. At this time, OTC sunscreen drug products may bear UVA claims provided that they (1) Contain sunscreen active ingredients that absorb UVA radiation (e.g., dioxybenzone, lawsone with dihydroxyacetone, octocrylene, octyl methoxycinnamate, red petrolatum, sulisobenzone, and titanium dioxide), and (2) meet the agency's enforcement policy which allows claims that were available in labeling prior to the beginning of the OTC drug review to appear in the labeling of currently marketed products until the rulemaking for OTC sunscreen drug products is completed, and the regulation for this class of products becomes effective (Ref. 16).

The agency does not believe that a separate call for data is necessary to address OTC sunscreens that provide UVA protection. Some data have already been submitted to this rulemaking, and this publication informs interested persons how the agency is proceeding. Any interested person may submit data and information in response to the publication of this proposed rule. If necessary, an amendment to this tentative final monograph will be published in a future issue of the Federal Register to address any comments concerning UVA claims and testing procedures received in response to this proposal.

The agency emphasizes that ingredients not included in the monograph, and new chemical entities that protect against UVA exposure, are considered to be new drugs; as new drugs they must be the subject of an approved application before they may be marketed in the United States with UVA claims. The agency's detailed comments on the data are on file in the Dockets Management Branch (Ref. 17).

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(17) Letters from W.E. Gilbertson, FDA, to T.P. Koestler, Westwood Pharmaceuticals, Inc., K.M. O'Brien, Schering-Plough Corporation, S. Kortschak, Mary Kay Cosmetics, Inc., N.J. Lowe, UCLA School of Medicine, M. A. Pathak, Harvard Medical School, coded LET44, LET46, LET48, LET49, and LET51, respectively, in Docket No. 78N–0038, Dockets Management Branch.

54. One comment suggested that the first sentence of the indications section (§ 352.50(b)) be revised as follows: "The labeling of the product contains a statement of the indications under the heading 'Indication(s)' and is limited to one or more of the following phrases, which may be combined to eliminate duplicative words or phrases." The comment contended that the phrase "which may be combined to eliminate duplicative words or phrases" appears in other OTC drug monographs and allows the inclusion of all pertinent information without redundancy.

The agency agrees that wherever practicable duplicative words and phrases in the indications should be eliminated. The agency has applied this principle in developing the indications proposed in this tentative final monograph. The agency has combined some of the Panel's recommended indications, revised others, and provided several optional ways for stating some indications. (See comments 56, 57, and 58.) Additionally, the agency has revised its labeling policy to allow for more alternatives in stating the indications for all OTC drug products. (See comment 39.) Therefore, it is not necessary to make the revision suggested by the comment.

55. One comment believed that sunscreen drug products with an SPF of 2 should not be allowed to make a claim for sunburn protection. The comment felt that the laboratory conditions under which an SPF is determined are artificial and are not likely to duplicate actual usage conditions. The comment stated that sunbathers apply sunscreens while in constant physical activity, and therefore rubbing against clothing, towels, etc., is almost unavoidable. This activity plus high temperature, humidity, and sweating collectively reduce the efficacy of a sunscreen in sunlight. The comment submitted a published paper (Ref. 1) discussing studies that it contended found a poor correlation between the indoor (laboratory) SPF value and the SPF value determined in sunlight. The SPF value determined in sunlight was significantly lower, which the authors attributed to heat, perspiration, etc., during outdoor testing. Thus, according to the comment, a product with a laboratory SPF of 2 will provide virtually no protection in sunlight, and a consumer using such a product will have "a false sense of safety." The comment stated that it is widely recognized that chronic UV radiation damage is a cumulative phenomenon, with every exposure contributing to the final damage. The comment contended that individuals who are allegedly "not-sun-sensitive" and use sunscreen products with low SPF values are at risk if they use products with an SPF of 2. The comment stated that every effort should be made to "spare" individuals from unnecessary UV exposure and, therefore, the lowest allowable SPF value should be 4.

The Panel discussed various skin types and the categories of sunscreen products recommended for each skin type (43 FR 38206 at 38213 to 38215). The Panel determined that there are six skin types based on the different reactions of individuals to sunlight, i.e., whether they burn easily, moderately, or not at all. Of the six skin types, the Panel listed three types, i.e., IV, V, and VI, for individuals who burn minimally, rarely burn, or never burn. For Skin Types IV and V, the Panel recommended sunscreen products that provide a minimal amount of protection with SPF values of 2 to under 4. For individuals with Skin Type VI, the use of a sunscreen product was not recommended.

Because there is a population who could use sunscreen products providing minimal protection, the agency believes that it would be inappropriate to eliminate these products from the marketplace. Such products offer protection to those individuals who burn minimally or rarely burn. Therefore, the agency does not accept the comment's recommendation. The agency is proposing a product category designation of "minimal" for sunscreen drug products that have an SPF value of 2 to under 4 and offer minimal protection against sunburn. As part of required labeling information, the agency is proposing a Recommended Sunscreen Product Guide that will provide consumer information on skin types and corresponding recommended SPF values of sunscreen drug products. (See comment 43.)

The agency has considered the paper submitted by the comment that shows a difference between the indoor (laboratory) SPF value and the outdoor (sunlight) SPF value (Ref. 1). The agency notes that the authors stated that the study demonstrated that the solar simulator can accurately reproduce the sunburn erythemogenic effect of natural solar radiation. However, the authors also stated that factors other than UV radiation enter into the determination of the SPF of a sunscreen product (e.g., environmental factors, such as skin temperature). The authors contended that if these environmental conditions are controlled, the SPF value obtained with a solar simulator is similar to that obtained using natural sunlight. A later study by some of the same authors (Ref. 2) showed good correlation between the indoor and outdoor SPF's of sunscreens with high substantivity. (See comment 79 for further discussion of this subject.)

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56. Several comments urged the agency to adopt the Panel's recommended labeling in § 352.50(b)(1)(iv) that states, "Overexposure to the sun may lead to premature aging of the skin and skin cancer. The liberal and regular use over the years of this product may help reduce the chance of these harmful effects," and in § 352.50(b)(1)(v) that states, "Overexposure to the sun may lead to premature aging of the skin and skin cancer. The liberal and regular use over the years of this product may help reduce the chance of premature aging of the skin and skin cancer." One comment noted that a final rule published in the **Federal Register** of April 29, 1977 (42 FR 22018) required a warning on the labels of aerosolized products containing chlorofluorocarbons. In that rule, the agency stated that the use of aerosols containing those ingredients could contribute to degradation of the earth's ozone layer, resulting in an increase in UV radiation and a possible increase in

skin cancer. The comment stated that in recognizing the risk of skin cancer from exposure to UV radiation in that document, the agency advocated educating the public on the risk of excessive exposure to the sun. Stating that this "warning/indication" labeling is based on clear and convincing scientific evidence, the comment objected to the Commissioner's statement in the preamble to the Panel's report (43 FR 38206) that this labeling might be misleading or confusing to consumers.

A second comment contended that the Commissioner based his statement concerning the aging/cancer warning/indication labeling in part on a minority report of three of the seven Panel members, who were opposed to the use of these statements. The comment argued that the minority report did not question the conclusion of the Panel majority. According to the comment, the minority report addressed the majority's presupposition that a person will use a sunscreen product correctly and that there may be skin alterations not yet manifested that could result in skin cancer whether or not the product is used. With respect to pre-existing skin conditions that could lead to cancer, the comment stated that "no drug product will aid in the prevention of a disease condition once that condition has occurred." The comment further stated that the minority report did not fully consider the language of these statements. The comment explained that, although the statements inform the consumer that the product may help prevent the harmful effects of the sun, they do not promise that the product will absolutely prevent the harmful effects. The comment urged the Commissioner to discount the minority report and to adopt the labeling recommended by the Panel majority. The comment concluded that the proposed statements would be an effective means of educating the public to use a sunscreen product early, regularly, and liberally in order to minimize the detrimental effects of long-term overexposure to UV radiation from the sun.

The comment also suggested adding to the above statements terminology that describes premature aging of the skin due to overexposure to UV radiation, e.g., "wrinkling of the skin." Noting the Panel's statement that "Premature aging of the skin refers to the thinning, dryness, and fine wrinkling produced by the exposure of the skin to sunlight" (43 FR 38206 at 38211), the comment contended that addition of such information to the Panel's recommended statements would aid consumers' understanding of the consequences of overexposure to the sun, and would implement the Panel's recommendations.

Two comments objected to labeling sunscreen drug products with claims concerning premature aging of the skin and skin cancer. One comment maintained that such labeling is unnecessary because everyone knows that exposure to the sun may lead to premature skin aging and skin cancer. The other comment stated that sunscreen products will not prevent skin cancer on skin that sunburns easily. This comment argued that any mention of helping to prevent cancer on the label of sunscreen products should be avoided because it may mislead people into a false sense of security. Referring to a sunscreen lotion labeled with the statement "May help prevent harmful effects * * * skin cancer," the comment recommended that the qualifying phrase "Not in high altitude" be added to the label. Referring to personal experience, the comment added that a basal cell epithelioma still developed even though a sunscreen lotion was used all summer and sun exposure was avoided between the hours of 10:00 a.m. and 4:00 p.m.

Three comments supported the indication "may reduce harmful effects of the sun" recommended by the Panel minority (43 FR 38212). One comment added that the recommended indication would be good if the word "may" is legible because consumers do not read fine print. A second comment suggested combining this indication with part of the Panel's recommended indications in § 352.50 (b)(1)(iv) and (b)(1)(v), as follows: "May reduce harmful sun rays that may lead to premature aging of the skin and skin cancer." A third comment suggested that the recommended indications in § 352.50 (b)(1)(iv) and (b)(1)(v), which refer to "liberal and regular use," should be revised to state "proper and regular use" or "when used regularly as directed."

Another comment contended that the wording of the Panel's recommended statements in § 352.50 (b)(1)(iv) and (b)(1)(v) will be exploited by advertisers and that consumers will be misled. The comment stated that it agreed to a certain extent with the report of the Panel minority (43 FR 38206 at 38212) in that "any claim of this nature should only be approved if it is supported by experimental data." According to the comment, it is not scientifically correct to state that any sunscreen will reduce the harmful effects of the sun because the protection afforded by a sunscreen product with an SPF value of 8 or more (PCD designation maximal, ultra) is being equated with that afforded by a product having an SPF value of 2. In addition, the comment stated that the term "skin cancer" in the indication statement should be changed to "nonmelanoma skin cancer" because the claim that the regular use of sunscreens may help reduce the chance of melanoma skin cancer should be investigated before approval. Stating that the word "nonmelanoma" has no meaning to consumers, a reply comment disagreed with the recommendation that "skin cancer" be changed to "nonmelanoma skin cancer." The reply comment also contended that even an SPF of 2 will provide twice the skin's natural protection from disease states that may be caused by long-term overexposure to UVB radiation.

The agency has reviewed recently published literature (Refs. 1 through 11) that was not available to the Panel. This literature supports the Panel's view that (1) exposure to sunlight/UV radiation is related to skin cancer and premature aging (i.e., skin aging), and (2) the regular use of sunscreens will reduce individuals' risk of skin aging and skin cancer due to the sun (43 FR 38206 at 38210 to 38211). The Panel recommended that the labeling of sunscreen drug products should alert the consumer to the harmful effects of sunlight (43 FR 38211); however, the indications suggested by the Panel in § 352.50 (b)(1)(vi) and (b)(1)(vii) of its monograph are optional labeling. The agency agrees with the Panel that consumers should be alerted to the risks of premature skin aging and skin cancer due to exposure to the sun. The agency also agrees with one comment that such labeling would be an effective means of educating the public to use sunscreens to minimize the detrimental effects of long-term exposure to the sun. Because of the seriousness of these adverse effects, the agency is proposing labeling in this tentative final monograph that will require all sunscreen drug products to inform consumers that the sun may damage the skin and that using sunscreens may help to reduce the risk of damage. After carefully considering the Panel's recommendations in § 352.50 (b)(1)(iv) and (b)(1)(v), which identified the risks of skin aging and skin cancer due to the sun, the recommendations of the Panel minority which did not identify the specific risks (43 FR 38206 at 38212), the available literature (Refs. 1 through 11), and the comments regarding these labeling recommendations, the agency is proposing to revise the Panel's recommendations in § 352.50 (b)(1)(iv) and (b)(1)(v) (as described below) and

including the revised statement in § 352.52(e)(6) of this tentative final monograph.

The agency disagrees with the comment that stated that the indications that warn of harmful effects of the sun should not apply to all sunscreens, because sunscreens with low SPF values are not equivalent in protection to sunscreens with high SPF values. While the use of sunscreens with high SPF values provides greater protection from the harmful effects of the sun, any reduction in exposure to the sun, regardless of SPF value, may be of benefit in reducing the risks of harmful effects. Furthermore, consumers with nonsensitive skin who only need to use sunscreens with low SPF values should also be warned of the harmful effects of sunlight. In addition, the agency believes that a statement relating to the harmful effects of the sun should be required in the labeling of all sunscreen drug products.

The agency does not agree that the indications recommended by the Panel in § 352.50 (b)(1)(iv) and (b)(1)(v) should warn the consumer that the sunscreen product will not help protect the consumer from skin cancer at high altitudes. The amount of incident light is affected by many factors, only one of which is altitude. While the comment has merit, the agency finds it impractical to include in the labeling just one of many factors that may increase exposure. Further, this information could be misleading unless all factors that may increase exposure were included. The agency sees no reason to require such labeling. However, the agency is not opposed to such descriptive information appearing in the labeling of sunscreen drug products if manufacturers wish to include it, provided that the information does not appear in the required labeling, is truthful, and is not misleading.

The agency does not believe that "premature aging" of the skin should be defined as "wrinkling" in the indications recommended by the Panel in § 352.50 (b)(1)(iv) and (b)(1)(v). Wrinkling is only a part of the process of premature aging of the skin due to excessive exposure to UV radiation and should not be elevated to greater significance than other signs of premature skin photoaging. In addition to wrinkling, photoaged skin displays a variety of benign, premalignant and malignant neoplasms, accentuated skin furrows, sags and bags, and a leathery, nodular, yellow surface with telangiectatic (i.e., a vascular lesion formed by the dilation of a group of small blood vessels) traceries. The most drastic of these visible aspects reflect the profound structural changes in the dermis (Ref. 5). (For a discussion of the agency's tentative conclusion regarding the use of the term "anti-aging" or similar terms in the labeling of OTC sunscreen drug products, see part II. paragraphs B.51, 52, and 53—Summary of the Agency's Changes.)

The agency believes that changing the term "skin cancer" to "nonmelanoma skin cancer" in the indications recommended by the Panel in § 352.50 (b)(1)(iv) and (b)(1)(v), as suggested by one comment, is unnecessary. Most consumers are not likely to recognize the term or would need a specific definition to decide whether or not to use sunscreens to help reduce the chance of skin cancer. To avoid misleading those consumers who are aware of specific types of skin cancer, the agency is proposing language that refers to "some types of skin cancer" rather than "skin cancer."

The agency agrees with one of the comments that the indications proposed by the Panel in § 352.50 (b)(1)(iv) and (b)(1)(v) should be revised and is proposing to replace the Panel's recommended phrase "the liberal and regular use over the years" with the phrase "regular use * * * over the years" because regular use is more important than liberal use. The agency notes that proper use of some sunscreen formulations does not require "liberal" application. In this tentative final monograph, the agency is proposing directions for OTC sunscreen drug products that are applicable to various dosage forms. (See comment 66.)

Because this proposed statement combines the attributes of an indication and a warning and is informational in nature, the agency believes that the statement should stand on its own and be distinctive in labeling. The agency is aware that some marketed products contain labeling entitled "Red Alert" to remind consumers to avoid the sun when the skin begins to burn (turn red). The agency agrees with using the term "ALERT" to readily gain consumers' attention when reading a label. However, the agency believes that for these products the term "SUN ALERT" is more informative to consumers. Further, consumers should be advised to be careful regarding all sun exposure, not only exposure after the skin has begun to burn. Therefore, in this tentative final monograph, the agency is proposing a new heading, "SUN ALERT."

The agency is further proposing that the heading "SUN ALERT" be followed by a statement that has been developed by simplifying the "skin aging/cancer" indications recommended by the Panel in § 352.50 (b)(v) and (b)(vi). This revision begins with a positive statement for which extensive scientific evidence exists: "The sun causes skin damage." The agency has determined that the term "overexposure," recommended by the Panel, is not necessary in this statement because any amount of sun exposure can potentially harm the skin. The amount of sun exposure that will cause harmful effects is relative to a person's skin type and predisposition to skin damage, and thus is not appropriate in labeling. The term "premature" has also not been included in the proposed statement because the agency believes that this term has different meanings to different individuals. The agency is not aware of any data showing that the term is generally understood by consumers when describing effects of the sun on the skin.

The new proposed statement includes the phrase "regular use of sunscreens over the years," which implies that any sunscreen may reduce the chance of the harmful effects due to the sun. Otherwise, the Panel's recommended statement "regular use over the years of this product" constitutes an endorsement of the specific sunscreen drug product on which the labeling statement appears. Evidence shows that any sunscreen when properly applied may help reduce the chance of the harmful effects of the sun. In addition, the term "liberal" has not been included in the statement because individual products provide adequate directions for use.

The agency invites specific comment on this proposed new "SUN ALERT" labeling statement. The agency encourages manufacturers to include this statement in the labeling of all sunscreen drug products. Until the final rule for OTC sunscreen drug products is published, manufacturers may use either the Panel's earlier recommended statement or this proposed "SUN ALERT" statement in their products' labeling. The final monograph will state the exact language that will need to be used when it becomes effective. (For further discussion of the "SUN ALERT" statement, see part II, paragraphs B.51, 52, and 53—Summary of Agency Changes.)

The agency has carefully examined the wording of the indications proposed by the Panel in § 352.50 (b)(1)(iv) and (b)(1)(v) and has revised the language to eliminate vague or unnecessary terms resulting in a single required statement. The agency believes that this statement should appear verbatim on all sunscreen drug products, regardless of any other labeling, and should be preceded by the

phrase "SUN ALERT." Any language in the product's labeling that does not relate skin aging or skin cancer as being "due to the sun" will cause the product to be misbranded under section 502 of the act (21 U.S.C. 352). (See Part II, paragraphs B.51, 52, and 53—Summary of the Agency's Changes, for labeling information that is appropriate for daily use (nonbeach products) as well as for products that are intended for occasional use (beach products).)

Therefore, in this tentative final monograph, the agency is proposing to replace the Panel's recommended § 352.50 (b)(1)(iv) and (b)(1)(v) with the following statement in § 352.52(b)(6): *For products containing any ingredient in § 352.10, the following statement may be used.* "SUN ALERT: The sun causes skin damage. Regular use of sunscreens over the years may reduce the chance of skin damage, some types of skin cancer, and other harmful effects due to the sun."

The agency is also proposing to include in § 352.52(e)(7) the following statement: *For products containing any ingredient identified in § 352.10.* Any variation of the statement in § 352.52(e)(6) that does not relate skin aging or skin cancer as being "due to the sun" will cause the product to be misbranded under section 502 of the act (21 U.S.C. 352).

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(10) "Focus on Photodamage," edited by the Skin Phototrauma Foundation, in OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

(11) Epstein, J. H., "Preventing Sun Damage," *The Skin Cancer Foundation Journal* 8:7 and 92–93, 1990.

57. One comment questioned the use of the word "before" in § 352.50(e), which states that the user may "Stay in the sun twice [4 times, etc.] as long as before without sunburning." The comment argued that "before" is very vague and could imply that a product is twice as effective as other products. The comment suggested that the statement should reflect the wording recommended by the Panel under "Additional indications" (§ 352.50(b)(2)) by stating that the user could stay in the sun two (four, six, etc.) times "longer than without sunscreen protection." Another comment suggested that the statement "Provides _____times your natural protection against sunburn" would be clearer than the Panel's recommended labeling.

Another comment contended that the application density used in the sunscreen testing procedures is often very different from the actual amount of sunscreen applied by a consumer during normal usage. Therefore, the claim "(this sunscreen product) provides x times your natural sunburn protection," where "x" equals the sunscreen's SPF, is usually false because the two preconditions that are necessary to support this claim are rarely met. The comment described the two preconditions as (1) the application density used by the consumer must be the same as that used in the sunscreen testing procedures, and (2) the SPF value of a sunscreen product must be the same whether tested indoors using artificial UV radiation sources or outside using the sun as the UV-radiation source.

In order to resolve this apparent dilemma, the comment suggested that the agency should disallow the claim that a sunscreen "provides x times your natural sunburn protection." The comment added that "Provides *up to* x times your natural sunburn protection" is a viable alternate claim. The comment maintained that if this claim were eliminated or altered as suggested, the SPF number on a product would continue to provide consumers with a means of comparing sunscreens but would be a relative, rather than an absolute, parameter for evaluating sun protection.

In § 352.50(b)(2) of its recommended monograph, the Panel included several indications that could be used in addition to the indications recommended in § 352.50(b)(1). These additional indications are based upon a product's PCD and include two basic indications that refer indirectly to the product's SPF value. For example, in § 352.50(b)(2)(i)(*f*), (b)(2)(ii)(*e*), (b)(2)(iii)(*g*), and (b)(2)(iv)(*e*), the Panel recommended that sunscreen products could display the following indication according to their PCD: "Allows you to stay in the sun [two, four, six, or eight] times longer than without sunscreen protection." In § 352.50(b)(2)(i)(*g*), (b)(2)(ii)(*f*), (b)(2)(iii)(*h*), and (b)(2)(iv)(*f*), the Panel recommended the following: "Provides [two, four, six, or eight] times your natural protection from sunburn." In § 352.50(e)(1), *Labeling claims for Product Category Designation (PCD)*, the Panel also recommended that the following labeling statement be placed on the principal display panel of sunscreen drug products in accordance with their PCD's: "* * * (SPF [2, 4, 6, 8, or 15]). Stay in the sun [twice, 4 times, 6 times, 8 times, or 15 times] as long as before without sunburning."

The agency believes that the concept of "up to the actual SPF value of the product" suggested by the comment provides a more accurate estimate of the protection a consumer can expect from a sunscreen product than the statements recommended by the Panel. Therefore, the agency is proposing to use the wording "up to" in applicable indications. In this tentative final monograph, the agency is not proposing the Panel's recommended indications in § 352.50(b)(2)(i)(*f*), (b)(2)(i)(*g*), (b)(2)(ii)(*e*), (b)(2)(ii)(*f*), (b)(2)(iii)(*g*), (b)(2)(iii)(*h*), (b)(2)(iv)(*e*), and (b)(2)(iv)(*f*), but is instead proposing the following indications in § 352.52 (b)(1)(iii) and (b)(1)(iv): "Allows you to stay in the sun up to (insert SPF of product up to 30) times longer than without sunscreen protection," and "Provides up to (insert SPF of product up to 30) times your natural protection from sunburn." The agency is proposing that the product's labeling display its tested SPF value, as determined by using the agency's proposed sunscreen testing procedures (see comment 45).

The agency agrees with the comment that the term "as long as before" used by the Panel in its recommended statements on product performance is vague and does not tell the consumer "before what." Moreover, the agency believes that the intent of the Panel's recommended phrase "stay in the sun [twice, 4 times, 6 times, 8 times, or 15 times] as long as before without sunburning" in the statements on product performance in § 352.50 (e)(1)(i) through (e)(1)(v) is adequately covered in the indications being proposed in

§ 352.52 (b)(1)(iii) and (b)(1)(iv) of this tentative final monograph. Therefore, the agency is not proposing the Panel's recommended phrase "stay in the sun [twice, 4 times, 6 times, 8 times, or 15 times] as long as before without sunburning" in § 352.52(e) "Statement on product performance" of this tentative final monograph. The indications that were proposed by the Panel in § 352.50 (b)(1)(iv) and (b)(1)(v) of its recommended monograph are being combined, and the combined indication is included in proposed § 352.52(b)(1)(vii). (See comment 56.)

58. Several comments contended that "tanning" and related terms with no "representation" for prevention of sunburn are not drug claims but are traditional cosmetic claims. The comments maintained that "tanning representations" may not properly be regulated in an OTC drug regulation. Accordingly, these comments suggested deleting all reference to "tanning" from the monograph and revising § 352.50(b), "Indications," to address only labeling regarding the prevention of sunburn.

One comment suggested three alternative means for regulating tanning claims. Its preferred alternative is for FDA to consider tanning claims to be cosmetic claims and to regulate them under section 602(a) of the act (21 U.S.C 362). The comment contended that the consumer perceives "tanning" to be a cosmetic benefit in terms of a "tan equals beauty" equation. The comment recommended that manufacturers be permitted the widest latitude in placing tanning claims on the labeling of their products. The comment added that consumers will be better informed regarding the selection of suitable tanning products if information regarding skin types and the quality of tan permitted by the product is placed on the labeling. The comment stated that section 602(a) of the act gives the Commissioner authority to act if a cosmetic claim is false or misleading. The comment also contended that this approach avoids regulation where none is needed; if regulation should be needed for tanning claims, it may be implemented by proposing additional cosmetic regulations.

The second alternative suggested by the comment is that tanning claims or "representations" are descriptive of product attributes and should not be regulated as indications. Remarking that indications relate to how an active ingredient functions relative to a disease or potential disease state, the comment stated that tanning is neither a disease nor a potential disease state. The comment contended that a product's permitting of tanning and the degree, depth, or scope of tanning are a function of the amount of sunscreen in the product and of the unique product formulation characteristics. Therefore, tanning is not an indication, but a descriptive product attribute. As a third alternative, the comment recommended that if tanning claims are included in the rulemaking as drug indications, then the monograph should be expanded to provide differential tanning information for each PCD group.

Two comments stated out that the Panel's recommended additional indications in § 352.50(b)(2)(i) and (b)(2)(ii) do not inform consumers of the degree of tanning that may be expected with minimal and moderate sunscreen products; whereas, on the other hand, the Panel allowed the following labeling for other sunscreen products: for extra sunscreen products, the phrases "limited tanning" and "extra protection;" for maximal sunscreen products, the phrases "limits tanning" and "maximal protection;" and for ultra sunscreen products, the phrases "prevents tanning" and "ultra protection." The comments added that the knowledge that individuals tan and burn to different degrees mandates that such information be provided to the consumer for all sunscreen products to permit a proper product choice. The comments argued for labeling information regarding sunscreen-containing products' tanning ability and product skin-type use information. The comments contended that without this information consumers seeking a dark, deep, or fast tan may use products that contain no sunscreens but that make claims such as "deep, dark tan."

One comment recommended that § 352.50(b)(2)(i) be expanded to include for minimal sunscreen products the statements "Permits darkest, deepest tan" and "Minimal (minimum) protection against sunburn," and that § 352.50(b)(2)(ii) be expanded to include for moderate sunscreen products the statements "Permits moderate (dark) tanning" and "Moderate protection against sunburn."

The other comment recommended that §§ 352.50(b)(2)(i) and (b)(2)(ii) be modified so that the indications will inform consumers about skin type information and the product's ability to permit increased tanning. The comment recommended that § 352.50(b)(2)(i) be expanded to include the following: "Permits fastest, darkest (maximum) tan (tanning);" "Minimal (minimum) protection against sunburn for persons who rarely burn and tan profusely;" and "Minimal (minimum) protection for persons who burn minimally and always tan well." The comment further recommended that § 352.50(b)(2)(ii) be expanded to include the following: "Permits fast, dark (moderate) tan (tanning)," and "Moderate protection for persons who burn (sunburn) moderately and tan gradually." The comment concluded that these recommendations should only be implemented if the agency determines that tanning claims are drug claims.

Although tanning claims have traditionally been considered to be cosmetic claims, based upon numerous factors discussed below, the agency has now tentatively determined that tanning claims used in conjunction with a sunscreen ingredient are drug claims. The Panel included tanning claims in its recommended monograph for OTC sunscreen drug products because such claims are very closely related to the sunscreening ability of the products. Both the sunscreen ingredient in the product and the SPF of the product directly influence the amount of tanning that occurs (i.e., the more radiation that a sunscreen product blocks or absorbs, the less tanning that the product permits). A "tanning" product that contains a sunscreen controls a physiological process (melanogenesis), i.e., it affects the function or structure of the body and is, therefore, a drug. Even if the sunscreening activity is not mentioned in the product's labeling, its intent clearly is (1) to prevent a disease (i.e, sunburn), and (2) to affect a function of the body (i.e., prevent melanogenesis). Both of these intended uses are drug activities under section 201(g) of the act (21 U.S.C. 321(g)).

The agency agrees with one of the comments that consumers will be better informed regarding the selection of suitable sunscreen products if information related to skin types and the quality of tanning permitted by the product is in its labeling. The agency believes that tanning claims should be included in the monograph because such claims help to more fully define the skin protection qualities provided by a sunscreen drug product and help consumers to determine which product is most appropriate for them to use. Failure to provide information pertaining to the tanning potential that exists with the use of a sunscreen might encourage consumers seeking a dark, deep tan or a fast tan to use products without a sunscreen ingredient, thus exposing them unnecessarily to possible skin damage. For these consumers, a sunscreen drug product allows the acquisition of a dark tan plus, more importantly, provides protection from harmful UV radiation.

The agency disagrees with one of the comments that tanning claims are

descriptive of product attributes and, therefore, are not indications. Based upon current scientific information, the agency believes that any reference to tanning on a product that contains a sunscreen ingredient is an indication that the product will affect a function of the body, that is, prevent melanogenesis. A finding of a 1989 NIH Consensus Development Conference was that, although tanning may provide some protection against further damage by UV radiation, all evidence indicates that UV radiation-induced tanning is itself harmful to the skin (Ref. 1). Tanning is accompanied by an increase in the number of DOPA-positive melanocytes, an increase in the number and melanization of melanosomes, and an increase in dendricity of melanocytes. UV radiation also increases the transfer of melanosomes from melanocytes to keratinocytes. Following UV radiation exposure, melanosomes diffusely distributed within the keratinocytes collect above the nucleus, forming a cap over it. Hawk and Parrish (Ref. 2) state that the induction of delayed tanning (i.e., the long-lasting tan induced by repeated exposure to UV radiation) follows UVB radiation doses of about 1.5 MEDs and is probably related to UV injury to melanocytes or keratinocytes. They add that melanocytes are probably always damaged by UV radiation before melanogenesis begins because ¼ MED or less of solar-simulating radiation can lead to DNA damage in basal cells. Based on the above, the agency now considers any reference to tanning in the labeling of a sunscreen drug product to be an indication regulated by the monograph for OTC sunscreen drug products. (For further discussion of the use of "tanning" claims on sunscreen-containing products, see comment 27.)

The agency does not agree with the comments that the Panel's recommended §§ 352.50(b)(2)(i) and (b)(2)(ii) should be expanded to further inform consumers of the degree of tanning that may be expected from a sunscreen drug product. The statements recommended by the Panel are adequate to inform the consumer that sunscreen drug products that provide minimal and moderate protection also permit tanning. The agency does not believe that additional qualifying phrases or terms are necessary. The quality of tanning depends upon many things including the individual's genetic predisposition to tanning, as one comment indicated and the Panel noted (43 FR 38206 at 38210), and the length of time that the individual remains in the sun.

Therefore, the agency is proposing the tanning claims that were set out in § 352.50(b)(2)(i)(*c*), (b)(2)(i)(*e*), (b)(2)(ii)(*c*), (b)(2)(iii)(*c*), (b)(2)(iv)(*b*), (b)(2)(v)(*b*), (b)(2)(v)(*e*), and (b)(2)(v)(*f*) of the Panel's recommended monograph. These tanning claims are included in § 352.52(b)(2) *"Additional indications"* of this tentative final monograph and may be used in addition to the required indications in § 352.52(b)(1) if the manufacturer wishes to do so. These claims can be included in the boxed area or under "APPROVED USES" in the labeling of OTC sunscreen drug products in accordance with § 330.1(c).

The other indications recommended by one of the comments, i.e., "Minimal (minimum) protection against sunburn" and "Moderate protection against sunburn," are substantially the same as the following claims recommended by the Panel in § 352.50(b)(2)(i)(*a*) and (b)(2)(ii)(*a*): "Affords minimal protection against sunburn" and "Affords moderate protection against sunburn." The agency believes that the Panel's recommended indications can be revised to accommodate the comment's suggestion by adding the word "minimum" to the Panel's recommended indication in § 352.50(b)(2)(i)(*a*). In addition, the agency believes that the word "Provides" may be better understood by consumers than the Panel's recommended word "Affords" and that the words "extra" and "maximal" should be revised to "high" and "very high" to reflect the agency's proposed revision of the PCD labeling. (See comment 45.) Therefore, the agency is proposing the following indications in §§ 352.52(b)(2):

(i)(A) (Select one of the following: "Provides minimal," "Provides minimum," "Minimal," or "Minimum") "protection against sunburn."

(ii)(A) (Select one of the following: "Provides moderate" or "Moderate") "protection against sunburn."

(iii)(A) (Select one of the following: "Provides high" or "High") "protection against sunburn."

(iv)(A) (Select one of the following: "Provides very high" or "Very high") "protection against sunburn."

(v)(A) (Select one of the following: "Provides the most" or "The most") "protection against sunburn."

With regard to one comment's concern that skin type information be made available to consumers, the agency is proposing a "Recommended Sunscreen Product Guide" that includes skin type information as part of the required labeling of OTC sunscreen drug products. (See comment 43.)

References

(1) "Sunlight, Ultraviolet Radiation, and the Skin," National Institutes of Health Consensus Development Conference Statement, Vol. 7, Number 8, May 8–10, 1989.

(2) Hawk, J. L. M., and J. A. Parrish, "Responses of Normal Skin to UV Radiation," *in* "The Science of Photomedicine," edited by J. D. Regan and J. A. Parrish, Plenum Press, New York, 1982, p. 242.

59. One comment objected to the use of indications that would state that a sunscreen drug product can completely prevent tanning. Referring to the Panel's recommended labeling for ultra sunscreen drug products (43 FR 38206 at 38214), the comment objected to the statement that the product "permits no tanning" because it is inconsistent with the scientific facts. The comment explained that the most effective products (ultra sunscreens) will significantly reduce the tanning response of an individual, but that the tanning ability of individuals varies, and this tanning ability is genetically predetermined. Explaining further, the comment added that an individual with Skin Type I or II will not tan as easily as an individual with Skin Type IV or V. The comment stated that an ultra sunscreen drug product which may not permit tanning in individuals with Skin Types I or II will certainly permit tanning, although at a reduced rate, in individuals with Skin Types IV or V. The comment requested that the statement "permits no tanning" be modified to reflect this fact. The comment suggested that this statement include the information that sunscreens with an SPF of 8 or more may not permit tanning in certain individuals (Skin Types I and II) who burn easily but tan poorly, but may permit some tanning in those individuals (Skin Types IV or V) who burn moderately or minimally. The comment also stated that tanning stimulated by UVA radiation cannot be blocked by the sunscreens that contain only the UVB absorbing active ingredients and that UVA radiation may cause tanning in individuals with a genetic predisposition and Skin Types III or IV.

The Panel's recommended indications for ultra sunscreens included "Prevents tanning and sunburn" in § 352.50(b)(2)(v)(*b*) and "Provides the highest degree of sunburn protection and permits no tanning" in § 352.50(b)(2)(v)(*e*). The Panel defined ultra sunscreens as follows: "Sunscreen products that provide an SPF value of 15 or greater, offer the most protection

from sunburning and permit no suntanning," (43 FR 38206 at 38213). The Panel stated, however, that "The tanning ability of an individual is genetically predetermined and is governed by the individual's capacity to produce melanin pigment within the pigment cells (melanocytes) when stimulated by UVB and UVA," (43 FR 38210).

The agency is proposing the term "ultra high" to describe sunscreen drug products that provide the most protection from UV radiation and is defining such products in § 352.3(b)(5) as follows: "Sunscreen products that provide an SPF value of 20 to 30, offer the most protection from sunburning, and permit no suntanning." The agency agrees that sunscreen drug products with the same SPF value may completely inhibit tanning in some individuals while perhaps permitting other individuals to tan. However, the labeling of a product cannot describe all possibilities without becoming cumbersome. The agency believes that the Panel's recommended labeling that refers to the different degrees of tanning permitted by various products is appropriate to inform the consumer regarding the protective qualities of that product. Therefore, the agency is including the labeling recommended by the Panel in § 352.50(b)(2)(v)(*b*) of its monograph in proposed § 352.52(b)(2)(v)(B).

The agency is combining the labeling recommended by the Panel in § 352.50(b)(2)(e) and (b)(2)(f) of its monograph and is including the revised additional indication in proposed § 352.52(b)(2)(v)(E) as follows: "Provides the highest degree of" (select one of the following: "sunburn" or "sunscreen") "protection and permits no tanning."

60. One comment objected to the Panel's definition of a "sunscreen opaque sunblock" in § 352.3(c) as "An opaque sunscreen active ingredient that reflects or scatters all light in the UV and visible range * * * and thereby prevents or minimizes suntan and sunburn." The comment argued that the definition of the term "sunblock" need not be limited to opaque substances and that this definition does not reflect what the comment felt to be consumer comprehension of a sunblock as a physical or chemical substance that prevents or minimizes sunburn. The comment stated that the Panel's recommended additional indication for ultra sunscreen products in § 352.50(b)(2)(v)(*b*), "Prevents tanning and sunburn," and suggested that if a sunblock prevents sunburn, and an ultra sunscreen prevents sunburn, then an ultra sunscreen must be a sunblock. The comment recommended that "sunblock" be included as an additional indication for ultra sunscreens in § 352.50(b)(2)(v) because this term is meaningful to consumers seeking a product that will prevent sunburn.

In its discussion of sunscreen agents, the Panel classified therapeutic sunscreens into categories based upon their UV radiation screening capacity (43 FR 38206 at 38213). One of the categories adopted by the Panel in its effort to find meaningful terms to describe the use of sunscreen agents was "sunscreen opaque sunblock agent," which it defined as "an opaque agent that reflects or scatters all light in the UV and visible range at wavelengths from 290 to 777 nm and thereby prevents or minimizes suntan and sunburn." Sunscreen active ingredients that are not opaque sunblocks act by absorbing UV radiation. These active ingredients do not necessarily absorb all UV radiation. Opaque sunblocks, however, reflect or scatter all light. Titanium dioxide is the only Category I sunscreen active ingredient recommended by the Panel that fits the definition of an "opaque agent" (43 FR 38206 at 38250). Zinc oxide, for which the agency is proposing a Category III classification, may also fit the definition of a sunblock. (See comment 36.) The Panel also noted that transparent sunblock agents are not yet available in the OTC drug marketplace. The comment did not submit any evidence supporting its contention that consumers think of a sunblock as a physical or chemical substance that prevents or minimizes sunburn. The agency believes that the term "sunblock" should refer to sunscreen drug products containing opaque sunscreen active ingredients.

The agency does not agree with the comment that if a sunblock prevents sunburn, and if an ultra high sunscreen prevents sunburn, then an ultra high sunscreen must be a sunblock. (See comment 45 for a discussion of new terminology for PCD's.) An ultra high sunscreen drug product may contain an opaque sunblock ingredient, or it may contain a sunscreen ingredient that is not an opaque sunblock ingredient so long as the final product provides an SPF of 20 to 30. A product with a high SPF may also contain an opaque sunblock ingredient or a sunscreen ingredient that is not an opaque sunblock ingredient so long as the final product provides an SPF of 12 to under 20. (For a discussion of SPF values as they relate to PCD's, see comment 45.) High and ultra high sunscreen products that contain a sunscreen opaque sunblock ingredient may display the indication in § 352.52(b)(3) *For products containing the active ingredient identified in § 352.10(s) that provide an SPF of 12 to 30, the following labeling statement may be used:* "Reflects the burning rays of the sun."

The agency does not agree with the comment's recommendation that "sunblock" be included as an additional indication for ultra high sunscreen drug products because the term "sunblock" is not an indication for use. Rather, it is a term that is descriptive of product performance or the name of a type of ingredient that may be used in a sunscreen drug product. The agency agrees with the comment that the descriptive term "sunblock" would be informative to users of OTC sunscreen drug products. The agency believes that the term "sunblock" may be used as an additional statement of product performance on sunscreen drug products that contain the ingredient titanium dioxide and provide an SPF of 12 or higher. Therefore, the agency is proposing the following additional statement in § 352.52(e)(5) *For products containing the active ingredient identified in § 352.10(s) that provide an SPF of 12 to 30, the following labeling statement may be used:* "Sunblock."

J. Comments on Warnings for Sunscreen Drug Products

61. Two comments urged that the Panel's recommended warnings in § 352.50(c)(2) (i) and (ii) be deleted. The warning in § 352.50(c)(2)(i) states that sunscreen products providing an SPF value of 2 to under 4 should be used on children under 2 years of age only with the advice of a physician. The warning in § 352.50(c)(2)(ii) states that sunscreen products providing an SPF value of 4 or greater should be used on children under 6 months of age only with the advice of a physician. Both comments stated that these warnings would dissuade the use of sunscreens on children, with one comment adding that children are in need of greater protection from the sun than adults.

One comment contended that these warnings could communicate to the parent that it is better to expose the child to the sun with no protection than to protect the child with a sunscreen product. This comment also stated that the Panel may have recommended these warnings because of its concern about the permeability of children's skin. The comment added that in 1976 Maibach had presented data to the Panel showing that within days after birth a child's skin behaves much the same as adult skin regarding permeability (Ref. 1). According to the comment, the greater

permeability of a child's skin as compared to an adult's skin has not been established. Consequently, the comment contended that "the risks attendant to inclusion of the warning far outweigh the benefits achieved by the deletion of the warnings."

A third comment disagreed with the Panel's conclusion at 43 FR 38217 that sunscreen products should not be used on children under 6 months of age. The comment strongly recommended that sunscreen products with high SPF values be used on babies if they are exposed to direct or indirect sunlight but added that direct exposure should be avoided.

The literature and data concerning sunscreens that the Panel reviewed included information on the percutaneous penetration of drugs and chemicals in infants and young children. The Panel did not find any convincing evidence that sunscreen active ingredients are safe for use on children under the age of 6 months and recommended that sunscreen products should not be used on children under 6 months of age. The Panel also recommended that sunscreen products with an SPF value of 2 to under 4 should not be used on children under 2 years of age (43 FR 38217). In other words, only sunscreen products providing a minimum SPF of 4 should be used on children between the ages of 6 months and 2 years. All sunscreen products, regardless of their SPF value, may be used on children 2 years of age and older.

The agency believes that sunscreen products may help to protect a child under the age of 6 months from the damaging effects of sunlight. However, the possible adverse effects of sunscreen active ingredients on a child of that age also must be considered. The agency, like the Panel (43 FR 38217), is concerned that biological systems that metabolize and excrete drugs absorbed through the skin may not be fully developed in children under the age of 6 months.

The agency agrees that children between 6 months and 2 years of age need sunscreen protection. Based on this need, the agency is proposing that only sunscreens that have a minimum SPF value of 4 or more be used on children in this age group. The agency does not believe that a sunscreen with an SPF value less than 4 provides enough protection for children in this age range. The agency also believes that children under 6 months of age should not be in the sun for prolonged periods of time. Therefore, they have little or no need for sunscreens. If, by chance, an infant under 6 months of age should need a sunscreen, the parent should ask a doctor which sunscreen to use. Therefore, the agency concurs with the Panel's age limitation recommendations for sunscreen drug products. The agency notes, however, that in the Panel's recommended monograph, the age limitations in the recommended warnings in § 352.50(c)(2)(i) and (c)(2)(ii) were also included in the directions in § 352.50(d)(1)(i) and (d)(1)(ii) (43 FR 38268). In other recently published tentative final monographs, the agency has been including age limitation information in the directions for use. Therefore, the agency is deleting the Panel's recommended warnings in § 352.50(c)(2)(i) and (c)(2)(ii), but the content of the warnings, with some minor format changes, is being proposed in the directions included in § 352.52(d). (See comment 66.)

Reference

(1) Transcript of the 27th Meeting of the Topical Analgesic Panel, November 18, 1976, pp. 4 to 44, in OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

62. One comment objected to the Panel's recommended warning in § 352.50(c)(1)(ii), "Avoid contact with the eyes." The comment contended that this warning might discourage consumers from using sunscreen products on the face. The comment asserted that such use of sunscreen products should be encouraged because the face is the part of the human body most often exposed to UV rays and skin cancer occurs more frequently on the face than on other parts of the body. The comment suggested the following warning instead, which, it stated, would not be so general as to discourage use of sunscreens in the eye area and would tell the consumer what to do if the product did enter the eye: "If contact with eyes occurs, flush eyes with tepid water." The comment stated that according to the Panel (43 FR 38206 at 38244), padimate O is not a primary irritant to the cornea or iris at concentrations of 2 and 5 percent; therefore, an eye-contact warning should not be required for products containing this ingredient. Adding that certain products such as lip balms with sunscreens are not indicated for use near the eyes, the comment requested that lip balms be exempt from any eye warning requirement.

The agency believes that the warning "Avoid contact with the eyes" should appear in the labeling of all sunscreen-containing products except for those products that are not intended for use around or near the eyes, such as lip balms and lipsticks. (See comment 52.) The agency considers this warning to be necessary because most sunscreen products are used on the face and can accidentally get into the eyes. Moreover, the agency believes that a warning statement similar to that suggested by the comment would be additional useful information to a consumer because any sunscreen used on a consumer's face could get into the eyes. Similar warnings (e.g., "Avoid contact with eyes. In case of contact, flush eyes with water" and "Avoid contact with eyes, eyelids and mouth. If contact occurs, rinse thoroughly with water.") currently appear on some OTC sunscreen drug products (Ref. 1). The agency notes that the comment has included the word "tepid" in the warning to describe the type of water that should be used to rinse the eyes. However, the comment did not provide any reason for this change. The agency is not aware of any reason to specify that "tepid" water must be used. Accordingly, the agency is proposing to amend the Panel's recommended warning in § 352.50(c)(1)(ii) as follows: "Avoid contact with the eyes. If contact occurs, rinse eyes thoroughly with water." and to include the revised warning in proposed § 352.52(c)(1)(ii).

The agency disagrees with the comment that products containing padimate O should not be required to bear the eye-contact warning. The Panel stated that 2 and 5 percent padimate O in mineral oil was not a primary irritant to the cornea and iris of test animals. The Panel noted that, in one study, 2 percent padimate O was at the upper limit of the mild primary irritant range in regard to its effect on this conjunctiva, as hyperemia was observed. In other eye irritation studies, 5 percent padimate O caused slight redness of the conjunctiva of each test animal on the first and second days following treatment (43 FR 38244). The Panel did not review all possible sunscreen drug product formulations. The agency believes that vehicles used to formulate the various sunscreen products may have different effects on the eye(s) and might also cause irritation. Therefore, if padimate O is included in the final monograph (see preamble discussion of padimate O above), products containing this active ingredient would not be exempted from the eye-contact warning.

Reference

(1) Labeling contained in OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

63. Several comments described adverse reactions resulting from the use of sunscreen drug products containing aminobenzoic acid. One comment

reported experiencing swelling of the face, swelling of the eyes causing them to close, and an allergic skin reaction after using a sunscreen drug product containing aminobenzoic acid in a cream formulation. The comment recommended that the labels of sunscreen drug products containing this ingredient display a prominent warning for the benefit of consumers with allergies. A second comment reported that several trials had shown aminobenzoic acid to sting and burn. (No supporting data or literature references were submitted.) The comment stated that only 3 percent aminobenzoic acid is allowed in Europe and that no European company uses aminobenzoic acid. The comment submitted an abstract of a presentation by Hodges, et al. (Ref. 1) regarding the sensitizing effect of aminobenzoic acid in a test on *Escherichia coli (E. coli)*. A third comment expressed concern that the warning on a sunscreen drug product containing aminobenzoic acid was not strong enough. The comment, from a consumer who once had skin cancer, reported experiencing a rash after using the product on a substantial area of the body. The comment added that many people who will use these sunscreens have had skin cancer or very sensitive skin. A fourth comment recommended that FDA publicize safety guidelines for sunscreen ingredients and, if hazards are present, weigh these hazards against the hazards of overexposure for sun-sensitive people.

One comment requested that the agency consider labeling sunscreen drug products in clear, bold letters as either "PABA SUNSCREEN" or "NON-PABA SUNSCREEN." The comment stated that products appropriately labeled will enable consumers to choose the proper sunscreen. Two other comments disagreed with this comment. One comment stated that because PABA (i.e., aminobenzoic acid) and its derivatives are active sunscreen ingredients, they must already be listed in the labeling of OTC sunscreen drug products. The comment maintained that consumers who are concerned about the presence of these ingredients need only check the active ingredient list to ascertain their presence in the sunscreen drug product. The comment added that requiring a statement in "bold letters" is unnecessary and urged the agency not to adopt this recommendation. The other comment stated that there is no reason to treat aminobenzoic acid differently from other sunscreen active ingredients.

The agency is aware that some individuals can have moderate or acute adverse reactions to active ingredients which cause no reactions in most people. The Panel, in reviewing the submitted literature on the safety of aminobenzoic acid, determined that the incidence of adverse reactions to aminobenzoic acid was low and individual intolerance was rare (43 FR 38206 at 38220). In the submitted abstract (Ref. 1), Hodges, et al. report on the survival levels of a repair deficient strain of *E. coli* following exposure to 313 nm UV radiation and to varying concentrations of aminobenzoic acid up to a maximum of 0.1 percent. The abstract states that the survival level of the bacteria decreases with increasing concentrations of aminobenzoic acid. The abstract does not explain how the effect of aminobenzoic acid on the survival level of a repair resistant strain of *E. coli* can be extrapolated to humans.

The agency has reviewed its adverse reaction files for the years 1979 to 1989; 14 cases of adverse reactions associated with the use of sunscreen products containing aminobenzoic acid were reported to FDA (Ref. 2). The reports show that allergic reaction, rash, pruritus, dermal exfoliation, and a few other problems occurred. However, only one report showed a serious reaction that might be attributed to aminobenzoic acid. Because the reported adverse reactions were mostly dermal problems, the agency agrees with the Panel that the appropriate warning for sunscreen products containing aminobenzoic acid would be "Discontinue use if signs of irritation or rash appear." However, the agency is proposing to add to the Panel's recommended warning additional guidance to the consumer, i.e., "If irritation or rash persists, consult a doctor." This addition to the warning is proposed in § 352.52(c)(1)(iii). The agency believes that these proposed warning statements are sufficient to alert consumers to the possibility of an allergic reaction to aminobenzoic acid or any other sunscreen active ingredient. Therefore, it is unnecessary for a product to be labeled as either a "PABA SUNSCREEN" or a "NON-PABA SUNSCREEN." In addition, the agency notes that the official name for PABA is aminobenzoic acid and that is the name that should be used in labeling (see comment 30).

References

(1) Hodges, N.D.M., S.H. Moss, and D.S.G. Davies, "The Sensitizing Effect of a Sunscreen Agent, Para-aminobenzoic Acid, on Near Ultraviolet Induced Damage in a Repair Deficient Strain of *Escherichia coli*," abstract of a paper presented at the 7th International Congress on Photobiology, September 1976, Rome.

(2) Department of Health and Human Services, Food and Drug Administration, Adverse Reaction Summary Listings for the years 1979 to 1989, OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

64. In response to the January 26, 1988 public meeting at which sunscreens with SPF values above 15 and sunscreen testing methods were discussed, one comment suggested that sunscreens with SPF values of 15 or above should include ingredients that offer UVA protection or prominently state that the product does not provide UVA protection. The comment indicated that the consumer is entitled to know if a high SPF product does or does not provide substantial protection against UVA because the scientific literature suggests that UVA is just as likely as UVB to contribute to photoaging and skin cancer and, in cases of prolonged exposure, erythema.

Another comment also indicated that the consumer is entitled to know if a high SPF product does or does not offer substantial broad spectrum protection. The comment contended that consumers purchasing high SPF products are as much interested in the antiaging and anticancer benefits of the products as they are in the erythema protection benefits. Moreover, the comment added, the proposed monograph encourages consumers to focus on photoaging and skin cancer concerns in that it permits manufacturers to claim that sunscreen drug products offer such protection. Because both UVA and UVB spectra contribute to photoaging and skin cancer, as well as erythema, the comment recommended that the agency consider requiring manufacturers to disclose the absence of UVA protection in high SPF products.

One comment was concerned that subjects taking part in the testing of high SPF sunscreen drug products will receive very high doses of intermediate and long-wave UVA radiation unless the product under test contains an agent that blocks out these wavelengths, or the solar simulator is appropriately filtered. The comment added that similar concerns apply, to some extent, to the use by consumers of products that do not include an appropriate UVA blocking agent. Another comment stated that for sunscreens with SPF values higher than 10, the amount of unfiltered UVA is such that aggression of tegument tissues is important. The comment added that this type of aggression is not detected by erythema, which is the recommended and available end point for the sunscreen testing procedures.

As stated in comment 53, the agency is aware that UVA radiation contributes to both acute and chronic skin damage

such as erythema, melanogenesis, carcinogenesis, drug-induced photosensitivity, and photoaging. Sunscreens with higher SPF values allow consumers to remain in the sun for long periods of time without burning, thus increasing UVA exposure. The agency believes that protection against UVA radiation may be as important to a consumer's well-being as protection against UVB radiation. Therefore, the agency is proposing in this tentative final monograph conditions under which an OTC sunscreen drug product may identify itself as a "broad spectrum" sunscreen. Such a product would be able to include UVA protection claims in its labeling as discussed in comment 53.

Regarding the comments' recommendation that manufacturers be required to disclose in labeling the absence of UVA protection in some high SPF products, the agency believes there is some merit to this recommendation. Persons using such products have a tendency to remain in the sun for long periods of time, with increased exposure to UVA radiation. The agency is proposing in this tentative final monograph that sunscreen drug products that provide both UVA and UVB protection be allowed to state that they are a "broad spectrum" sunscreen and that they provide protection against UVA radiation. FDA believes that the message that the comments have recommended (i.e., does not provide UVA protection) would be useful to consumers, and the agency wants to develop language that would be meaningful to consumers. (Normally, the labeling of OTC drug products does not contain "negative" statements—i.e., that the product does not do a certain thing. Some manufacturers have done so for ingredients voluntarily, e.g., "Contains no caffeine.") Possible language that could be used in this situation includes "does not provide UVA protection" or "does not provide broad spectrum protection." The agency invites further comment as to whether such information should be required in the labeling of OTC sunscreen drug products and how it could best be presented to users of these products. The agency also requests available data that show consumers' understanding and knowledge of terms such as "UVA," "UVB," and "broad spectrum" as related to sunscreen drug products. At this time, the agency is not proposing any specific language requiring a manufacturer to disclose the absence of UVA protection for a sunscreen product with an SPF value of 15 or above. The agency also invites comments as to whether such information should appear only in the labeling of sunscreen drug products with an SPF value of 15 or above or should appear in the labeling of any sunscreen drug product not providing such protection regardless of its SPF value. The agency will address this issue further in a future issue of the **Federal Register** after evaluating the comments received.

65. One comment stated that care must be taken in recommending sunscreens for chronic use because they suppress cutaneous vitamin D_3 synthesis. To support its contention, the comment cited a recent paper by Matsuoka, et al. (Ref. 1) in which a single application of an aminobenzoic acid-containing sunscreen (SPF 8) interfered with the cutaneous synthesis of vitamin D_3.

Although exposure of the skin to UVB radiation produces a variety of pathological effects such as sunburn, immunological changes, and skin cancer, UVB radiation is essential for the endogenous production of vitamin D_3. The relationship of sunshine to vitamin D_3 and the normal growth and development of the skeleton is well known (Ref. 2). The agency is aware that there is evidence that vitamin D_3 synthesis is inhibited by the use of sunscreen drug products. However, Matsuoka, et al. (Ref. 1) stated that the effect of sunscreen drug products to limit or prevent the cutaneous production of vitamin D_3 is probably of little consequence for children and young adults who obtain adequate vitamin D nutrition from their diet and frequent exposure to sunlight. They added that the elderly, who are more prone to developing vitamin D deficiency, could increase their risk of vitamin D deficiency if they consistently apply a sunscreen before going outdoors. The authors suggested that elderly chronic users of sunscreens should be routinely investigated for vitamin D deficiency. A 1989 NIH consensus development conference basically agreed that, in the United States, sunscreen inhibition of vitamin D_3 synthesis does not present a health hazard for the pediatric population, although deficiencies may exist in elderly populations (Ref. 2). Matsuoka, et al. (Ref. 1) recommended that elderly persons who might be at risk from constant use of a sunscreen may be advised to take supplemental vitamin D_3 or to omit sunscreen use and expose their skin only to suberythemal doses of sunlight. In the case of prolonged outdoor activities, a topical sunscreen may be applied immediately after the initial exposure.

The comment did not distinguish between the use of sunscreens by any age group. The agency does not believe that there should be a warning on sunscreen drug products regarding vitamin D_3 suppression, because such a warning might discourage the use of sunscreens, especially in children. Both Matsuoka, et al. (Ref. 1), and the NIH consensus development conference (Ref. 2) stated that the inhibition of vitamin D_3 synthesis by sunscreens does not present a health hazard for the pediatric population. Further, the agency considers the use of sunscreens in children to be especially important because much of the skin damage that appears in adulthood is a cumulative result of sun exposure in childhood (Ref. 3). The NIH consensus development conference stated that it is important for the public health that sunscreen drug products be used frequently and properly (Ref. 2). The agency concurs and is proposing labeling that it hopes will meet these objectives. The agency invites public comment on whether any of the above information related to the use of sunscreens by elderly persons should appear in the labeling of sunscreen drug products.

References

(1) Matsuoka, L.Y., et al., "Sunscreens Suppress Cutaneous Vitamin D_3 Synthesis," *Journal of Clinical Endocrinology and Metabolism*, 64:1165–1168, 1987.

(2) "Sunlight, Ultraviolet Radiation, and the Skin," National Institutes of Health Consensus Development Conference Statement, Vol. 7, Number 8, May 8–10, 1989.

(3) Stern, R.S., M.C. Weinstein, and S.G. Baker, "Risk Reduction for Nonmelanoma Skin Cancer with Childhood Sunscreen Use," *Archives of Dermatology*, 122:537–545, 1986.

(4) "Cancer of the Skin," edited by the Task Force on Pamphlets, American Academy of Dermatology, Evanston, IL, 1986.

K. Comments on Directions for Sunscreen Drug Products

66. Referring to the "Directions for use" in § 352.50(d), in which the Panel recommended that all sunscreen products be applied liberally, one comment contended that liberal or heavy application is not required for some formulations to be effective and, in some cases, may decrease efficacy. The comment stated that because certain vehicles "crack, peel or pill" when applied too heavily, these products require an even application to dry skin. The comment argued that, because sunscreen products are available in a variety of forms (oils, lotions, creams, sprays, etc.), the monograph should allow manufacturers to develop specific application

instructions based on clinical experience with the formulation.

The agency has reviewed the suggested changes and agrees with the comment that the proper use of some formulations does not require liberal or heavy application for the reasons stated by the comment. Therefore, to allow for variations in the application of different product formulations, the agency believes that the Panel's recommended directions in § 352.50(d) (1) and (2) may not be adequate for all types of sunscreen drug products.

To accommodate the various dosage forms of sunscreen drug products that are available, the agency is including in proposed § 352.52(d) only brief, required directions for sunscreen drug products. The monograph will also provide that manufacturers can voluntarily expand and supplement these required directions with more detailed instructions applicable to a particular product formulation and dosage form. In addition, as discussed in comment 105, the agency is proposing that manufacturers determine the waiting period (the time between applying a sunscreen drug product and exposing the test site to water, if applicable) for water resistant and very water resistant sunscreen drug products and include this information in the labeling. Accordingly, the agency is proposing the following directions in § 352.52(d):

(d) *Directions.* The labeling of the product contains the following information 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 that do not satisfy the water resistant or very water resistant testing procedures in § 352.76.* "Adults and children 6 months of age and over: Apply" (select one or more of the following, as applicable: "liberally," "generously," "smoothly," or "evenly") "before sun exposure. Reapply after swimming, excessive" (select one of the following: "sweating," or "perspiring,") "or anytime after towel drying. Children under 2 years of age should use sunscreen products with a minimum SPF of 4. Children under 6 months of age: consult a doctor."

(2) *For sunscreen products containing any ingredient in § 352.10 that satisfy the water resistant or very water resistant testing procedures in § 352.76.* "Adults and children 6 months of age and over: Apply" (select one or more of the following, as applicable: "liberally," "generously," "smoothly," or "evenly") "(insert appropriate time interval, if a waiting period is needed) before sun or water exposure. Reapply after" [select one of the following: "40 minutes" (if water resistant) or "80 minutes" (if very water resistant)] "of swimming or excessive" (select one of the following: "sweating," or "perspiring,") "or anytime after towel drying. Children under 2 years of age should use sunscreen products with a minimum SPF of 4. Children under 6 months of age: consult a doctor."

67. Referring to the directions for water resistant sunscreen drug products recommended by the Panel in § 352.50(d)(2)(i), one comment objected to the requirement for reapplication after 40 minutes in the water. Because a product must retain its original PCD after 40 minutes of swimming in order to qualify as water resistant, the comment found the requirement to reapply the product after this time period to be contradictory. The comment requested that the monograph be revised to allow manufacturers the option of testing to determine the minimum immersion period that would cause a reduction in the product's PCD value and then labeling the product with the reapplication instructions based on these test results. Alternatively, the comment stated that those manufacturers not wanting to conduct further tests would be required to use the 40-minute reapplication time. The comment added that these options should also apply to the directions for waterproof and sweat resistant products. (The agency is substituting the term "very water resistant" in place of the term "waterproof" in this tentative final monograph. See comment 50.)

Another comment stated that the Australian standard, AS2604–1986, allows only the claim "water resistant," but gives reasonable scope in that the label claim can include how long consumers can stay in the water before reapplication is necessary. For example, the comment noted that several products are now claiming "water resistant for up to two hours."

The agency disagrees with the comment's suggestion that the monograph be revised to allow manufacturers to test for the minimum immersion period that would cause a reduction in the product's PCD and to include this time for reapplication of the product in the directions for use. The directions to reapply a water resistant sunscreen drug product after 40 minutes in water are based on the testing guidelines for establishing that the product is water resistant. In order to be labeled as a water resistant sunscreen drug product, the SPF value of the product after water immersion testing must remain within the PCD range into which the product was originally categorized. This time is included in the monograph directions applicable to such a product because it ensures a safe lower limit of the effectiveness of the product.

The agency believes that permitting a proliferation of reapplication times, based upon the actual time period a product can retain its PCD while undergoing water immersion testing, would lead to consumer confusion and may be unsafe. In general, sunscreen drug products should be reapplied frequently in order to be most effective. The agency believes that consumers should be encouraged to reapply water resistant or very water resistant sunscreen drug products at minimal time intervals. A water resistant or very water resistant sunscreen drug product should enable an individual to maintain a certain level of protection from the harmful rays of the sun. This is especially important for individuals with a high risk of wash-off such as children who may be constantly in and out of the water and who may remain in a beach/pool environment for long periods of time. The agency considers two designations (i.e., water resistant for 40 minutes and very water resistant for 80 minutes) to be adequate as to the number of categories and times appropriate for the safe and effective use of such products. The agency believes that requiring the labeling to state that the product should be reapplied after 40 minutes for water resistant or after 80 minutes for very water resistant sunscreen drug products helps to ensure that consumers receive maximum protection from sunlight both when in and out of water.

Regarding the comment's statement that the options it suggested for water resistant products should also apply to very water resistant and sweat resistant sunscreen drug products, the agency agrees with the reapplication times included in the Panel's recommended directions in § 352.50(d)(2)(ii) for very water resistant sunscreen drug products. If the product maintains its PCD after 80 minutes of water immersion, it can be labeled "very water resistant" and contain directions for reapplication after 80 minutes. The agency is not including the Panel's recommended "sweat resistant" test or directions for use of products that satisfy the sweat resistance test in this tentative final monograph. A product that passes the water resistant or very water resistant tests is also permitted to make "sweat resistant" claims. (See comment 100.)

The agency believes that consumers should be directed to reapply water

resistant and very water resistant sunscreen drug products after 40 or 80 minutes, as appropriate. Therefore, the agency is including the Panel's recommended times for reapplication of water resistant and very water resistant sunscreen drug products in the directions for use of these products in proposed § 352.52(d)(2).

68. One comment recommended that labeling directions include the following statement in block letters: "FOR INFORMATION, ASK A PHARMACIST." The comment contended that consumers, especially the young, do not read directions and that a grading system for sunscreens would be confusing. The comment added that pharmacists could put up informative posters or displays and distribute leaflets prepared in English and Spanish at no cost to the government.

As discussed in comment 44, the grading system is clearly explained in the labeling recommended by the Panel and proposed in § 352.52(e). Therefore, the agency sees no need to require the labeling statement requested by the comment. The agency has stated many times that the pharmacist is a valuable source of health care information. Pharmacists are available to provide information about the grading system for sunscreens to consumers who require assistance.

L. Comments on Professional Labeling for Sunscreen Drug Products

69. Several comments requested labeling that includes indications for the use of sunscreens for pathological conditions. Some of these comments requested professional labeling, while others requested consumer labeling.

One comment stated that the Panel should have included a discussion of special types of sunscreens useful for patients with polymorphic photodermatitis, drug photosensitivity, and other types of photodermatitis. A reply comment agreed with the comment and suggested that a section for professional labeling be incorporated into the tentative final monograph to include an indication for patients with solar urticaria, polymorphic light eruptions, drug photosensitivity, and other types of photodermatitis where sunscreen therapy is indicated. The reply comment felt that the Panel recognized that some sunscreening agents, such as the benzophenones, provide protection through extended wavelength regions, and that opaque sunscreens containing a physical sunscreening agent, such as titanium dioxide, also provide broad-spectrum protection. This comment stated that it "would support indications for products with an appropriate absorption spectrum for the prevention of, or decrease exacerbation of, diseased states effected by the specific spectra screened by the screening products."

One comment from a person who has systemic lupus erythematosus (SLE) stated that this condition is exacerbated by exposure to sun, fluorescent lights, X-rays, etc. The comment added that people with this problem need accurate information on sunscreen preparations, such as how often to reapply the product, ability to protect, etc. The comment expressed support for appropriate labeling of a sunscreen product that might help persons with SLE to avoid flareups of fever and pain caused by the sun's rays.

One comment stated that there was a need in the proposed labeling system for "one more category" that would be for persons with reactions such as a rash on exposure to sunlight. The comment requested labeling information that would allow persons who develop a rash on exposure to sunlight to choose an effective sunscreen product without consulting a doctor.

Although many photodermatoses have been described, the exact etiology of most of these light-related skin diseases is not known (Ref. 1). The agency does not believe that the labeling for OTC sunscreen drug products should include indications for the use of sunscreens to protect against photodermatoses. In order to prescribe the appropriate sunscreen drug product for a particular photodermatosis, it is necessary to know the action spectrum (i.e., limits of the wavelength region) that causes a particular photodermatosis (Ref. 2) because that portion of the spectrum must be blocked in order to protect against the photodermatosis. Pathak, et al. (Ref. 2) have identified various action spectra for responses of human skin to solar radiation. The condition of variegate porphyria can be caused by a range of wavelengths between 390 and 600 nm with a maximum effect between 390 and 420 nm. Drug photosensitivity reactions can be caused by wavelengths between 300 and 400 nm with a maximum reaction between 320 and 380 nm. The range of effective wavelengths implicated in certain solar urticaria is 290 to 380 nm with a maximum reaction between 290 and 320 nm (Ref. 2). In order to successfully protect against a photodermatosis with a sunscreen drug product, the agency believes that a clinical diagnosis is necessary. Sun protection measures in persons with photodermatoses must be individualized to reflect the nature of the disorder, the causative wavelengths of sunlight, the individual's exposure habits, and the severity of the disease. The recommended measures for individuals with photodermatoses vary from disease to disease and may be very different from the recommendations for individuals without such conditions (Ref. 3). Because such determinations cannot be made by the consumer, the agency concludes that indications for the use of sunscreen drug products for protection against photodermatoses should only be made in a professional context.

Regarding professional labeling specific to photodermatoses, the comments suggested indications for special types of sunscreen products that may be useful for persons with photodermatitis. However, the comments did not provide any data to establish appropriate indications for such use. Therefore, the agency has no basis at this time for including professional or consumer labeling in the tentative final monograph. Nevertheless, the agency invites the submission of data that would establish appropriate professional labeling for sunscreen drug products for persons with photodermatitis and the other conditions described by the comments. (See comment 33.) Any data submitted on specific claims for specific sunscreen ingredients will be reviewed by the agency and addressed in the final monograph.

The agency notes that many of the conditions described by the comments may be caused by or exacerbated by exposure to UVA radiation (Ref. 2). If a Category I sunscreen ingredient is shown to have an absorption spectrum that extends to 360 nm or above in the UVA range, and a product containing that ingredient can demonstrate UVA protection using appropriate testing procedures that the agency is proposing be developed, that product may include UVA protection claims in its labeling. (See comment 53.) Such a claim would imply nonspecific protection against UVA induced photodermatoses.

References

(1) Ippen, H., "Photodermatoses," *in* "The Science of Photomedicine," edited by J.D. Regan and J.A. Parrish, Plenum Press, New York, pp. 349–350, 1982.

(2) Pathak, M., et al., "Protection of Skin Against Solar Radiation," *in* "The Science of Photomedicine," edited by J.D. Regan and J.A. Parrish, Plenum Press, New York, pp. 447–450, 1982.

(3) American Academy of Dermatology Consensus Statement, "Photoaging/Photodamage as a Public Health Concern," Consensus Conference on Photoaging/

Photodamage, Boston, p. 7, March 3 and 4, 1988.

M. Comments on Combination Sunscreen Drug Products

70. One comment requested that allantoin combined with aminobenzoic acid be reclassified from Category III to Category I as a sunscreen drug product. The comment noted that the Panel accepted the safety of allantoin combined with aminobenzoic acid, but requested further chemical data affirming that this formulation is a discrete chemical entity (a complex) and not a mixture, as well as additional data confirming its effectiveness as a sunscreen complex. The comment stated this formulation is a true chemical entity as shown by (1) the IR and UV absorption curves of allantoin combined with aminobenzoic acid, and (2) the fact that the solubility of the complex is 1 to 2 percent or more, whereas the solubility of a mixture is only 0.5 to 0.75 percent. The comment added that the complex acts synergistically and contributes to the formulation's moisturizing properties. In the case of a mixture of allantoin and aminobenzoic acid, the comment contended each component acts independently and not synergistically. The comment argued that testing in over 500 subjects demonstrates that allantoin combined with aminobenzoic acid is effective, safe, soothing, moisturizing, and is an anti-irritant. The comment concluded that the submitted data confirm the safety and effectiveness of allantoin combined with aminobenzoic acid in concentrations from 2 to 6 percent with an SPF value from 6 to 15 (Ref. 1).

As mentioned by the comment, the Panel determined that allantoin combined with aminobenzoic acid is safe, but concluded that the data are insufficient to demonstrate effectiveness. The Panel recognized that allantoin-aminobenzoic acid in combination has shown sunscreening activity equivalent to aminobenzoic acid alone. However, the submitted studies did not show that the combination of allantoin and aminobenzoic acid possesses any greater sunscreen potential than aminobenzoic acid alone (43 FR 38256). In addition, data submitted to the Panel referred to allantoin combined with aminobenzoic acid as a complex; however, the studies did not show that there was complexation involved between allantoin and aminobenzoic acid or that any modification had resulted which would alter in any way the individual characteristics of the parent compounds (43 FR 38206 at 38256 to 38257).

The agency has reviewed the data submitted by the comment, which include UV and IR spectroscopy curves that were originally submitted to the Panel, and other chemical, clinical, and safety data (Ref. 1). The agency concludes that the chemical data are insufficient to demonstrate clearly that allantoin and aminobenzoic acid form a discrete chemical entity whose properties are different from those exhibited by the mixture described by the comment. From the data, it is not possible to conclude that a complex is formed that exhibits chemical and physical properties not shown by a mixture of the components. In addition, the data do not address the effectiveness of allantoin combined with aminobenzoic acid as a sunscreen agent. Therefore, the agency is proposing that allantoin combined with aminobenzoic acid remain in Category III in this tentative final monograph when labeled only as a sunscreen. The agency's detailed comments and evaluation of the data are on file in the Dockets Management Branch (Refs. 2 and 3).

The agency notes, however, that 0.5 to 2 percent allantoin is proposed as a Category I skin protectant active ingredient (see the tentative final monograph for OTC skin protectant drug products published in the **Federal Register** of February 15, 1983; 48 FR 6832) and that Category I sunscreen active ingredients may be combined with Category I skin protectants. (See comment 71.) Therefore, aminobenzoic acid, a Category I sunscreen, may be combined with allantoin, a Category I skin protectant, provided the combination is labeled as both a sunscreen and a skin protectant.

References

(1) Comment No. C00040, Docket No. 78N–0038, Dockets Management Branch.

(2) Letter from W.E. Gilbertson, FDA, to S.B. Mecca, Schuylkill Chemical Co., coded ANS 81/01/09 to C00040, Docket No. 78N–0038, Dockets Management Branch.

(3) Letter from W.E. Gilbertson, FDA, to S.B. Mecca, Schuylkill Chemical Co., coded C00073/ANS, Docket No. 78N–0038, Dockets Management Branch.

71. One comment stated that the Panel discussed its desire to permit combinations of sunscreen and nonsunscreen active ingredients, but failed to provide for these combinations in its recommended monograph. To remedy this oversight, the comment recommended that the following section be established in the monograph: "§ 352.30 *Combination of sunscreen and nonsunscreen active ingredients.* Two or more sunscreen active ingredients may be combined with other active ingredients provided that the ingredients are generally recognized as safe and effective."

Although the Panel concluded that "sunscreen active ingredients may be combined with other active ingredients, e.g., skin protectants, provided that the ingredients are generally recognized as safe and effective, i.e., Category I active ingredients" (43 FR 38206 at 38217), it did not include any such combinations in its recommended monograph nor did the comment provide any information on specific combinations. The agency's combination policy for OTC drugs in § 330.10(a)(4)(iv) provides for the combination of two or more safe and effective active ingredients when each ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population. In addition to the above requirements, the agency's "General Guidelines for OTC Drug Combination Products" (Ref. 1) provide that Category I active ingredients from different therapeutic categories may be combined to treat different symptoms concurrently only if each ingredient is present within its established safe and effective dosage range and the combination meets the OTC combination policy in all other respects.

In some cases, the agency believes that combination drug products containing Category I sunscreens and active ingredients from other therapeutic categories may be rational. In situations where the skin is subjected to the combined effects of the sun and wind that could result in irritating and potentially harmful effects such as chafing, cracking, and windburn as well as sunburn, the agency believes that a combination drug product containing a sunscreen and a skin protectant is a rational combination. Certain skin protectant ingredients (i.e., allantoin, cocoa butter, dimethicone, glycerin, petrolatum, shark liver oil, and white petrolatum) are used to help prevent and temporarily protect chafed, chapped, cracked, or windburned skin and lips. (See § 347.50(b)(2) of the tentative final monograph for OTC skin protectant drug products (February 15, 1983; 48 FR 6820 at 6832).) The agency notes that several products submitted to the Topical Analgesic Panel contained ingredients such as lanolin, cocoa butter, allantoin, glycerin, or petrolatum in combination with sunscreen ingredients. In addition to sunscreening

claims, these products displayed skin protectant labeling claims such as "Protects from drying by sun, wind, water," and "Moisturizes skin to help protect against dryness and chapping due to exposure to sun and wind," (Refs. 2, 3, and 4). The agency believes that the data submitted to the Topical Analgesic Panel (Refs. 2 and 3) support the safety and effectiveness of such products. Moreover, because the pharmacological action of Category I sunscreens is similar (i.e., the ingredients screen or scatter the UV radiation from the sun) and because the pharmacological action of certain skin protectants is similar (i.e., the ingredients are chemically inert compounds that form a barrier on the skin and protect it against drying and other irritations), the agency concludes that any Category I sunscreen active ingredient can be safely and effectively combined with the following Category I skin protectant active ingredients: allantoin, cocoa butter, dimethicone, glycerin, petrolatum, shark liver oil, and white petrolatum. Accordingly, the agency is proposing to include new paragraphs (b) (1) and (2) in § 352.20, to read as follows: "(b)(1) Any single sunscreen active ingredient when used in the concentration established in § 352.10 may be combined with one or more skin protectant active ingredients identified in § 347.10 (a), (d), (e), (f), (h), (i), and (j) of this chapter, provided the finished product has a minimum SPF value of not less than 2 as measured by the testing procedures established in subpart D of this part and provided the product is labeled according to § 352.60" and "(b)(2). Two or more sunscreen active ingredients when used in the concentrations established in § 352.20(a)(2) may be combined with one or more skin protectant active ingredients identified in § 347.10 (a), (d), (e), (f), (h), (i), and (j) of this chapter, provided the finished product has a minimum SPF value of not less than 2 as measured by the testing procedures established in subpart D of this part and provided the product is labeled according to § 352.60." (See comment 37 for a discussion of minimum dosage limits for combination sunscreen drug products.)

The agency does not consider all skin protectant active ingredients to be appropriate for combining with a sunscreen. Certain skin protectant ingredients (i.e., aluminum hydroxide, calamine, kaolin, zinc acetate, zinc carbonate, and zinc oxide) are indicated only for drying the oozing and weeping of poison ivy, poison oak, and poison sumac. There does not appear to be any need to combine these ingredients with sunscreen ingredients, nor is the agency aware of any such products currently being marketed. Accordingly, such combinations are not being proposed in this tentative final monograph. However, the agency invites comment on this proposal.

The agency has determined that appropriate labeling for combination products containing sunscreen and skin protectant active ingredients would be any applicable sunscreen indication proposed in § 352.52(b) along with the skin protectant indication proposed in § 347.50(b)(2). Because consumers use a sunscreen-skin protectant drug product primarily as a sunscreen and because proper application is important to the safe and effective use of a sunscreen drug product, the combination product should be labeled with the sunscreen directions for use in § 352.52(d) of this tentative final monograph that are appropriate to the indication used on the product, the dosage form, and the substantivity of the product (e.g., a lipstick that contains a sunscreen and displays the indication "Filters out the sun's rays," should bear the following directions: "Apply liberally as often as necessary."). (See comments 52 and 66 for further discussion of these directions.) The agency does not believe that any special labeling is necessary for the warnings required on sunscreen-skin protectant drug products. The warnings for each ingredient as established in the warning sections of the respective OTC drug monographs are appropriate, except the agency does not find the general warning proposed in § 347.50(c)(3) for OTC skin protectant drug products to be necessary for sunscreen-skin protectant drug products. This warning states: "If condition worsens or does not improve within 7 days, consult a doctor." Based on the above, the agency is proposing to include the following labeling requirements for the indications and directions of sunscreen-skin protectant combination drug products in § 352.60 *Labeling of combination sunscreen drug products*, (b), (c), and (d), respectively.

"For permitted combinations containing a sunscreen and a skin protectant identified in § 352.20(b). In addition to any or all of the indications for sunscreens in § 352.52(b), the indication for skin protectants in § 347.50(b)(2) of this chapter should be used."

"For permitted combinations containing a sunscreen and a skin protectant identified in § 352.20(b). The warning for skin protectants in § 347.50(c)(3) is not required."

"For permitted combinations containing a sunscreen and a skin protectant identified in § 352.20(b). The directions for sunscreens in § 352.52(d) should be used."

The agency believes that labeling specific to combination drug products need appear only in one monograph, which should be the one most pertinent to the intended target population of the combination product. The agency believes that a drug product intended and labeled for use as a sunscreen and as a skin protectant is primarily a sunscreen and that labeling for such a product should appear in the monograph for OTC sunscreen drug products. However, the agency will include a cross-reference to this combination in the final monograph for OTC skin protectant drug products so that interested parties will know where to find the pertinent information about these products.

Similarly, a combination of a sunscreen and hydroquinone, a skin bleaching active ingredient, may be included in the final monograph for OTC skin bleaching drug products to be published in a future issue of the **Federal Register**. That combination product is primarily for skin bleaching, and its labeling is included in § 358.50 of the skin bleaching tentative final monograph. For informational purposes, the agency is proposing to include a cross-reference to that combination in § 352.20(c) of this tentative final monograph to read as follows *"For sunscreen and skin bleaching combinations.* See § 358.50 of this chapter."

The agency does not find any other combination products containing sunscreen and nonsunscreen active ingredients appropriate at this time. The agency invites further comments and supporting data on such combination drug products.

References

(1) Food and Drug Administration, "General Guidelines for OTC Drug Combination Products," September 1978, Docket No. 78D–0322, Dockets Management Branch.

(2) OTC Vol. 060002.

(3) OTC Vol. 060065.

(4) OTC Vol. 060076.

N. General Comments on Testing Procedures for Sunscreen Drug Products

72. Several comments agreed that testing is necessary to ensure that OTC sunscreen drug products meet the standards set forth in the monograph. However, these comments argued that testing procedures should be in the form of guidelines that outline a currently acceptable method of evaluating OTC

sunscreen drug products and should not be included in the monograph. Two comments stated that the agency had proposed this approach in other OTC drug monographs such as the monograph for OTC antiperspirant drug products. Another comment stated that such an approach would be highly desirable for SPF measurement in view of the international character of the sunscreen drug products market, where many identical formulations are sold in various countries around the world.

One comment added that maintaining the testing procedures for OTC sunscreen drug products in the form of guidelines would allow a company to use either the method specified in the guidelines or any other properly validated method that can be shown to assess performance at least as accurately as the guideline method. One comment stated that once alternative methods were validated, they would enjoy the same status as the proposed guidelines without the need to be submitted and approved through a rulemaking procedure. Another comment stated that the agency should explicitly state that other validated methods, or validated modifications of the methods proposed, are acceptable provided they are shown to evaluate performance consistently with and at least as accurately as the guideline method.

Some comments argued that establishing the testing procedures for sunscreen drug products as guidelines would build flexibility into the system and allow for easier handling of advances and improvements to the testing methodology. One comment maintained that mandating specific test protocols that must be followed to substantiate efficacy tends to stifle scientific and technological investigation in these areas. The comment contended that parties affected by the rules are often unwilling to support additional research because any changes proposed would have to go through a lengthy rulemaking procedure before being accepted. The comment added that other advances would be likely to cause the whole procedure to be repeated again and again. One comment stated that it is essential to have the best data available on which to base regulatory decisions and that the best way to have current data available is to provide for new and improved testing methods to be used.

The agency does not agree with the comments that testing procedures should be guidelines rather than be included in the monograph. The agency notes that the seriousness of the consequences that may result if a consumer relies upon an inaccurately labeled sunscreen (e.g., one that promises more protection than it actually affords) mandates that the final formulation of OTC sunscreen drug products be tested using standardized and validated testing procedures. Labeled SPF values should be based on testing conducted under the most carefully controlled conditions so that results are as accurate as possible. The outcome of an accurate and reproducible testing procedure ensures that competitive products on the market with the same SPF value provide essentially the same degree of protection. The agency believes that this can be accomplished best by requiring all manufacturers to use fully evaluated and validated testing procedures for testing the final formulation of OTC sunscreen drug products. The data from this testing need not be submitted to FDA by the manufacturer. The agency intends to use the testing procedures set forth in the final monograph for any necessary compliance testing of these products. The agency concludes that these testing procedures should be codified in the Code of Federal Regulations (CFR).

The agency agrees that it is essential to have the best data available on which to base regulatory decisions and encourages the development of new methods for testing sunscreen drug products. (See comment 53.) Properly validated, alternate methods for determining the SPF value of OTC sunscreen drug products would be acceptable so long as they have been evaluated and accepted by the agency. Such methods must be submitted to the agency as a petition under the rules established in § 10.30 of this chapter. The petition should contain data to support the modification or data demonstrating that an alternative testing procedure provides results of equivalent accuracy. All information submitted will be subject to the disclosure rules in Part 20 of this chapter. If acceptable, these alternative methods could be included in the monograph. The petition process is included in § 352.77 of this tentative final monograph.

Regarding one comment's statement that the agency had agreed to permit testing guidelines in the case of antiperspirant drug products, the agency notes that the consequences of a consumer using an ineffective antiperspirant drug product are not as serious as those that might be expected should a consumer use an ineffective sunscreen drug product. (For further discussion of the adverse effects of sunlight and the serious consequences that may occur if a consumer uses an ineffective sunscreen, see comments 27, 53, and 56.)

Final formulation testing procedures are included in the monographs for OTC antacid drug products in 21 CFR part 331 and for OTC first aid antibiotic drug products in 21 CFR part 333. Such testing procedures are also included in the tentative final monograph for first aid antiseptic drug products published in the **Federal Register** of July 22, 1991 (56 FR33644). The agency points out that several revisions to the antibiotic testing procedures have been accomplished in a timely fashion by using the normal OTC drug review rulemaking procedures. Accordingly, the agency finds no valid reasons not to include the testing procedures for OTC sunscreen drug products in this tentative final monograph.

O. Comments on Testing Procedures for UVA Sunscreen Drug Products

73. In response to the January 26, 1988 public meeting at which sunscreen testing methods were discussed, several comments addressed testing methodologies for sunscreens that absorb UVA radiation. One comment stated that increasing concern over the long-term effects of UVA radiation has generated a new interest in the development of UVA sunscreens. Despite this concern, the comment noted that the agency had not proposed any methodology for assessing the photoprotective properties of such sunscreens. Another comment noted that there have been significant discussion and some publications regarding the appropriate way of claiming a protection factor against UVA radiation. The comment recognized that protection against UVA radiation is important for reducing the harmful effects of UVA radiation on the skin as well as for reducing the risks of photosensitization in susceptible individuals. The comment mentioned the difficulty in evaluating the direct effects of UVA radiation in nonphotosensitized individuals (a large dose of UVA radiation is needed to produce a measurable endpoint). The comment suggested the use of topical 8-methoxypsoralen (8–MOP) plus UVA irradiance as one way of determining a phototoxic protection factor (PPF) for UVA protective sunscreens. (8–MOP is one of several photosensitizing chemicals which when applied topically or taken orally causes the skin to become abnormally sensitive to certain wavelengths, usually in the UVA range.)

One comment stated that the determination of a UVA radiation-induced MED value ratio with and

without topical application of sunscreen is appropriate for assessing UVA absorbing sunscreens. However, the comment maintained that methods involving the determination of a minimum phototoxic dose ratio in the presence of a topically applied 0.1-percent solution of 8–MOP and subsequent UVA irradiation in the presence and absence of UVA absorbing sunscreens have limited value. Although the comment did not submit an alternative approach, it did assure the agency that the Photobiology Task Force of the AAD would cooperate in developing a test for evaluating UVA sunscreens.

Another comment stated that many currently marketed sunscreen products contain a UVA absorbing active ingredient. However, a universally acceptable quantitative measure of the UVA protection afforded by such products has not been established. Therefore, the comment considered it necessary for the agency to provide manufacturers with guidelines for a testing methodology for UVA absorbing sunscreens. The comment stated that published results for benzophenone-3 and Parsol 1789 demonstrate UVA protection factors ranging from slightly more than 1 to almost 5. Maintaining that the techniques used for obtaining those results involve human evaluations that include (1) measurements of 8–MOP or anthracene phototoxicity, (2) delayed erythema, (3) immediate tanning, and (4) delayed tanning, the comment added that all but the latter produce a clearly defined end-point in Type I and Type II individuals. The comment stated that although phototoxicity studies give higher protection factors than the other techniques, the erythemal effectiveness spectrum for sensitized skin is different from that for normal skin, and the results obtained from phototoxicity studies cannot be extrapolated to a "normal" situation. The comment stated that, for the above reasons, delayed erythema in unsensitized subjects is the most meaningful parameter for evaluating UVA protection. The comment maintained that a UVA protection factor expressed in terms of protection against delayed erythema would be analogous to the SPF and would have similar advantages and disadvantages. The advantage is that sunburn or delayed erythema is a measurable end-point, and sunburn protection is needed. A disadvantage is that the relevance of sunburn protection to protection from skin cancer and photoaging are not known, particularly in the case of UVA radiation. The comment acknowledged that the dose requirements for UVA erythema are high and require prohibitively long exposures. However, it maintained that this problem could be solved by using a modified solar simulator with a quartz lens that concentrates the UVA energy within a small area.

One comment claimed that the additional UVA protection afforded by higher SPF's has been advanced as the main reason to allow unlimited SPF label claims. The comment stated that if the primary benefit of SPF's over 30 is protection from UVA radiation, then a methodology should be devised to measure and quantify the amount of this protection. The comment maintained that merely raising the SPF number, which is an indication of UVB protection, is a misdirected effort toward accomplishing this goal. Another comment also recommended that the agency develop appropriate terminology for the protection factor of UVA absorbing sunscreens. Stating that the term "sun protection factor" or "SPF" is well accepted for UVB absorbing sunscreens, the comment maintained that the term "SPF" should not be applied to UVA protection.

The agency believes that including UVA protection information in the labeling of those OTC sunscreens that provide such protection is important in order to fully inform the consumer. However, currently there is no generally acceptable method for determining a meaningful UVA protection factor that is analogous to the SPF. Several methods have been used with varying degrees of success. In one study (Ref. 1), photoprotection against UVA radiation by three sunscreens was evaluated in humans, with delayed erythema, immediate pigmentation, or delayed melanogenesis used as endpoints in normal skin, in skin sensitized with 8–MOP, and in skin sensitized with anthracene. The individual protection factor for each of these endpoints was calculated as the ratio of the threshold dose in the protected skin to that in unprotected skin. UVA protection factors were found to be significantly higher in sensitized skin compared with normal skin. However, the investigators concluded that UVA protection factors obtained in sensitized skin are probably not relevant to normal skin and that pigmentation, either immediate or delayed, is a reproducible and useful endpoint for the routine assessment of photoprotection of normal skin against UVA.

In another study (Ref. 2), the UVA erythema-protective effectiveness of a sunscreen containing an investigational new drug, butyl methoxydibenzoylmethane, in combination with a Category I OTC sunscreen, padimate O, was evaluated using subjects sensitized with 8–MOP. One portion of the study was done outdoors using natural sunlight, and the other portion was done indoors using a solar simulator. A PPF was derived from the ratio of the minimal phototoxic dose of UVA that produced delayed erythema (72 hours) on sunscreen-protected and unprotected skin. The study demonstrated that the combination of 3 percent butyl methoxydibenzoylmethane and 7 percent padimate O provided significantly greater protection than the other sunscreen formulations and that the PPF values determined indoors and outdoors were comparable. The investigator noted that this method has a number of advantages. First, it avoids the long exposure times and larger doses of UVA radiation required to produce erythema in nonsensitized skin. Second, it minimizes a potential source of error by reducing the thermal component of UVA erythema that is a consequence of long exposures with high intensity UVA sources. Third, the use of topical 8–MOP rather than oral 8–MOP to sensitize small areas of skin reduces the time of UVA exposure, the need for ocular protection, and the risk of other adverse reactions associated with systemic 8–MOP. Fourth, shorter UVA exposure times make the study more practical for both the investigator and the subject and reduce the erythemogenic effects of any contaminating UVB radiation to insignificant levels. However, the investigator also pointed out that the PPF values achieved by this method are applicable to subjects sensitized with 8–MOP and are not necessarily applicable to normal individuals.

In 1985, at the agency's request, the Dermatologic Drugs Advisory Committee evaluated a study (Ref. 3) similar to the one described above (Ref. 2) except that some of the subjects were sensitized with orally-ingested 8–MOP and others were sensitized with topically-applied 8–MOP. PPF values were derived from erythema reactions at 48 and 72 hours. Melanogenic protection factors (MPF) were derived from pigmentation responses at 12 to 14 days. The Committee agreed that the use of 8–MOP to accelerate the subject's response to UVA radiation is an acceptable method to qualitatively determine UVA protection. It also concluded that PPF values derived from 48- and 72-hour erythema reactions and MPF values derived at 12 to 14 days are appropriate endpoints.

The agency believes that a testing method similar to the one described by Lowe, et al. (Ref. 2) could be used to demonstrate that an ingredient provides protection against UVA radiation. However, at this time, the agency does not have enough information or data to propose a method for determining UVA protection in this tentative final monograph. A method should be developed and validated in the same manner as was the sunscreen testing procedure for protection against UVB radiation that is being proposed in this tentative final monograph. Any such method should clearly demonstrate that a particular product provides significant protection against UVA radiation. It should include the use of a control sunscreen preparation that absorbs UVA radiation and that can be used to assure the reliability of the testing procedure and equipment. Even though it may not result in a meaningful PPF or UVA protection factor, a standardized UVA testing method should demonstrate that a sunscreen ingredient either does or does not protect against UVA radiation. Therefore, the agency is requesting comments and data regarding an appropriate testing methodology for OTC sunscreen drug products that afford UVA protection.

At this time, the agency does not believe that it is appropriate for an OTC sunscreen drug product to display a PPF value in its labeling because a PPF value is obtained with methods that use chemically photosensitized skin and is not necessarily relevant to the protection of normal skin. Other UVA testing methods that use normal skin are not sufficiently developed or standardized to produce valid UVA protection factors. If a testing method is developed that results in a meaningful PPF or UVA protection factor, the agency will consider allowing that factor to be included in OTC sunscreen labeling. The agency's comments on the data are on file in the Dockets Management Branch (Ref. 4).

References

(1) Kaidbey, K., and R. W. Gange, "Comparison of Methods for Assessing Photoprotection Against Ultraviolet A In Vivo," *Journal of the American Academy of Dermatology*, 16:346–353, 1987.

(2) Lowe, N. J., et al., "Indoor and Outdoor Efficacy Testing of a Broad Spectrum Sunscreen Against Ultraviolet A Radiation in Psoralen-sensitized Subjects," *Journal of the American Academy of Dermatology*, 17:224–230, 1987.

(3) Summary Minutes of the 26th Meeting of the Dermatologic Drugs Advisory Committee, Food and Drug Administration, November 18, 1985, OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

(4) Letters from W. E. Gilbertson, FDA, to T. P. Koestler, Westwood Pharmaceuticals, Inc., K. M. O'Brien, Schering-Plough Corporation, N. J. Lowe, UCLA School of Medicine, and M. A. Pathak, Harvard Medical School, coded LET45, LET47, LET50, and LET52, respectively, in Docket No. 78N–0038, Dockets Management Branch.

P. Comments on the Standard Preparation for the Testing Procedures for Sunscreen Drug Products

74. Referring to the Panel's discussion of a standard homosalate-containing sunscreen used in the method for determining SPF values (43 FR 38206 at 38259), one comment stated that the formula for this standard was prepared and evaluated by a collaborative industry group consisting of several independent industrial photobiology laboratories and investigators. The validity of the testing methodology and confirmation of an SPF value of 4 for the standard homosalate sunscreen were submitted to the Panel (Ref. 1). After the submission of these data, however, it was observed during routine shelf-life evaluations of the standard that the stability of this formulation was not adequate for use as a standard. Thus, a revised formulation with improved stability characteristics was prepared and again evaluated by five independent laboratories and investigators. Subsequently, the comment submitted the results of this testing to the agency and concluded that the "revised" formulation is more appropriate for validating the test methodology at the SPF 4 level (Ref. 2). The comment recommended that § 352.40 of the Panel's report be amended to include the revised formulation and its manufacturing directions.

The agency has determined that the improved stability characteristics of the revised 8-percent homosalate standard formulation make it more appropriate for use as a sunscreen standard than the standard preparation originally submitted to the Panel. The agency notes that the SPF of the revised preparation is 4.47 with a standard deviation of 1.279, while the SPF of the standard reviewed by the Panel was 4.24 with a standard deviation of 1.14. However, the results of the collaborative study performed on the revised formulation (Ref. 2) indicate that general agreement between laboratories performing SPF testing can be achieved using this revised standard formulation. In addition, the results from SPF testing recently submitted to the agency (Refs. 3 and 4) demonstrate the reliability of the revised 8-percent homosalate preparation. (See comment 75.) The agency is aware that the revised 8-percent homosalate formulation is currently being used by most manufacturers of OTC sunscreen drug products as a reference control for their sunscreen testing procedures (Ref. 5). Therefore, the agency is including the revised formulation and its manufacturing directions in proposed § 352.70(a) and (b) as follows:

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

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

COMPOSITION OF PREPARATION A AND PREPARATION B OF THE STANDARD SUNSCREEN

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

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.

The agency's comments on the data are on file in the Dockets Management Branch (Ref. 6).

References

(1) OTC Vol. 060169.

(2) "Comparative Study on a New Standard Sunscreen Formula," Comment No. C00046,

Docket No. 78N–0038, Dockets Management Branch.

(3) Comment No. 00080, Docket No. 78N–0038, Dockets Management Branch.

(4) Comment No. 00083, Docket No. 78N–0038, Dockets Management Branch.

(5) Letter from G.N. McEwen, Jr., The Cosmetic, Toiletry and Fragrance Association, Inc., and W.W. Bradley, The Proprietary Association, to W.E. Gilbertson, FDA, coded LET75, Docket No. 78N–0038, Dockets Management Branch.

(6) Letter from W.E. Gilbertson, FDA, to J.D. Cope, Nonprescription Drug Manufacturers Association, coded LET40, Docket No. 78N–0038, Dockets Management Branch.

75. The agency's initial evaluation of the Panel's report and of the comments received raised some questions regarding the use of the 8-percent homosalate formulation as the standard for the validation of sunscreen drug product testing. Results from two collaborative studies submitted to the agency (Refs. 1 and 2) were inconsistent and produced SPF values that placed the 8-percent homosalate standard formulation into different PCD's. From this information, the agency concluded that the SPF and PCD of the 8-percent homosalate formulation had not been precisely established. Therefore, in the notice announcing a public meeting to discuss sunscreen testing procedures (52 FR 33598 at 33600), the agency reopened the administrative record. The agency asked whether new data had become available since the 8-percent homosalate standard formulation was originally tested that would provide additional information regarding the reliability of that formulation.

In response, the agency received several comments favoring retention of a revised 8-percent homosalate preparation as the standard for validation of sunscreen testing procedures (Ref. 2). (For a discussion of the revised homosalate formulation that was submitted to the agency in response to the Panel's report, see comment 74.) Two comments stated that the homosalate preparation is not a standard in the normal meaning of the word. The comments asserted that the preparation actually is a reference control to ensure that the testing facility and the equipment being used to conduct the SPF evaluations provide results within an acceptable range of variation. One comment added that use of the reference control ensures that the SPF calculated for a test product is valid and reproducible. Another comment referred to the results of interlaboratory testing of the 8-percent homosalate formulation that placed it in two different PCD's. The comment maintained that such results are not unexpected because the nominal SPF value of the preparation is on the PCD boundary. Thus, according to the comment, these results are not in themselves an indication of excessive variation.

The comment further suggested that the sunscreen monograph contain guidelines as to how testing laboratories should use the results obtained from the testing of the "control" formulation. For example, the comment asked if all the test results should be invalidated if the "control" SPF is outside the 90-percent confidence interval expected for the control. The comment also stated that the control should be as well characterized as possible, including its physical and chemical stability.

Another comment stated that currently there is no mandatory rejection of data based upon the results of the control. Testing facilities are not required to test the 8-percent homosalate control along with each product test. The comment suggested that, for each test panel, an appropriate control sunscreen should also be tested, and the validity of the test should depend upon the results of the testing of the control sunscreen. If the results of the control sunscreen are found to be significantly different from the "nominal" value, then the sample sunscreen test should be invalid. The comment believed that such a requirement would ensure compliance by various testing laboratories to a common reference system. Another comment stated that the collaborative studies submitted previously to the Panel and the agency (Refs. 1 and 2) established consistent results among laboratories for the 8-percent homosalate standard and established its PCD as "Moderate Sun Protection" and its SPF value as 4. The comment maintained that after 12 years of consistent use of the 8-percent homosalate preparation, it was satisfied that the preparation has adequately fulfilled its purpose as a reference control. The comment added that the current 8-percent homosalate standard is the revised formulation that was previously submitted to the agency (Ref. 2). The comment was not aware of any new comparative testing done on this formulation, and stated that there was no particular need to change the current standard. The comment noted, however, that any changes regarding testing methodology, especially those affecting statistics or application density, will also affect the SPF and PCD of the 8-percent homosalate standard or any other standard that might be chosen.

Stating that it had used the 8-percent homosalate standard for the past 9 years or more, one comment stated that it had evaluated the SPF value of this formulation in nearly 500 volunteers. The testing occurred both under indoor conditions using UV radiation from a solar simulator equipped with a xenon-arc lamp and under outdoor conditions using natural sunlight. The comment maintained that if the formulation is correctly manufactured and used within 3 to 6 months of preparation, it provides an SPF of 4.0 ± 0.5 when a solar simulator is used as the source of UV radiation. However, under outdoor conditions, the comment added that the 8-percent homosalate preparation provides an SPF of 2.5 to 3.0. Maintaining that the homosalate formulation is useful, adequate, and acceptable for use as an internal standard for testing sunscreen formulations having SPF values in the range of 4 to 8, the comment recommended that the agency retain this internal standard.

The CTFA stated in 1987 that over the past 10 years, the industry has developed a massive block of test data that substantiates the validity of the 8-percent homosalate preparation. CTFA submitted new data from sunscreen testing conducted by four laboratories during 1985 through 1987 (Ref. 3) and contended that the results show a consistent response for the homosalate control both within and between laboratories. The comment asserted that these data substantiate the reliability of the 8-percent homosalate control for sunscreen testing of products over the entire range of SPF's currently marketed. Another comment also submitted recent data and stated that these data confirm that the formula is predictable and reliable as used in its testing facilities (Ref. 4).

The agency believes that the new data (Refs. 3 and 4) that have been submitted support the reliability of the revised 8-percent homosalate standard preparation for testing sunscreens with SPF values of 15 or below. The data submitted by CTFA (Ref. 3) include information accumulated on over 1,700 subjects over 2 to 3 years by four different laboratories. These data indicate a mean SPF value equal to approximately 4, with a standard deviation around 0.7 for the 8-percent homosalate standard. The other data submission (Ref. 4) contains results from 100 subjects, with a mean SPF value of 4.35 and a standard deviation of 0.61. These data are consistent with the results of the CTFA submission (Ref. 3). The agency notes that these new data (Refs. 3 and 4) are consistent with the initial test results of the revised formulation of the 8-percent homosalate

preparation, which indicate a mean SPF of 4.47 with a standard deviation of 1.279 (Ref. 2). (See comment 74.)

The agency notes that one comment suggested that the homosalate standard is appropriate for testing sunscreens with SPF values of 4 to 8. Another comment believed that it was appropriate for sunscreen testing of products over the entire range of SPF's currently marketed. The agency agrees with the Panel that an 8-percent homosalate preparation may be used to validate the testing procedures for products with SPF's up to and including 15. However, there is currently not enough information available for the agency to determine that the use of this standard is valid for testing sunscreens with SPF values above 15. (See comments 77 and 78.)

The agency considers the 8-percent homosalate formulation not to be a standard within the normal meaning of that word. Rather, it is a control that should be used to validate the testing procedure, equipment, and facilities. As such, it plays no part in the calculation of the SPF value for the test product. However, the agency believes that the homosalate control should be tested at the same time as the test product for every SPF determination. If the SPF of the homosalate preparation is within acceptable limits of variability of the validated mean, then the SPF determined for the test product can be considered valid, if it meets all other requirements for acceptable limits of variability. The 95-percent confidence interval for the mean SPF of the data from the control product should contain the value 4. If it does not, the study should be considered invalid. These provisions are included in the sunscreen testing procedures being proposed in this tentative final monograph.

Regarding one comment's statement that the 8-percent homosalate preparation provides an SPF of 2.5 to 3.0 under outdoor conditions, the agency is not including outdoor testing procedures in this monograph. (See comment 79.) The agency's comments on the data are on file in the Dockets Management Branch (Ref. 5).

References

(1) OTC Vol. 060169.

(2) "Comparative Study on a New Standard Sunscreen Formula," Comment No. C00046, Docket No. 78N–0038, Dockets Management Branch.

(3) Comment No. 00080, Docket No. 78N–0038, Dockets Management Branch.

(4) Comment No. 00083, Docket No. 78N–0038, Dockets Management Branch.

(5) Letters from W.E. Gilbertson, FDA, to M.B. McTernan, Johnson and Johnson, and E.E. Kavanaugh, Cosmetic, Toiletry and Fragrance Association, coded LET39 and LET57, respectively, Docket No. 78N–0038, Dockets Management Branch.

76. Referring to the Panel's discussion of a standard sunscreen (43 FR 38206 at 38259), one comment contended that the international sunscreen testing experience with a homosalate formulation as a sunscreen standard is rather poor. The comment recommended that 5 percent PABA (aminobenzoic acid) should be used as the standard sunscreen because the international literature mentions it as a widely-known formulation. The comment asserted that in sunscreen testing it is important that the sunscreen standard have an SPF value of at least 4 or, preferably, an SPF value of 6.

The comment did not provide any literature references to support its contention that 5 percent aminobenzoic acid is frequently referred to in the international literature. Also, no data were submitted to demonstrate that 5 percent aminobenzoic acid should be preferred over the Panel's proposed 8 percent homosalate formulation as a sunscreen standard. The agency is aware that the Panel reviewed data from a collaborative study involving comparative testing of standard sunscreen products. In this study, two different sunscreen preparations containing either 8 percent homosalate or 4 percent aminobenzoic acid were tested by six laboratories (Ref. 1). The results showed that individual subjects using the 4-percent aminobenzoic acid sunscreen in an alcoholic vehicle had mean SPF values ranging from a low of 6.4 to a high of 9.7. The mean SPF value for the entire group of 60 volunteers was approximately 7, with a standard deviation of 1.61. The SPF values for the 8-percent homosalate formulation were not as scattered or as variable as the SPF values for the 4-percent aminobenzoic acid formulation. The results for the 8-percent homosalate gave an individual mean SPF that ranged from a low value of 3.8 to a maximum value of 6.0. When all the data were compiled for the homosalate formulation, the mean SPF value was 4.24 with a standard deviation of 1.14. The investigators reporting on the comparative testing of aminobenzoic acid and homosalate as sunscreen standards suggested that the 4-percent aminobenzoic acid in alcohol appears to be more difficult to spread uniformly on the test site. This difficulty might have contributed to the wide variation in the test results.

The agency is unaware of any data demonstrating that a 5-percent aminobenzoic acid formulation referred to in the comment is superior as a sunscreen standard to the 8-percent homosalate formulation proposed by the Panel and revised by the agency. Furthermore, additional data supporting the reliability and wide acceptance of the revised 8-percent homosalate standard were submitted to the agency in 1987 (Refs. 2 and 3). (These data are discussed in comments 74 and 75.) The agency tentatively concludes that the revised 8-percent homosalate formulation is suitable to use in the testing procedures to ensure the uniform evaluation of OTC sunscreen drug products. The agency is including the revised formulation for the 8-percent homosalate standard and directions for its manufacture in proposed § 352.70(b). (See comment 74.)

References

(1) OTC Vol. 060169.

(2) Comment No. C00080, Docket No. 78N–0038, Dockets Management Branch.

(3) Comment No. C00083, Docket No. 78N–0038, Dockets Management Branch.

77. In the notice of public meeting to discuss appropriate testing methods for OTC sunscreen drug products (52 FR 33598 at 33602), the agency asked for comment and supporting data on the following question: "Can these higher SPF values be accurately determined using currently available sunscreen testing procedures?" The agency also asked for the submission of appropriate testing methods if the currently recognized sunscreen testing procedures are not considered adequate.

Six comments responded to the agency's question regarding the adequacy of using currently available testing procedures for sunscreen drug products claiming to have SPF values in excess of 15. The comments agreed that the current testing methods are adequate for evaluating such formulations. However, only two comments provided data from actual studies.

One comment (Ref. 1) submitted data on a sunscreen formulation that was tested at two different laboratories which utilized the methods found in the Panel's testing procedures in subpart C of its recommended monograph (43 FR 38206 at 38265). In one laboratory, test results from 21 subjects produced a mean SPF value of 36.88. Results from the 25 subjects tested at the second testing facility produced a mean SPF value of 34.1. The comment also submitted data on another sunscreen formulation. The test results from 20 subjects resulted in a mean SPF value of 29.16. Furthermore, the comment claimed that in vitro testing, consisting of optical measurement, yielded SPF values of 32 and 26.5, respectively, for these two formulations. The comment

noted that because no recognized alternate validating methodology is available, it is impossible to answer whether these results are "accurate." However, the comment maintained that the results are reproducible and consistent with optical transmission properties measured in vitro on the skin. The comment added that the principles of testing are the same for both high SPF and low SPF products and that there are no physiological differences in the responses that would necessitate a different testing procedure.

Another comment (Ref. 2) submitted the results of five studies, each involving about 20 subjects. Three of the studies were performed in one laboratory, while the other two were performed in another testing facility. The studies were basically designed according to the Panel's recommended testing procedure. All five studies used test products which produced mean SPF values that exceeded 15. These values ranged from 24.4 to 36. The standard deviation of the results ranged from 1.6 to 5.05, and the standard error percentage of the mean ranged from 0.91 to 2.95.

Regarding the data submitted by the first comment (Ref. 1), the agency believes that the results of tests on the same formulation on humans at two testing laboratories give some indication of reproducibility. Moreover, the results support the use of the Panel's method for evaluating sunscreens with SPF values higher than 15. The in vitro results may also be supportive, but the comment did not submit those data.

It is unclear from the data submitted by the second comment (Ref. 2) whether the test products were the same formulation and should have produced the same mean SPF value, or whether they were different products. In addition, it could not be determined whether the 8-percent homosalate control was used in two of the studies (Refs. 3 and 4), and the light source was not well defined in another two studies (Refs. 5 and 6). The agency acknowledges that it is possible to obtain consistent SPF values above 15 in the context of one study. The unresolved problems are whether high SPF values are reproducible among testing laboratories, and whether such values are valid.

The agency notes that the 8-percent homosalate control used in some of these submitted studies has an SPF value of approximately 4. The agency is proposing that one or more standard preparations with SPF values higher than 4 be developed for testing sunscreens with higher SPF values (see comment 78). Also, such standard preparations, when developed and validated, would be used to develop new testing procedures or to validate existing testing procedures for sunscreen drug products with SPF values higher than 15. At this time, such standards are not available.

The agency has determined that the submitted data are not sufficient to demonstrate that the testing methods currently used to evaluate sunscreen drug products with SPF values up to 15 are equally applicable to evaluating sunscreen drug products with SPF values above 15. The agency believes that collaborative studies using an appropriate control preparation are necessary. The agency invites further comment on this matter. If necessary, the agency will publish an amendment to this tentative final monograph to address any new data submitted regarding testing procedures for sunscreens with high SPF values (above 15), so that the public may comment before a final rule is published. The agency's comments on the data are on file in the Dockets Management Branch (Ref. 7).

References

(1) Comment No. C00083, Dockets No. 78N–0038, Dockets Management Branch.

(2) Comment No. C00080, Dockets No. 78N–0038, Dockets Management Branch.

(3) Kaidbey, K., "The Evaluation of a Suncare Product for its Ability to Resist Wash-Off, Protocol 1308," unpublished report in Appendix 16, Comment No. C00080, Docket No. 78N–0038, Dockets Management Branch.

(4) Kaidbey, K., "Evaluation of a Suncare Product for its Ability to Resist Wash-Off, Protocol 1588," unpublished report in Appendix 17, Comment No. C00080, Docket No. 78N–0038, Dockets Management Branch.

(5) Epinette, W.W., and A. McCarthy, "Final Report: Sunscreen Evaluation, Project No. CN–0028," unpublished report in Appendix 15, Comment No. C00080, Docket No. 78N–0038, Dockets Management Branch.

(6) Epinette, W.W., and C.L. Hughes, "Final Report: Sunscreen Evaluation, Project No. CN–0043," unpublished report in Appendix 18, Comment No. C00080, Docket No. 78N–0038, Dockets Management Branch.

(7) Letters from W.E. Gilbertson, FDA, to M.B. McTernan, Johnson and Johnson, and E.E. Kavanaugh, Cosmetic, Toiletry and Fragrance Association, coded LET38 and LET41, respectively, in Docket No. 78N–0038, Dockets Management Branch.

78. In the notice of a public meeting to discuss appropriate testing procedures for OTC sunscreen drug products, the agency stated that it was concerned about using a standard preparation that may have a relatively low SPF value of 4 to validate a sunscreen testing procedure that is supposed to determine a wide range of SPF values (currently SPF 2 to SPF 30 and higher) (52 FR 33598 at 33600). The agency asked whether standard formulations with SPF values higher than 4 would make the determination of SPF values higher than 8 and 15 more accurate. The agency stated that it believed that two or three standard preparations should be available having SPF values representing the entire range of possible SPF values (e.g., SPF 8 and SPF 20 or SPF 4, SPF 15, and SPF 25). The agency also asked if sunscreen preparations were available that would be appropriate for use as standard preparations when testing sunscreen drug products with estimated SPF values greater than 15. If so, the agency requested that data on such preparations be submitted.

Several comments agreed with the agency that additional standard or control preparations with SPF values higher than 4 should be available for sunscreen drug product testing. One comment agreed with the agency on the usefulness of a low and a high SPF control and recommended that the homosalate control be retained for low SPF products. The comment stated that it is aware of prototype control formulations that would fulfill the requirements for a high SPF control. Another comment recommended that two standard preparations with SPF values of 4 and 9 should be available and added that it is essential that a choice be left to the investigator to use either of the standards depending upon the expected SPF testing range. Another comment suggested that standard formulations should have SPF values of 4 and 12.

Some comments recommended that, in addition to the SPF 4 standard control, a standard preparation with an SPF of 15 should be available. One comment stated that one or two additional standards should be available and that one of these standards should have an SPF value of greater than or equal to 15. The comment added that both the level of absorbers and the vehicle (sunscreen base) of the standard preparation must be clearly defined. Another comment stated that for testing sunscreens with SPF values under 15, the 8-percent homosalate standard, as defined and recommended by FDA, or the 2.7 percent cinnamate, as defined and recommended by DIN, should be used. However, for evaluating sunscreen preparations with SPF values higher than 15, the comment recommended that a standard which has an SPF of at least 15 and which does not contain substances known as reflectors should be used. The comment stated that this standard may contain either UVB filters with extended absorption in the UVA

range or a pure UVA absorber plus a UVB absorber.

One comment suggested that the sunscreen testing methodology should spell out which control formulation should be used with which range of expected SPF values. For example, the SPF 4 control should be used where the expected SPF of the test product is 2 to less than 8, and the SPF 15 control should be used where the expected SPF is 8 to 30. Another comment stated that the control standards should be run at least once a year in the laboratory test, but another comment proposed that the standard should be run twice a year.

One comment stated that the use of a high SPF control would improve the accuracy of the testing procedure and provide a benchmark of compliance for testing laboratories. The comment stated that it is willing to provide formulations for use as high SPF (and waterproof) reference standards, but because these formulations are proprietary, they could not be disclosed publicly. The comment stated that it could provide finished products with SPF values of "8+" and "20+" (both waterproof) to the industry for a fee in line with the costs of producing, validating, and distributing the materials and submitted data on the SPF testing of these products (Ref.1). Another comment noted that it was planning to submit data in support of a control for high SPF testing, but realized that such data could not be submitted before the administrative record closed in April, 1988. The comment stated that it would submit the data as part of a petition to reopen the administrative record to consider these data and requested that the agency give favorable consideration to such a petition. [No such petition has been submitted to date.] The comment stated its willingness to work with the agency to develop and validate an additional control.

The agency believes that the 8-percent homosalate standard preparation proposed in this tentative final monograph is suitable for testing sunscreens with lower estimated SPF values (which may include values up to and including 15). (See comment 75.) However, the agency believes that one or more additional standard preparations with SPF values higher than 4 (e.g., SPF 15, 20, or 25) may be desirable for testing sunscreens with higher SPF values (i.e., SPF values higher than 15). Depending on the SPF values of the additional standard preparations, one of those preparations may be deemed more appropriate to use to test products with an estimated SPF value of 15. At this time, the agency does not have enough data or information to reach a conclusion regarding the use of other suitable standards or their formulations. Only one comment submitted data on higher SPF standard preparations, one with an SPF of "8+" and one with an SPF of "20+" (Ref. 1). These data are not sufficient to verify the reliability of these preparations. For the preparation with an SPF of "8+," the comment submitted data on 120 subjects, but for the preparation with an SPF of 20, it submitted data on only 20 subjects. In both cases, mean SPF values higher than the expected SPF value were obtained. The agency would need more within-laboratory data as well as data from different laboratories before it could determine if these standard preparations were appropriate. In addition, the agency notes that the formula of any standard preparation required by an OTC drug monograph must be in the public domain so that the preparation can be prepared in any laboratory.

The agency appreciates the interest shown by two comments in developing standard preparations for the testing of higher SPF sunscreens. However, no data or information regarding additional standard preparations has been submitted at this time. The administrative record will be open for 1 year following publication of this document to accept new data relating to these proposals. If additional data are submitted, the agency will, if necessary, publish an amendment to the tentative final monograph in a future issue of the **Federal Register** to state its proposals regarding appropriate standard preparations for testing of higher SPF sunscreens.

Regarding the suggestion that the standard preparation should be run once or twice a year, the Panel recommended in § 352.40(a) of its monograph that the standard preparation should be run every time (i.e., concomitantly) a sunscreen drug product is tested. The agency agrees and is including this requirement in proposed § 352.70(a).

Reference

(1) Comment No. C00083, Docket No. 78N–0038, Dockets Management Branch.

Q. Comments on Indoor vs. Outdoor Testing Procedures for Sunscreen Drug Products

79. One comment disagreed with what it believed was the Panel's opinion that determination of the SPF value under laboratory conditions (with artificial light sources) will produce more reliable and reproducible SPF values than those achieved using natural light. Referring to personal experience in testing sunscreen products, the comment stated that artificial light sources have given a higher SPF value than natural sunlight and offered to submit such data if requested. The comment pointed out that the physical properties of sunscreen products always tend to be altered when tested under natural light, and that the combined effects of UVB, UVA, visible, and IR radiation are more pronounced under outdoor conditions. In view of the availability of reliable meters to measure light fluences (amounts of light) and of good facilities to conduct outdoor testing, the comment concluded that the Panel should have insisted that at least one study be conducted under outdoor conditions in order to obtain a true SPF value, adding that the cost of such testing is not an excuse when the principal issue concerns the health of people and when the major objectives are to minimize or prevent skin cancer and wrinkling of the skin. For these reasons, the comment argued that indoor as well as outdoor testing should be mandated by FDA.

A second comment agreed with the Panel's recommendation that both artificial and natural light can be used in the testing of sunscreens (43 FR 38206 at 38259). However, the comment suggested that final sunscreen formulations should be required to undergo at least one outdoor simulated-use test with natural sunlight. The comment maintained that artificial light sources should be used only in research and development programs to identify formulations that appear to have merit under laboratory conditions and to partially evaluate formulations with very high protective factors, explaining that the SPF of such formulations "might range from 8X to 18X in the laboratory environment, but that range narrows considerably (from 4X to 6X with some formulations) when the products are tested under natural sunlight-simulated-use conditions." The comment concluded that it would be reasonable to require all sunscreens (even those with protection in the range of 8X or greater) to demonstrate performance under natural sunlight-simulated-use conditions. The comment requested that the tentative final monograph explain the role of artificial and natural light testing in the development of sunscreen drug products, and provide guidelines for natural sunlight testing and recommendations for preferred simulated-use conditions.

One reply comment questioned the validity of the above comments and supported the Panel's recommendations regarding both solar simulator testing

and natural sunlight testing. The reply comment stated that it believed laboratory conditions using artificial light can be constructed to parallel outdoor conditions without the variables associated with outdoor testing. It believed that "solar simulator testing provides a means of standardization, a means of assuring reproducible results and ultimately, and most importantly, a means of insuring uniform product labeling." The reply comment contended that the same amount of erythemic energy is required to produce a sunburn using either a xenon arc solar simulator or natural sunlight, and that, as long as other environmental factors are reproduced, the SPF of a sunscreen drug product is reproducible under laboratory conditions using a xenon arc solar simulator. The reply comment submitted a published paper (Ref. 1) and the results of studies, previously submitted to the Panel for review, which it said demonstrated reproducible results in various laboratories, using the xenon arc solar simulator (Ref. 2).

Another comment, responding to the January 26, 1988 public meeting to discuss sunscreen testing procedures, stated that it did not support an outdoor test. The comment maintained that although sunscreens are applied for use in natural sunlight, this source of UV radiation is too variable and too unpredictable for routine use in the assessment of a large number of commercial sunscreen products.

The Panel did not recommend the use of an artificial light source over natural sunlight for determining SPF values. In discussing testing procedures for determining the SPF value of a sunscreen product, the Panel considered the use of artificial light (i.e., a solar simulator) and the use of natural sunlight as light sources (43 FR 38206 at 38259 and 38260). The Panel discussed the advantages and disadvantages of using these light sources for determining SPF values. The Panel described an artificial light source in § 352.41(a) and discussed the use of a natural light source in § 352.41(b) of its recommended monograph. It outlined procedures for determining SPF values using an artificial light source in § 352.43 and for the determination of SPF values using sunlight in § 352.44. However, the Panel did not favor one method over the other.

The use of SPF values evolved from research and development efforts involving both natural and artificial light sources. The agency believes that labeled SPF values should be based on testing conducted under the most carefully controlled conditions so that the results are as accurate and reproducible as possible. Accurate and reproducible testing procedures ensure that competitive products with the same SPF values have essentially the same effectiveness.

The agency agrees with the reply comment that indoor testing using a properly filtered and calibrated solar simulator provides an appropriate means of standardizing SPF measurements by providing controls over most of the variables that cannot be controlled in outdoor testing. (For a discussion of solar simulators, see comment 86.) The agency believes that indoor testing ensures reproducible results because it is easier to control significant variables such as temperature and humidity. Outdoor testing of sunscreen products is not reproducible from day to day because of uncontrollable variables such as changing cloud cover, changing radiation intensity with time, changing sun angle to the body surface with time, and variable heat-induced sweating. A solar simulator produces a constant spectrum at a constant angle with a high output in the UV range of 290 to 400 nm (43 FR 38260). It is a more reliable source of UV radiation than the sun whose spectrum changes continuously depending upon angle, altitude, pollution, and the amount of ozone in the atmosphere (Ref. 3). Additionally, although there is not enough sunlight in a day to conduct outdoor testing of sunscreens with high SPF values, testing of these products may be done quickly and efficiently using a high intensity solar simulator.

The agency has reviewed the published paper and the results of a study submitted by the reply comment (Refs. 1 and 2) as well as a later publication not available to the Panel (Ref. 4). The agency tentatively concludes that SPF values determined by indoor testing compare favorably with SPF values determined by outdoor testing. The study by Sayre, et al. (Ref. 1) showed that the MED for unprotected skin induced by a solar simulator was similar to the MED values obtained in outdoor testing using natural sunlight. SPF values obtained for products tested indoors using solar simulators were consistently higher than the SPF values obtained outdoors using natural sunlight. However, the study demonstrated that if certain critical environmental conditions, such as temperature, are controlled, the SPF value of a sunscreen product determined with an artificial light source is similar to that obtained using natural sunlight. A subsequent study by Sayre, et al. (Ref. 4) suggests that when testing sunscreens for substantivity (resistance to water wash-off), varying environmental conditions are not considerations because the substantiveness of the sunscreen formulation negates the effects of heat and humidity on the SPF determination. The data in this study demonstrate good correlation between the indoor and outdoor testing results of substantive sunscreen formulations.

The agency believes solar simulator testing is a more accurate method of determining SPF values for product labeling than outdoor testing. Carefully controlled solar simulator testing provides a convenient means of standardization among laboratories and is not affected by variable outdoor environmental conditions. Therefore, the agency is proposing only general testing procedures in § 352.72 that use an artificial light source, as specified in § 352.71, for determining SPF values. Accordingly, the agency is not including the Panel's recommended § 352.41(b) "Natural light source (sunlight)" and § 352.44 "Determination of SPF value using natural light source (sunlight)" in this tentative final monograph. In addition, the Panel's reference to natural sunlight testing in § 352.42(h) "Response criteria" is not being proposed.

References

(1) Sayre, R. M., et al., "The Correlation of Indoor Solar Simulator and Natural Sunlight," *Archives of Dermatology*, 114:1649–1651, 1978.

(2) Comment No. SUP002, Docket No. 78N–0038, Dockets Management Branch.

(3) Urbach, F., "The Biological Effects of Ultraviolet Radiation," Pergamon Press, New York, pp. 359–373, 1969.

(4) Sayre, R. M., et al., "Performance of Six Sunscreen Formulations on Human Skin," *Archives of Dermatology*, 115:46–49, 1979.

80. One comment suggested that a conversion factor of 0.7 be used to correct for the observation that the calculated SPF of sunscreen drug products is higher when tested indoors using an artificial UV light source than when tested outdoors using natural sunlight. The comment maintained that this approach would also provide for retaining the 2 milligram/centimeter squared (mg/cm^2) application density in the sunscreen testing procedures. At the same time, it would result in an SPF value that would better reflect the actual sunscreen protection the consumer would experience in natural sunlight.

The agency does not believe that the testing procedures should include a conversion factor of 0.7 to adjust a calculated SPF that has been determined using an artificial light

source. The proposed sunscreen testing method using an artificial light source is reasonably, but not absolutely, comparable to sun exposure conditions. As discussed in comment 79, there are inherent variables in sunscreen testing done under outdoor conditions. The agency believes that indoor testing with an artificial light source is a more accurate method of determining SPF values than is outdoor testing. Furthermore, the comment did not submit data to demonstrate a constant relationship between SPF values determined using an artificial light source and SPF values determined under natural sunlight conditions. Nor were data provided to support the suggested conversion factor. Therefore, the agency is not including a conversion factor in the proposed sunscreen testing methods.

81. Referring to the Panel's discussion of environmental conditions for testing sunscreen products in sunlight (43 FR 38206 at 38260 and 38266), one comment provided possible specifications for the testing of the standard sunscreen formulations in natural sunlight. To circumvent environmental variables, the comment suggested the following possible specifications for weather (and environmental) conditions: no intermittent clouds (less than 2 percent), ambient temperature of 84 °F to 88 °F, haze (minimal), and humidity of 50 to 70 percent. Among other environmental variables affecting the testing of standard formulations, the comment listed wind, air quality index, and other exposure conditions, such as latitude and the time of the year. The comment did not suggest any specifications for these conditions. The comment predicted that test failures would result if cloudiness became excessive. Therefore, the comment urged the agency to place very strict limits on weather variations during the testing of standard formulations.

The Panel discussed the effect of atmospheric conditions and geographic latitude on the development of the MED in fair-skinned people (43 FR 38206 at 38210). Atmospheric conditions alter the solar erythemic intensity and, depending upon the latitude, also affect the exposure time required to induce one MED. Although testing of sunscreen products in natural sunlight provides useful information, such testing is associated with many variables, such as those mentioned by the comment. Accordingly, the agency is not proposing natural sunlight testing as a regulatory standard. For a discussion on the determination of SPF values using an artificial light source, see comment 79.

82. Noting the subject selection procedures in § 352.42(a), one comment stated that the selection of subjects with Skin Types I, II, and III seems appropriate for evaluations using artificial light. For natural sunlight testing, however, the comment contended that subject selection should be restricted to test subjects with moderate skin pigmentation. The comment argued that restricting the skin type for natural sunlight tests should decrease subject variation in evaluating the test and control formulations. The comment added that the conditions of simulated use during natural sunlight testing of sunscreens should be specified. It cited "no swimming" and "schedule of exercise" as examples of conditions that should be specified.

As described in comment 79, natural sunlight testing of sunscreen drug products provides SPF values that vary too greatly to be useful in assigning PCD claims. Therefore, the agency is proposing only artificial light testing procedures. Thus, it is not necessary to specify conditions for natural sunlight testing of sunscreens.

R. Comments on Artificial Light Sources

83. One comment disagreed with the Panel's statement that solar simulators of 150 Watts (W) usually produce 10 or 12 solar constants (43 FR 38206 at 38260). The comment explained that solar simulators "based on the principle reported by Berger, where the radiation is reflected from visible light and an IR reflecting dichroic mirror, produce the equivalent of ten to twelve times the amount of UV radiation contained in mid-latitude noon sunlight." The comment added that if most of the visible light and IR radiation were not removed from the beam, severe burns would result. Therefore, the comment felt that the Panel's statement is too broad and incorrect. For similar reasons, the comment also objected to the Panel's statement concerning solar simulators producing 40 solar constants (43 FR 38260) and contended that because not all solar simulators are built on the Berger principle, they will emit a variety of intensities of UV radiation depending on their design and construction.

The Panel defined a solar constant as "the total amount of energy at all wavelengths per square meter, available from the sun, at the earth's surface" (43 FR 38260); however, as the comment stated, solar simulators recommended for sunscreen testing emit only UV wavelengths of radiation. A true solar constant also includes energy from visible light and IR radiation. The agency believes that the Panel's report would have been more precise had it read "solar constants of UV radiation." Concerning the comment's objection that solar simulators will emit a variety of intensities of UV radiation depending on their design, the Panel stated that the "more powerful instruments can produce up to 40 solar constants." The Panel recognized that solar simulators may emit a variety of intensities of UV radiation when it qualified its statement by saying "up to" 40 solar constants.

84. One comment questioned the Panel's statement, in its discussion of light sources and monitoring (43 FR 38206 at 38260), that the UV intensity of a solar simulator will be reported in J/m^2. The comment stated that if the J/m^2 refers to "the total output of a solar simulator without specifying spectrum, the results in terms of numbers will be most misleading." Further, the comment claimed that the statement is technically incorrect because Joules represent the dose of radiation and not the intensity, which is measured in Watts per meter squared (W/m^2). The comment maintained that a solar simulator's effectiveness for sunscreen testing should be measured by multiplying its output spectrum by an agreed upon action spectrum for erythema. The comment added that the dose of radiation should be expressed as "erythema effective Joules/m^2," and the intensity of radiation should be expressed as "erythema effective Watts/m^2." The comment stated that a number of action spectra for skin erythema have been published and that it is of particular importance for the sunscreen rulemaking that "the FDA specify one action spectrum which will then be used for appropriate integrations." The comment added that because the majority of the sun's energy output is in the visible and IR range, and the UV radiation component rarely exceeds a few percent of the total and changes rapidly with time, measurement of the sun's intensity without making the corrections suggested above will produce useless results. Therefore, the comment felt that radiometers for measuring the sun's intensity should also be calibrated in "erythema effective Joules/m^2," if a dose is being measured, or in "erythema effective Watts/m^2," if intensity is being measured.

A second comment felt that, although the monograph appropriately does not specify the scale to be used in measuring the output of solar simulators, the Panel's report is confusing regarding the units in which radiometers should be calibrated. The comment cited the following statements from the Panel's report (43 FR 38260):

"The output of a solar simulator is measured in units of Joules * * * The UVL [UV light] intensity of a solar simulator will be reported in J/m^2." The comment stated that this requirement would restrict the use of monitoring devices (such as the widely used Robertson-Berger (R-B) meter) that meet all other Panel-recommended requirements for radiometers but that provide output in terms of sunburn units/hour. The comment suggested that the Commissioner clarify that the radiation of solar simulators need not be measured in terms of Joules.

The first comment is correct regarding the Panel's use of "intensity" instead of "dose" in its discussion of solar simulators. The agency believes that the proper nomenclature should be the currently accepted CIE definitions of units applicable to all radiation (Refs. 1, 2, and 3). The acceptable quantities are "radiant power," which has units of Watts, and "radiant energy," which has units of Joules. "Irradiance" is the radiant power incident upon a surface per unit area of the surface and is expressed in W/m^2. "Radiant exposure" is the energy equivalent of irradiance and is expressed in J/m^2. Additionally, the term "spectral irradiance" refers to the irradiance of the source restricted to a narrow wavelength band of the spectrum, and is expressed in terms of Watts per square meter per nanometer (W/m^2-nm).

In § 352.43, "*Determination of SPF value using artificial light source,*" the Panel defined UV radiation exposure in units of time. The agency believes that it is more accurate to express dose as the "erythema effective exposure," in units that define the total amount of erythema effective energy applied to the testing subsite, i.e., as J/m^2. Thus, in order to determine the erythema effective exposure, the measured output from the solar simulator (spectral irradiance, W/m^2-nm) must be weighted using an agreed-upon erythema action spectrum. And this spectrum must have weighting factors that have a different effectiveness for producing erythema with different wavelengths of UV radiation.

The agency is aware that although various erythema action spectra have been published, none have been universally adopted (Ref. 4). The agency agrees with the first comment that an action spectrum for erythema should be agreed upon. The CIE has proposed a reference action spectrum based upon a statistical analysis of the results of several published studies carried out since 1964 (Ref. 4). The agency believes that the CIE's proposed reference action spectrum is appropriate for use in the testing procedures for OTC sunscreen drug products. The following equations describe the proposed reference spectrum:

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

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

$$V_i(\lambda) = 10^{0.015(139-\lambda)} (328 < \lambda < 400 \text{ nm})$$

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

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

where:

E=Erythema Effective Exposure (dose)
V_i=Weighting Factor (Erythema Action Spectrum)
I=Spectral Irradiance (W/m^2-nm)

The agency believes that adoption of this erythema action spectrum would represent a significant step forward in the development of standardized equipment for the testing of sunscreen drug products. Therefore, the agency is proposing to modify § 352.43 of the Panel's recommended monograph to include this action spectrum and the proposed calculation to determine the erythema effective exposure. This information appears in proposed § 352.73(a), (b), and (c).

The agency is using the term "erythema effective exposure" in place of the term "exposure time interval" in the SPF calculation as follows:

SPF value=the ratio of erythema effective exposure (J/m^2) (MED (PS)) to the erythema effective exposure (J/m^2) (MED (US)) The agency invites comments on this proposal.

The agency agrees with the second comment that the Panel's report is confusing regarding the units in which radiometers should be calibrated. The agency does not agree, however, that the radiation of solar simulators need not be measured in terms of Joules. The agency believes that the CIE units mentioned above should be used in all sunscreen testing, including the calibration of equipment. The agency acknowledges that requiring the output of a solar simulator to be measured in Joules does mean that the "widely used" R–B meter cannot be used to measure the output of solar simulators. However, radiometers, including the R–B meter, have limited value for measuring the output of simulators. Considering present technology, the agency recommends the use of spectroradiometers or similar spectrally sensitive devices for measuring the radiant energy output from solar simulators (Refs. 5 and 6). (See comment 88.)

Because natural sunlight is not being proposed as a testing light source in this tentative final monograph, the agency is not addressing the requirements for radiometers to measure natural sunlight. However, any specifications for instruments to be used for measuring solar simulators may also be used for measuring natural sunlight.

References

(1) Ben-Hur, E., and I. Rosenthal, editors, "Photomedicine Vol. III," CRC Press, Inc., Boca Raton, FL, pp. 110–117, 1987.

(2) Sliney, D., and M. Wolbarsht, "Safety with Lasers and Other Optical Sources," Plenum Press, New York, pp. 54–60, 1980.

(3) Kaufman, J.E., editor, "Measurement of Light and Other Radiant Energy," *in* "IES Lighting Handbook," Illuminating Engineering Society of North America, New York, 1984.

(4) McKinlay, A.F., and B.L. Diffey, "A Reference Action Spectrum for Ultraviolet Induced Erythema in Human Skin," *CIE-Journal*, 6:17–22, 1987.

(5) Diffey, B.L., "A Comparison of Dosimeters Used for Solar Ultraviolet Radiometry," *Photochemistry and Photobiology*, 46:55–60, 1987

(6) Sliney, D., and M. Wolbarsht, "Safety with Lasers and Other Optical Sources," Plenum Press, New York, pp. 439–466, 1980.

85. Referring to the Panel's statement that approximately 6×10^6 J/m^2, as measured by a recording radiometer, will evoke 1 MED in Skin Types I and II (43 FR 38206 at 38262), one comment stated that the number is meaningless and that such a dose can be obtained from the sun without any UVB being

present in the beam. The comment felt that all such doses should be reported as "erythema effective J/m^2." The comment also objected to the Panel's statement at 43 FR 38262 that "duration of sun exposure will be documented in Joules/m^2 or in R–B counts." It is not duration of sun exposure, the comment claimed, but UVB dose that should be documented, particularly since J/m^2 or R–B counts refer to dose. Likewise, the comment felt that the number 4.5×10^6 J/m^2, presented as an example of an MED for a type I subject in the Panel's discussion of a test protocol design (43 FR 38262), is another meaningless number. The comment stated that dose should always be expressed in erythema effective J/m^2. The comment added that the doses presented in the Panel's discussion of the calculation of the SPF value using a recording radiometer (43 FR 38263) should also be expressed in "erythema effective J/m^2."

The agency agrees with the comment that the quantities 6×10^6 J/m^2 and 4.5×10^6 J/m^2, alone, without reference to a band of the solar spectrum are not useful. The Panel used these figures as examples of appropriate amounts of solar exposure needed to evoke 1 MED in subjects with Skin Types I and II. Likewise, in the Panel's report (43 FR 38206 at 38263), 6×10^6 J/m^2 is used in an example given for the determination of the SPF value from an MED obtained using a recording radiometer. Although it is possible to receive a dose of 6×10^6 J/m^2 of radiant energy from the sun without any UVB being present, it is unlikely that exposure to natural sunlight would be completely devoid of any UVB radiation. Further, the Panel only used these numbers as examples in its discussion of the methods involved in determining the SPF value of a sunscreen product using natural sunlight as a light source.

The agency is not proposing the Panel's recommended testing procedures for the determination of SPF values using natural sunlight testing (see comment 79). Therefore, it is not necessary to address the comment's concerns about the dose of natural solar radiation measured in sunscreen drug product testing. However, with respect to indoor testing using a solar simulator, the agency now prefers to express dose as the "erythema effective exposure," in units that define the total amount of erythema effective energy applied to the testing subsite (J/m^2). (See comment 84.) In order to ensure that only erythema effective radiation emitted by a solar simulator is measured for sunscreen drug product testing, an action spectrum for erythema and the units of radiant energy must first be established. The agency has proposed an action spectrum for erythema and discussed the appropriate units for measuring radiant energy elsewhere in this document. (See comment 84.)

86. One comment stated that the artificial light source used in testing to determine SPF values should not be restricted to xenon lamps. The comment referred to the Panel's statement that the xenon arc solar simulator is the preferred artificial light source (43 FR 38206 at 38259 and 38260). The comment suggested that, in the tentative final monograph, the agency should de-emphasize the use of the xenon arc lamp over other artificial light sources unless it can be demonstrated to be superior through corroborative testing. The comment contended that Westinghouse FS 40 sunlamps provide a useful laboratory source for UVB radiation and have two advantages over the xenon arc lamp: (1) the absence of discomfort to the subject during the challenge to UV radiation, and (2) an area of coverage of over 20 times greater than that of a 150 W xenon arc lamp. The comment argued that the FS 40 sunlamp results in greater effectiveness in laboratory studies because the exposure of 16 to 24 treatment sites in testing of a product with SPF values of 8 or 10 can be completed within 16 to 20 minutes. The same experiment with one subject and a 150 W xenon arc lamp would take about 1½ hours.

A second comment stated that experience with xenon arc solar simulators is insufficient to determine whether a correlation exists between SPF values determined using them as the light source and SPF values determined using natural sunlight. The comment suggested that the Panel's testing procedures also allow for the use of other light sources, such as the Weinsberger Solarium or Osram Vitalux.

A reply comment contended that the light sources suggested by the above comments, e.g., the FS series of fluorescent sunlamps and the filtered intermediate pressure mercury vapor sunlamp (such as the Osram Vitalux) do not adhere to the Panel's recommendations for an appropriate light source and could cause misevaluation of the sunscreen product. The comment stated that these two types of light sources emit radiation shorter than 290 nm and, as a result, may produce erythemal responses with nonsolar radiation. The comment added that the Osram lamp also emits a line spectrum that is not continuous. Therefore, the lamp deviates from natural sunlight and from the Panel's recommendations for an appropriate light source. The comment supported the Panel's recommendation to use solar simulator light sources that emit a continuous UVB spectrum of 290 to 320 nm with not more than 1 percent of the emitted radiation shorter than 290 nm.

In the notice of public meeting to discuss sunscreen testing procedures (52 FR 33598 at 33599), the agency questioned the variability of the data submitted to the Panel in support of the recommended testing methods and proposed several possible modifications to these testing methods in an effort to improve them. In response to the publication and the subsequent meeting held on January 26, 1988, the agency received several comments that addressed the solar simulator as a possible source of error in the sunscreen testing procedures.

Four of these comments suggested that light sources other than the xenon arc solar simulator were appropriate for use in sunscreen testing. Stating that the light source is one of the remaining variables in the existing methods for SPF determination, one comment submitted testing results obtained in France (Ref. 1). This comment maintained that these data suggest that the use of different light sources now specified by existing methods is unlikely to affect results significantly. Another comment stated that a frequent problem of the xenon arc solar simulators is that their spectral characteristics can change following alteration or damage to the filtration system used with these machines. Noting that there are alternative UV sources that are utilized for sunscreen testing, the comment stated that four Osram lamps are used in the DIN methods. The comment added that high pressure mercury halide sources have also been used. The comment maintained that even though these sources are not as solar simulating as a perfectly filtered xenon arc source, their spectral characteristics remain constant. The comment subsequently presented data purporting to show that similar SPF values are derived when using either an appropriately filtered xenon arc solar simulator or a high pressure mercury halide source even though the high pressure mercury halide lamp emits a discontinuous spectrum (Ref. 2). Stating that both instruments have advantages, the comment noted that the advantages of the mercury halide source include ease of use and stable spectral output reliability. The comment suggested that alternative UV sources be permitted providing that they possess appropriate quantities of UVA and UVB as terrestrial sunlight. The comment also suggested that nonxenon arc sources be tested with SPF assays and

compared to xenon arc simulators prior to acceptance of an allowed UV radiation source.

Two comments cited a recent publication (Ref. 3) to support a contention that, for testing sunscreen products with an SPF under 15, either a xenon arc or a mercury halide lamp can be used with similar results. However, both comments claimed that for sunscreens with an SPF over 15, a xenon arc solar simulator should be used. Another comment maintained that the testing of sunscreen drug products with an SPF of 15 or higher is best achieved by using high-intensity xenon arc lamps of 1 kilowatt (kw) or greater and that the Panel-recommended 150 W xenon arc lamp is inadequate for this purpose. One comment noted that an Ultravitalux lamp, which is a "line source mercury arc," has very little emission in the UVA range. This comment stated that when UVA absorbers are added to sunscreen formulations, the Ultravitalux lamp will overestimate the efficacy of protection against a solar source.

Five comments maintained that the solar simulator should be the light source of choice for sunscreen drug product testing. Three comments suggested that the sunscreen monograph should include specifications for acceptable light sources for testing sunscreens. One comment initially suggested that the solar simulator should be filtered to match the spectrum of the sun at a 60° angle; however, the comment subsequently recommended that the light source should be filtered to match the spectrum of the sun at 75° above the horizon. Another comment recommended that because the sun angle rarely exceeds 80° elevation, except in the tropics, a spectrum similar to an 80° elevation should be used and should give adequate safety factors. One of the comments stated that the xenon arc light source should be filtered with "WG 320, 1 mm thickness."

One comment explained that because the biological effectiveness of UV radiation wavelengths from 295 to 400 nm drops rapidly by a factor of over 1,000, the emission spectrum (i.e., spectral power distribution) of the UV radiation source will greatly influence SPF values. The comment stated that: (1) The sun emits a polychromatic continuum of different wave lengths; (2) low pressure fluorescent sun lamps emit a continuum mainly in the UVB, or mainly in the UVA range; (3) high pressure mercury arcs provide discontinuous line spectra; and (4) high intensity solar simulators, based on xenon, xenon-mercury, or doped tungsten may mimic solar UV radiation, but they require special filtration to shape the UVB spectrum and to remove intense visible and IR radiation. The comment added that the age of the lamp, temperature of the bulb or arc, and the age of the filters will influence both spectral power distribution and irradiance.

The comment recommended that for purposes of SPF testing, light sources with a spectral power distribution closely representing that of sunlight should be used and that the light source should not emit radiation below 290 nm. Stating that the power consumption (i.e., 150 W, 2500 W, etc.) is immaterial, the comment maintained that only the spectral power distribution counts. Adding that accurate spectroradiometry methods are now available, the comment stressed that it is important that the spectral power distribution of the light source be known exactly and that equipment be monitored regularly. According to the comment, spectral power distribution and irradiance of filtered light sources vary in the first minutes of operation. For that reason, testing should not begin until 30 minutes after the equipment has been turned on to allow all systems to come to operating temperature and spectrum. This practice is particularly important when new lamps or filters are installed, in which case the solar output of the light source should be monitored frequently during the early times of operation.

The agency points out that the Panel (43 FR 38206 at 38265) did not restrict the artificial light source for sunscreen drug product testing to xenon arc solar simulators; they were recommended as the preferred artificial light source (43 FR 38260). The agency believes that the Panel recommended xenon arc solar simulators as the preferred light source because it had more information and more experience with these light sources than with other light sources.

The agency does not consider the data submitted by two of the comments (Refs. 1 and 2) sufficient to demonstrate that light sources with emission spectra different from that of sunlight can produce results equivalent to those obtained using a xenon arc lamp. In one study (Ref. 1), the investigators determined the SPF of the standard preparation used in the DIN sunscreen testing procedure using a modified DIN testing procedure in which a xenon arc solar simulator replaced the solar simulator normally used. Using 22 subjects and the modified DIN method, they determined that the geometric mean of the SPF was 3.53 and concluded that this result compared favorably with the SPF of 3.7 obtained when the DIN standard preparation is evaluated using the normal DIN testing procedures. However, for a true comparison, the same batch of sunscreen standard should have been evaluated by both methods on the same 22 subjects. The agency also notes that these data merely indicate that the light source may have no effect on the determination of a low SPF. There are no data showing that the light source will not affect the determination of a high SPF such as 15.

The second set of data (Ref. 2) consists of two SPF values for each of five sunscreens. One SPF was determined using a metal halide light source, and the other was obtained using a xenon arc source. No other information or data were included. These data are not adequate to demonstrate the comparability of light sources for sunscreen testing procedures.

At this time, the agency agrees with the Panel that xenon arc solar simulators are the preferred light source for sunscreen testing because they emit a continuous spectrum that can be filtered to match sunlight. However, the agency acknowledges that other light sources may be used providing that they meet the specifications being proposed in § 352.71. (See comment 87.)

The agency believes that the light source is a significant factor that can affect the outcome of sunscreen testing. It is important, therefore, that the monograph testing procedures include adequate specifications describing an appropriate light source. The Panel defined an appropriate solar simulator for sunscreen testing as a light source having "(1) A continuous emission spectrum in the UVB (290 to 320 nm); (2) Less than 1 percent of its total energy contributed by nonsolar wavelengths (wavelengths shorter than 290nm); and (3) No more than 5 percent of its erythemically effective energy contributed by nonsolar wavelengths," (45 FR 38259 and 28260). The Panel provided these specifications for a solar simulator in § 352.41(a) of its recommended monograph, but did not identify any specific light source which would meet these criteria.

The knowledge regarding solar simulators, the erythema action spectrum, and the role of UVA in the production of skin damage has increased greatly since the Panel's report was published in 1978. The agency believes that the specifications for a solar simulator recommended by the Panel for sunscreen testing should be revised based on this new information. Although the Panel recommended that the solar simulator

used for sunscreen testing should emit a continuous UV spectrum from 290 to 320 nm (UVB radiation), the agency now believes that the solar simulator used to determine the SPF value of a sunscreen product should mimic the harmful spectrum of the sun as closely as possible and should include both the UVB and UVA spectra. The agency notes that the Panel's recommended labeling claims for Category I sunscreens include photoprotection against harmful rays of the sun that cause sunburn, cancer, and premature aging of the skin (i.e., skin aging). Although UVA radiation has been traditionally thought to contribute little to the deleterious effects of the sun, recent studies have shown that UVA is erythemogenic (Refs. 4 and 5). One study strongly suggests that UVA wavelengths of 315 to 340 nm, which are abundant in solar UVA, are most responsible for UVA induced photoaging (Ref. 6). UVA radiation can also augment the acute and chronic effects of UVB radiation (Refs. 7 through 11). In addition, the agency notes that some of the Category I sunscreens protect against UVA radiation as well as UVB radiation. The agency, therefore, concludes that the solar simulator used for sunscreen testing should emit a continuous UV spectrum from 290 to 400 nm (UVB and UVA radiation), similar to that of the sun at sea level. (For a discussion of sunscreens that protect against UVA radiation and UVA labeling claims, see comment 53.)

Regarding which sunlight spectrum should be used as the model that a solar simulator should mimic, the agency notes that one comment recommended matching sunlight at an 80° solar elevation. Another comment initially recommended matching sunlight at a 60° solar elevation but later recommended a 75° solar elevation. There are two ways of describing the position of the sun in the sky. The comments' method uses the angle of the solar elevation above the horizon to describe the position of the sun. The other method uses the angle of the sun measured from the sun's zenith. A solar elevation of 80° equals a zenith angle of 10°. In this rulemaking, the agency is using the zenith angle to describe the position of the sun in the sky.

The agency is aware that the spectral quality of the sun is not constant and is dependent upon the effective thickness of the atmosphere through which the radiation must pass. The effective thickness of the atmosphere is dependent upon various factors including the latitude and altitude of the observer and the zenith angle of the sun (Ref. 12). The agency realizes the importance of specifying which sunlight spectrum should be used for testing sunscreen drug products and believes that a zenith angle of 10° represents a reasonable angle to specify in the testing procedures. Therefore, the agency is proposing that the solar simulator used for sunscreen testing should have a spectrum similar to sunlight at sea level from the sun at a zenith angle of 10°. The agency invites comment on this proposal.

Regarding one comment's recommendation that the xenon arc light source should be filtered with "WG 320, 1 mm thickness," the agency is not including specific filters in its specifications for solar simulators. The agency is not restricting the light source for sunscreen testing to xenon arc lamps, but is including specifications that the light source used for sunscreen testing must meet. In order to fulfill these specifications, light sources must be appropriately filtered. However, the filters necessary to obtain the proper spectrum depend upon the unfiltered output of the light source. Therefore, it would be inappropriate for the monograph to specify specific filters. However, the agency is proposing that a solar simulator be properly filtered so that its output simulates sunlight at sea level from the sun at a 10° zenith angle between 290 and 400 nm.

The agency is aware that, due to fluctuations in electrical supply and ambient temperature, the spectral output of solar simulators can change significantly during the period of time immediately after being switched on (Ref. 13). This is more pronounced when optical filters are used. Thus, the agency is proposing in § 352.71 that a solar simulator should not have significant time-related fluctuations in radiation emissions after an appropriate warm-up period. The investigator should carefully evaluate the solar simulator being used in order to determine the time period required for warm-up. Because a uniform exposure is important to the outcome of sunscreen testing, the agency is also proposing that the solar simulator have good beam uniformity (within 10 percent) in the exposure plane. The agency is also proposing that a solar simulator be measured periodically with an accurately calibrated recording instrument. (See comment 87.)

The Panel recommended that a solar simulator should have less than 1 percent of its total energy output contributed by nonsolar wavelengths shorter than 290 nm and not more than 5 percent of its total energy output contributed by wavelengths longer than 400 nm (43 FR 38206 at 38259). However, the Panel's reasons for choosing these limits are not clear. Ideally, a solar simulator used for testing sunscreen drug products should emit only solar UV radiation. Extraneous radiation only adds to the error of the testing method. Although the Panel's recommended limits are adequate and are being proposed in this document, the agency believes that these limits could be more narrowly defined because the design of solar simulators is better today than when the Panel report was published. For example, it is possible that a solar simulator could have less than 0.1 percent of its total energy output contributed by nonsolar wavelengths shorter than 290 nm and not more than 1 percent of its total energy output contributed by wavelengths longer than 400 nm. Therefore, the agency is requesting comments on the amount of extraneous radiation that should be allowed in the output of a solar simulator.

The agency is revising the specifications proposed by the Panel in § 352.41(a) of its monograph to reflect these changes and is including new specifications in proposed § 352.71 to read as follows:

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

The agency invites further comment on these proposed specifications.

References

(1) Comment No. C00076, Docket No. 78N–0038, Dockets Management Branch.

(2) Comment No. C00089, Docket No. 78N–0038, Dockets Management Branch.

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

(4) Kaidbey, K. H., and A. M. Kligman, "The Acute Effects of Longwave Ultraviolet Radiation in Human Skin," *Journal of Investigative Dermatology*, 72:253–256, 1978.
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(10) Forbes, P.D., et al., "Simulated Stratospheric Ozone Depletion and Increased Radiation Effects on Photocarcinogenesis in Hairless Mice," *Cancer Research*, 42:2796–2803, 1982.
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(12) Forbes, P.D., "Workshop on Production and Measurement of Ultraviolet Light: Light Sources for Solar Simulation in Photocarcinogenesis Studies," International Conference on Ultraviolet Carcinogenesis, National Cancer Institute Monograph No. 50, 1977.
(13) Diffey, B.L., "The Stability of Light Sources: Implications for Photobiological Studies," *Photochemistry and Photobiology*, 47:317–320, 1988.

87. One comment questioned the Panel's exemption of the xenon lamp from validation by "corroborating natural sunlight testing." The comment stated that validation was required for all other artificial light sources, even though these might have a UV spectrum comparable to "xenon light" (43 FR 38206 at 38260). The comment believed that industry has interpreted the Panel's report to mean that the xenon lamp replaces and is more desirable than natural sunlight testing. The comment felt that the Panel's position is faulty because it does not recognize the limitations of solar simulators, i.e., that simulated sunlight is not natural sunlight, and that "simulators are often used in a laboratory environment under conditions that don't even approximate (let alone simulate) use conditions." A second comment noted that the activity of all xenon arc solar simulators is not based on the same principle, i.e., radiation reflected from visible light and an IR reflecting dichroic mirror. Therefore, the comment stated xenon lamps will emit a variety of intensities of UV radiation, depending on their design and construction. A reply comment questioned the validity of the objections by the first comment and stated that at least two highly reputable and respected manufacturers currently produce xenon arc lamps under sufficiently controlled procedures to effectively eliminate concerns about the standardization of these light sources between manufacturers.

The agency agrees with the Panel that a properly filtered xenon arc solar simulator is the preferred artificial radiation source. The xenon arc solar simulator was first described in 1969 by Berger (Ref. 1), and solar simulators have been widely used in photobiological research since then. According to Sayre (Ref. 2), the design of these instruments has changed little. According to Diffey (Ref. 3), the technology of optical radiation sources is well established, and the factors that can affect the stability and the life of these lamps is well documented. Currently, a number of xenon arc solar simulators systems are commercially available to provide solar simulated radiation (Ref. 2). The agency notes that in the Panel's recommended monograph and in proposed § 352.71, a specific type of light source is not mandated; only the specifications of the light source are described. These specifications ensure that the solar simulator emits a spectral distribution of UV radiation that is most similar to that produced by the sun. (See comments 85 and 86 for further discussion of artificial light sources.)

Regarding one comment's belief that industry has interpreted the Panel's report to mean that indoor testing is preferable to natural sunlight testing, the agency has determined that indoor testing is as accurate and more reproducible than outdoor testing. (See comment 79.)

As the second comment noted, all xenon arc solar simulators do not produce identical intensities of UV radiation. While one type of xenon arc solar simulator may produce a spectral distribution very similar to that produced by natural sunlight, another xenon simulator may produce a slightly different spectrum. Solar simulators may also emit different spectra as the lamp and its filters age. Therefore, the agency emphasizes that all artificial light sources, including xenon arc solar simulators, must be measured periodically with an accurately calibrated spectroradiometer system or equivalent instrument. Testers must ensure that the lamps used deliver the appropriate spectrum of UV radiation and comply with the specifications in proposed § 352.71. (See comment 88 below for a detailed discussion on the monitoring for artificial light sources.) Therefore, the agency is revising the last sentence of the Panel's recommended § 352.41(a) to read as follows: "To ensure that the solar simulator delivers the appropriate spectrum of UV radiation, it must be measured periodically with an accurately-calibrated spectroradiometer system or equivalent instrument." Also, as noted in comment 86, this revised sentence is included in proposed § 352.71. The agency invites comment as to whether a specific time period (e.g., "measured every 3, 6, or 12 months") should be substituted for "measured periodically" in the above statement.

References

(1) Berger, D. S., "Specification and Design of Solar Ultraviolet Simulators," *Journal of Investigative Dermatology*, 53:192–199, 1969.
(2) Sayre, R. M., "UV Solar Simulation," *Photochemistry and Photobiology*, 47:52S, 1988.
(3) Diffey, B. L., "The Stability of Light Sources: Implications for Photobiological Studies," *Photochemistry and Photobiology*, 47:317–320, 1988.

88. Referring to the Panel's discussion regarding monitoring of the xenon arc solar simulator (43 FR 38206 at 38260), one comment stated that thermopiles are useful in measuring UV, visible, and IR radiation. The comment stated that the Panel, however, did not mention using appropriate filters to screen out visible and IR radiation for obtaining the UV flux incident on the skin surface. The comment added that using filters is important not only for monitoring the correct dosimetry of UV radiation, but also for eliminating IR radiation that is significantly present in the xenon arc emission.

The agency agrees with the intent of the comment. However, considering present technology, the agency believes that spectroradiometry (measurement of wavelengths in the form of spectra), or similar spectrally sensitive techniques, should be used to characterize the output from a solar simulator (Ref. 1). Although the Panel recommended the use of calibrated thermopiles to measure the output of solar simulators (43 FR 38260), the agency believes that the thermopile is not an appropriate instrument for performing measurements of solar simulators. For measuring the output from a solar simulator, a radiometer must have accurate sensitivity in the UV spectral region and be equipped with an appropriate mechanism to filter out any visible light or IR radiation that may be emitted by the solar simulator. Even a

properly calibrated radiometer, if unfiltered, will measure the total energy output of the light source regardless of the wavelengths present or the intensities of those wavelengths. As a solar simulator ages, it frequently emits progressively less UV radiation although its emissions in the visible and the IR spectrum continue to remain relatively constant. An unfiltered radiometer may not detect these changes.

There are several ways to determine radiometric values which, when correctly used, yield the same physical values. The agency is not requiring a specific method. The following suggestions are offered to establish the important parameters; physically equivalent alternatives are also acceptable.

Measurements should be performed using generally accepted radiometric principles and techniques. The quantity to be measured should be reported in spectral irradiance values which have units of W/cm^2-nm. For solar simulators, all measurements should be made on the complete device consisting of the light source and any related housing, filtration, or attachments manufactured or assembled for use with the device. Although filtered radiometers may be used to measure the output of solar simulators, the agency believes that such meters have limited value because they do not measure the spectral distribution of the light source. Accordingly, the agency recommends that spectroradiometers, or similar spectrally-sensitive instruments, be used. Spectroradiometry is the most fundamental method for measuring the radiant energy output (Refs. 2 and 3). Sophisticated instruments for the measurement of spectral irradiance should be used to adjust for spectral output distribution changes caused by such factors as filtration, distance from the source, warm-up time, and lamp age. Additionally, in order to use biological weighting functions, the spectral distribution of the source must be determined.

The spectroradiometric measurements on the solar simulator should be made at the same distance from the lamp that will be used for the sunscreen testing exposures. The measurements on the continuum part of the spectrum should be made at intervals of no more than 10 nm in the UV wavelength region below 400 nm. In addition, the spectral lines in the emission should be measured with a sufficiently narrow spectral bandpass (≤ 2nm) so as to adequately measure the level of radiation being emitted in those lines.

The measurements should be made with instruments calibrated against standards of spectral irradiance. These standards should have been calibrated either by the U.S. National Institute for Standards and Technology (NIST) (formerly the National Bureau of Standards (NBS)) or by another laboratory against standards calibrated by NIST using NIST-recommended or generally accepted techniques. The instruments should be calibrated on a regular basis, sufficient to document the integrity of the data.

The use of other types of radiometers may be of limited value if properly calibrated and used. There have been attempts to develop radiometers with spectral responses incorporating biological weighting functions. Because biological weighting functions change dramatically with wavelength in the UV spectral region, it is imperative that radiometers be carefully designed for useful results. There are radiometers that measure the photopic (spectral response similar to what the human eye sees) functions well, but this is not the case for other weighting functions (Ref. 3). The principal problem is measuring UV radiation while rejecting all visible light and IR radiation. In addition, because the agency's proposed erythema action spectrum (see comment 84) covers the entire solar UV spectral region from 290 to 405 nm, a radiometer that measures the entire UV spectrum is needed.

As stated above, a spectroradiometer system or equivalent instrument is preferred for measuring the output of a solar simulator. The agency is specifying in § 352.71 that an "accurately calibrated spectroradiometer system or equivalent instrument" be used. (See comment 87.)

References

(1) Ben-Hur, E., and I. Rosenthal, editors, "Photomedicine Vol. III," CRC Press, Inc., Boca Raton, FL, pp. 110–117, 1987.

(2) Diffey, B. L., "A Comparison of Dosimeters Used for Solar Ultraviolet Radiometry," *Photochemistry and Photobiology*, 46:55–60, 1987.

(3) Sliney, D., and M. Wolbarsht, "Safety with Lasers and Other Optical Sources," Plenum Press, New York, pp. 439–466, 1980.

(4) Berger, D. S., "The Sunburning Ultraviolet Meter: Design and Performance," *Photochemistry and Photobiology*, 24:587–591, 1976.

89. One comment suggested that, in addition to the R–B meter, the Panel should have recommended other UV measuring instruments that are reliable, well calibrated, give radiant energy in Watt-seconds per square centimeter, and have continuous measurement capability. Arguing that the R–B meter is an expensive research instrument that is not readily available, the comment described another, less expensive instrument that it had found to be very reliable for both the indoor and outdoor measurement of UV radiation. Another comment stated that specific references to the R–B meter should be deleted from § 352.44. The comment stated that, if proper control formulations are used to validate test results and calculate the SPF value, the monitoring device becomes secondary to the control formulation. The comment mentioned that the R–B meter is available from only one commercial source, and this limitation could place unnecessary restraints on natural sunlight-simulated use testing. The comment recommended that § 352.44 either be expanded to be more representative of the available instrumentation or be generalized with no reference to specific instrumentation. Another comment stated that the wording of § 352.44 is adequate because it provides that radiometers other than the R–B meter may be used. Another comment stated that the R–B meter is widely used and widely available.

The Panel discussed the use of the R–B meter for monitoring the amount of exposure to natural sunlight during the testing of a sunscreen drug product (43 FR 38206 at 38260). Citing a compilation of data from various radiation studies (Ref. 1), the Panel stated that the R–B meter has proved to be successful in monitoring and reproducing solar erythemic exposures. The Panel also stated that other recording radiometers are in use that perform a similar function. The Panel did not limit its recommendation for radiometric instruments to the R–B meter only. Concerning the comment's recommendation that the agency delete references to the R–B meter in § 352.44 and expand this section to include other types of radiometric instrumentation, the agency is not including the Panel's recommended § 352.44 in this tentative final monograph. (See comment 79.)

The agency earlier discussed the R–B meter as a monitor of the output of solar simulators used in sunscreen drug product testing. (See comment 84.) The R–B meter is only one of the recording radiometers that can be useful, and the agency is not mandating any specific instrument for monitoring solar simulators.

Reference

(1) Measurement of Ultraviolet Radiation in the United States and Comparisons with Skin Cancer Data, OTC Volume 06A185, Docket No. 78N–0038, Dockets Management Branch.

90. One comment stated that a major factor that affects the erythema response of individuals and the resulting SPF and

PCD determinations is the xenon arc lamp solar simulator and its four major components: the quartz bulb, dichroic mirror, W. G. cut-off filters used at the UV radiation exit site, and the line voltage. The comment stated that the first three of these components become coated with dust particles, smoke, and laboratory-derived gaseous films from acids, ammonia, etc. To minimize variations in UV intensity, the comment recommended that the light box be kept covered with a black cloth cover when not in use, and that variations in line voltage be minimized by a voltage stabilizer.

The comment's recommendations appear reasonable in the absence of any contrary evidence. Parties who conduct tests on OTC sunscreen drug products should consider these recommendations as part of their test procedures.

S. Comments on the Design of the Testing Procedures for Sunscreen Drug Products

91. Referring to the agency's public meeting on sunscreen testing procedures and statistical methods held on January 26, 1988, one comment recommended that the testing procedures specify product "blinding." The comment stated that many laboratories already include "blinding" as part of their testing procedures but felt that this procedure should be mandatory to eliminate any product bias during subjective evaluation of the MED.

In a supplementary submission (Ref. 1), the comment maintained that potential investigator bias in clinical studies involving SPF determinations can be eliminated or reduced in several ways. Stating that sunscreen formulations (e.g., lotions, creams, gels, and solutions) can be packaged in identical appearing containers prior to testing, the comment maintained that such a blinding procedure is essential when the person applying the products is also evaluating the erythema on the test sites 16 to 24 hours later. However, the comment added that this blinding procedure can only be completely successful if all the formulations are identical in consistency and color. Moreover, the comment pointed out that the major disadvantage with this procedure is the need to retest repackaged units to ensure that the concentration of the active ingredients has not changed during repackaging. The comment added that this procedure does not contribute much to the study blinding if a mixture of sunscreen formulations (e.g., gel and cream) are evaluated in the same study or if sunscreens of different SPF estimates are used.

According to the comment, a second way to eliminate investigator bias is to randomize the application of sunscreen formulations to the test sites. Such randomization (generated from computer or random number tables) eliminates investigator bias with respect to evaluation of erythemal scores on a specific test site or sites. An untreated test site may be included in the randomization if necessary. Because the erythemal score on the untreated irradiated area is used in the SPF calculation of all sunscreens evaluated, the comment stated that any investigator bias in reading the erythemal scores on the untreated, irradiated area will be constant for all formulations.

In order to eliminate bias, the comment stated that it is imperative to blind the erythemal evaluator with respect to the application of the products to the treatment sites and, if possible, to the times of UV irradiation. The comment maintained that prior knowledge of these variables may easily influence the reading of the MED by the evaluator, which would ultimately affect the calculated SPF.

The Panel did not require "blinding" in its recommended testing procedures for sunscreen drug products. However, the agency agrees with the comment that blinding would be a desirable part of the sunscreen testing procedures. The agency believes that the person who applies the sunscreen to the test site and administers the doses of UV radiation should not evaluate the erythema end points after the waiting period. In addition, if two or more sunscreens are being tested at the same time, they should be applied to the testing subsites in a randomized manner. If only one sunscreen is being tested, the agency believes that the doses of UV radiation should be applied in a random manner. In addition to being run the day prior to the test, a MED(US) (i.e., an untreated control site) should be run concurrently with the test sunscreen(s). The agency is proposing such a requirement in § 352.73(b). (See section II.B.—*Summary of Agency's Changes*, paragraph 40, of this document.)

The agency is aware that including an untreated control site in the randomization scheme could expose the test subject to an excessive dose of UV radiation on unprotected skin. To prevent this from occurring, the agency is proposing that the untreated control site be exposed to a series of UV radiation doses that are appropriate to determining the test subject's inherent MED as proposed in § 352.73. The agency is also proposing that the appropriate standard preparation be included in the randomization pattern. Therefore, the agency is proposing that a standard preparation, as specified in § 352.70, be run every time a sunscreen drug product is tested. If the SPF of the sunscreen standard falls outside its specified range, the entire test should be considered invalid. (See comment 78.)

The comment suggested that one way to eliminate potential bias in clinical studies involving SPF determinations is to package the test sunscreen formulations in identical packages. If the above procedures are followed, the agency does not believe that test sunscreen formulations need to be packaged in identical containers.

The agency believes that blinding procedures should be included in the sunscreen testing procedures and, thus, is proposing to revise the Panel's recommended § 352.42(e), *Application of test materials*. The following sentences are being added to the end of paragraph (e): "If two or more sunscreen drug products are being evaluated at the same time, the test products and the standard sunscreen, as specified in § 352.70, should be applied in a blinded, randomized manner. If only one sunscreen drug product is being tested, the testing subsites should be exposed to the varying doses of UV radiation in a randomized manner." The agency is also proposing revisions in the Panel's recommended § 352.42(h), *Response criteria*, by adding the following sentence at the beginning of the paragraph: "In order that the person who evaluates the MED responses does not know which sunscreen formulation was applied to which site or what doses of UV radiation were administered, he/she must not be the same person who applied the sunscreen drug product to the test site or administered the doses of UV radiation." The agency is including these revisions in proposed § 352.72(e) and § 352.72(h), respectively.

Reference

(1) Comment No. C101, Docket No. 78N-0038, Dockets Management Branch.

92. One comment, submitted in response to the Panel's report, suggested that the testing of sunscreen agents with the solar simulator should also be performed on skin areas below the belt line, where no sun has typically changed skin color. The comment asserted that most people have tanned skin areas on the back from the neck to the belt line. Another comment referring to the subject selection procedures for testing sunscreen drug products was submitted in response to the public meeting held on January 26, 1988. At that meeting and in the notice

announcing the meeting (52 FR 33598 at 33599), the agency expressed concern regarding the apparent variability of data generated by the testing procedures recommended by the Panel. The comment stated that guidelines for the selection of subjects are not rigidly defined in the Panel's recommended monograph. The comment suggested that deviations in SPF determinations may result from the enrollment of subjects that do not meet the necessary criteria. Stating that volunteers of Skin Types I, II, and III are essential for evaluating the SPF value of the test product, the comment added that these subjects must not have undergone sunbathing or been exposed at a tanning salon for at least 30 days prior to enrollment as a test volunteer. The comment stated that the site for product application must be clearly defined, and products should not be tested on the habitually sun-exposed areas of the upper back (suprascapular region) or on the anterior forearms. The comment considered any fair-skinned subject who claims to be Skin Type I, II, or III, but who has a tanned back or who exhibits an intense immediate pigment darkening (IPD) reaction, as contributing to significant deviations in the determination of SPF values. The comment recommended that such subjects be dropped from the study after MED tests have been performed on day one of the test. The comment emphasized that fair-skinned individuals with untanned backs of Skin Types I, II, and III should be selected for the evaluation of sunscreen test products; individuals with tanned backs or those who have recently been exposed to the sun should be excluded. The comment added that the MED values of different regions of any test subject vary [e.g., the MED of the upper back (suprascapular) is always higher than the MED of the lower or central back (infrascapular)]. The comment maintained that the MED near the anterior cubital region of the upper arm is less than the MED of the volar antibrachial region of the lower arm due to the variations in the thickness of the stratum corneum and pigment content of the epidermis. The comment stated that such variations significantly influence the SPF determination. The comment concluded that to achieve uniformity in test results, the site for evaluation of sunscreen formulations should be specified, and it should preferably be the back area involving the infrascapular region.

The agency agrees with the second comment. Procedures for the selection of test subjects should be clearly defined, and the site for product application should be the carefully inspected back between the beltline and the shoulder blades (scapulae) lateral to the midline. The Panel's recommended sunscreen testing procedures clearly define the criteria for the selection of test subjects and test sites. In § 352.42 of the Panel's recommended monograph, only fair-skinned volunteers with Skin Types I, II, and III are to be selected for enrollment in testing a sunscreen product. If a test subject has areas on the back that are unsuitable for testing a sunscreen product, then that subject should not be included in the study. In discussing the procedure for inspecting the test site of a potential test subject, the Panel recommended that a physical examination should determine the presence of sunburn, suntan, scars, active dermal lesions, and uneven skin tones on the areas of the back to be tested (43 FR 38206 at 38265).

The Panel also considered the areas of the body that are suitable for sunscreen testing and recommended the area of the back between the belt line and the shoulder blade, and lateral to the midline (43 FR 38265). The Panel stated that the back offers a large surface area which is best suited for testing and comparing a number of sunscreen samples. Also, the back has been traditionally used by manufacturers for testing new sunscreen agents. It is important to use the same skin site on the body for testing because comparisons must be made between treated and untreated areas, and areas treated with different ingredients. Using the same skin site helps to minimize testing result differences that are due to variations in skin sites rather than to actual differences between ingredients.

The first comment did not specify particular areas below the belt line that would be suitable for sunscreen testing, nor did it submit data that would demonstrate that the use of such areas will provide consistent test results that allow accurate comparisons between treated and untreated areas. Therefore, the agency accepts the Panel's recommendation that the area to be tested shall be the back between the beltline and the shoulder blade (scapulae) and lateral to the midline and is proposing this requirement in § 352.72(d).

The second comment did not provide any data to demonstrate that test subjects who exhibit an intense IPD reaction contribute to erroneous test results. In § 352.42(h), the Panel recommended that all immediate responses, including "immediate darkening or tanning" be recorded. The Panel did not, however, recommend that subjects who displayed immediate reactions be excluded from testing. The agency is not now proposing to revise the Panel's recommendation. However, if adequate data are submitted demonstrating that an intense IPD reaction contributes to the variability of sunscreen test results, the agency will consider excluding such subjects by modifying § 352.72(h) concerning response criteria and/or § 352.72(i) concerning rejection of test data.

93. In its notice of a public meeting to discuss appropriate testing procedures for OTC sunscreen drug products (52 FR 33598 at 33601), the agency questioned the amount of test sunscreen and standard sunscreen that should be applied to the test subject. The agency noted that the Panel had recommended application of 2 mg/cm^2 (the application density). An independent sunscreen testing expert had suggested to the agency that 1 mg/cm^2 may be a more appropriate amount of sunscreen to use in the testing procedure because 1 mg/cm^2 more accurately reflects the amount of product normally used by a consumer. The agency commented that use of 1 mg/cm^2 would undoubtedly produce lower SPF values and suggested that this may be a way to accommodate the new higher SPF values because using this amount of the product may produce SPF values that more closely approximate the time a product will provide protection.

The agency received 24 comments in response to its question. The majority of the comments, including two manufacturer's associations in the United States, advocated continuing the use of an application density of 2 mg/cm^2. Nine comments, including one from a European manufacturer's association, suggested or recommended that the standard density of sunscreen product per application should be in the range of 1 to 1.5 mg/cm^2.

Comments advocating an application density of 1.5 mg/cm^2 stated that this particular issue is one which goes far beyond the simple question of how much sunscreen a consumer may typically apply. These comments stated that the published data on the application rates of sunscreens seem to be confusing because they vary over a wide range. One comment stated that, based on published studies and unpublished communications (Ref. 1), there is not a "universal" application amount which will be appropriate in all cases. The product type, its viscosity, the product container, consumer use habits, and the areas of the body to which the sunscreen is being applied are among the factors which determine

how much product a consumer may typically apply. Therefore, the comment noted, it should not be surprising that the application density amounts found in the literature vary from about 0.6 mg/cm^2 to 20 mg/cm^2. The comment stated that, although at first glance it may appear not to make any difference which amount one chooses to use for the test conditions, it is important that the testing procedure result in SPF values which reflect actual consumer protection.

The comment stated that several studies and comments have demonstrated that most products tested according to the current United States procedure (using 2 mg/cm^2) have sun protection values which promise a higher protection than is usually experienced by a typical consumer under actual use conditions in natural sunlight (Ref. 1). The comment added that the test procedure should result in SPF values which are, in the majority of cases, reflective of actual consumer protection in natural sunlight. Otherwise, according to the comment, currently allowable label claims such as "Stay in the sun X-times as long as before without sunburning" are misleading and incorrect for the majority of consumers. The comment stated that using a smaller application amount, such as 1.5 mg/cm^2, will result in SPF values which more accurately reflect the actual protection a typical consumer will enjoy in natural sunlight. The comment contended that the DIN method for evaluating sunscreens, which uses an application amount of 1.5 mg/cm^2±10 percent, results in SPF values more clearly reflecting actual consumer protection in natural sunlight. The comment felt that reducing the application amount to 1 mg/cm^2 may result in SPF numbers that are too low. The comment concluded that an application density of 1.5 mg/cm^2 would be the most appropriate to use for determining SPF values. According to the comment, use of this density would be a significant step towards a uniform, worldwide testing procedure that would ensure a certain level of protection from a product regardless of where in the world it was purchased.

A majority of comments, however, strongly advocated retention of 2 mg/cm^2 as the specified application density. Acknowledging that an international reference system of SPF values is a desirable goal, one comment stated that until all other details of the testing protocol are also identical (e.g., the light source used for testing), a change in the application density to a common level will not accomplish that end. The comment added that a review of the literature supports the use of 2 mg/cm^2 as a meaningful test density that has been in use for 10 years.

Another comment noted that no other countries' standards use an amount as low as 1 mg/cm^2. The Australian standard is 2 mg/cm^2, and Japan and Britain generally follow the proposed FDA guidelines. Germany uses an application density of 1.5 mg/cm^2 ± 10 percent. Another comment stated that insofar as international uniformity is sought, 2 mg/cm^2 is a more appropriate figure than 1.5 mg/cm^2. The comment maintained that climate, geography, latitude, population diversity and size, and the multitudes of lifestyles that include year-round sunbathing make the United States a more reliable international model upon which to base sun exposure standards than Germany.

One comment noted that there are many published studies which discuss the average use level of lotions or sunscreen drug products. It cited a study by Schlagel and Sanborn (Ref. 2) which demonstrated that ointments or creams were applied to skin at a use rate of 2.4 mg/cm^2 when used to cover the whole body. The comment also mentioned a study by Hoppe (Ref. 3) in which the average use rate for sunscreen drug products was determined to be 4.0 mg/cm^2 for creams, 2.1 mg/cm^2 for lotions, and 0.75 mg/cm^2 for oils. The comment concluded that, for two of the three categories of sunscreen drug products, the use rate was greater than 2 mg/cm^2. The comment added that the results of a study by Lynfield and Schechter (Ref. 4), in which they investigated how vehicles were applied, demonstrated that application rates varied among individuals up to 100 percent, confirming that sunscreen application is a highly subjective exercise. The comment stated that this study found usage of a sunscreen lotion to be 1.3 mg/cm^2 1.3 mg/cm^2. The comment maintained that it is especially interesting that 1.3 mg2 was the average application density when the subject was instructed to apply "thinly," whereas in the United States, the labeling of sunscreen products generally encourages "liberal" application.

The comment also discussed a study by Stenberg and Larko (Ref. 5) which indicated that the actual application of sunscreen preparations by individuals results in a layer thickness closer to 1 mg/cm^2 than 2 mg/cm^2. It stated that a publication of the Skin Cancer Foundation (Ref. 6) interpreted the study (Ref. 5) to mean that some individuals may be using "inadequate" amounts of sunscreen for achieving proper sun protection and emphasized the need to use enough sunscreen to protect against sunburn and long-term skin damage. The comment noted that the Skin Cancer Foundation reiterated its support of the 2 mg/cm^2 level "recommended by dermatologists" (Ref. 6). The comment concluded that it is more in the public interest to encourage liberal use of sunscreens than it is to change the application density of SPF testing.

The comment further stated that, in over 10 years of testing sunscreens by the proposed FDA guidelines, it has become apparent that 2 mg/cm^2 is an amount which can be uniformly applied to the test site. The comment stated that use of a smaller amount makes uniform application much more difficult, and that some dosage forms cannot be uniformly applied at lower levels. The comment mentioned the wealth of preclinical information in the scientific literature regarding the effects of sunscreens in preventing skin cancer and premature aging. The comment stated that such tests have generally been conducted using the 2 mg/cm^2 sunscreen application rate. The comment expressed concern that a change in the application density will make past scientific studies difficult to interpret for comparative purposes. As a result, the comment contended that the scientific community would lose 10 years of valuable historical data that are the basis of much of the educational position of the AAD and the Skin Cancer Foundation. The comment emphasized that there is no scientific support indicating that any other application amount, including 1 mg/cm^2 or 1.5 mg/cm^2, is better, more accurate, or more reflective of consumer use. Another comment stated that a change in the application density ought to be considered by the agency only when the results are necessary for adequate protection of the public health.

Several comments noted that consumers have learned by experience what level of labeled SPF they need individually to help prevent sunburn. These comments asserted that radically altering the system for determining SPF values would lead to confusion and inappropriate choices of sunscreen products. One comment stated that consumers in the United States now have over 10 years of experience with products tested at 2 mg/cm^2, they have become familiar with the benefits provided by these SPF's based on that testing, and they purchase products on the basis of that familiarity. The comment maintained that lowering the application density in the SPF determination would, in many cases, alter the SPF value, leading to industry-

wide relabeling and/or reformulation of most sunscreen drug products. The comment felt that, from the consumer's point of view, such a change would require a complete revision in his or her sunscreen buying habits. Noting that an individual who burns moderately and tans gradually typically wants and uses an SPF 4, the comment contended that a product with an SPF of 4 based on a 1 mg/cm^2 application density would provide more protection than he or she expects or wants. The comment felt that it is not sound public policy for FDA to disturb an established labeling scheme when the change will confuse consumers and the agency has no information that the change will provide any real benefits.

Another comment agreed with the comment above and strongly recommended retention of the 2 mg/cm^2 application density. Noting that its sunscreen products are labeled with a toll free number to allow consumers to readily report their concerns or complaints, the comment stated that during the past 2 years, data from this consumer contact line, along with all other correspondence, indicate that only 10 reports of sunburning are received per one million units of sunscreen product distributed. The comment contended that these data suggest that consumers are not being misled by SPF claims and are choosing the products appropriate to their skin type and sun exposure habits. The comment added that its sunscreen products include the instructions to apply "liberally" or "generously." The comment asserted that from the low incidence of reported sunburn it can be inferred that these instructions are being followed. The comment concluded that consumers are adequately choosing and applying sunscreen products with the proper SPF and that the current testing methodology is using the appropriate amount of sunscreen for determining SPF values.

The agency agrees with the majority of the comments. Changing the amount of sunscreen used in the sunscreen testing procedures from 2 mg/cm^2 to 1.5 or 1 mg/cm^2 would negatively affect consumers and the scientific community.

The agency agrees with one comment that using 2 mg/cm^2 of sunscreen product in the testing procedure ensures a more uniform application over the test area and thus contributes to a more accurate method of determining SPF values for product labeling. According to published literature (Refs. 2 through 5), actual application density of sunscreen drug products by consumers varies greatly, ranging from a high amount of 4.0 mg/cm^2 to a low amount of 0.75 mg/cm^2 (Ref. 3). Because of the thickness and viscosity of some sunscreen formulations, amounts smaller than 2 mg/cm^2 may be difficult to apply uniformly. If the application density is not uniform across all the testing sites, the resultant MED's are not indicative of the true protection provided by the test product. The SPF calculated from those MED's would be meaningless. Labeled SPF values should be based on testing conducted under the most carefully controlled conditions, so that the results are as accurate and reproducible as possible. The outcome of an accurate and reproducible testing procedure ensures that competitive products with the same SPF values provide essentially the same degree of protection.

Most consumers accept and understand the currently used SPF system. This system effectively communicates to consumers the amount of protection that can be expected from the product. The agency believes that changing this aspect of the SPF system would result in unnecessary consumer confusion and would not be in the public interest.

The agency points out that the SPF value is not an absolute predictor of sunscreen protection. There are many variables involved in sunscreen use (e.g., skin type, latitude, altitude, whether the consumer is at the beach or in a city, and spreading characteristics of the product). The value of the SPF is that it is derived by strictly standardized testing procedures and, therefore, provides a convenient means of product-to-product comparison. The SPF provides consumers a means to evaluate and compare sunscreen drug products based upon the consumer's previous experience in the sun and previous use of products with an identified SPF value. The agency believes that currently there is no scientific need to change the sunscreen testing procedures to include an application density lower than 2 mg/cm^2.

Based on the above discussion, the agency is proposing that 2 mg/cm^2 be the amount of sunscreen used in the testing procedures in § 352.72(e).

References

(1) Comment No. APE003, Docket No. 78N–0038, Dockets Management Branch.

(2) Schlagel, C. A., and A. B. Sanborn, "The Weights of Topical Preparations Required for Total and Partial Body Inunction," *Journal of Investigative Dermatology*, 42:253–256, 1964.

(3) Hoppe, U., "Photostabilitat und Hautaffinitat," *Journal of the Society of Cosmetic Chemists*, 25:667–680, 1974.

(4) Lynfield, Y. L., and S. Schechter, "Choosing and Using a Vehicle," *Journal of the American Academy of Dermatology*, 10:56–59, 1984.

(5) Stenberg, C., and O. Larko, "Sunscreen Application and its Importance for the Sun Protection Factor," *Archives of Dermatology*, 121:1400–1402, 1985.

(6) Skin Cancer Foundation, "Sunscreen Skimping," *Sun and Skin News*, 3:2, 1986.

94. In § 352.42 of its recommended monograph, the Panel stated that groups of 20 subjects should be used for each test panel for determining SPF values. The Panel added that "the standard error shall not exceed ±5 percent of the mean. An appropriate number of additional subjects shall be used to determine the PCD, if a PCD does not fall within the limits of the standard error."

One comment mentioned an apparent contradiction between the Panel's definition of standard error for a 20-subject test group (i.e., 25 percent divided by $\sqrt{20}$, which equals 5.59 percent) and the Panel's later statement that the "standard error" should not exceed ±5 percent of the mean (43 FR 38206 at 38261). The comment assumed that the Panel intended that the standard deviation of the sample should be used to calculate the standard error because the stated standard error for 20 subjects exceeds 5 percent by the definition given. The comment suggested that an additional definition of standard error is required. The comment recommended that the required number of subjects be based on the confidence interval of the mean at a 90-percent level and that the minimum number of subjects should be eight. The comment added that to categorize a product as being within a PCD, the 90-percent confidence interval should fall entirely within a PCD.

Another comment stated that when the Panel initially considered test subject populations, it had considered subject populations ranging from 8 to 12 subjects. However, based upon the collaborative study on standard sunscreen product testing submitted to the Panel by CTFA and NDMA (Ref. 1), the Panel concluded that 20 test subjects would provide a better estimate of a product's SPF value and PCD. The comment stated that this study demonstrates that the inherent standard deviation of the tests performed should not exceed 25 percent of the average SPF for the test formula, regardless of the laboratory in which the test was performed. The comment maintained, therefore, that the Panel felt no advantage accrued from using confidence limits that are dependent upon the standard error or standard

deviation of the test results. The comment asserted that the standard error could be specified thereby controlling the precision of the categorization. The comment suggested that the statistical method proposed by the previous comment (i.e., number of subjects based on the confidence interval of the mean at a 90-percent level with the minimum number of subjects set at eight) should be rejected and the method included in the Panel's recommended § 352.42(g) should be used.

Another comment suggested revising the last sentence of the Panel's recommended § 352.42(g) as follows: "An appropriate number of additional subjects should be used to determine the PCD, if the mean of the SPF test when combined with the allowable minus standard error result in a value below the minimum limit of the PCD." One comment requested that the last sentence of § 352.42(g) be replaced by the following statement: "If the standard error exceeds 5 percent, an appropriate number of additional subjects shall be used to determine the PCD so that the standard error is within this limit."

In the notice announcing a public meeting on sunscreen testing procedures (52 FR 33598 at 33600), the agency stated that it was considering revising the Panel's recommended § 352.42(g) as follows: *"Number of subjects.* Groups of at least 20 subjects shall be used for each test panel. The panel size shall be fixed in advance and additional subjects shall not be added." The agency asked that, if this change is not acceptable, what is the best method for evaluating sunscreen test data to determine if additional subjects are needed to obtain a valid SPF value, and what is the minimum number of subjects required? The agency invited public comment on the possible change.

Most of the comments agreed that (1) test panels should consist of at least 20 subjects, (2) the size of the test panel should be fixed in advance, (3) the limitations that the standard error should be less than ±5 percent should not apply, and (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. One comment maintained that any SPF value derived from a minimum of 8 subjects per test product would not provide convincing data of SPF values acceptable at 99 percent confidence limits.

Another comment, agreeing that at least 20 subjects are needed to complete a test with acceptable data, recommended that the agency recognize the following specific conditions requiring the rejection of data and the subsequent addition of subjects to the test panel: (1) When the exposure series of a given subject fails to elicit an MED response on either the treated or unprotected skin sites, and (2) when responses on the treated sites are randomly absent. The comment also suggested that if a subject withdraws from the test due to illness, schedule or work conflicts, etc., it should be permissible to replace such subjects on an "as-needed" basis because over-recruitment for a study in anticipation of such withdrawals is expensive, inefficient, and unnecessary.

One comment agreed that the agency should allow a limited number of subjects (e.g., 3 to 5) to be added to a test panel if the criteria for PCD are not met due to deviations resulting from inconclusive SPF data. Another comment recommended that the total number of "replaceable" test panel members be limited to 5; if this number is exceeded, the entire test should be repeated. The comment added that the requirement that "the standard error shall not exceed ±5 percent of the mean" is an arbitrary and unsubstantiated limitation and should not be applied.

One comment stated that it has been a common practice to use data from a smaller panel for a preliminary SPF determination and to supplement this panel with enough test subjects to bring the total panel size to a minimum of 20 for the final SPF determination. The comment recommended that this concept should be recognized in the final monograph. The comment proposed that § 352.42(g) be revised to read as follows: "Number of subjects. Group of at least 20 subjects shall be used for each test panel. The panel size shall be fixed in advance and additional subjects shall not be added unless individuals need to be dropped from the study for noncompliance or other legitimate, not test-related reasons or if their response to the test conditions is such that it will not allow a statistical evaluation. The total number of replaceable individuals shall not exceed 5 individuals. It is not required that the entire panel be subjected to the test at the same time."

Conversely, one comment suggested that 20 subjects appears to be the maximum needed for each test panel. It added that a lower number may be possible provided that criteria are built into the method that lay down maximum tolerances on the deviations between readings on each subject. Another comment suggested that panels could be restricted to 10 or 12 persons if the MED of each person is determined in advance and the product's SPF is approximated. One comment stated that it could neither concur with nor refute the adequacy of 20 subjects based upon the documentation provided for review.

One comment stated that experience in Australia demonstrates that a panel size of 10 subjects yields results similar to those obtained on the same formulation in the United States when 20 subjects are used. The comment suggested that the upper limit on panel size should be fixed, for example at 25, and that the test data should be rejected if, for example, 20 valid results are not obtained. The comment added that it is appropriate to retain the Panel's proposed limit on the standard error of the mean.

One comment agreed with the agency's position stated in the notice of public meeting (52 FR 33598 at 33600) that substitutions or additions to a panel should not be allowed. The comment maintained that where all sites on the sunscreen protected area show erythema, these data should be incorporated into the estimate of the mean instead of merely rejecting them as indeterminate results. The comment suggested that if any panelist showed all irradiated spots on the sunscreen protected site, statistical analysis should automatically be handled by a nonparametric test, such as the modified median test or the Wilcoxon signed ranks test. The comment stated that the purpose of using such methods is to ensure that detrimental (yet valid) test results be included in the determination of the SPF estimate and not excluded because they were nondetermined. The comment maintained that this method would more conservatively estimate the protection provided by the test sunscreen.

One comment stated that the final monograph should be very specific in outlining criteria that would disqualify a test subject; the monograph should allow for subsequently replacing that individual on the test panel. For example, the comment stated that if a test subject were erythematous on all subsites, one could not calculate an SPF value and using another test subject should be permissible. Likewise, it should be acceptable to replace a test subject because of noncompliance or other reasons unrelated to the test. Another comment stated that criteria for adding additional subjects are outlined in the Panel's report (43 FR 38206 at 38266) and recommended retaining this procedure. The comment stated that the statistical procedures should provide for the addition of test subjects in the event that the SPF variability precludes

placing the product in the desired PCD. Additional subjects should be limited to the smallest number necessary to classify the mean SPF value ±5percent standard error of the mean or to classify the mean SPF with a power coefficient of 0.8.

The agency recognizes the possibility that during the testing of sunscreen drug products some subjects may not produce data suitable for analysis. Additionally, there may be instances where a subject must withdraw from a study and a question may arise about replacing this subject. Nevertheless, once a subject enters a study, the subject should be considered as part of the study. If the subject withdraws before any data are obtained, the subject may be replaced because the person has not really become part of the study. However, once data are obtained on a subject, the person should not be replaced but should be considered as producing nonvalid data for analysis. The reason for this approach is that preliminary data obtained may influence a subject's decision to leave the study and thus may introduce biases. In general, the guiding principle should be that new subjects are not allowed. Therefore, the agency has determined that the appropriate approach is for test panels to start at a fixed number (the agency is proposing that that number not exceed 25), from which at least 20 subjects must produce valid data for analysis. Nonvalid test data should be rejected, but the subjects should not be replaced. If there are more than five nonvalid subjects, the study should be considered a failure.

The agency agrees that the standard error criterion recommended by the Panel in § 352.42(g) is confusing. Accordingly, that criterion is not being proposed. Instead, the agency is proposing a one-sided t-test to analyze the data obtained from the sunscreen testing procedures. The analysis of sunscreen testing data is discussed further in comment 97.

Therefore, the agency is proposing the following in § 352.72(g): "*Number of subjects.* A test panel shall consist of not more than 25 subjects with the number fixed in advance by the investigator. From this panel, at least 20 subjects must produce valid data for analysis."

All subjects producing valid data must be used in the analysis. Likewise, any subject producing nonvalid data must be omitted from the analysis. Nonparametric tests, such as the modified mean test or the Wilcoxon signed ranks test, should not be used to analyze indeterminate tests results. In § 352.42(i) "Rejection of test data," the Panel recommended the following as valid reasons to reject subject data: (1) The exposure series fails to elicit an MED response on unprotected skin sites; or (2) responses on treated sites are randomly absent, which indicates the product was not spread evenly. The agency agrees with the Panel, but believes that subject noncompliance is an additional reason for rejecting data. Therefore, the agency is proposing to revise the Panel's recommendation by adding the phrase "or if the subject was noncompliant (e.g., subject withdraws from the test due to illness or work conflicts, subject does not shield the exposed testing site from further UV radiation until the MED is read, etc.)." The information on "Rejection of test data" appears in proposed § 352.72(i).

The agency agrees with one comment's suggestion that it is not necessary or practical to test the entire panel of test subjects at the same time. Testing a limited number of subjects per day over a period of several days should not compromise the testing so long as the testing is properly controlled (e.g., the light source is calibrated, concomitant testing of the standard preparation is done, the SPF of the standard preparation falls within the range specified in § 352.70, etc.). However, the agency does not believe that it is necessary to include such a stipulation in the monograph.

Reference

(1) Comment No. SUP002, Docket No. 78N–0038, Dockets Management Branch.

95. Several comments presented suggestions and recommendations to clarify the definition and precision of measurement of the "minimal erythemal dose (MED)" recommended by the Panel in §§ 352.42(h) and 352.43 of its testing procedures. Three comments stated that the MED should be defined as the minimal erythema producing uniform redness and sharp borders (or erythema reaching all borders). One comment stated that using "any perceptible change" or "just perceptible change" as the endpoint of erythemal response will result in doubtful determinations. The comment stated that one of the great problems in deciding upon a definition of "MED" occurs when high SPF sunscreens are tested with solar simulators, because these sunscreens are very effective in absorbing UVB radiation and very long irradiation times are needed. Therefore, significant amounts of UVA radiation are delivered to the skin, so that erythema at the sunscreen-protected sites is mainly due to UVA radiation. In patients with Skin Type II and III, immediate pigmentation is produced, some of which lasts for 24 hours. Consequently, sites will appear faintly tanned with doses well below those producing erythema and the question of "just perceptible change" becomes difficult to answer. The comment also maintained that it has been shown that it takes significantly less UVA energy to produce erythema with a high irradiance UVA emitting radiation source than with a less intense one (Ref. 1). Because modern solar simulators are designed to give high irradiance (up to 100 milliwatts/cm^2 UVA) so as to shorten irradiance times, the comment stated that MED values (determined using "just perceptible erythema" criteria) may vary greatly between investigators depending upon the radiation source used.

The comments suggested various postexposure (after irradiation) time limits for the evaluation of an erythema reaction to UV radiation: 22 to 24 hours, 22 to 24 hours (±10 percent), and 22 hours (±10 percent). Maintaining that erythema due to UVA radiation has an earlier onset than that of UVB, but has a prolonged peak, one comment concluded that 22 to 24 hours should be satisfactory for both.

Three of the comments suggested environmental conditions under which MED values should be determined. Two maintained that the MED should be read under a tungsten light source. Another comment suggested that the erythema response of the skin of all test subjects should be evaluated under the same conditions of illumination. If natural light is not available, the comment suggested all test subjects be examined under a 100–W tungsten light bulb. The comment added that fluorescent light should not be used to assess the MED because major deviations in MED values can result if some subjects are examined under natural light and some are examined under cool, white fluorescent light. All three comments stated that the posture or body position should be the same for all test subjects. One comment maintained that the visually recognizable erythema response often varies with the posture (e.g., the exposed back when examined in a prone position versus a vertical or standing position). Another comment contended that the MED should be read with the subject in the same position as during irradiation. Two of the comments suggested that the MED readings be done in rooms where the external temperature is between 20 and 25 °C.

In §§ 352.42(h) and 352.43 of its recommended monograph, the Panel defined the MED as "the time of exposure that produces the minimally perceptible erythema at 16 to 24 hours postexposure." The agency believes that

this definition should be clarified and narrowed. The Panel stated that immediate pigmentation fades in 30 to 60 minutes (43 FR 38206 at 38266). However, more recent information indicates that immediate pigmentation or immediate tanning may persist with higher doses of UV radiation for 1/2 to 1 hour, up to 24 hours, or (rarely) for 36 to 48 hours after prolonged exposure (Ref. 2). Therefore, the agency agrees with the comments that immediate pigmentation may interfere with an investigator's perception of minimally perceptible erythema. This is especially true when testing a high SPF sunscreen product, where a large dose of UV radiation is required, or if the MED evaluation is done at 16 hours postexposure. Sunscreen testing results will be more accurate and comparable if the MED is defined as the smallest dose of UV radiation that produces redness reaching the borders of the exposure site, and if the MED is determined at 22 to 24 hours postirradiation rather than 16 to 24 hours postirradiation. This time is consistent with those requested by the comments.

The agency has considered the comments' suggested environmental conditions under which the MED should be determined (i.e., light source, position of the body, and temperature of the room). The Panel did not include such conditions in § 352.42(h) of its recommended monograph. Nonetheless, the agency agrees with the comments that some environmental conditions should be included in the sunscreen testing procedures.

In discussing testing procedures, the Panel stated that when reading the MED, the investigator should use a constant light source such as an incandescent or warm white fluorescent lamp at a fixed distance (43 FR 38206 at 38260). The agency believes that there is little difference between the light emitted from an incandescent (i.e., tungsten) light and a warm white fluorescent light. The illumination level at the site of inspection is more important than the source of illumination. The agency notes that various illumination levels are recommended for other types of critical observations (i.e., 300 lux for medication preparation areas, 500 lux for emergency room treatment areas, and 22,000 lux for the emergency table in an operating room) (Ref. 3). The agency believes that 500 lux is an appropriate illumination level for evaluating the MED. Therefore, the agency is proposing in § 352.72(h) that the source of illumination should be either a tungsten light bulb or a warm white fluorescent light bulb that provides a level of illumination at the test site within the range of 450 to 550 lux.

The agency agrees with the comments that the MED should be assessed with the subject in the same position used when the test site was irradiated. Hawk and Parrish (Ref. 2) state that MED assessments should always be made with the subject in the same position to prevent MED variations. The agency is proposing this requirement in § 352.72(h). However, the agency does not believe it is necessary to specify a particular position.

There is insufficient information to determine whether the temperature of the room in which the MED is assessed has an effect on the MED. Therefore, the agency is not proposing a specific temperature, but is requesting further comment.

Based on the above, the agency is proposing to include in § 352.72(h) the following: "* * * the MED is determined 22 to 24 hours after exposure. The erythema responses of the test subject should be evaluated under the following conditions: the source of illumination should be either a tungsten light bulb or a warm white fluorescent light bulb that provides a level of illumination at the test site within the range of 450 to 550 lux, and the test subject should be in the same position used when the test site was irradiated. Testing depends upon determining the smallest dose of energy that produces redness reaching the borders of the exposure site at 22 to 24 hours postexposure for each series of exposures * * *." The agency is also proposing in § 352.73 that the MED is the lowest dose of radiation that produces uniform redness reaching the borders of the exposure site at 22 to 24 hours postexposure.

The agency is also proposing to provide a definition of MED in § 352.3 by adding new paragraph (a) as follows: "*Minimal erythema dose (MED).* The smallest dose of ultraviolet (UV) radiation (expressed as Joules per meter squared) that produces redness reaching the borders of the exposure site." Other definitions in § 352.3 are being renumbered to adjust for the addition of new paragraph (a).

References

(1) Kagetsu, N., R. W. Gange, and J. A. Parrish, "UVA-Induced Erythema, Pigmentation, and Skin Surface Temperature Changes Are Irradiance Dependent," *The Journal of Investigative Dermatology*, 84:445–447, 1985.

(2) Hawk, J. L. M., and J. A. Parrish, "Responses of Normal Skin to Ultraviolet Radiation," *in* "The Science of Photomedicine," edited by J. D. Regan and J. A. Parrish, Plenum Press, New York, pp. 227, 240, and 241, 1982.

(3) "Institutions and Public Buildings; Health Care Facilities," *in* "IES Lighting Handbook," 1981 Application Volume, edited by J. E. Kaufman and H. Haynes, Illuminating Engineering Society of North America, New York, pp. 7–4 to 7–17, 1981.

96. Two comments argued that in the Panel's sunscreen testing procedures smaller increments in exposure time would provide more accuracy in determining SPF values that exceed 15. In § 352.43 of its recommended monograph, the Panel included a geometric series of time intervals represented by $(1.25)^n$, such that each exposure time interval is 25 percent greater than the previous time (43 FR 38206 at 38265 to 38266). One comment requested that § 352.43 be revised to read "The time intervals selected shall be a geometric series represented by $(1.X)^n$, where X is greater than zero but less than or equal to 25." Several comments suggested that this section be revised to read, "The time intervals selected shall be a geometric series represented by $(1.X)^n$ wherein each exposure time interval is X percent greater (X must not exceed 25 percent) than the previous time * * *."

In its notice of a public meeting to discuss appropriate sunscreen testing procedures, the agency stated that exposure times are crucial to the accurate determination of SPF values and PCD's (52 FR 33598 at 33601). However, the agency expressed concern over the Panel's recommended time intervals. The agency stated that there may be little justification for geometrically increased exposure time intervals because use of such intervals offers less precision in the upper SPF ranges. The agency added that precision in the upper SPF ranges has become increasingly important because of the appearance on the OTC market of sunscreen drug products with SPF values much higher than 15 (i.e., up to 30). Because the MED can be measured with equal precision across the full range of an arithmetically arranged series of exposure times, the agency stated it was considering using an arithmetical progression of at least 11 exposure times increasing in 4-second increments, beginning with a 10-second exposure and ending with a 50-second exposure time (i.e., 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, and 50 seconds).

A number of comments objected to the proposed arithmetic progression. Most of the comments preferred a geometric progression method similar to the one recommended by the Panel in § 352.43. Several comments added that this method has been successfully used

by industry for many years. Some comments contended that the fundamental relationship between SPF values and sunscreen spectral absorbency is logarithmic and, therefore, the correct approach is the use of geometric progressions. Another comment stated that the SPF is a ratio of two independently determined values; statistically, ratio values are treated with geometric techniques in order to compensate for the higher expected variance simply because the value is a ratio of two independently-variable measurements. The comment maintained that the precision of the SPF ratio depends on both variables, i.e., the protected skin MED (numerator) and the unprotected skin MED (denominator), but more critically on the denominator which is the smaller quantity. The comment argued that the agency's proposed arithmetic progression would, in many instances, use larger exposure intervals for the unprotected irradiated sites than the Panel's recommended 25-percent exposure intervals, and would compromise rather than improve precision.

One comment contended that a valid scientific rationale for using geometrically increasing time intervals is to relate the SPF values to the time exposures. The comment stated that available data provided only limited ability to examine the need for geometric time increments. The comment added that careful consideration should be given to the spacing of the geometric progression to ensure that there are not large intervals at the upper end of the range of exposure times, thereby eliminating overestimations of the SPF values. One comment maintained that there is little in the photobiologic literature to support arithmetic progressions. Other comments stated that the references cited in the meeting notice (52 FR 33598 at 33602) in support of the agency's proposal do not contain any data supporting use of arithmetic progressions for sunscreen testing.

Two comments stated that an arithmetically arranged series of exposures would result in differences in redness between exposure sites that are too small for the trained human eye to distinguish, i.e., the agency's geometric dosing schedule is based on MED determination sensitivity of which the human eye is incapable. Thus, such a procedure would make the results more subjective rather than more precise as the agency intended.

Many comments expressed concerns for the well-being of the test subjects. They maintained that the agency's proposed arithmetic progression would subject the test subjects to at least 11 UV radiation exposures, resulting in great risk, discomfort, injury, and unnecessary UV radiation exposure. One comment stated that for a single SPF determination the agency's proposed arithmetic progression would require a minimum of 33 irradiated sites (including the standard), more than half of which could develop a sunburn reaction. The comment added that the agency's proposal would increase the time that a test subject would be exposed to the solar simulator. In order to test a sunscreen with a theoretical SPF of 22, the comment asserted that the exposure time would be increased from about 60 minutes to 135 minutes. The comment concluded that this proposed procedure would make it impractical to test samples with an SPF higher than 22. Another comment agreed that the risk of exposure to UV radiation to test subjects, the time required for testing, and the number of testing sites would increase with the agency's proposed methodology. The comment stated that the increase in the number of testing sites becomes critical when testing water resistant sunscreen drug products, which require additional test sites.

Two comments suggested that a preliminary range-finding pilot study involving 3 subjects should be performed prior to testing an experimental product on a 20-person test panel. A pilot study would prevent the needless overexposure and "UV burn" of a large number of test subjects that results from the occasional overestimation of a product's SPF or from the underestimated substantivity of a "wash-off" sunscreen drug product. One comment recommended that the maximum erythema on the protected skin not be induced by more than twice the MED on the protected skin. Several comments stated that the radiation exposure times specified by the agency in the public meeting notice (52 FR 33598 at 33601) are not applicable to all xenon arc radiation sources, because some xenon arc sources may require longer or shorter time exposures due to higher wattage or radiation intensity.

Another comment considered the use of a geometric or arithmetic progression in determining the relevant exposure times. If a geometric progression series is used, the comment asserted that the important issue is that the "multiplicator factor has to be determined very carefully."

Several comments suggested various methods of determining the exposure intervals to accommodate OTC sunscreen drug products with SPF values in excess of 15. One comment contended that a better approach would be to use a geometric series of 5 exposure times rather than the agency's proposal for an arithmetic progression of 11 exposure times. The comment suggested that the exposure intervals of the geometric series should be calculated as follows: (1) (1.25)X for products with an estimated SPF less than 8, (2) (1.20)X for products with an estimated SPF from 8 to 15, and (3) (1.15)X for products with an estimated SPF greater than 15. Two comments from a manufacturers' association added that industry should have the option of choosing smaller increments than 25 percent, if desired, in order to achieve greater precision when testing for SPF values. For example, the time intervals selected should be a geometric series represented by $(1.X)^N$ such that each exposure time interval is X percent times greater (X must not exceed 25 percent) than the previous time interval. Another comment recommended a two-tier approach with a cut-off point between SPF 6 and 8. Below SPF 6 or 8, a geometric series based on $(1.25)^n$ would be used. Above SPF 6 or 8, "smaller increments of $(1.25)^n$ corresponding to $(1.12)^n$" would be used.

One comment strongly recommended that the agency adopt the delivery of UV radiation in terms of mJ/cm^2, and not in seconds or minutes. Several comments added that the term "light exposures" discussed in the "Exposure times section" of the public meeting notice (52 FR 33598 at 33601) should be expressed in the context of "dose" rather than "time." According to the comments, the term "dose" would allow for the use of both radiance and time as variables.

The agency agrees with several comments that the expression of radiation exposures be in terms of dose rather than time. The term "dose" is more appropriate because it allows for the use of both radiance and time as variables. Although the Panel defined UV radiation exposure in units of time, the agency believes 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 (J/m^2). (The agency is using the term "exposure dose" rather than "exposure time" in this tentative final monograph. See comments 84 and 85.)

The agency agrees with the suggestion that a preliminary range-finding study be performed prior to testing a new sunscreen product on a test panel. The study would prevent unnecessary risks of discomfort, injury, and overexposure to UV radiation to the test subjects.

However, there is insufficient information to establish specific requirements for a preliminary range-finding study at this time. Therefore, the agency is not now proposing such a study in the monograph, but is inviting additional comments and data as to appropriate requirements for such a study.

The agency also agrees that an arithmetic progression of determining exposure doses in the SPF testing for OTC sunscreen drug products is not the method of choice, for the following reasons: the arithmetic progression of exposure doses would: (1) Expose the test subjects to higher doses of UV radiation than necessary, particularly at the higher end of the exposure series; (2) provide differences in redness between exposure sites that are too small for the trained eye to distinguish; (3) prolong the time required to deliver exposure doses to the test subjects; and (4) reduce flexibility in exposure doses needed to accommodate different solar simulators. A geometric progression that is modified to take into account the higher SPF values is more appropriate for determining exposure doses, for the following reasons: (1) It reduces the risk of exposure to UV radiation to the test subjects by decreasing testing time and the number of exposure sites, and (2) a geometric series covers a larger range of exposure doses with fewer exposures.

The agency believes that a geometric series with only five exposure doses may produce overestimations of the true SPF values, thereby producing biased estimates. The possible production of biased estimates is illustrated in the following example: if the MED(US) is 30 J/m^2 and the product being tested has an expected SPF of 8, the exposure doses would be 0.69X, 0.83X, 1.0X, 1.2X, and 1.44X, using 1.20 as the base in a geometric series. Here, X is set to yield the estimated SPF, e.g., X=30 J/m^2×8=240 J/m^2 of exposure doses. The exposures would be 165.6, 199.2, 240, 288, and 345.6 J/m^2, respectively.

For the above example, a substantial number of MED(PS) would be observed at 240 J/m^2, as well as 199.2 and 288 J/m^2. If the same number of subjects are observed at the 199.2– and 288–J/m^2 exposure doses, the mean SPF would be greater than the expected SPF of 8. For example, if out of 20 subjects, 10 MED(PS) were observed at 240 J/m^2, 5 at 199.2 J/m^2, and 5 at 288 J/m^2, the corresponding SPF values for these MED(PS) values are 8.00, 6.64, and 9.6, respectively. In this example, an MED(PS) of 288 produces an SPF of 9.6, which is 1.6 units above the expected SPF value of 8, while an MED(PS) of 199.2 produces an SPF of 6.64, which is only 1.36 units different from the expected value of 8. Because the exposure dose of 288 J/m^2 is a greater distance from 240 than 199.2 is from 240, each time a MED(PS) greater than 240 is produced, it is assigned an undue extra large value. Ultimately, the effect produces an overestimation of the average SPF value.

The major reason for the overestimation is that the geometric series is implemented in such a way that it has a nonsymmetric assignment of SPF values. When an MED(PS) exceeds the expected MED(PS), it produces a corresponding SPF farther away from the expected SPF value than when the observed MED(PS) is below the expected SPF value.

The agency believes that exposure doses are crucial to the accurate determination of SPF values and PCD's. A geometric series similar to that proposed by the Panel, but modified to include 2 additional exposure doses equally spaced around the expected SPF, would eliminate the overestimation of the true SPF value of a product with a high SPF value. This procedure would also restrict the testing range for products with low SPF values. The doses selected would consist of a geometric series of 5 exposures where the middle exposure is placed to yield the expected SPF plus 2 other exposures, placed symmetrically around the middle exposure.

The agency agrees with one comment that different exposure doses are appropriate for determining different SPF values for greater accuracy. The exposure doses for the geometric series should be calculated as follows: (1) (1.25)X for products with an estimated SPF less than 8, (2) (1.20)X for products with an estimated SPF from 8 to 15, and (3) (1.15)X for products with an estimated SPF greater than 15. The use of dosage intervals smaller than 25 percent is necessary to eliminate bias in the testing and to ensure accurate SPF determinations of sunscreen drug products with high estimated SPF values. The agency is proposing that the exposure intervals selected be a geometric series represented by $(1.X)^n$ such that each exposure dose is X percent greater than the previous dose (X must not exceed 25 percent).

For products with expected SPF values less than 8, the exposure doses could be 0.64X, 0.80X, 0.90X, 1.00X, 1.10X, 1.25X, and 1.56X, where X represents the expected SPF of the product. For products with expected SPF values between 8 and 15, the exposure doses could be 0.69X, 0.83X, 0.91X, 1.00X, 1.09X, 1.20X, and 1.44X, where X represents the expected SPF of the product. For products with expected SPF values greater than 15, the exposure doses could be 0.76X, 0.87X, 0.93X, 1.00X, 1.07X, 1.15X, and 1.32X, where X represents the expected SPF of the product. Accordingly, the agency is proposing to revise the Panel's recommended determination of SPF values (§ 352.43) by including a new paragraph in proposed § 352.73(c) as follows:

Determination of individual SPF values. A series of UV radiation exposures expressed as Joules per meter squared (adjusted to the erythema action spectrum calculated according to § 352.73(a)) is administered to the subsite areas on each subject with an accurately calibrated solar simulator. A series of seven exposures shall be administered to the protected test sites to determine the MED of the protected skin (MED(PS)). The doses selected shall consist of a geometric series of five exposures, where the middle exposure is placed to yield the expected SPF plus two other exposures placed symmetrically around the middle exposure. The exact series of exposures to be given to the protected skin shall be determined by the previously established MED(US) plus the expected SPF of the test sunscreen. For products with an expected SPF less than 8, the exposures shall be the MED(US) times 0.64X, 0.80X, 0.90X, 1.00X, 1.10X, 1.25X, and 1.56X, where X equals the expected SPF of the test product. For products with an expected SPF between 8 and 15, the exposures shall be the MED(US) times 0.69X, 0.83X, 0.91X, 1.00X, 1.09X, 1.20X, and 1.44X, where X equals the expected SPF of the test product. For products with an expected SPF greater than 15, the exposures shall be the MED(US) times 0.76X, 0.87X, 0.93X, 1.00X, 1.07X, 1.15X, and 1.32X, where X equals the expected SPF of the test product. The MED is the lowest dose of radiation that produces uniform redness reaching the borders of the exposure site at 22 to 24 hours postexposure. The SPF value of the test sunscreen is then calculated from the dose of UV radiation required to produce the MED of the protected skin and from the dose of UV radiation required to produce the MED of the unprotected skin as follows: SPF value=the ratio of erythema effective exposure (Joules per meter squared) (MED(PS)) to the erythema effective exposure (Joules per meter squared)(MED(US)).

Reference

(1) Magnus, I., "Reductions of Normal Skin to UVR and to Visible Light," *in* "Dermatological Photobiology," Blackwell

Scientific Publications, Oxford, pp. 117–163, 1976.

T. Comments on the Statistical Analysis of Results from the Testing Procedures for Sunscreen Drug Products

97. Many comments questioned aspects of the Panel's recommended testing procedures and statistical methods for determining the SPF and the PCD of sunscreen drug products. The agency discussed these comments in the notice of public meeting to discuss sunscreen testing procedures (52 FR 33598 at 33599 and 33600), and proposed two approaches to analyzing the data generated by sunscreen drug product testing. The first method utilizes the testing procedures proposed by the Panel but adds one step to the determination of the PCD. The added step is equivalent to performing a one-sided t-test at the 0.05 level of significance, where the null hypothesis is that the mean SPF is less than the minimal SPF of the assigned PCD. The second method concentrates on the boundaries between the PCD's rather than on the actual SPF values of the sunscreen drug product. Following the establishment of a MED for unprotected skin, protected skin is tested at exposure times chosen so that the corresponding SPF's are slightly less that the lower bounds of the intervals defining the various PCD's. This procedure does not distinguish between SPF's in the same PCD but does distinguish between SPF's in different PCD's. The agency requested comments on the Panel's proposed procedure for sunscreen testing as well as the two methods outlined in the notice of public meeting.

The agency received many comments opposing the binomial method. The comments supported the Panel's recommended testing procedure as modified by adding a one-sided t-test to determine SPF values and PCD categories. Several comments stated that the current procedure is a fair and conservative method for categorizing observed SPF measurements into PCD determinations. The comments stated that no rationale was presented by the agency as to why the simple descriptive method currently in use is not adequate and acceptable. One comment maintained that the fact that the current method has been in use for nearly 12 years provides tangible evidence that it is reasonable and appropriate.

Another comment emphasized that an SPF value is not an absolute, but is instead an indication of relative performance. The comment stated that statistical procedures must be adequate for analyzing and classifying sunscreen drug products in a manner that is understandable and meaningful to the consumer. The comment concluded that the system that has been in place for over 10 years accomplishes this purpose. The comment acknowledged that refinements can be accomplished by adopting the one-sided t-test or the Wilcoxon signed ranks test as an acceptable method.

Several comments stated that the modified Panel method allows for the determination of SPF values as well as PCD categories. One comment stated that the PCD is an arbitrarily assigned limit, while the SPF is an experimentally derived value. This comment asserted that it is not necessary to be too stringent in compliance with PCD's so long as the SPF is accurately determined. The comments maintained that a distinct advantage of the t-test is that it encompasses the current procedure for conducting SPF testing; plus, it provides a simple computational procedure for a statistical test that projects the results to the entire population.

One comment suggested that if more precision is needed in assessing the PCD by the "t" test method, the significance level may be set at 0.01 rather than at 0.05 when SPF values are evaluated. Another comment recommended the following modification to make the t-test even more useful. It stated that if the significance level were set at 0.10 rather than 0.05, this would allow for slightly more variability in the SPF range and still enable the product to be placed in the PCD that is appropriate for its mean SPF, without adverse impact on consumers.

Three comments stated that, although preferable to the binomial method, the t-test method has one difficulty: Variability, even from high outlying values, can cause the product being tested to fall below the intended PCD. One comment stated that variability is inherent in the results from this type of testing, particularly with higher SPF products. Two comments stated that such variability can be minimized by allowing for dosing increments smaller than 25 percent, especially when testing products with higher SPF values. One comment added that a minimum of exposures can reduce the chance for variability.

Many comments maintained that the binomial procedure proposed by the agency is not appropriate for classifying observed SPF data into PCD categories. Some comments opposed adoption of the binomial method of analysis because it does not provide for the determination of SPF values. One comment cited data from a consumer survey (Ref. 1) that purports to demonstrate that SPF numbers are a major factor that consumers use in selecting an appropriate sunscreen drug product. Another comment added that the binomial method does not distinguish between SPF's in the same PCD category and that products with very similar SPF's may be classified into different PCD's. Two comments stated that the binomial method lacks the sensitivity of the t-test, and it is more difficult to reject the null hypothesis using the binomial analysis than using the t-test.

Some comments pointed out that the binomial method may result in unnecessary UV exposure. Three comments stated that using the set exposure times in this method would expose a panelist to much more UV radiation than necessary and might even cause severe sunburn. One comment stated that the exposure of a panelist to 14.9 X MED(US), when the proposed protection factor for the product is SPF 2 to 4, would result in severe over exposure. The comment added that the fixed exposure schedule would not allow the current flexibility in modifying the exposure schedule to more closely fit the expected SPF of the product. Another comment stated that because the exposure levels proposed in the binomial procedure are not currently used, there is a lack of historical data on this method. The comment contended that predictions on the effects of using this test are difficult to surmise without a historical perspective.

One comment stated that neither of the proposed methods was adequate and that simpler calculations would be preferable. The comment suggested that the variability inherent in the use of sunscreen drug products by consumers is so high that the statistical refinement suggested is unnecessary in calculating SPF values. The comment added that, if the proposed method is adopted, manufacturers may be forced to aim for higher mean SPF values to allow inclusion of products in current PCD categories. The comment asserted that this will be an unnecessary cost with no real benefit to the consumer. The comment maintained that consumers have had several years to work out which products are suitable for their use and that a change in labeling now would necessitate a further period of adjustment. The comment added that there are very few complaints that sunscreen drug products fail to provide the expected level of protection. Two other comments stated that the agency should reject each of the methods proposed and accept the Panel's recommendation.

Some comments recommended that any scientifically valid statistical analysis method should be permitted to calculate the results of sunscreen product testing. Some comments suggested the Wilcoxon rank sum test as an equally valid method. According to the comments, this method could be used with the current exposure techniques and still have the benefits of the binomial procedure (i.e., no assumption of a normal distribution and less sensitivity to outlying values). One comment added that the Wilcoxon test takes advantage of the interval nature of the data and, therefore, is more sensitive than the binomial procedure and close in sensitivity to the t-test procedure. As stated above, another comment mentioned that the Wilcoxon signed ranks test could provide refinements in the existing procedures.

The agency agrees with the majority of the comments that the Panel's recommended method, as modified by the addition of a one-sided t-test, is the preferred method for calculating SPF values and for categorizing sunscreen drug products into PCDs. The statistical procedure used to calculate the relative protection provided by sunscreen drug products should be based upon the determination of SPF values. Consumers understand and depend upon SPF values when choosing a sunscreen. The Panel's recommended method as modified by the one-sided t-test being added in this tentative final monograph provides an SPF value that can be used to place the product into a PCD for labeling purposes.

The one-sided t-test employs the mean of its observations (i.e., SPF values) as a point estimator, and it incorporates the variability of the data (i.e., the standard deviation). This method classifies a sunscreen drug product into a PCD only where there is statistically significant assurance that the product belongs in the PCD. The agency also points out that this statistical procedure has good power. Further, the modified method is safer than the binomial method because the test subject is exposed to less UV radiation.

The agency is proposing that a sunscreen drug product may display its tested SPF value in its labeling rather than the lowest SPF value in the PCD as the Panel recommended. (See comment 44.) However, a product should only be labeled with a particular SPF if there is sufficient statistical evidence to conclude that the true SPF is at least as high as the label SPF. In order to provide statistical significance to the SPF value that consumers use when choosing products, the agency is proposing that the SPF value permitted in labeling be the largest whole number that is excluded by a 95-percent one-sided confidence interval for the mean SPF.

Regarding the suggestions for making the t-test more useful by setting the significance level at 0.10 or 0.01 rather than 0.05, there is no basis for allowing for more variability in the SPF range with a 0.10 level of significance, or for being more rigid by using a 0.01 level of significance. The agency considers a 0.05 level of statistical significance to be a standard; it should not be changed without compelling reasons.

The agency recognizes that the Panel's method modified by the addition of the t-test is not the only valid method available. However, it is the best method currently available and is being proposed in § 352.73. By knowing in advance the statistical analysis to be used, there will not be an incentive for an investigator to select a method that will produce the desired SPF or PCD for a particular data set. Further, the agency believes it is desirable to have all data for different manufacturer's products analyzed by the same method. Therefore, the agency is proposing § 352.73 to include a one-sided t-test as follows:

(d) *Determination of the test product's SPF value and PCD.* Use data from at least 20 test subjects with n representing the number of subjects used. First, for each subject, compute the SPF value as stated in § 352.73(b) and (c). Second, compute the mean SPF value, $\bar{x}$, and the standard deviation, s, for these subjects. Third, obtain the upper 5-percent point from the t distribution table with n-1 degrees of freedom. Denote this value by t. Fourth, compute $ts/\sqrt{n}$. Let this quantity be denoted by A (i.e., $A = ts/\sqrt{n}$). Fifth, calculate the SPF value to be used in labeling as follows: The label SPF equals the largest whole number less than $\bar{x} - A$. Sixth and last, the drug product is classified into a PCD as follows: if $20 + A < \bar{x}$, the PCD is Ultra High; if $12 + A < \bar{x} < 20 + A$, the PCD is Very High; if $8 + A < \bar{x} < 12 + A$, the PCD is High; if $4 + A < \bar{x} < 8 + A$, the PCD is Moderate; if $2 + A < \bar{x} < 4 + A$, the PCD is Minimal; if $\bar{x} < 2 + A$, the product shall not be labeled as a sunscreen drug product and may not display an SPF value.

Reference

(1) Comment No. C00083, Appendix 3, Docket No. 78N–0038, Dockets Management Branch.

98. Several comments recommended the use of a geometric mean rather than an arithmetic mean when calculating the SPF value. One comment maintained that the geometric mean will dampen the variability of the widely ranging data often present in SPF test data. Another comment stated that the DIN testing procedures use the geometric mean rather than the arithmetic mean.

The agency believes that it is invalid to use the geometric mean in the t-test that is being proposed for use in calculating the SPF. The standard deviation is based on the arithmetic mean, and a "t" ratio of the geometric mean to the standard deviation based on the arithmetic mean is meaningless. Also, an attempt to use the geometric mean in the computation of the standard deviation would produce a meaningless measure of dispersion. Therefore, the agency is proposing to calculate the arithmetic mean of the data to determine the SPF value of the product.

However, it might be useful to modify the statistical analysis procedure further by performing the t-test on logs of the SPF data. Analysis of the logs of the SPF is equivalent to using the geometric mean as a measure of the average for the original data. This procedure might be useful if the data have a few very large SPF values which have a detrimental effect on the standard deviation computed on the original data. The agency invites comment on this modification.

99. In response to the agency's two proposed statistical methods for analyzing data (i.e., the one-sided t-test and the binomial method), one comment submitted an alternative method based upon statistical tolerance intervals. This comment suggested that sunscreen drug products should be labeled with interval PCD's. The comment stated that the determination of the interval range for an SPF would be based on the value of the lower 95-percent confidence interval for the mean or a procedure based on the binomial distribution. The comment stated that SPF determinations become more variable as the SPF value gets higher. In these cases, the average SPF value is not representative of the data because of the wide range of the SPF values. Therefore, the comment recommended that product SPF labeling should not be based solely on a product's average SPF. The comment maintained that its recommendation would not change if PCD intervals were used as a labeling device rather than individual SPF values. In either case, according to the comment, the variability of the individual SPF values using the testing procedures currently in place do not permit sufficient precision in the

estimation of the mean SPF value for a sunscreen product.

The comment contended that a product should be labeled on the basis of a 95-percent lower confidence interval for the mean SPF value. The comment stated that a disturbing feature of the lower confidence limits is that most of them exclude a high percentage of the individual SPF values. The comment maintained that confidence intervals provide a lower boundary on the mean SPF value for a product but do not provide limits for individual SPF values. The comment asserted that for a given product the lower confidence interval will exclude a higher percentage of the individual SPF values as the sample size is increased. According to the comment, the SPF values excluded will approach a limit of approximately 50 percent, because the lower limit will approach the true mean SPF value.

The comment maintained that if the intent of SPF labeling is to ensure that individual users of sunscreen products are provided with the protection indicated on the label of a product, SPF labeling should not be based solely on a lower confidence interval for a product's mean SPF value. The comment added that this recommendation, like the previous one, is equally applicable to the labeling of products by SPF values and by PCD intervals.

The comment stated that if each of the above recommendations were followed, the current methods for product labeling would be discarded. The comment asserted that a statistical tolerance intervals test would ensure that products are adequately labeled to protect consumers. Also, the statistical tolerance intervals test would establish an acceptable measure of the variability of test results in the determination of SPF designations. The comment maintained that a tolerance interval provides a lower bound on the SPF values for individuals, rather than for the mean of a population of individuals as does a confidence interval. The comment added that a tolerance interval is as easy to implement as a confidence interval. The comment stated that the form for a lower tolerance interval for an individual SPF value is $y - ks < SPF$, where y and s are the average and sample standard deviation of a sample of n SPF values, and k is a factor obtained from statistical tables for tolerance intervals.

The comment maintained that tolerance limits are much lower than the confidence limits and that they generally cover the entire sample of individual SPF values. The comment also stated that the lower tolerance interval is closer to actual data values when the SPF values exhibit small variability. Thus, the comment concluded that the tolerance intervals satisfy the two criteria stated above and lead to a third recommendation that product SPF labeling should be based on a lower tolerance interval for an individual consumer's SPF value.

Stating that this third recommendation has a solid statistical foundation, the comment maintained that it addresses one of the key underlying problems with the implementation of clinical testing of sunscreen products: the incorporation of the variability of test results in the setting of SPF values. The comment stated that, unlike the confidence interval approach, the tolerance intervals approach incorporates the variability of individual SPF values, not just the variability of the estimate of the mean SPF value. The comment added that the tolerance intervals approach has the seemingly undesirable effect of resulting in lower assigned SPF values for a product. However, the comment stated that, in reality, it is simply an acknowledgement of the variability inherent in the current testing procedures. The comment stated that the tolerance intervals approach, however, does not alleviate the problem of variability, because it would utilize the lower confidence limit for the mean to determine in which interval a product would be placed. Thus, the difficulties with the use of a lower confidence limit discussed above still apply to PCD designations using this proposal.

The comment stated that a product that has an SPF mean around the limit of a PCD could, through the variability associated with the test results, be assigned to one PCD or a bordering PCD almost at random and that this could imply to a consumer that the product has more protection than it actually has. Further, the labeling of SPF values using statistical tolerance intervals eliminates the need for PCD designations. Under this method, tolerance intervals directly address the key problem, protection of the individual consumer, rather than attempting to address a related but clearly not equivalent problem, the variability of average SPF values. The comment stated that the consumer would be protected with tolerance intervals through lower SPF designations when variability is excessive.

The agency agrees with the comment that the use of a 95-percent lower confidence interval for SPF labeling is preferable to the use of only the calculated average SPF in the labeling of sunscreen drug products and is proposing such as the fifth step in § 352.73(d). (See comment 97.) However, the agency does not agree that a statistical tolerance intervals test is an acceptable alternative to the one-sided t-test. The one-sided t-test makes a statement about the mean or average SPF. It does not make inferences about particular individuals. Some individuals will receive less protection than the stated SPF, but others will receive more protection. The tolerance intervals procedure makes a statement about the range of SPF values that most of the population of users would achieve. This inference is not usually made in drug testing, and the agency believes that there is no justification for using this procedure for sunscreen drug products. In addition, the validity of the suggested tolerance intervals procedure depends upon the assumption of normality of the underlying distribution. No justification has been presented for this assumption. Unlike the t-test, which tends to be valid if the underlying distribution is not normal, the tolerance intervals procedure depends heavily upon the normality of the underlying distribution for its validity. Therefore, the agency is not including a tolerance intervals statistical analysis method, but instead is proposing that the statistical analysis of sunscreen testing data be done using a one-sided t-test. (See comment 97.)

U. Comments on Water Resistant and Very Water Resistant Testing Procedures for Sunscreen Drug Products

100. Referring to the Panel's statement that a water immersion test is a more severe test of a sunscreen product than a sweat resistance test (43 FR 38206 at 38263), one comment stated that a product that passes the water resistance test should also be permitted to use the term "sweat resistant" and any other claims permitted for products passing the sweat resistance test.

A reply comment disagreed with the above comment and argued that the physical mechanism of removal of the sunscreen product is clearly different in the two tests. The water immersion test recommended by the Panel in § 352.46 requires that the sunscreen product resist removal by water applied "over" the product; the "sweat resistance" test recommended in § 352.45 requires that the sunscreen product resist removal by sweat emerging from "underneath" the product. Contending that there is no assurance that a product that resists removal by one physical action will also resist removal by the opposite physical action, the reply comment pointed out

that the difference between the chemistry of water and the chemistry of sweat requires different test standards. The reply comment further stated that if §§ 352.45 and 352.46 remain in the monograph, separate tests should be maintained for product performance claims of "water resistance" and "sweat resistance." Another comment recommended that the determination of the SPF value of a product be conducted under the combined stress of sweating and swimming.

The agency agrees with the Panel that the "water resistant" test is a more severe test of a sunscreen product than the "sweat resistant" test (43 FR 38206 at 38261). The water resistant tests have a longer time of exposure to water and include a 40- to 80-minute period of moderate activity. The agency disagrees with the reply comment that the difference in the chemistry of water and sweat requires different test standards. The composition of sweat and water differ, but the composition of each is variable. The composition of sweat varies from subject to subject and the composition of tap water varies depending on the source. Sweat is composed predominantly of water (Refs. 1 and 2) and has only traces of lactate, urea, ammonia, sodium chloride, potassium, and other substances (Ref. 3). The Encyclopedia of Biochemistry (Ref. 1) states that "the composition of sweat is about 99 percent water * * *." White et al. (Ref. 2) states that the sweat glands release virtually pure water. Sweat, which is about 99 percent water with a pH from 5 to 7.5 (Ref. 1), can be considered similar to various types of water. The degree of variability in the content of treated water, untreated water, or different sources of water can be high. (See comment 104.) In addition, swimming pool and sea water contain different quantities of other minerals and chemicals, and the pH varies depending on the water source. Therefore, the agency believes that, for the purposes of sunscreen drug product testing, sweat and water are sufficiently similar so as not to require different test standards.

The agency agrees with the reply comment that the physical mechanisms by which a sunscreen product resists removal by sweat and water immersion are different. However, the "wash-off" effects of sweat emerging from underneath the product can be expected to be less than the "wash-off" effects from water over the product. The requirement for a "water resistant" claim is for the product to retain the same PCD after 40 minutes of swimming as it had before being exposed to water. If any sunscreen product can withstand 40 minutes of water immersion and retain its original PCD or can withstand 80 minutes of water immersion required for a "very water resistant" claim (see comment 50) and retain its original PCD, the agency and Panel agree that the product can also withstand 30 minutes of sweating and retain its PCD (see the Panel's recommended § 352.50(e)(2)(i)(*a*)(*3*) and (*b*)(*3*)). Therefore, the agency believes that it is appropriate for a product that passes the water resistance and very water resistant tests to also be permitted to make claims that satisfy the sweat resistance test.

The agency agrees that a sunscreen product that passes the "water resistant" test should be permitted to use the claim "sweat resistant." The agency has reviewed the available information and concludes that for sunscreen drug products that have passed the tests in § 352.76 of this tentative final monograph for water resistant and very water resistant claims, an additional test to support a sweat resistance claim is unnecessary and possibly hazardous.

The agency is concerned that those who serve as subjects for "sweat resistant" testing could be unduly harmed by heat stress. The Panel's recommended procedure in § 352.45 for determining sweat resistance includes inducing copious sweating for 30 minutes by exposing the subjects to a temperature of 35 to 38 °C (95 to 100 °F) and 70 to 80 percent humidity, with little air movement. The Panel cautioned that, for safety purposes, older people should not be used and subjects should have their pulse and temperature taken every 15 minutes. Even with these safeguards, however, the agency believes that this test presents an unnecessary risk when the less-hazardous water resistance testing can be used in support of a sweat resistant claim. Further, the agency is unaware of any sunscreen products that make "sweat resistant" claims but do not also make "water resistant" claims. Accordingly, the agency concludes that the potential benefits of the sweat resistance test do not outweigh the possible risks to the test subject.

The agency disagrees with the recommendation that the SPF value of a product should be done under the combined stress of sweating and swimming. The determination of an SPF value is a test independent of stress. The requirement that the product be labeled with the appropriate PCD provides sufficient information for consumers to choose the proper sunscreen product for their individual needs.

In summary, the agency is proposing to permit the use of the terms "sweat resistant," "perspiration resistant," "resists removal by sweating," or "resists removal by perspiring" for a sunscreen drug product that qualifies for the claim of "water resistant" or "very water resistant." The agency is proposing the phrase "sweat resistant" or "perspiration resistant" in § 352.52 (e)(2) and (e)(3) and is not proposing § 352.50(e)(2)(i)(*c*) as recommended by the Panel (see comment 103). The agency is not including the Panel's recommended "sweat resistant" test in the testing procedures and is proposing only the procedures for "water resistant" and "very water resistant."

References

(1) Williams, R. J., and E. W. Lansford, Jr., editors, "The Encyclopedia of Biochemistry," Reinhold Publishing Corporation, New York, pp. 774–775, 1967.

(2) White, A., et al., "Principles of Biochemistry," 7th Ed., McGraw-Hill Book Company, New York, p. 152, 1983.

(3) Sato, K., "Eccrine Sweat Glands," *in* "Dermatology in General Medicine," edited by T. B. Fitzpatrick, et al., McGraw-Hill Book Company, New York, pp. 195–209, 1987.

101. Referring to the Panel's recommended procedures for testing water resistance and waterproof claims in § 352.46 (a) and (b), one comment stated that the criteria for these tests are not defined. The comment mentioned that both procedures simply state that "A sunscreen product that can withstand 40 (80) minutes of water immersion may claim to be water resistant (waterproof)." However, the Panel's discussion of these tests (43 FR 38206 at 38263) and the sweat resistance test (§ 352.45) require that the product demonstrate the same PCD before and after water immersion. The comment requested that this standard also be included in the water resistance and waterproof testing procedures.

The agency agrees with the comment that the criteria for passing the Panel's recommended tests in § 352.46 (a) and (b) should be defined and included in the testing procedures. Therefore, the agency is proposing in § 352.76(a) to replace the Panel's recommended sentence "A sunscreen product that can withstand 40 minutes of water immersion may claim to be water resistant" with the following sentence: "If the sunscreen product retains the same PCD after 40 minutes of water immersion as it had before water immersion, the claim of 'water resistant' may be made." In § 352.76(b), the agency is proposing to replace the Panel's recommended sentence "A sunscreen product that can withstand 80 minutes of water immersion may claim to be waterproof" with the following sentence: "If the sunscreen

product retains the same PCD after 80 minutes of water immersion as it had before water immersion, the claim of 'very water resistant' may be made." (See comment 50 regarding use of the term "very water resistant" instead of "waterproof.")

102. One comment believed that the Panel's recommendations to use an artificial light source for substantiating the claim of sweat resistance (43 FR 38206 at 38262) are ideal but far from being realistic or achievable. If the Panel feels that a sunscreen product should retain the same PCD after the sweat test as before the sweat test, the comment explained, "there will be a tendency on the part of the regulatory agency to disapprove such claims for failure in compliance; because, every sunscreen product, no matter how good it is, will not give the same protection factor value before and after the stress of swimming. The product after the stress of sweating will always be giving a lower protection factor value (hence, a lower PCD designation)."

The comment offered the following example: Products with an SPF value of 12 or more (PCD maximal or ultra) tend to show a decreased SPF value after the stress of swimming or sweating, e.g., an SPF of 12 may decrease to an SPF of only 8 (a decrease of nearly 33 percent). The same SPF value cannot be achieved for various reasons (e.g., elution changes due to the partition coefficient, thinning of the applied film, alteration in physical properties, etc.). Another comment also contended that the same SPF value will never be obtained after swimming because 15 to 20 percent of the sunscreen effectiveness will be lost depending on the base (vehicle) used in the product. The first comment concluded that, if the criteria recommended by the Panel are retained, the tendency on the part of the manufacturer will be to claim a low SPF value. Thus, in order to have a claim of "sweat resistance" or "water resistance," the comment argued, a manufacturer could only claim an SPF value of 8.

The comment felt that less effective products (i.e., products with a low SPF value but which retained the original SPF value after the stress of sweating) had a marketing advantage because these products could not be denied a claim of sweat resistance. The comment gave the following example: a product with an SPF value of 4 (before and after sweating) could have a claim of sweat resistance, whereas a superior product with an SPF value of 8 or more could not qualify for such a claim because its SPF value decreases to 6 after the stress of sweating. The comment felt this problem could be resolved by allowing the sweat resistance claim if the SPF value differences before and after the stress of sweating are less than 20 percent, provided the initial SPF value is at least 8 or 10.

The agency is not proposing the Panel's recommended testing procedure for a sweat resistance claim in this tentative final monograph (see comment 100). Accordingly only the comments' concerns about the test for water resistance are being addressed. The agency is aware of two studies, conducted since publication of the Panel's report, that determined the water resistance effectiveness of single-ingredient and combination sunscreen products (Refs. 1 and 2). One study (Ref. 1) used the protocol recommended by the Panel, and the second study (Ref. 2) used a similar protocol involving a 10-minute whirlpool treatment. In both studies, the SPF values for several different sunscreen ingredients alone and for combinations of sunscreen ingredients were determined before and after the water treatment. A decrease in the SPF values occurred for all of the products tested, including sunscreen drug products previously determined to be water resistant. With some products, e.g., 5 percent aminobenzoic acid, the decrease in the SPF values after the water treatment was significant. In other cases, e.g., 8 percent octyldimethyl aminobenzoic acid plus 3 percent oxybenzone, the decrease in the SPF value after the water treatment was minimal. Because every product was affected, the agency believes that some allowance for a decrease in SPF values after the water test should be made.

The Panel recommended that a sunscreen drug product must retain the same PCD, not the same SPF value, after the test as it had before the test (43 FR 38263). A product can experience a reduction in SPF value and still remain in the same PCD. For example, a product with a PCD of very high has an SPF value of 12 to under 20. If the product has an SPF value of 20 before the water test, it must have an SPF value of 12 or above after the test in order to retain the same PCD and make the claim for water resistance. The SPF value of the product could decrease by as much as 40 percent and the product would still be classified under the same PCD. Even sunscreen drug products that offer less protection, e.g., products with a moderate PCD, can undergo a reduction in SPF value after exposure to water and still remain in the same PCD. Therefore, the agency believes that the range of SPF values listed for each PCD recommended by the Panel is sufficiently broad to provide for a reduction in the SPF value after the water test. This criterion in the test for water resistant and very water resistant claims is proposed in § 352.76. (See comment 101.)

References

(1) Kaidbey, K. H., and A. M. Kligman, "An Appraisal of the Efficacy and Substantivity of the New High-Potency Sunscreens," *Journal of the American Academy of Dermatology*, 4:566–570, 1981.

(2) Sayre, R. M., et al., "Performance of Six Sunscreen Formulations on Human Skin," *Archives of Dermatology*, 115:46–49, 1979.

103. One comment referred to the Panel's recommended testing procedure in § 352.46 for determining whether a sunscreen product is water resistant or waterproof. The comment stated that: (1) The terms "water resistant" and "waterproof" should be defined; (2) the criteria are unrealistic, arbitrary, and scientifically not established; (3) 2 water immersion periods of 20 minutes with moderate activity in water (a total of 40 minutes) are not essential for ascertaining the water resistance of a sunscreen product because the average person rarely remains in water for 40 minutes; and (4) 3 water immersion periods of 20 minutes with moderate activity in water (a total of 60 minutes) are totally unrealistic. A similar comment stated that it is inconsistent that FDA would demand proof that the 8-percent homosalate standard is validated before accepting and promulgating the in vivo sunscreen testing procedures, and at the same time, promulgate in vivo water resistant testing procedures which have not been validated. The comment maintained that the same exacting standards should be required for all in vivo testing procedures that substantiate labeling claims upon which consumers rely. Another comment added that it would not differentiate between water resistant and waterproof because several studies have shown that the average swimming time is not more than 10 minutes.

The agency believes that the term "waterproof" has a different meaning from that intended by the Panel for a sunscreen product; therefore, the agency is proposing the term "very water resistant" instead of the term "waterproof." (See comment 50.) Although the Panel recommended testing procedures for determining whether sunscreen drug products are "water resistant" or "waterproof" (§ 352.46(a) and (b)), the agency does not agree with the comment that these terms are not defined. A "water resistant" sunscreen resists removal for at least 40 minutes in the water, and a "very water resistant" (waterproof)

sunscreen resists removal for at least 80 minutes in the water. (For a further discussion of these terms, see comment 50.)

The comments did not elaborate on the statement that the testing criteria necessary to establish a claim of water resistant or very water resistant are unrealistic, arbitrary, and scientifically not established. At the time of the Panel's deliberations there were no adequate standards on which to base water resistant and very water resistant claims. Thus, to establish criteria for testing water resistant and very water resistant sunscreen products (Ref. 2), the Panel proposed a testing method that it considered to be a reasonable and fair representation of swimming habits. Since the Panel completed its deliberations, the procedures it recommended have been tested and found to provide a good measure of the water resistance of sunscreen products. Studies have shown that the substantivity of such products has improved over the years (Refs. 3 and 4). Kaidbey and Kligman (Ref. 3) evaluated sunscreen products using the Panel's recommended procedures and found that certain sunscreen products, especially some of the newer products, were more resistant to wash-off than others. Further, such products, after undergoing water treatment, maintained an SPF number closer to the original SPF number. In addition, in a communication with the agency, the Nonprescription Drug Manufacturers Association, a trade association of OTC drug manufacturers, stated that the Panel's recommended testing methods are frequently used in determining water resistant and waterproof claims (Ref. 5). Thus, the agency disagrees with the comments' assertions that these procedures are unrealistic, arbitrary, and scientifically not established.

The agency also does not accept one comment's claim that a total of 40 minutes of moderate activity in water is not essential for ascertaining the water resistance of a sunscreen product because the average person rarely remains in the water for 40 minutes. The comments did not provide any evidence to support their statements that the average person rarely remains in the water for 40 minutes or that the average swimming time is not more than 10 minutes. Likewise, the agency disagrees with one comment's claim that 60 minutes of moderate activity in water is an unrealistic time period to determine that a sunscreen product is waterproof. The Panel concluded that two 20-minute periods of moderate activity in water (for a total of 40 minutes) is an appropriate test for determining the water resistance of a sunscreen product. Likewise, four 20-minute periods of moderate activity in water (for a total of 80 minutes) was recommended to establish that a product is very water resistant. The Panel chose the 20-minute water immersion periods because unpublished marketing data revealed that a typical population of adults and children under 12 years of age goes into the water 3.6 times for an average duration of 21 minutes per immersion at the beach or pool, and has an average total immersion time of approximately 80 minutes (Ref. 1). Further, the data indicated that 38 percent of users do not reapply a sunscreen product after swimming. By selecting a water immersion period of 40 minutes for a water resistance claim and 80 minutes for a very water resistant claim, the Panel chose reasonable average times that a product should withstand removal by water in order to show effectiveness as a water resistant or very water resistant sunscreen product. The agency considers a sunscreen drug product that can be removed by water in less than 40 minutes as not appropriate as a water resistant or very water resistant sunscreen. A water resistant or very water resistant sunscreen product should enable an individual to maintain a certain level of protection from the harmful rays of the sun after an average period of swimming without the need to reapply the product. For example, children are constantly in and out of the water, and may stay for hours at a time in the beach/pool environment. These individuals are at the greatest risk for "wash-off." They are also at the greatest risk of subsequent adverse effects if the SPF value of a sunscreen is overstated based on test methods that underestimate the exposure time to water immersion of very active individuals. Therefore, the agency believes that test times must approach the longer times that some consumers will be immersed in water, rather than "average" times which would significantly underestimate immersion times of a high-risk group. The agency concurs with the Panel's recommendations concerning testing procedures for water resistant claims in sunscreen drug product labeling; however, as noted above, the agency is proposing to replace the Panel's recommended term "waterproof" with the term "very water resistant."

References

(1) OTC Vol. 060168.

(2) Summary Minutes of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Treatment and Prevention Drug Products, March 4 and 5, 1976, OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

(3) Kaidbey, K. H., and A. M. Kligman, "An Appraisal of the Efficacy and Substantivity of the New High-Potency Sunscreens," *Journal of the American Academy of Dermatology*, 4:566–570, 1981.

(4) Sayre, R. M., et al., "Performance of Six Sunscreen Formulations on Human Skin," *Archives of Dermatology*, 115:46–49, 1979.

(5) Comment No. C00075, Docket No. 78N–0038, Dockets Management Branch.

104. One comment contended that the Panel's recommended testing procedure, in § 352.46, for determining if a sunscreen is water resistant or waterproof cannot be controlled because of the high degree of variability in the content of fresh water. (The test is to be performed in an indoor fresh water pool.) The comment stated that fresh water has, depending on its source, different pH values and different amounts of minerals and chemicals (such as chlorine and fluoride), which may influence the solubility of the sunscreen ingredient in the product. Because the Panel did not define the term "fresh water," the comment stated that FDA must provide, in the regulation, specifications for the fresh water in order to standardize the procedures for testing the effectiveness of water resistant and waterproof sunscreen products.

FDA proposes to define "fresh water" for the purpose of this tentative final monograph as clean drinking water that meets the standards established by the United States Environmental Protection Agency (EPA). Tap (piped) water for drinking and domestic use is generally supplied by rivers, lakes, wells, and springs. Water from a public water system is filtered and treated with chemicals in water treatment plants to kill bacteria, soften the water, and improve its taste (if it is to be consumed). The treated water might even go to another reservoir such as a swimming pool or a whirlpool and undergo further treatment if it is used by the public for swimming, in a factory, or a sunscreen testing laboratory, etc.

The EPA is responsible for establishing the minimum standards for all water systems that provide water suitable for human consumption to the public. Service to the public includes factories and private housing developments, communities, camping sites, etc. EPA regulations provide the maximum contaminant levels for organic and inorganic chemicals other than fluoride, for disease-causing microorganisms, etc., in drinking water. (See the National Interim Primary Drinking Water Regulations in 40 CFR

Part 141.) FDA does not believe that additional specifications for the water used for sunscreen testing are necessary. Accordingly, FDA is defining "fresh water" in § 352.76 as clean drinking water that meets the standards in 40 CFR Part 141.

105. One comment stated that the Panel's recommended instructions concerning the waiting period between applying a sunscreen drug product and exposing the test site are inconsistent with the testing procedures for water resistant and waterproof claims in the Panel's report. The general testing procedure in § 352.42(f) specifies a waiting period of at least 15 minutes after application of the sunscreen before exposing the test site; whereas, the procedures in § 352.46(a)(1) and (b)(1) for testing water resistant and waterproof claims require that application of the sunscreen be followed by the waiting period indicated on the sunscreen drug product's labeling. The comment further noted that a waiting period is not included under the product labeling requirements of the Panel's recommended monograph. The comment suggested that, for uniformity, the individual testing procedures should all reference § 352.42 *"General Testing Procedures."*

The Panel intended for the *"General Testing Procedures"* in § 352.42 to apply to the individual testing procedures for water resistant and very water resistant claims (see comment 50 on the substitution of the term "very water resistant" for the term "waterproof"). However, the Panel did not find it necessary to restate in § 352.46 the detailed general testing procedures for the determination of the SPF value. The agency believes that a cross-reference would be useful for clarity. Therefore, the agency is proposing to add a statement to the introductory text of § 352.76 that states: "The general testing procedures in § 352.72 should be used as part of the following tests, except where modified in this section."

The agency disagrees with the comment's claim that the Panel's recommended waiting periods are inconsistent. One waiting period (in § 352.42(f)) refers to the time between applying a sunscreen drug product and exposing the test site to the UV radiation source. The other waiting period (in § 352.46(a)(1) and (b)(1)) refers to the time between applying a sunscreen drug product and exposing the test site to water. In the *General Testing Procedures* in § 352.42, the Panel recommended a waiting period of at least 15 minutes. This waiting period occurs prior to exposing the test site to the UV radiation source for the determination of the product's SPF value. Every sunscreen drug product must have its SPF value measured according to these procedures. For products claiming to be water resistant or very water resistant, the static (i.e., initial) SPF is measured after a 15 minute waiting period, according to § 352.42. When determining the water resistant SPF, another waiting period, as determined by the manufacturer, elapses before the test site is exposed to water in accordance with § 352.46. After exposure to water, the SPF of the product is again determined. If the product maintains the same PCD after the amount of water exposure specified in either § 352.46 (a) or (b), it can be labeled with either a water resistant or a very water resistant claim. (See comment 102.)

For products that make water resistant and very water resistant claims, the Panel recommended that the waiting period should be that indicated on the product labeling (43 FR 38206 at 38266 and 38267). The agency agrees with the Panel that the waiting period for each water resistant and very water resistant product should be individually determined by the product's manufacturer. Water resistant and very water resistant sunscreen drug products are specifically formulated to withstand wash-off by water. The degree of water resistance of such products varies and is greatly influenced by the vehicle in which the sunscreen ingredient is incorporated. As stated by the Panel at 43 FR 38218, "the persistence, penetration, and resistance of the active ingredients to abrasion, sweating, and washing often depends upon the vehicle." A waiting period may be necessary for some water resistant products (e.g., to allow the product to dry) in order to provide better resistance to water, and the waiting periods for different sunscreen products may vary. For these reasons, the agency is proposing the Panel's recommendations regarding waiting periods in §§ 352.72(f) and 352.76(a)(1) and (b)(1).

With regard to the comment's statement that waiting periods are not included in the Panel's recommended monograph labeling, the agency believes that consumers should be informed if a waiting period is necessary for the most effective use of water resistant and very water resistant sunscreen drug products. Therefore, the agency is proposing that the manufacturers determine the waiting periods for the most effective use of their products and include this information in the directions for their product (see comment 66).

106. Four comments addressed the Panel's recommended testing procedure in § 352.46 for determining if a sunscreen product is water resistant or waterproof. (The agency is using the term "very water resistant" rather than waterproof. See comment 50.) One comment requested that: (1) A whirlpool testing method be included as an alternative testing procedure for water resistant and very water resistant claims; (2) the 20-minute drying periods between immersion periods be deleted; and (3) in analyzing data, the projected slope technique not be excluded from acceptability to product labeling. The comment maintained that such techniques as linear regression and least square techniques require data obtained for different amounts of water exposure, and could not be used under the present proposed procedure. The comment contended that the complexity of the Panel's proposed procedure (e.g., the time an investigator must spend with each subject, the number of subjects required, and the requirement for the testing facilities to be close to a swimming pool) makes conducting these tests very expensive in terms of manpower, equipment, and resources. In addition, without access to a close indoor pool, water resistant and very water resistant testing would require the use of an outside swimming pool, which would limit periods of testing to good weather only. Further, if that were to occur, the testing would be subject to many uncontrolled environmental variables such as the weather. The comment added that if the swimming pool is not located in the same facility as the testing area and solar simulator, transportation of the subjects between the pool and the testing facility would be required, thereby adding further variability in test results between laboratories. The comment concluded that the proposed requirements could eliminate most comparative testing of sunscreen products and stop laboratories from performing such tests.

The comment contended that a testing method using a whirlpool would be more economical and accessible than a method using an indoor swimming pool, provide better standardization of the test environment, and provide better control of environmental variables such as sun exposure, water temperature, and chlorination. In addition, the whirlpool could be located close to the solar simulator testing area.

The comment submitted a summary of the results of tests conducted to determine if a sunscreen is water resistant or very water resistant using the procedure proposed in § 352.46 and using a whirlpool. The tests compared results obtained in large or small whirlpools to those obtained in a

swimming pool for a number of sunscreen products with various SPF values. All SPF determinations for water resistant and very water resistant were performed with solar simulators in accordance with the Panel's recommended procedures, except that not all studies included 20 test subjects. Based on the results obtained, the comment concluded that under indoor laboratory testing conditions using a whirlpool bath: (1) The environment and the well-being of the volunteers can be more carefully monitored, and indoor heating can be carefully controlled to maintain the volunteer's temperature; (2) the solar simulators can be more rigorously maintained; (3) an acceptable laboratory test using an indoor whirlpool can lead to "a better discussion and treatment of other environmental factors not directly applicable in a swimming pool environment," e.g., the influence of temperature, humidity, and wind; and (4) testing can be performed year-round.

The comment added that its data indicate there is no difference in product effectiveness introduced by inclusion of the Panel's recommended 20-minute drying period between water exposure periods. The comment concluded that this condition appeared to needlessly complicate the testing procedure, and requested that it be deleted. However, the comment did not submit data comparing test results with and without the 20-minute drying period.

A second comment proposed a water resistance test using either a jacuzzi or a swimming pool for sunscreen drug products with an SPF value of 15 or more. The proposed water resistance testing involved the application of the sunscreen product followed by a 15-minute waiting period at room temperature before entering the water. The subject would then bathe in a pool or jacuzzi (temperature between 25 and 30 °C) for 20 minutes. This would be followed by a 20-minute drying period, then by a 10-minute mild shower (temperature between 33 and 37 °C, minimum 2 liters/minute), and then by a 10-minute drying period. The MED of the protected skin would be determined before the procedure for bathing and immediately after the last drying period. The comment stated that the ratio of "bathings/no bathing" of protected sites should be better than 0.8 (i.e., the decrease in SPF should not be more than 20 percent after the test). The comment stated that a product that does not fulfill this water resistance test could not claim to belong to "class I" or to "ultra-sun protection."

A third comment recommended that specific guidelines be provided for water immersion testing. The comment did not provide any guidelines for such testing but did indicate that guidelines for factors such as temperature, method of agitation, and movement should be specified for manufacturers to employ in determining substantivity.

A fourth comment opposed adding a requirement for a very water resistant standard control to the water resistant testing procedures. The comment stated that the current static standard is adequate to fulfill the purpose of the control and can be used in conjunction with the very water resistant testing without a problem. The comment concluded that nothing would be gained by adding a requirement for a very water resistant standard control.

The agency agrees that a whirlpool or jacuzzi is an acceptable alternate to an indoor swimming pool in the testing procedure recommended by the Panel in § 352.46. These facilities provide an appropriate means of standardizing water resistant testing among laboratories by providing control over most of the variables. Whirlpools and jacuzzi are similar to an indoor swimming pool in that they provide: (1) Adequate control of environmental factors, e.g., temperature and humidity; (2) proximity to the testing sites; and (3) year-round testing capabilities because testing would not be weather dependent. Additionally, whirlpools and jacuzzi are economical and provide a more rigorous water challenge to test the water resistant properties of the sunscreen drug product. The agency believes that indoor testing helps ensure reproducible results because it is easier to control indoor environmental variables such as temperature and humidity. An accurate and reproducible testing procedure can ensure that competitive products with the same water resistant labeling have essentially the same effectiveness (see comment 79). Therefore, the agency is proposing that the testing procedure (§ 352.46) be revised to state that an indoor fresh water pool, whirlpool, and/or jacuzzi maintained at 23 to 32 °C shall be used in the testing procedures to determine if a sunscreen drug product is water resistant or very water resistant. This revised testing procedure is in proposed § 352.76.

The agency does not agree with one comment's suggestion that a total of only 30 minutes of water immersion is adequate for ascertaining the water resistance of a sunscreen drug product. The Panel concluded that two 20-minute periods of moderate activity for a total of 40 minutes in the water is an appropriate test for determining water resistance (43 FR 38206 at 38263). Likewise, the Panel recommended four 20-minute periods of moderate activity in water (for a total of 80 minutes) to establish that a product is very water resistant. (See discussion in comment 103.) The comment did not provide any test data or other evidence to support its suggestion for moderate activity in water for 30 minutes.

The agency also disagrees with another comment's request to delete the Panel's recommended 20-minute drying period between immersion periods. The Panel reviewed an unpublished consumer marketing survey (Ref. 1) that studied typical water immersion behavior patterns among sun care product users and used these data to establish the 20-minute water immersion periods. Although the survey did not specifically address the amount of time spent out of the water between the immersion periods, the agency considers the Panel's 20-minute drying periods reasonable and a fair representation of the swimming habits of individuals at the beach or swimming pool. The survey indicates that the typical population does spend time out of the water and then reenters the water several times. The agency believes that a water resistant or very water resistant sunscreen drug product should enable an individual to maintain a certain level of protection from the harmful rays of the sun after an average period of swimming, including time spent out of the water between immersions, without the need to reapply the product. If data are submitted that support deleting the 20-minute drying periods between immersion periods, the agency will consider revising the testing procedure to delete the drying periods.

Regarding specific guidelines for water immersion testing, the agency notes that the Panel required that the water temperature be 23 to 32 °C. Further, the Panel stated that the pool and air temperature and the relative humidity should be recorded. The agency agrees with these Panel recommendations and, in addition, agrees with the comments that more specific guidelines (e.g., water and air temperature, humidity, and minimum size of the whirlpool or jacuzzi) should be included in the testing procedures for sunscreen drug products. However, the comments provided no specific guidelines that might be used for water resistant testing procedures or data concerning the use of such guidelines. Therefore, the agency is proposing in § 352.76 that the water temperature of the indoor pool, whirlpool, or jacuzzi be maintained at 23 to 32 °C and is

requesting comment and data on including other specific environmental guidelines, such as those noted above, that would improve the water resistant testing procedures.

The agency agrees with one comment that an additional control standard for water resistant testing serves no added benefit because the current 8-percent homosalate standard adequately fulfills the purpose of serving as a control for the SPF testing procedure. The Panel stated in its recommended water resistant testing procedures in § 352.46 that "The standard sunscreen is not used in these tests." The agency is concerned that this statement could imply that the 8-percent homosalate standard is not required for the SPF testing procedure. Therefore, the agency is not proposing this sentence in § 352.76.

Regarding the acceptability of a projected slope technique for the analysis of data for product labeling, the statistical analysis of data from sunscreen drug product testing is addressed in comment 97.

Reference

(1) OTC Vol. 060168, Docket No. 78N–0038, Dockets Management Branch.

V. Comments on In Vitro Testing for Sunscreen Drug Products

107. Referring to the Panel's recommended testing procedure in § 352.46 for determining if a sunscreen is water resistant or waterproof, one comment recommended that an in vitro substantivity test with isolated specimens of epidermis be used. The comment described the procedures for the in vitro test as follows: (a) Obtain small specimens of skin (5 inches by 2 inches) from postmortem cases; (b) isolate the epidermis by treating the skin specimen at 60 °C for 30 to 60 seconds; (c) measure the transmission spectra of the isolated and untreated epidermis between a spectral range of 200 to 400 nm; (d) apply the sunscreen lotion (2 mg or 2 microliters/cm^2), select the minimum and the maximum time for diffusion of the applied sunscreen agent, determine the chemical conjugation of the sunscreen, and measure the transmission spectra after 30- and 60-minute intervals; (e) immerse the specimen in water with constant mechanical stirring for varying periods of time ranging from 10 to 90 minutes; (f) measure the transmission spectra of the specimen after immersion in water for these varying intervals of time; (g) determine the amount of sunscreen agent left on the specimen before and after immersion in water; (h) determine the percent transmission changes in the spectral range of 200 to 400 nm; and (i) calculate the substantivity or water resistance. The comment added that the variables in this test can be controlled.

Another comment submitted in response to the January 1988 public meeting to discuss sunscreen testing methods acknowledged that human testing is the accepted method for determining SPF values. The comment added that in vitro methods are nevertheless being developed and should be encouraged.

The agency agrees that in vitro testing of sunscreen drug products may be useful and encourages the development of such testing methods. The agency has reviewed the in vitro substantivity test suggested by the comment and believes it may be suitable for obtaining an approximate measure of a sunscreen product's water resistance. However, the agency needs further details about the procedure to properly evaluate it. The protocol offered by the comment is very brief and does not contain enough information for adequate performance of the test and interpretation of the results. While the protocol appears to have merit, it needs to be expanded, developed, and compared to in vivo methods for determining water resistance. Sayre, et al. (Ref. 1) have tested a similar in vitro procedure for determining the water resistance of several sunscreen products using the epidermis of hairless mice in a spectrophotometric assay. The results showed clear differences in substantivity among several sunscreen ingredients using this in vitro method. The results from the in vitro method were reported to be similar to those determined by the in vivo method.

The agency points out that while data from in vitro tests using isolated skin samples may offer some supportive evidence of water resistance, in vivo tests for determining the effectiveness and substantivity of a sunscreen product are still required. Isolated skin specimens do not behave like natural living skin, e.g., they do not sweat, vary in temperature, or develop erythema. Therefore, such in vitro tests alone are not suitable for determining the effectiveness or substantivity of a sunscreen drug product. In addition, comparative evaluations between in vitro and in vivo methods must be performed in order to establish a direct correlation between these methods. Therefore, the agency believes that additional studies with in vitro procedures using isolated skin samples need to be performed and evaluated before these methods can be considered for inclusion in a monograph.

Reference

(1) Sayre, R. M., et al., "Sunscreen Testing Methods: In Vitro Predictions of Effectiveness," *Journal of the Society of Cosmetic Chemists*, 31:133–143, 1980.

W. Comment on Safety Testing for Sunscreen Drug Products

108. Stating that the 3 methods of patch testing recommended by the Panel for final products or Category III ingredients are acceptable methods (43 FR 38206 at 38218), one comment requested that a routine patch test method proposed by the International Contact Dermatitis Research Group (ICDRG) also be included as an acceptable method. The comment cited two references in which the ICDRG method is described (Refs. 1 and 2) and added that many sunscreen products have been previously evaluated by this patch test method, which is an accepted method in Europe.

The 3 methods of patch testing recommended by the Panel are part of a general discussion of test methods applicable to human safety testing of Category III ingredients or final-formulated products (43 FR 38218). Because these tests have proven valuable in predicting skin irritancy and potential sensitization, the Panel recommended that these methods be considered for providing adequate data to establish the safety of OTC sunscreen ingredients. The Panel did not recommend that any specific patch test be included in the monograph.

The agency has not addressed specific testing methods for determining the safety of OTC sunscreen drug products in this tentative final monograph; the agency is not, therefore, recommending the use of a particular patch test. Each manufacturer or sponsor should determine which scientifically valid patch test to use to evaluate the safety of its sunscreen drug product. Before utilizing a new patch testing method for sunscreen drug products, the sponsor may want to discuss the use of the method with the agency.

References

(1) International Contact Dermatitis Research Group, "Routine Patch Test Series: 1974," *British Journal of Dermatology*, 89:437–438, 1973.

(2) Magnusson, B., "Patch Testing," in "Sunlight and Man," edited by M. A. Pathak, et al., Tokyo University Press, Tokyo, pp. 799–812, 1974

III. The Agency's Tentative Conclusions and Adoption of the Panel's Report

A. Summary of Ingredient Categories and Testing of Category II and Category III Conditions

1. *Summary of ingredient categories.* The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and is proposing to reclassify padimate A from Category I to Category II for concentrations of 5 percent and higher and to Category III for concentrations less than 5 percent. As a convenience to the reader, the following list is included as a summary of the categorization of sunscreen active ingredients recommended by the Panel and the proposed categorization by the agency. In this list, sunscreen active ingredients are identified by their current established name. If the current established name is different from that used by the Panel, the Panel's designation is indicated by footnote.

Sunscreen active ingredients	Panel	Agency
Allantoin/aminobenzoic acid complex.	II	III
Aminobenzoic acid	I	I
Bomelone	III	III
Cinoxate	I	I
Diethanolamine methoxycinnamate[1].	I	I
Digalloyl trioleate	I	I
Dioxybenzone	I	I
Dipropylene glycol salicylate.	III	III
Ethyl 4-[bis(hydroxypropyl] aminobenzoate.	I	I
2–Ethylhexyl 4-phenylbenzophenone-2 carboxylic acid.	II	II
Glyceryl aminobenzoate	I	I
Homosalate	I	I
Lawsone with dihydroxyacetone.	I	I
Menthyl anthranilate	I	I
3-(4-methylbenzylidene)-camphor.	II	II
Octocrylene[2]	I	I
Octyl methoxycinnamate[3]	I	I
Octyl salicylate[4]	I	I
Oxybenzone	I	I
Padimate A (up to 5 percent).	I	III.
Padimate A (5 percent or higher)[5].		II
Padimate O	I	I
Phenylbenzimidazole sulfonic acid[6].	I	I
Red petrolatum	I	I
Sodium 3,4-dimethylphenylglyoxylate.	II	II
Sulisobenzone	I	I
Titanium dioxide	I	I
Trolamine salicylate[7]	I	I
Zinc oxide[6]		III

[1] Identified by the Topical Analgesic Panel as diethylanolamine p-methoxycinnamate.
[2] Identified by the Topical Analgesic Panel as 2-ethylhexyl- 2-cyano-3, 3-diphenylacrylate.
[3] Identified by the Topical Analgesic Panel as ethylhexyl p-methoxycinnamate.
[4] Identified by the Topical Analgesic Panel as 2-ethylhexylsalicylate.
[5] Not evaluated by the Topical Analgesic Panel.
[6] Identified by the Topical Analgesic Panel as 2-phenylbenzimidazole-5-sulfonic acid.
[7] Identified by the Topical Analgesic Panel as triethanolamine salicylate.

2. *Testing of Category II and Category III conditions.* The Panel recommended testing guidelines for sunscreen drug products (43 FR 38206 at 38258 and 38259). Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any sunscreen ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the **Federal Register** of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). That policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Changes

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the Panel's report and recommended monograph with the changes described in FDA's responses to the comments above and with other changes described in the summary below. A summary of the changes made by the agency follows.

1. The agency is placing the labeling sections of this tentative final monograph in Subpart C. In addition, the agency is renumbering the testing sections, §§ 352.40 through 352.46, of the Panel's recommended monograph as §§ 352.70 through 352.76 and is placing these sections in Subpart D.

2. Because the term "ultraviolet radiation" is preferred when speaking of the wavelengths between 100 and 400 nm, the agency is using the term "ultraviolet radiation" instead of "ultraviolet light" throughout the tentative final monograph. (See comment 2.)

3. To clarify that the scope of this monograph extends only to drug products and to be consistent with the format of other OTC drug monographs, the word "drug" is being added to § 352.1 to read as follows: "An over-the-counter sunscreen drug product in a form suitable for topical administration * * *." (See comment 25.)

4. The agency is proposing to provide a definition of MED in § 352.3 by adding new paragraph (a) as follows: "*Minimal erythema dose (MED).* The smallest dose of ultraviolet (UV) radiation (expressed as Joules per meter squared) that produces redness reaching the borders of the exposure site." The other definitions in § 352.3 are being renumbered to adjust for the addition of new paragraph (a). (See comment 95.)

5. The agency is proposing to revise the Panel's recommended definitions in § 352.3(a)(3), (4), and (5) to reflect new terminology and SPF ranges for PCD's and is including the revised definitions in § 352.3(b)(3), (4), and (5). (See comments 44 and 45.)

6. The agency is revising the Panel's recommended definition for a sunscreen active ingredient in § 352.3(b) and is including the revised definition in proposed § 352.3(c) as follows: "*Sunscreen active ingredient.* An active ingredient that absorbs at least 85 percent of the radiation in the UV range at wavelengths from 290 to 320 nanometers, but may or may not transmit radiation at wavelengths longer than 320 nanometers." (See comment 17.)

7. Based upon data showing that padimate A is a weak phototoxic agent, the agency is classifying padimate A at 5 percent and higher concentrations in Category II and in concentrations less than 5 percent in Category III. (See comment 35.)

8. Although the Panel did not include zinc oxide in its report on OTC sunscreen drug products, the agency is proposing in this tentative final monograph to classify zinc oxide in Category III. (See comment 36.)

9. Because a sunscreen active ingredient's performance is not totally dependent upon the concentration of the active ingredient in the drug product, the agency is proposing only maximum concentrations in § 352.10. However, because the agency is concerned that each ingredient of a combination drug product contributes to the effect of the product, the agency is proposing minimum concentrations for sunscreens used in combination with one another in § 352.20. (See comment 37.)

10. The agency is proposing that any Category I sunscreen active ingredient can be safely and effectively combined with certain Category I skin protectant active ingredients (allantoin, cocoa

butter, dimethicone, glycerin, petrolatum, shark liver oil, and white petrolatum) in § 352.20(b)(1) and (2) as follows: "(1) Any single sunscreen active ingredient when used in the concentration established in § 352.10 may be combined with one or more skin protectant active ingredients identified in § 347.10(a), (d), (e), (f), (h), (i), and (j) of this chapter, provided the finished product has a minimum SPF value of not less than 2 as measured by the testing procedures established in Subpart D of this part and provided the product is labeled according to § 352.60" and "(2) Two or more sunscreen active ingredients when used in the concentrations established in § 352.20(a)(2) may be combined with one or more skin protectant active ingredients identified in § 347.10(a), (d), (e), (f), (h), (i), and (j) of this chapter, provided the finished product has a minimum SPF value of not less than 2 as measured by the testing procedures established in Subpart D of this part and provided the product is labeled according to § 352.60." (See comment 71.)

11. The agency concludes that OTC sunscreen drug products with SPF values higher than 15 are beneficial to consumers and is proposing in §§ 352.50 and 352.52 that the upper limit for SPF values be 30. The agency is also proposing that a sunscreen drug product should display its tested SPF value up to 30. The agency believes that SPF values should be displayed on the principal display panel of OTC sunscreen drug products and is, therefore, proposing a new § 352.50 that requires SPF values to appear on the principal display panel.

The agency is proposing to renumber the Panel's recommended § 352.50 "*Labeling of sunscreen products*" as § 352.52. (See comments 45, 46, and 47.)

12. The agency believes that including both a static and a water resistant SPF value in the labeling of water resistant and very water resistant sunscreen drug products will be beneficial to the consumer. Therefore, the agency is proposing such labeling in § 352.50(b). (See comment 51.)

13. The agency has determined that some of the Panel's recommended indications can be combined and simplified. In this tentative final monograph, the agency is combining the indications recommended by the Panel in § 352.50(b)(1)(ii) and (b)(1)(iii) and is proposing the combined indication in § 352.52(b)(1)(ii) as follows: (Select one of the following: "Filters" or "Screens") 'out the sun's" (select one of the following: "burning" or "harsh and often harmful") "rays to prevent sunburn." The agency is also combining the additional indications recommended by the Panel in § 352.50(b)(2)(v)(*e*) and (b)(2)(v)(*f*) and is proposing the combined indication in § 352.52(b)(2)(vi)(E) as follows: "Provides the highest degree of" (select one of the following: "sunburn" or "sunscreen") "protection and permits no tanning."

14. The agency has determined that sunscreen-containing products that are not indicated for the prevention of sunburn, but only for added protection against the sun are drug products. Because such products are not adequately addressed by the Panel's recommended monograph, the agency is proposing to include the following new indications in § 352.52(b)(1) as follows: § 352.52(b)(1)(v) (Select one of the following: "Filters" or "Screens") "out the" (select one of the following: "sun's rays," "sun's harsh rays," or "sun's harmful rays") "to help prevent" (select one or more of the following: "lip damage," "skin damage," "freckling," or "uneven coloration"), and § 352.52(b)(1)(vi) (Select one of the following: "Protects from" or "Shields from") (select one of the following: "the harmful rays of the sun" or "the sun"). (See comment 52.)

15. The agency is proposing to replace the Panel's recommended labeling in § 352.50(b)(1)(iv) and (b)(1)(v) with the following statement in § 352.52(e)(6): "SUN ALERT: The sun causes skin damage. Regular use of sunscreens over the years may reduce the chance of skin damage, some types of skin cancer, and other harmful effects due to the sun." This statement will be required on all sunscreen drug products. The agency is also proposing the following in § 352.52(e)(7): "Any variation of the statement in § 352.52(e)(6) that does not relate skin aging or skin cancer as being 'due to the sun' will cause the product to be misbranded under section 502 of the act (21 U.S.C. 352)." (See comment 56.)

16. The agency believes that the information in the Panel's indications in § 352.50(b)(2)(i)(*f*), (b)(2)(i)(*g*), (b)(2)(ii)(*e*), (b)(2)(ii)(*f*), (b)(2)(iii)(*g*), (b)(2)(iii)(*h*), (b)(2)(iv)(*e*), and (b)(2)(iv)(*f*) and in the phrase "Stay in the sun (twice, 4 times, 6 times, 8 times, or 15 times) as long as before without sunburning" in the statements on product performance in § 352.50(e)(1)(i) through (e)(1)(v) can be better presented to consumers if those indications and phrases are revised. Therefore, the agency is not including those recommendations from the Panel, but is instead proposing the following in § 352.52(b)(1)(iii) and (b)(1)(iv), respectively: "Allows you to stay in the sun up to (insert SPF of product up to 30) times longer than without sunscreen protection," and "Provides up to (insert SPF of product up to 30) times your natural protection from sunburn." (See comment 57.)

17. The agency is proposing to revise the Panel's recommended indications in § 352.50(b)(2)(i)(*a*), (b)(2)(ii)(*a*), (b)(2)(iii)(*a*), (b)(2)(iv)(*a*), and (b)(2)(v)(*a*) and to include the revised indications in § 352.52(b)(2)(i)(A), (b)(2)(ii)(A), (b)(2)(iii)(A), (b)(2)(iv)(A), and (b)(2)(v)(A). (See comment 58.)

18. In order to be consistent with other recently published tentative final monographs, the agency is proposing to delete the Panel's recommended warnings in § 352.50(c)(2)(i) and (c)(2)(ii). The content of the warnings with some minor format changes is proposed in the directions included in § 352.52(d). (See comment 61.)

19. The agency is proposing to revise the Panel's recommended warning in § 352.50(c)(1)(ii) as follows: "Avoid contact with the eyes. If contact occurs, rinse eyes thoroughly with water." The revised warning is proposed in § 352.52(c)(1)(ii). (See comment 62.)

20. The agency is proposing to revise the Panel's recommended warning in § 352.50(c)(1)(iii) by adding the sentence "If irritation or rash persists, consult a doctor." The revised warning is proposed in § 352.52(c)(1)(iii). (See comment 63.)

21. The agency believes that sunscreen-containing lip balms and lipsticks do not require the warning recommended by the Panel in § 352.50(c)(1)(i). Therefore, the agency is proposing new § 352.52(c)(3), "*For products containing any ingredient identified in § 352.10 formulated as a lip balm or lipstick.* The warning in paragraph (c)(1)(i) of this section is not required." (See comment 52.)

22. The agency does not believe that sunscreen-containing lipsticks should be required to display the warning "Avoid contact with the eyes. If contact occurs, rinse eyes thoroughly with water." Therefore, the agency is proposing to add new § 352.52(c)(4) "*For products containing any ingredient identified in § 352.10 formulated as a lipstick.* The warning in paragraph (c)(1)(ii) of this section is not required." (See comment 52.)

23. To accommodate the various dosage forms of sunscreen drug products that are available, the agency is including only brief, required directions that can be expanded with more detailed instructions applicable to a particular product formulation and dosage form. In addition, the agency is

proposing that manufacturers determine the necessary waiting period between applying a sunscreen drug product and exposing the test site to water, if applicable, for water resistant and very water resistant sunscreen drug products and include this information in the directions for use. Accordingly, the agency is proposing these requirements in the directions in § 352.52(d). (See comment 67.)

24. The agency is combining the directions recommended by the Panel in § 352.50(d)(1)(i) and (d)(1)(ii) and is proposing the combined directions in § 352.52(d)(1). The agency is also combining the directions recommended by the Panel in § 352.50(d)(3)(i) and (d)(3)(ii) and is proposing the combined directions in § 352.52(d)(3) of this tentative final monograph.

25. The agency is also proposing specific directions for sunscreen-containing drug products such as lip balms, make-up preparations, skin preparations, and lipsticks in § 352.52(d) as follows:

"(4) *For products containing any ingredient identified in § 352.10 labeled with only the indications in § 352.52(b)(1)(v) and/or (b)(1)(vi) and formulated as a make-up preparation or lipstick.* 'Apply liberally as often as necessary.'

(5) *For products containing any ingredient identified in § 352.10 labeled with only the indications in § 352.52(b)(1)(v) and/or (b)(1)(vi) and formulated as a lip balm or skin preparation.* 'Adults and children 6 months of age and over: Apply liberally as often as necessary. Children under 2 years of age should use sunscreen products with a minimum SPF of 4. Children under 6 months of age: consult a doctor.'" (See comment 52.)

26. The agency is proposing to allow manufacturers the option of using the word "perspiration" for "sweat" and the word "perspiring" for "sweating" in §§ 352.50(b) and (c) and 352.52(d) and (e). (See comment 49.)

27. The agency is not proposing the Panel's recommended term "waterproof" in this tentative final monograph, but is proposing instead the term "very water resistant" in §§ 352.50(c) and 352.52 (d) and (e). (See comment 50.)

28. The agency is proposing to revise the Panel's recommended PCD labeling in § 350.50(e) to more accurately reflect the actual protective values of sunscreen drug products and that PCD labeling claims be optional. The agency is also proposing the terms "minimal," "moderate," "high," "very high," and "ultra high" to identify PCD's. The agency is proposing this revised PCD labeling in § 352.52(e). (See comments 44 and 45.)

29. The agency believes that it is appropriate for a sunscreen drug product that passes the water resistance and very water resistance tests to be permitted to make claims regarding sweat resistance in addition to making claims regarding water resistance. Therefore, the agency is proposing to permit the use of the terms "sweat resistant," "perspiration resistant," "resists removal by sweating," or "resists removal by perspiring" for a sunscreen drug product that qualifies for the claim of water resistant or very water resistant. The agency is proposing the phrase "sweat resistant" or "perspiration resistant" in § 352.52(e)(2) and (e)(3) and is not proposing § 352.50(e)(2)(i)(c) as recommended by the Panel. In addition, the agency is not including the Panel's recommended sweat resistant test in § 352.46 in the sunscreen testing procedures. (See comment 100.)

30. The agency is proposing the following additional statement in § 352.52(e)(5): "*For products containing the active ingredient identified in § 352.10(s) that provide an SPF of 12 to 30, the following labeling statement may be used.* 'Sunblock.'" (See comment 60.)

31. The agency is proposing to include the following labeling requirements for the indications, warnings, and directions of sunscreen-skin protectant combination products in § 352.60 (b), (c), and (d), respectively, concerning labeling of combination sunscreen drug products: "*For permitted combinations containing a sunscreen and a skin protectant identified in § 352.20(b).* In addition to any or all of the indications for sunscreens in § 352.52(b), the indication for skin protectants in § 347.50(b)(2) of this chapter should be used."

"*For permitted combinations containing a sunscreen and a skin protectant identified in § 352.20(b).* The warning for skin protectants in § 347.50(c)(3) is not required."

"*For permitted combinations containing a sunscreen and a skin protectant identified in § 352.20(b).* The directions for sunscreens in § 352.52(d) should be used."

The agency is also proposing a new § 352.20(c) to include a cross reference to the combination of a sunscreen active ingredient and a skin bleaching active ingredient. Labeling for this combination will be included in the final monograph for OTC skin bleaching drug products. (See comment 71.)

32. Because the improved stability characteristics of a revised 8-percent homosalate standard make it more appropriate for use in the testing procedures for sunscreen drug products than the standard originally submitted to the Panel, the agency is proposing the revised formulation and its manufacturing directions in § 352.70(a) and (b). In addition, the agency is including in § 352.70(a) the following statement: "In order for the SPF determination of a test product to be considered valid, the SPF of the standard sunscreen must fall within the standard deviation range of the expected SPF (i.e., 4.47 ± 1.279), and the 95-percent confidence interval for the mean SPF must contain the value 4." (See comments 74 and 75.)

33. The agency is not including the Panel's recommended § 352.41(b) "*Natural light source (sunlight)*" and § 352.44 "*Determination of SPF value using natural light source (sunlight),*" in this tentative final monograph. In addition, the Panel's reference to natural sunlight testing in § 352.42(h) "*Response criteria*" is not being included. (See comment 79.)

34. The agency is revising the light source specifications proposed by the Panel in § 352.41 of its monograph and is proposing new specifications in § 352.71. Also in § 352.71, the agency is specifying that an "accurately-calibrated spectroradiometer system or equivalent instrument" be used to measure the output of a solar simulator. (See comments 86 and 88.)

35. The agency believes that blinding procedures should be included in the sunscreen testing procedures. Therefore, the agency is proposing blinding procedures in § 352.72(e) "*Application of test materials*" and § 352.72(h) "*Response criteria.*" (See comment 91.)

36. In this tentative final monograph, the agency is not including the Panel's recommended § 352.42(g) but is proposing the following in § 352.72(g): "*Number of subjects.* A test panel shall consist of not more than 25 subjects with the number fixed in advance by the investigator. From this panel, at least 20 subjects must produce valid data for analysis." In addition, the agency is proposing to revise the Panel's recommended § 352.41(i) "*Rejection of data*" by adding the phrase "or if the subject was noncompliant (e.g., subject withdraws from the test due to illness or work conflicts, subject does not shield the exposed testing site from further UV radiation until the MED is read, etc.)" and is including the revised section in § 352.72(i). (See comment 94.)

37. The agency is proposing that § 352.72(h) include the following: "* * * The MED is determined 22 to 24 hours after exposure. The erythema

responses of the test subject should be evaluated under the following conditions: the source of illumination should be either a tungsten light bulb or a warm white fluorescent light bulb that provides a level of illumination at the test site within the range of 450 to 550 lux, and the test subject should be in the same position used when the test site was irradiated. Testing depends upon determining the smallest dose of energy that produces redness reaching the borders of the exposure site at 22 to 24 hours postexposure for each series of exposures * * *." The agency is also proposing in § 352.73 that the MED is the lowest dose of radiation that produces uniform redness reaching the borders of the exposure site at 22 to 24 hours postexposure. (See comment 95.)

38. In § 352.73(c) the agency is proposing to revise the Panel's recommended determination of SPF values in § 352.43 to include a geometric series of 5 exposures plus 2 other exposures placed symmetrically around the middle exposure. In addition, the agency is proposing that the exposure doses for the geometric series shall be calculated as follows: (1) (1.25)X for products with an estimated SPF less than 8, (2) 1.20X for products with an estimated SPF from 8 to 15, and (3) (1.15)X for products with an estimated SPF greater than 15. (See comment 96.)

39. The agency is proposing an erythema action spectrum and a proposed calculation to determine the erythema effective exposure in § 352.73. The agency is also proposing to replace the term "exposure time interval" in the SPF calculation in § 352.73 with the term "erythema effective exposure." (See comments 84 and 85.)

40. The Panel recommended in § 352.43 of its monograph that the MED(US) be determined on the day before evaluating the MED(PS) of the test sunscreens and the standard sunscreen. The agency agrees that it is necessary to establish the inherent MED of the test subject prior to evaluating a test sunscreen drug product so that the investigator can select appropriate doses of UV radiation to administer to the test subsites based upon the individual's predetermined MED(US) and the expected SPF of the test product. The agency is proposing that an MED(US) be determined on a day prior to the testing of the sunscreen drug product and that this previously established MED(US) be used to determine the testing doses of UV radiation. However, the agency also believes that the MED(US) and the MED(PS) that are used in the calculation of the SPF value of a sunscreen drug product should be determined on the same day. Such concomitant testing will eliminate any discrepancies resulting from day to day variations that may exist in the testing environment. Therefore, the agency is proposing in § 352.73 that, in addition to establishing an MED(US) on a day prior to the testing of the sunscreen drug products, a second MED(US) must be established on the same day as the MED(PS). The MED(US) that is established concomitantly with the MED(PS) is to be used in the calculation of the test product's SPF value.

41. The agency is including a statistical analysis based upon the t-test to be used in analyzing the results of the testing procedures for sunscreen drug products. Therefore, in § 352.73, the agency is proposing to include a one-sided t-test. The agency is also proposing the use of a 95-percent lower confidence interval to establish a statistically significant SPF value for use in OTC sunscreen drug product labeling. (See comment 97.)

42. In § 352.76(a) the agency is proposing the following sentence at the end of the section: "If the sunscreen product retains the same PCD after 40 minutes of water immersion as it had before water immersion, the claim of 'water resistant' may be made." In § 352.76(b), the agency is proposing the following sentence at the end of the section: "If the sunscreen product retains the same PCD after 80 minutes of water immersion as it had before water immersion, the claim of 'very water resistant' may be made." (See comment 101.)

43. The agency is proposing in § 352.76 of this tentative final monograph a definition of "fresh water" as clean drinking water that meets the standards in 40 CFR Part 141. (See comment 104.)

44. To clarify that the procedures in *"General Testing Procedures"* in § 352.72 apply to the individual testing procedures for water resistant and very water resistant claims, the agency is proposing a cross reference in § 352.76 as follows: "The general testing procedures in § 352.72 should be used as part of the following tests, except where modified in this section." The agency is also deleting the Panel's recommended statement in § 352.46 that states that "The standard sunscreen is not used in this test," and requiring that the 8-percent homosalate standard be used in the general testing procedures in § 352.72. (See comments 105 and 106.)

45. The agency is proposing testing procedures in § 352.76 to state that an indoor fresh water pool, whirlpool, and/or jacuzzi maintained at 23 to 32 °C shall be used in the water resistant or very water resistant testing procedures. (See comment 106.)

46. The agency is proposing to amend the cosmetic regulations in 21 CFR Part 700 by adding § 740.19 as follows: *"Suntanning preparations.* The labeling of suntanning preparations that do not contain a sunscreen ingredient must display the following warning: 'Warning—This product does not contain a sunscreen and does not protect against sunburn.'" (See comment 29.)

47. The agency is also proposing to revise the cosmetic regulations in 21 CFR Part 700 by adding § 700.35 to state that if a cosmetic product uses the word "sunscreen" anywhere in its labeling, the term "sunscreen" must be qualified by describing the cosmetic benefit provided by the sunscreen. (See comment 27.)

48. Because the trade correspondence TC–61 will be superseded by the requirements of the final monograph for OTC sunscreen drug products, the agency intends to revoke TC–61 and will publish a notice of revocation and the final monograph for OTC sunscreen drug products concurrently. (See comment 27.)

49. In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs to substitute the word "doctor" for "physician" in OTC drug monographs on the basis that the word "doctor" is more commonly used and better understood by consumers. Based on comments received to these proposals, the agency has determined that final monographs and other applicable OTC drug regulations will give manufacturers the option of using either the word "physician" or the word "doctor." This tentative final monograph proposes that option.

50. For an active ingredient to be included in an OTC drug final monograph, it is necessary to have publicly available sufficient chemical information that can be used by all manufacturers to determine that the ingredient is appropriate for use in their products. The recent discovery of a nitrosamine contaminant in sunscreens containing padimate O (see discussion above) illustrates the importance of requiring that sunscreen ingredients are adequately characterized and that these standards are published in an official compendium. Only a few of the sunscreen active ingredients that the Panel classified as Category I are standardized and characterized for quality and purity and are included in official compendia. Aminobenzoic acid, cinoxate, dioxybenzone, oxybenzone and titanium dioxide are currently

included as articles in the U.S.P. (Ref. 1). The remaining sunscreen active ingredients, including the homosalate control preparation used in the sunscreen testing procedures, are currently not adequately characterized.

The agency believes that it would be appropriate for interested parties to develop with the United States Pharmacopoeial Convention appropriate standards for the quality and purity of the sunscreen ingredients that are not already included in official compendia. In this tentative final monograph diethanolamine methoxycinnamate, digalloyl trioleate, ethyl 4-[bis(hydroxypropyl)] aminobenzoate, glyceryl aminobenzoate, homosalate, lawsone with dihydroxyacetone, menthyl anthranilate, octocrylene, octyl methoxycinnamate, octyl salicylate, phenylbenzimidazole sulfonic acid, red petrolatum, sulisobenzone, and trolamine salicylate are proposed in Category I. However, should interested parties fail to provide necessary information so that appropriate standards may be established, these ingredients will not be included in the final monograph. The same standards should also be developed for any Category II or III ingredients for which data are submitted for inclusion in the final monograph.

Reference

(1) "United States Pharmacopeia XXII—National Formulary XVII," United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 63, 312, 455, 986, and 1380, 1989.

51. The agency has determined that the medical literature supports the Panel's conclusion that overexposure to sunlight/UV radiation is related to skin cancer and premature aging of the skin. (See comments 46 and 56.) The Panel recognized the epidemiological evidence that skin cancer and degenerative skin changes (elastotic degeneration), referred to as premature aging of the skin, are related to chronic exposure to the UV radiation from the sun (43 FR 38206 at 38211 and 38212). This damage is cumulative, and many years may pass before skin changes appear.

The agency notes that premature aging of the skin caused by excessive exposure to the sun is a distinct process very different from normal chronologic or intrinsic aging of the skin. Some of the differences observed between photoaged skin and chronologically aged skin were discussed in a 1986 review article (Ref. 1). For example, photoaged skin displays massive quantities of elastic fibers that degenerate into an amorphous mass while normally aged skin displays a slightly increased, but almost normal, amount of elastic tissue. Although, the dermis of photoaged skin becomes thicker than normal, the dermis of normally aged skin becomes thinner. Photoaged skin contains an increased number of hyperactive fibroblasts, an increased number of mast cells, and a mixed inflammatory infiltrate. In normally aged skin, the fibroblasts are decreased in number and inactive, the mast cells are decreased in number, and there is no inflammation. The agency emphasizes that the use of sunscreens has no effect on the normal process of aging, either aging of the skin or of the entire body.

The Panel noted that dermatologists routinely instruct their patients who have skin cancer on sun-exposed areas to wear long sleeves and a wide-brim hat, to avoid sun exposure between 10 a.m. and 2 p.m. solar time, and to use a sunscreen liberally every day (43 FR 38206 at 38212). The reason that most physicians recommend sunscreens for skin cancer patients is to reduce the risk of skin cancer that may not appear for 10 to 20 years, resulting from current exposure to the sun. It is not intended that the use of sunscreens will heal damage resulting from sun exposure that occurred years earlier.

The agency recognizes that many consumers could benefit from protection against everyday chronic exposure to UV radiation in addition to obtaining protection against periodic, acute exposure such as is encountered at the beach. For example, daily protection from exposure to UV radiation could be useful for many outdoor workers (e.g., construction workers, traffic policemen) and other persons involved in long-term outdoor activities. These individuals would require the most frequent sunscreen application. In addition, individuals who jog, play tennis, walk, drive, or garden may also need protection from UV radiation exposure. The AAD notes that 90 percent of all skin cancers occur on parts of the body that are unprotected by clothing. Farmers, outdoor workers, sports enthusiasts, and others who by choice or necessity spend numerous hours in the sun are likely candidates for leathery complexions and solar keratoses (Ref. 2). The AAD recommends that for optimal protection against developing skin cancer, people should avoid constant overexposure to the sun from infancy through adulthood. By selecting appropriate clothing and applying the proper sunscreens, persons can enjoy outdoor activities in the sunshine while still maintaining healthy and attractive skin throughout life.

The agency is unaware of specific data demonstrating a need for protection from UV light generated indoors, such as in an office building. Most scientific sources, including an NIH Consensus Development Conference (Ref. 3), have concluded that daily sun protection is needed for routine outdoor exposure but have not made recommendations regarding the need for protection indoors. A statement issued by the NIH Consensus Development Conference (Ref. 3) recognizes that unshielded fluorescent bulbs used for illumination are a potential source of artificial UV radiation. An unresolved issue is the amount of UVA emitted by such sources and the long-term effects of this exposure. More research on indoor sources of radiation is needed to identify possible problems. In the absence of definitive data, the AAD provides no recommendations on the use of sunscreens indoors. The agency invites comments, data, and information on the usefulness of sunscreens indoors.

Because of the documented importance and value of sunscreen drug products for many consumers, the agency concludes that the marketing of sunscreen drug products for daily use is beneficial, provided the products are appropriately labeled. Therefore, in this tentative final monograph, the agency is proposing labeling that is appropriate for daily use (nonbeach products) as well as for products that are intended for occasional use where intense sun exposure is likely to occur (beach products). (See comment 52.)

The Panel's recommended monograph included the following two indications for all sunscreen drug products: (1) "Over-exposure to the sun may lead to premature aging of the skin and skin cancer. The liberal and regular use over the years of this product may help reduce the chance of these harmful effects," and (2) "Overexposure to the sun may lead to premature aging of the skin and skin cancer. The liberal and regular use over the years of this product may help reduce the chance of premature aging of the skin and skin cancer."

The Panel recommended these indications because it (1) believed that overexposure to sunlight/UV radiation is related to skin cancer and premature aging of the skin and (2) the regular use of sunscreens will reduce consumers' risk of these adverse effects (43 FR 38206 at 38210 and 38211).

The agency agrees that it is important that consumers be alerted to the risks of premature aging and skin cancer that may result from overexposure to the sun. The agency believes that including such information on all sunscreen drug

products would be an effective means of educating the public to use sunscreens to minimize the detrimental effects of long-term exposure to the sun. Therefore, because of the seriousness of these adverse effects, the agency is proposing not to include the statement as an optional indication but rather as a required statement in the labeling of all sunscreen drug products. The agency is proposing a different statement than that recommended by the Panel, however, because it believes that this statement will better alert and inform consumers that the sun may damage the skin and that using sunscreens may help to reduce the risk of damage. This statement is proposed in § 352.52(e)(6) of this tentative final monograph under the heading "SUN ALERT" as follows: "The sun causes skin damage. Regular use of sunscreens over the years may reduce the chance of skin aging, some types of skin cancer, and other harmful effects due to the sun." (See comment 56.)

It is very important that the labeling of sunscreen drug products convey accurate information to consumers and that consumers are not misled. The agency believes that any labeling on sunscreen drug products that refers to skin aging or skin cancer should not be taken out of context, and that the labeling should directly relate the skin aging or skin cancer as being due to sun exposure. Labeling that does not directly relate these adverse effects as being due to sun exposure is misleading. Therefore, in § 352.52(e)(7) of this tentative final monograph, the agency is proposing the following: "Any variation of the statement in § 352.52(e)(6) that does not relate skin aging or skin cancer as being "due to the sun" will cause the product to be misbranded under section 502 of the act (21 U.S.C. 352)." The agency will evaluate claims made on OTC sunscreen drug product labels on a product-by-product basis, under section 502 of the act (21 U.S.C. 352), to determine whether those claims are false or misleading.

For examples of acceptable and unacceptable labeling, (see section II.B.52 and 53—*Summary of Agency Changes* of this document.

References

(1) Kligman, L. H., and A. M. Kligman, "The Nature of Photoaging: Its Prevention and Repair," *Photodermatology* 3:215–227, 1986.

(2) "Cancer of the Skin," edited by the Task Force on Pamphlets, American Academy of Dermatology, Evanston, IL, 1986.

(3) "Sunlight, Ultraviolet Radiation, and the Skin," National Institutes of Health Consensus Development Conference Statement, Vol. 7, Number 8. May 8–10, 1989.

52. The agency is aware that most manufacturers of sunscreen skin care products have recognized that the specific term "anti-aging" or similar absolute terms are not appropriate for use in labeling of either an OTC drug or cosmetic product. At the agency's urging, the majority of manufacturers are not currently using such terms on products containing Category I sunscreen ingredients.

The agency issued a number of regulatory letters (Ref. 1) to companies marketing skin creams and lotions with therapeutic labeling claims. None of the products were marketed or promoted as beach products. Most of the products did not contain sunscreens and were marketed as facial creams with claims such as the following: "anti-aging total skin supplement," "anti-age daytime skin treatment," "reverses signs of facial aging," "prevent, postpone, and minimize the effects of the aging process," "recreate the structure of a youthful skin," "helps to rebuild the intercellular structure of your skin," and "cause cells to divide and reproduce faster." However, some of the products contained sunscreen ingredients and, in addition to anti-aging claims similar to those described above, displayed claims such as "enhanced with two sunscreens: Filters for UVA and UVB," "helps prevent lines and wrinkles by guarding against UV damage," "special UVA and UVB screening agents help prevent permanent tissue damage caused by sun exposure * * * designed to shield the skin against the specific factors that accelerate the signs of aging," and "filters out damaging UV light rays."

In its regulatory letters, the agency pointed out that such claims represent and suggest (1) that the product is intended to affect the structure and function of the human body and (2) that the product is adequate and effective for such uses as recreating the structure of young skin, rebuilding the intercellular network of skin, and other claims. The agency stated that such claims cause the product to be regarded as a drug as defined in section 201(g) of the act (21 U.S.C. 321(g)). The agency also stated that because it was unaware of any substantial scientific evidence that demonstrated that the products were generally recognized as safe and effective for their intended uses, these products were "new drugs" within the meaning of section 201(p) of the act (21 U.S.C. 321(p)). In addition, many of the products that contained sunscreen ingredients were not labeled with adequate directions for use. Moreover, some products contained a purported sunscreen ingredient that was not generally recognized as safe and effective for its intended use and were, therefore, unapproved new drugs.

One regulatory letter was sent to a company that marketed a product, "ANTI-AGING COMPLEX," that contained a sunscreen among other ingredients. According to the letter (Ref. 2), the labeling of the product stated or suggested that the product minimizes the aging effects that can result from ultraviolet rays, aids maturing skin while new cells rise to the surface through a special balance of skin cell protectors, and helps the skin hold vital moisture deep within the epidermis. The agency stated that these claims cause the product to be a drug, and that, because the drug is not generally recognized as safe and effective for its intended use, the product is a new drug. In a written response to the agency (Ref. 3), the company insisted that it had consistently labeled the product as an OTC drug/cosmetic in compliance with the act and the proposed rule for OTC sunscreen drug products. The company stated that the use of the name "Anti-Aging" for its product is not false or misleading because, when taken in the context of the claims, indications, and declaration of active ingredients, the terms clearly demonstrate that the product is intended to minimize the visible signs of aging associated with incidental sun exposure. According to the company, the product's labeling included the following claims, among others: (1) "With proper care and protection, it is possible to moderate the influence of environmental factors, helping to minimize the visible signs of aging," (2) "Minimizes the aging effects which can result from incidental sun exposure during everyday activities," and (3) "A unique formula that contains ingredients designed to shield your skin against specific factors that accelerate the signs of aging." As support for such claims, the manufacturer pointed to the indications proposed by the Topical Analgesic Panel in § 350.50 (b)(iv) and (b)(v) of its recommended monograph for OTC sunscreen drug products (e.g., "Overexposure to the sun may lead to premature aging of the skin and skin cancer. The liberal and regular use over the years of this product may help reduce the chance of these harmful effects." See 43 FR 38206 at 38267.) The company added that although its claims do not follow the language of the monograph verbatim, they are consistent with the language in the monograph and that consistency is all

that is required under the agency's OTC labeling "flexibility policy."

Another regulatory letter (Ref. 4) was issued regarding "AGE-LESS ANTI-AGING DAILY FACE CAPSULES." The letter cited labeling statements such as the following: "AGE-LESS ANTI-AGING DAILY FACE CAPSULES * * * HELPS PREVENT THE VISIBLE SIGNS OF AGING. Your skin starts aging from the very first day it's exposed to the environment. But this skin aging can be controlled. AGE-LESS is a highly effective protective complex. It filters out damaging UV light rays * * *." The agency stated that these claims suggest that the product is adequate and effective for such uses as preventing the visible signs of aging and controlling skin aging. The agency added that it was not aware of any substantial scientific evidence that demonstrates the safety and effectiveness of this product for its intended use, nor was it aware that this drug was generally recognized as safe and effective for its intended uses. In a reply letter (Ref. 5), the company stated that its products were labeled in accordance with the proposed monograph for OTC sunscreen drug products. The letter included a lengthy discussion regarding the value of incorporating a sunscreen into daily-use products. The company also submitted proposed new labeling as follows: "AGE-LESS Anti-Aging Daily Face Capsules with Sunscreen. Sunscreen may help prevent the premature aging of the skin caused by overexposure to the sun. SPF 4."

As mentioned above, much of the industry is not currently using such labeling information and has recognized that the specific term "anti-aging" is not appropriate. It should be further noted that the term "anti-aging" does not relate the aging in question to either skin or the sun. The agency objects to the use of that term in the labeling of OTC sunscreen drug products or any other topically applied OTC drug product. The agency is not aware of any scientific studies that establish the safety and effectiveness of a topically-applied OTC drug for the intended use of reversing or delaying the intrinsic aging process, as implied in the "anti-aging" labeling claim. There is no support for such a claim in the Panel's recommended monograph, which does not include the specific term "anti-aging" among its indications (43 FR 38206 at 38267 and 38268). The agency is not proposing the term "anti-aging" as an allowable labeling claim in this tentative final monograph. Therefore, any claim that includes the term "anti-aging" or any similar term is Category II.

The agency does not believe that "premature aging" of the skin should be defined as "wrinkling." Wrinkling is only a part of the process of premature aging of the skin from excessive exposure to UV radiation (Ref. 6). Wrinkling should not, therefore, be elevated to greater significance than other signs of premature skin photoaging. In addition to wrinkling, photoaged skin displays a variety of benign, premalignant and malignant neoplasms, accentuated skin furrows, sags and bags, and a leathery, nodular, yellow surface with telangiectatic (i.e., a vascular lesion formed by the dilation of a group of small blood vessels) traceries. The most drastic of these visible aspects reflect profound structural changes in the dermis.

The agency also objects to the use of the term "anti-aging" or similar terms (e.g., AGELESS) in the product names of OTC sunscreen drug products. As stated in 21 CFR 201.128, the intended use of a product may be evidenced by labeling claims, other oral or written statements, or other circumstances in the labeling or marketing indicating that the product is offered for a purpose for which it is neither labeled nor advertised. The agency considers a product's name to be an integral part of the labeling of the drug. A drug product's intended use can be inferred from the product's name. The agency believes that use of the term "anti-aging," or equivalent language, in a sunscreen drug product's name could lead consumers to assume that the product will protect against chronological aging, a use for which the product is not labeled and is not generally recognized as safe and effective. The agency considers such terms in a sunscreen product's name to be inappropriate and misleading.

The agency is aware that the phrase "photoaging of the skin" has been used in the labeling of sunscreen drug products as an alternative to the phrase "premature aging of the skin due to overexposure to the sun." Although the scientific community may equate the term "photoaging of the skin" with "premature aging of the skin," the agency is not aware of specific information demonstrating that the average consumer recognizes that the phrase "photoaging of the skin" refers to premature aging of the skin caused by sunlight. Therefore, in this tentative final monograph, the agency is requesting comment on whether "photoaging of the skin" is an appropriate alternative phrase for the phrase "skin aging due to the sun."

In order to provide guidance regarding alternative language for claims pertinent to skin aging due to the sun, the agency is providing in this document some examples of acceptable and unacceptable language that may appear on sunscreen drug products. Acceptable language clearly links the effect (i.e., skin aging) with the cause (i.e., the sun or ultraviolet radiation). Examples of some acceptable language regarding premature aging of the skin include the following:

(1) "Sunscreen may reduce the chance of skin aging caused by exposure to the sun."

(2) "While biological aging is inevitable, sunscreen may help protect skin from aging caused by exposure to ultraviolet radiation from the sun."

(3) "Skin can age prematurely from exposure to the sun. Sunscreen may help reduce the chance of this type of aging."

(4) "May help inhibit the signs of skin aging caused by exposure to ultraviolet rays from the sun."

Sunscreen labeling relating to skin aging caused by the sun that does not clearly link the cause to the effect is unacceptable. The agency considers the following examples pertaining to premature aging of the skin unacceptable:

(1) Statements that include only the term "anti-aging." As discussed above, the agency does not believe that the term "anti-aging" by itself is adequate language to describe the action of a sunscreen drug product and is in fact misleading.

(2) "Helps prevent lines and wrinkles by guarding against UV damage." As discussed above, "premature aging of the skin" cannot be defined as "wrinkling" or "lines" because wrinkling is only a part of the process of premature aging of the skin and should not be elevated to greater significance than other signs of premature skin photoaging.

(3) Statements including terms such as stops, reverses, or reduces the signs of aging. These statements make no reference to premature aging of the skin or that such aging is due to the sun. The agency is not aware of any data showing that the use of a sunscreen stops, reverses, or reduces the signs of aging.

(4) "Helps to minimize the visible signs of aging," when used in conjunction with a sunscreen ingredient. This statement makes no reference to aging of the skin or that the skin aging is due to the sun. As noted above in (3), the agency is not aware of any data showing that the use of a sunscreen has any affect on aging.

(5) "Prevent (or reduce) skin aging caused by exposure to ultraviolet rays." The agency objects to the absolute term "Prevent (or reduce)" used in this claim

The statement proposed in § 352.52(e)(6) of this tentative final monograph is a qualified statement that use of a sunscreen drug product "may reduce the chance of * * *" adverse effects of the sun. The agency concludes that a qualified statement is appropriate, and that the use of absolute terms such as "prevent" is not justified in the labeling of sunscreen drug products.

(6) "Reverses aging of the skin caused by exposure to the sun." The agency is aware of some investigations showing that sunscreens can promote the repair of UV radiation-induced dermal damage (Refs. 6 and 7). However, these results are not conclusive. Therefore, at the present time the use of such claims on sunscreen drug products would be premature.

The agency invites comments on these and any other related statements that might be used in the labeling of OTC sunscreen drug products.

References

(1) Letters from D. L. Michels, FDA, to L. Lauder, Estee Lauder; I. Alfin, Alfin Fragrances, Inc.; H. B. Waldron, Avon Products, Inc.; J. Correze, Cosmair, Inc.; W. Slater, Christian Dior Perfumes, Inc.; A. Philip, Shiseido Co., Ltd.; P. Rogers, Clarins, USA Inc.; F. Borghese, Orlane/Caron Group; A. Arpel, Adrian Arpel; M. Huber, Max Huber Research Labs, Inc.; R. Perelman, Germaine Monteil Cosmetiques Corp.; J. F. Ronchetti, Elizabeth Arden, Inc.; R. Stephens, Princess Marcella Borghese, Inc.; C. D'Alessio, Chanel, Inc.; I. Forsythe, Jacqueline Cochran la prairie; J. Correze, Biotherm (Division of Cosmair, Inc.); T. Munchak, Frances Denney, Inc.; M. Lowenthal, Almay, Inc.; P. Berge, Charles of the Ritz; R. Baliatico, Prince Matchabelli Inc.; J. Light, Jason Natural Cosmetics; R. Perry, Rachel Perry, Inc.; and J. Harmon, Coty Division of Pfizer, in OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

(2) Letter from G. E. Vince, FDA, to R. R. Rogers, Mary Kay Cosmetics, Inc., dated February 12, 1990, in OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

(3) Letter from T. R. Tunnell, Mary Kay Cosmetics, to D. L. Graham, FDA, dated March 7, 1990, in OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

(4) Letter from J. J. Faline, FDA, to R. Perelman, Revlon, Inc., dated September 28, 1988, in OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

(5) Letter from A. J. Lorman, for Revlon, Inc., to I. Flaum, FDA, dated October 27, 1988, in OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

(6) Kligman, L. H., and A. M. Kligman, "The Nature of Photoaging: Its Prevention and Repair," *Photodermatology*, 3:215–227, 1986.

(7) Kligman, L. H., et al., "Sunscreens Promote Repair of Ultraviolet Radiation-Induced Dermal Damage," *The Journal of Investigative Dermatology*, 81:98–102, 1983.

53. Skin cancer is a serious concern to all consumers. According to the American Cancer Society, more than 600,000 people were diagnosed with basal-cell and squamous cell carcinomas in 1990, up from 400,000 in 1980. In addition, 35,000 more people were diagnosed with melanoma in 1990 (Ref. 1). Because of the seriousness of skin cancer, the agency believes that sunscreen drug product labeling related to skin cancer should be especially limited and carefully stated. It is very important that the labeling of sunscreen drug products not include any phrases or terms that may induce a false sense of security in sunscreen users.

Although there is extensive epidemiological evidence supporting the direct role that UV radiation plays in basal cell and squamous cell carcinomas, the relationship between UV radiation exposure and melanoma is not as clear (Ref. 2). As noted in comment 56, the labeling statement proposed by the agency in § 352.52(e)(6) of this tentative final monograph takes into account the likelihood that all skin cancers may not be correlated to UV radiation exposure. This labeling information states that "Regular use of sunscreens * * * may reduce the chance of * * * some types of skin cancer * * * due to the sun."

In addition, skin cancer is a long-term consequence of exposure to UV radiation. It normally manifests itself several years after the causative UV radiation exposure. Using a sunscreen now does not protect consumers against the development of a skin cancer that was initiated by UV exposure that occurred 20 or 30 years ago.

The agency is aware of at least one product, SKIN CANCER GARDE, that displays labeling that emphasizes the product's purported effectiveness in preventing skin cancer (Ref. 3). The product displays labeling statements such as: (1) Skin Cancer Garde" in which the word "skin" is substantially smaller and less distinct than the words "Cancer Garde," and (2) "Many skin cancers may be avoided by taking adequate precaution against excessive sun exposure."

The agency considers the use of the term "Cancer Garde" in the labeling of the product "SKIN CANCER GARDE" misleading. It is an overly positive statement that may lead consumers to assume that use of the product will absolutely prevent skin cancer, when such is not necessarily the case. The proposed statement related to premature aging of the skin and skin cancer proposed by the agency in this tentative final monograph is qualified, i.e., "may reduce the chance of * * * skin cancer," and any skin cancer prevention language that is displayed in the labeling of sunscreen drug products should reflect the tentativeness of the FDA approved labeling. Such language should also clearly relate the skin cancer to exposure to the sun or ultraviolet rays.

The agency believes that the following claims are examples of acceptable labeling pertaining to skin cancer for sunscreen drug products:

(1) "May reduce the chance of some kinds of skin cancers caused by exposure to the sun that would otherwise appear 20 years from now."

(2) "Regular, everyday use of this product from childhood on, may reduce the chance of some types of skin cancers caused by exposure to the sun".

These statements accurately reflect the intent of the "premature aging/cancer" statement proposed by the agency in this tentative final monograph. The agency believes that this is important information that should be provided to consumers; however, the information must be stated in such a manner so that consumers are not mislead to believe that the product will provide more protection than it actually does.

The agency considers the following claims as examples of unacceptable labeling pertaining to skin cancer:

(1) "Cancer Garde" or "Cancer Guard" as the name of a product.

(2) "Prevents skin cancer that may result from exposure to the sun".

As discussed above, the agency considers such labeling to be misleading because consumers may be led to believe that use of the product will absolutely prevent cancer, when such is not the case.

The agency invites comments on these and any other related statements that might be used in the labeling of OTC sunscreen drug products.

References

(1) Greeley, A., "No Safe Tan," *in* FDA Consumer, May, 1991, pp. 16–21.

(2) "Sunlight, Ultraviolet Radiation, and the Skin," National Institutes of Health Consensus Development Conference Statement, Vol. 7, Number 8, May 8–10, 1989.

(3) OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

IV. Recent Developments

A. Padimate O Safety Concerns

In the advance notice of proposed rulemaking for OTC sunscreen drug products, the Topical Analgesic Panel recommended that 21 ingredients, including padimate O, be generally recognized as safe and effective for use

in OTC sunscreen drug products. Padimate O is octyl dimethyl aminobenzoic acid ester. In evaluating the safety of padimate O, the Panel reviewed animal and human toxicological data that included oral LD_{50} results, primary irritation and sensitization studies, and eye irritation studies (43 FR 38206 at 38244). However, the Panel did not review any mutagenicity or carcinogenicity data for padimate O or for any other sunscreen ingredient.

Recently, FDA identified a new nitrosamine contaminant isolated from sunscreen drug products that contain the ingredient padimate O. Chou, Yates, and Wenninger (Ref. 1) developed a method for the identification and determination of this new nitrosamine, N-methyl-N-nitrosoaminobenzoate octyl ester (NMPABAO), chemically known as 2-ethylhexyl 4-(N-methyl-N-nitrosamino) benzoate. They used this method to analyze 17 commercially available sunscreen drug products containing padimate O and demonstrated that 14 of the products contained NMPABAO at levels ranging from 60 to 1,960 parts per billion (ppb). The presence of NMPABAO in all samples with more than 1,000 ppb was confirmed by mass spectroscopy.

Three discreet problems arose as a result of discovering the NMPABAO contamination of padimate O-containing sunscreen drug products: (1) Because NMPABAO was a new nitrosamine, its mutagenic and carcinogenic potential was unknown, (2) many questions were raised regarding the validity of the analytical methods used by the agency to isolate the nitrosamine, and (3) the photostability of NMPABAO was not known.

1. Toxicological Data

An unpublished report describing the results from an Ames test of NMPABAO was submitted to the agency (Ref. 2). The results of this test were purported to indicate that NMPABAO might be mutagenic. The agency is also aware of unpublished studies examining NMPABAO for mutagenicity in tests using *Salmonella typhimurium* (Ref. 3) and mouse lymphoma cells (Ref. 4). The results of another study were submitted to the agency in which the carcinogenic potential of NMPABAO was tested by measuring unscheduled desoxyribonucleic acid (DNA) synthesis (UDS) in the Rat Hepatocyte Primary Culture/DNA Repair Assay (Ref. 5). The agency has also tested NMPABAO and padimate O using the same assay (Ref. 6).

In the unpublished report describing positive results from an Ames test (Ref. 2), an ingredient purported to be NMPABAO was tested with two Salmonella strains (*Salmonella typhimurium* TA 100 and TA 1535) with and without in vitro metabolic activation by Aroclor-induced rat liver S–9 preparation. Doses ranged from 0.5 to 50 micromoles (µmoles) per plate in the presence of the metabolic activation system. The data for the experiments without metabolic activation are from strain TA 1535 only, and doses ranged from 1 to 50 µmoles per plate. Concurrent solvent and positive controls were performed with each experiment.

No increase in mutant counts was seen in strain TA 1535 in the absence of metabolic activation. In the presence of metabolic activation, increases in mutant counts occurred at doses of 10 µmoles per plate and higher, and these increases were dose related up to the 50 µmole maximum dose. In strain TA 100, in the presence of metabolic activation, increases exceeded a doubling of the spontaneous count at doses of 1 µmole per plate and higher. These increases were dose related up to the 50 µmole maximum dose. This indicates that the test sample used is mutagenic, but that its mutagenic activity is not very strong in the assay as performed. Impurities in the sample could account for the mutagenic activity at this dose and at higher doses.

The methodology used for these experiments is not explained in any detail, and the report contained no information on the purity of the compound. For example, the amount of S–9 used per plate is not given. The report does not state whether a plate incubation protocol or a preincubation protocol was used. The report states that the positive responses seen exceed those seen with the well-known carcinogen dimethylnitrosamine (DMN). The agency notes that DMN is generally considered to be a very weak mutagen and gives a positive response only under proper conditions in the *S. typhimurium* mutagenicity assay.

The report on this Salmonella assay (Ref. 2) states that interpretation of these results should include the following considerations: (1) Metabolic activation in this assay was provided by liver enzymes, and, therefore, the results cannot be extrapolated to assume that skin enzymes would also activate this compound to a mutagenic form, (2) the results obtained with rat enzymes cannot be extrapolated to human enzymes; and (3) the report noted that mutagenic activity does not imply carcinogenic activity.

The agency points out that there are a number of nitrosamines that give very weak responses in the standard plate incorporation Salmonella assay. The mutagenicity of such compounds can often be better detected by using a preincubation protocol or by using Syrian golden hamster S–9 rather than rat S–9 for the metabolic activation system.

In another study (Ref. 3), other investigators were unable to duplicate the positive results described in the above assay (Ref. 2). NMPABAO and a structurally related positive control, N-nitrosopiperdine, were tested for mutagenicity in the *S. typhimurium* assay (Ref. 3). The two compounds were initially tested in the Salmonella plate incorporation assay using dimethyl sulfoxide (DMSO) as the solvent. NMPABAO was negative with all five Salmonella tester strains without metabolic activation and with liver S–9 preparations from Fischer 344 rats and Syrian golden hamsters. In contrast, N-nitrosopiperdine induced positive responses in tester strains TA 98 and TA 100 but only in the presence of hamster S–9.

Because it has been reported that neither the plate incorporation assay nor the use of DMSO may be the optimal conditions for expression of a mutagenic response for some nitrosamines, the compounds were retested with *Salmonella* using a preincubation procedure and acetone as the solvent. Under these conditions, the results were the same with NMPABAO as those obtained in the plate incorporation assay. There were no increases in the number of revertants in any of the five tester strains. With N-nitrosopiperidine, dose-related responses were obtained with TA 98, TA 100, and TA 1535, in the presence of hamster S–9. The investigators concluded that NMPABAO is not mutagenic in *S. typhimurium*.

NMPABAO and two positive control chemicals, 3-methylcholanthrene (MCA) and ethyl methanesulfonate (EMS), were tested in the mouse lymphoma (L5178Y) mutagenesis assay (Ref. 4). NMPABAO was negative with and without Aroclor-induced rat liver S–9 metabolic activation using either DMSO or acetone as the solvent. In contrast, the direct-acting mutagens, EMS and MCA, in the presence of rat liver S–9, induced mutations.

In another test for genotoxicity (Ref. 5), NMPABAO was tested for its ability to induce DNA repair in primary rat hepatocytes. The positive control in this test was 4-(methylnitrosoamino)-1-(pyridyl)-1-butanone (NNK). NMPABAO and the positive control, NNK, were examined at three concentrations: 10^{-2}, 10^{-3}, and 5×10^{-3} moles (*M*). NMPABAO showed no apparent

induction of UDS at all test concentrations. In contrast, the positive control, NNK, showed significant and dose-dependant induction of UDS at 10^{-2} and 5×10^{-3} *M*.

Although the results of this assay were negative, indicating that NMPABAO is not genotoxic, the agency notes that there were several problems in the performance of this test. Because all the slides in this experiment were not scored, the agency questions the suitability of the hepatocyte preparation. If cell attachment and survival are poor, a very potent inducer of UDS may score positive with only a few cells. However, a weak inducer of UDS may be missed. Because this report does not include data on cell survival (cell attachment or cytotoxicity), it is difficult to evaluate the cell status on UDS data alone.

A recently published consensus report on the Primary Rat Hepatocyte Assay for UDS (Ref. 7) states the need for three experiments per data point and an initial screening experiment for an assessment of cytotoxicity. Another report, by Swierenga, et al. (Ref. 8), also stresses the need for information on cytotoxicity.

In 1991, the agency tested both NMPABAO and padimate O for UDS in primary rat hepatocytes (Ref. 6). Two UDS experiments were performed. One experiment tested NMPABAO at dose levels ranging from 0.713 to 2.92 micrograms/milliliter (µg/mL), and the second tested padimate O at dose levels ranging from 0.010 to 10 microliters/milliliter (µl/mL). The controls were (1) a solvent control (1 percent DMSO), (2) a negative medium control, and (3) a positive control of 2-acetylaminofluorene (2–AAF) at 1.0 and 2.5 µg/mL.

Both NMPABAO and padimate O were soluble in DMSO. However, doses of 0.73, 1.46, and 2.92 mg/mL of NMPABAO and 1, 5, and 10 µl/mL of padimate O were insoluble when added to the aqueous cell culture medium. Heavy, oil-like droplets that dispersed evenly in the aqueous medium when vortexed were noted at the above doses of NMPABAO and padimate O. Although faint turbidity was observed at lower dose levels, no heavy oil droplets were apparent as were with the higher doses.

The data show that neither NMPABAO nor padimate O induced UDS in rat hepatocyte cultures. Values for both net nuclear grain count and percent cells in repair were similar to the negative control and solvent control values. In contrast, the positive control, 2–AAF, induced a dose dependent increase in net nuclear grain counts.

Cytotoxicity was qualitatively evaluated as cell number and morphology. Intermediate doses of NMPABAO (11.4 to 365 µg/mL) and padimate O (0.1 to 0.5 µl/mL) showed evidence of cytotoxicity compared to control values. Cytotoxicity was not observed at the lower doses of NMPABAO (0.71 to 5.7 µg/mL) or padimate O (0.01 to 0.05 µl/mL) nor at the higher doses of NMPABAO (730 to 2920 µg/mL) or padimate O (1 to 10 µl/mL). However, the heavy oil appearance of the test agents in media at these higher dose levels suggests that the compounds may not have reached the cells attached to the bottom of the culture dish. The agency, however, concludes that, in these experiments, neither NMPABAO nor padimate O appears to induce UDS at cytotoxic or non-cytotoxic dose levels.

The agency believes that the results of this study confirm the lack of solubility of NMPABAO at concentrations of 0.73 to 2.92 mg/mL and the moderate solubility of NMPABAO at concentrations of 182.5 and 365 µg/mL, thus explaining some of the questions raised by the results of the first DNA repair assay (Ref. 5) discussed above. Furthermore, cytotoxicity was evident in hepatocyte cultures between 11.4 and 365 µg/mL NMPABAO, which suggests that NMPABAO reached the cells at the bottom of the culture dish at these dose levels. NMPABAO and padimate O do not appear to damage DNA, as evaluated by the DNA repair assay, at non-toxic doses when the chemical is soluble in the medium, at cytotoxic doses when the chemical is both soluble and partially soluble in the medium, and at non-cytotoxic doses when the chemical is insoluble in the medium.

The structure-activity relationships in carcinogenesis by N-nitroso compounds have been reviewed (Ref. 9). Some 250 N-nitroso compounds have been studied in rats, and many have been studied in mice and hamsters, to provide reliable carcinogenesis data. The similar carcinogenic actions of certain groups of N-nitroso compounds can be related to their generation of similar simple moieties having certain organs as their target.

Although NMPABAO has not been tested in an animal bioassay for carcinogenesis, certain predictions can be made based on its chemical structure. Most nitrosamines that are carboxylic acids or esters are not carcinogenic, probably due primarily to their being ionized (esters are likely to be hydrolyzed), which prevents their entry into cells; and also possibly because of electronic effects (Ref. 9). For example, N-nitrosopiperdine (which is structurally related to NMPABAO) produces tumors of the nasal mucosa, esophagus, and liver of the rat. An esterified derivative, α-phenyl-2-piperidinacetic acid methyl ester, tested negative for carcinogenesis in the rat. Based on this correlation, esterification of a carcinogenic nitrosamine greatly reduces or eliminates the carcinogenic potential of the compound. Chemically, NMPABAO is an ester of a carboxylic acid and, based on its chemical structure, would not be predicted to be carcinogenic in an animal bioassay.

2. Analytical Methods

The agency informed industry trade associations of this potential problem and a need for immediate examination in letters dated July 25, 1989, to the CTFA (Ref. 10) and the NDMA (Ref. 11). In those letters, the agency stated that it intended to reopen the administrative record for OTC sunscreen drug products for the submission of information and data regarding (1) the presence of nitrosamine contaminates in padimate O and other sunscreen ingredients with a related chemical structure and (2) the effect such contaminants may have on the safety of these ingredients. After those letters were issued, it became apparent that this problem was more complex than originally thought and that it could not be resolved immediately. Because industry and the agency began addressing this problem quickly, the agency determined that it was not necessary to reopen the administrative record for the rulemaking for OTC sunscreen drug products prior to the publication of this tentative final monograph.

After these letters were sent to CTFA and NDMA, a comment was submitted to the agency (Ref. 12) asserting that the FDA assay method for nitrosamines is inappropriate for sunscreen-containing drug products. The comment stated that this method actually creates conditions for artifact nitrosation to occur during the sample preparation phase. The comment submitted a proposed alternative assay method for determining trace levels of NMPABAO in commercial sunscreens. The comment asserted that the design of its method overcomes potential artifact nitrosation. The assay method proposed by the comment utilizes a HPLC/Thermal Energy Analyzer. The comment maintained that its method avoids the technical pitfalls of the FDA method (1) by using hexane in place of dichloromethane as the extracting solvent and (2) by not using extraneou. quenching agents, such as ammonium sulfamate. Stating that its method is simple, direct, and does not involve

"foreign" reagents, the comment added that the method demonstrates excellent recovery of NMPABAO from spiked samples. The comment added that, in limited trials, recovery of NMPABAO from spiked samples has been demonstrated to be up to 90 percent depending upon the complexity of the sample being assayed. The comment maintained that, conversely, one sample assayed by the FDA method showed approximately 1,500 ppb of NMPABAO. However, the same sample showed less than 20 ppb (lowest detectable limit) of NMPABAO when assayed by the comment's proposed HPLC/Thermal Energy Analyzer method. The comment maintained that this discrepancy is further evidence that the FDA method generates artifact nitrosamines.

The agency recently received new data (Ref. 13) purporting to verify the validity of the alternative assay method proposed by the comment (Ref. 12). A series of experiments were undertaken by two independent laboratories. These experiments included studies to establish the linearity of the HPLC-Thermal Energy Analyzer detector response, to measure the original background levels of NMPABAO in the lotion, to determine the recovery and reproducibility of NMPABAO from spiked lotion, and to ascertain if the method itself promotes artifactual formation of NMPABAO. Both laboratories used the same SPF 15 sunscreen lotion containing 8 percent padimate O and the same batch of purified NMPABAO. The results obtained by both laboratories agree well and demonstrate that the proposed alternative method can be performed by analysts in different laboratories to yield reproducible and accurate determinations of NMPABAO in commercial sunscreen drug products. The data demonstrate that the method is applicable to all vehicle systems evaluated thus far, including lotions, creams, gels, and oils. The results show a minimum detectable limit of approximately 30 ppb by this procedure, NMPABAO recovery of greater than 80 percent, and high reproducibility. The results demonstrate that the procedure does not generate NMPABAO artificially during the sample preparation.

The proposed alternative assay method was used by one of the laboratories to evaluate 22 randomly selected commercial sunscreen drug products for NMPABAO levels. Four of these sunscreen drug products contained NMPABAO at levels higher than 100 ppb. The highest level of NMPABAO detected was 216 ppb.

The submission concluded that these studies, as well as the biological studies submitted to the agency (Ref. 5), indicate that the presence of NMPABAO in sunscreen drug products containing padimate O is not a public health concern. The submission contended that, when analyzed using a scientifically validated method, commercial sunscreen drug products appear to have insignificant levels of NMPABAO. The submission concluded that the results of these tests support the long history of padimate O as a safe and effective sunscreen ingredient.

The agency recently reevaluated its method for the identification and determination of NMPABAO (Ref. 14). Its reevaluation included recovery studies for NMPABAO from representative sunscreen drug products, as well as studies of possible chromatographic interference with NMPABAO and of the nitrosation potential of the test reagents. The tests also investigated, by use of inhibitors and a secondary amine marker, the occurrence of artifact nitrosation. The basic method used for detecting nitrosation potential of the sample preparation system involved the addition of a readily-nitrosatable secondary amine (marker) to the product prior to analysis. Detection of the nitrosated marker would suggest that one or more components of the system had the potential for causing artifact nitrosation during sample preparation.

The agency found that the solvents and reagents used in its procedure for assaying NMPABAO contained no compounds that would interfere with the HPLC/Thermal Energy Analyzer determination of NMPABAO. The studies also demonstrated that the presence of nitromusk fragrances in sunscreen drug products would not interfere with the HPLC/Thermal Energy Analyzer determination of NMPABAO. The evaluation of Celite for nitrosation potential demonstrated that some batches contained a nitrosating agent. Therefore, to avoid artifact nitrosation resulting from Celite used in this method, each batch of Celite must be tested for nitrosating potential before use. Results of these studies also showed that ammonium sulfamate, mixed tocopherols, ascorbyl palmitate, squalene, Volpo 5, and ammonium sulfamate mixed with Volpo 5 are not effective as nitrosation inhibitors in sunscreen matrices.

The agency method was corroborated by recovery studies in which a known quantity of NMPABAO and a known quantity of padimate O were added to a nitrosating agent-free sunscreen drug product that did not contain padimate O. The results of the recovery studies indicate that this analytical method adequately recovers NMPABAO from sunscreen matrixes.

In June 1990, the agency agreed to participate in a joint laboratory study to compare the recovery efficiency of its analytical method for NMPABAO and the proposed alternative method developed by a manufacturer of sunscreen drug products (Ref. 15). The agency recommended that the manufacturer prepare the samples for the study and submit them to FDA as "blind" samples. The manufacturer submitted to FDA four 50 gram (g) samples, in duplicate, fortified with NMPABAO at different levels. The manufacturer also provided duplicate 100 g blank lotions containing padimate O with no added NMPABAO for blank and artifact determinations, and a reference NMPABAO standard in isooctane. The manufacturer disclosed to FDA the NMPABAO fortification levels after the analyses were completed. The FDA method utilized a column chromatographic extraction of a sample-Celite mixture with organic solvents, concentration of the resulting eluate, and determination of NMPABAO by HPLC coupled to a Thermal Energy Analyzer (Ref. 16). The proposed alternative method involved partition of a sample with organic solvent, concentration of the extract, reconstitution in an organic solvent, centrifugation, and analysis by HPLC coupled to a Thermal Energy Analyzer (Ref. 13). Both methods utilized a nitrosation inhibitor to prevent artifactual formation of NMPABAO during sample analysis. The agency analyzed the test samples using both its and the proposed alternative methods. The manufacturer analyzed the samples by the proposed alternative method. The agency made two modifications to the proposed alternative method before analyzing samples: (1) A valve between the HPLC and the Thermal Energy Analyzer, specified in the proposed alternative method to divert the HPLC mobile phase from the Thermal Energy Analyzer, was omitted because it was not available in the FDA laboratory, and (2) a single HPLC column was used instead of the prescribed two-column system, because satisfactory separation of the components of interest could be obtained with one column.

Using its methodology for NMPABAO detection, the agency performed duplicate analyses of each sample and obtained good agreement between analyses of the same samples. The recovery of added NMPABAO using the FDA method ranged from 39 to 83

percent, with an overall average of 58 percent. The same samples were analyzed using the modified proposed alternative method. Recovery of added NMPABAO ranged from 56 to 93 percent, with an overall average of 77 percent. Using its own method, the manufacturer reported recoveries ranging from 79 to 100 percent, with an overall average of 86 percent. The agency concludes that NMPABAO was more efficiently recovered from the sunscreen matrix by the proposed alternative method than by the FDA method. Data obtained by the proposed alternative method in both laboratories were in good agreement throughout the entire NMPABAO fortification range.

The agency has determined that partial losses of NMPABAO by the FDA method occurred by premature elution of the N-nitrosamine during the petroleum ether wash of the silica gel column. Similar losses previously observed using the FDA method were found to be caused by inactivation of the silica gel by samples containing significant water levels. The FDA method was modified to improve recovery efficiency of NMPABAO from samples containing substantial amounts of water. Reanalysis of the sunscreen samples by the modified FDA method resulted in recoveries of NMPABAO ranging from 78 to 88 percent, with an average of 83 percent.

The agency concludes that the proposed alternative method, as modified by FDA, and the FDA method, modified to accommodate matrices with high levels of water, result in comparable recoveries of NMPABAO from a sunscreen drug product. Although the proposed alternative method provides the most accurate recoveries of NMPABAO, either method can successfully detect NMPABAO in sunscreen drug products without artifact formation.

3. Photostability Data

One comment submitted data (Ref. 13) that included the results of photostability studies of NMPABAO. The results show that NMPABAO, even in films containing UV absorbers, is extremely unstable when exposed to UV light. When added to sunscreen lotions of both low (SPF 4) and high (SPF 25) photoprotection levels, NMPABAO decomposed rapidly. After exposure to radiation for 1 minute, approximately 50 percent of the NMPABAO in the SPF 25 product and 80 percent of the NMPABAO in the SPF 4 product were degraded. After exposure for 4 minutes, the extent of NMPABAO decomposition was 91 percent for the SPF 25 product and 97 percent for the SPF 4 product.

The agency also conducted a study designed to investigate the photodecomposition of NMPABAO in a model system and in a commercial sunscreen drug product with an SPF of 15 (Ref. 17). The model system consisted of dimethyl silicone as the carrier base, approximately 3,000 ppb NMPABAO, and either 0 or 4 percent padimate O. The commercial sunscreen drug product contained padimate O and approximately 14,000 ppb NMPABAO. Samples of the model system and the sunscreen product were exposed to UV radiation from a high intensity solar simulator for periods of up to 60 minutes, with 1 minute of exposure being approximately equivalent to 0.2 MED. The samples were spread on glass plates as films of approximately 20 micrometer (μm) for the model system and approximately 150 μm for the commercial product. NMPABAO concentrations were determined by HPLC separation and Thermal Energy Analyzer detection before and after UV radiation exposure. NMPABAO in the model system was totally decomposed following exposure of 1 minute (i.e., radiation equivalent to approximately 0.2 MED) even in the presence of 4 percent padimate O. The decomposition of the NMPABAO in the commercial sample was found to follow first order reaction kinetics; the half-life was 2.6 minutes, i.e., approximately 0.5 MED. The results of this study indicate that NMPABAO decomposes upon exposure to UV radiation and corroborate the photodegradation results submitted to the agency (Ref. 13).

4. Conclusions

Two analytical methods with which NMPABAO contamination of OTC sunscreen drug products can be accurately determined are available: (1) The agency's method (Refs. 1 and 14), and (2) the method submitted by one of the comments (Ref. 12). Either method can successfully detect NMPABAO in OTC sunscreen drug products.

Regarding the safety concerns associated with the presence of NMPABAO in padimate O-containing sunscreen drug products, the agency notes that the toxicological data available to the agency at this time indicate that NMPABAO does not have mutagenic or carcinogenic potential. Although the agency does not contemplate additional toxicological testing at this time, it cannot be stated with certainty that NMPABAO is not carcinogenic. This can only be resolved by a carcinogenic bioassay. The agency is not planning any such studies nor is it aware of any such studies currently in progress. However, the agency believes that the risk associated with NMPABAO contamination of sunscreen drug products is very low. For example, in addition to low mutagenicity and carcinogenicity potential, photostability studies dome with NMPABAO demonstrate that the nitrosamine decomposes rapidly when exposed to UV radiation (Refs. 13 and 17).

The agency believes that padimate O, if formulated in a sunscreen drug product properly, is a safe and effective sunscreen ingredient. The presence of NMPABAO in padimate O-containing sunscreen drug products is the result of poor manufacturing practices, and demonstrates that the product has not been formulated properly. For example, the agency recently analyzed 25 commercially available sunscreens for NMPABAO (Ref. 18). NMPABAO was found in 11 samples at levels up to 21,020 ppb. Four of these samples also contained 2-bromo-2-nitro-1,3-propanediol, an indirect nitrosating agent. If these products were formulated without the nitrosating agent, there would be no nitrosamine contamination.

According to § 330.1(a), OTC sunscreen drug products must be manufactured in compliance with current good manufacturing practices, as established in 21 CFR Parts 210 and 211. The agency believes that the presence of NMPABAO in sunscreen drug products indicates that the product has not been manufactured under current good manufacturing practices, and therefore, the product is adulterated under section 501(a) of the act (21 U.S.C. 351(a)). The agency is considering establishing limits for the amount of NMPABAO that may be present in a sunscreen drug product. If these limits were surpassed, the product would be considered to be adulterated. Although not proposed in this tentative final monograph, the agency is including for comment a proposal that OTC sunscreen drug products must contain less than 500 ppb of NMPABAO.

As stated above, the agency believes that padimate O is a safe and effective OTC sunscreen ingredient. Therefore, in this tentative final monograph, padimate O remains in Category I.

References

(1) Chou, H. J., R. L. Yates, and J. A. Wenninger, "2-Ethylhexyl 4-(N-methyl-N-nitrosoamino) Benzoate in Commercial Sunscreen Preparations," Comment No. REF001, Docket No. 78N–0038, Dockets Management Branch.

(2) "Report on Testing of RH–III–30112–5–8 in the Ames Assay," OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

(3) "Summary of Mutagenicity Data for NPABAO," draft of an unpublished study, OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

(4) "Mouse Lymphoma Assay (L5178Y TK +/–)," draft of an unpublished study, OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

(5) Letter from D. Hoffman, America Health Foundation, to J. A. Wenninger, FDA, dated June 13, 1989, OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

(6) "Evaluation of 4-(Methylnitro-soamino) benzoic acid-2-ethylhexylester (MNBEHE) [also known as MNPABAO] and Padimate O by Autoradiographic Measurements of Unscheduled DNA Synthesis (UDS) in the Rat Hepatocyte Primary Culture/DNA Repair Test," draft of unpublished study, OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

(7) Butterworth, B. E., et al., "A Protocol and Guide for the In Vitro Rat Hepatocyte DNA/Repair Assay," *Mutation Research*, 189:113–121, 1987.

(8) Swierenga, S. H. H., et al., "Recommended Protocols Based on Survey of Current Practice in Genotoxicity Testing Laboratories: I. Unscheduled DNA Synthesis Assay in Rat Hepatocyte Cultures," *Mutation Research*, 246:235–253, 1991.

(9) Linjinsky, W., "Structure-activity Relations in Carcinogenesis by N-nitroso compounds," *Cancer and Metastasis Reviews*, 6:301–356, 1987.

(10) Letter from W. E. Gilbertson, FDA, to E. Kavanaugh, The Cosmetic, Toiletry and Fragrance Association, dated July 25, 1989, coded LET030 in Docket No. 78N–0038, Dockets Management Branch.

(11) Letter from W. E. Gilbertson, FDA, to J. Cope, Nonprescription Drug Manufacturers Association, dated July 25, 1989, coded LET029 in Docket No. 78N–0038, Dockets Management Branch.

(12) Letter from J. M. Clayton, Schering-Plough Corporation, to J. A. Wenninger, FDA, dated July 10, 1989, coded C100 in Docket No. 78N–0038, Dockets Management Branch.

(13) Letter from E. E. Kavanaugh, The Cosmetic, Toiletry and Fragrance Association, to W. E. Gilbertson, FDA, dated April 30, 1990, coded RPT4 in Docket No. 78N–0038, Dockets Management Branch.

(14) "Evaluation of the FDA Method for Determination of 2-Ethylhexyl-P-(N-Nitroso-N-Methylamino) Benzoate in Commercial Sunscreen Products," coded RPT3 in Docket No. 78N–0038, Dockets Management Branch.

(15) Letter from J. A. Wenninger, FDA, to J. M. Clayton, Schering-Plough Corporation, dated June 1, 1990, OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

(16) "Comparative Study of FDA's and Schering-Plough's Analytical Methods for the Determination of NMPABAO in Sunscreen Products," draft of unpublished study, OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

(17) "Study of the Photodecomposition of N-Nitroso-N-Methyl-p-Aminoben-zoic Acid Octyl Ester on Exposure to Ultraviolet Light," coded RPT3 in Docket No. 78N–0038, Dockets Management Branch.

(18) "Technical Plan Project Quarterly Report," draft of unpublished study, OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

B. Sunless Tanning/Tanning Accelerator Products

The agency is aware of several sunless tanning/tanning accelerator products that are available commercially (Ref. 1). These products include various ingredients that are purported to either: (1) Give the user the appearance of a tan by coloring the skin, or (2) accelerate the actual tanning process.

In the first case, the tanning effect is accomplished either by an externally applied dye such as dihydroxyacetone or by orally ingested carotenoid dyes (tanning pills) such as canthaxanthin. Products containing dihydroxyacetone rely upon a Schiff Base formation between dihydroxyacetone (or its glyceraldehyde tautomar) and amino or imino moieties associated with the keratin of the stratum corneum. These Schiff Bases then undergo condensation-polymerization reactions to yield dark-colored melanoidins (Ref. 2). Dihydroxyacetone is approved for use in externally applied drugs and cosmetics to impart color to the human body. (See 21 CFR 73.1150 and 73.2150.) Dihydroxyacetone may also be combined with lawsone as a Category I sunscreen ingredient in this tentative final monograph.

The Panel concluded that lawsone in conjunction with dihydroxyacetone is safe and effective for OTC use as a sunscreen. The Panel reviewed a marketed product composed of two lotions packaged together and labeled to be applied separately and in sequence. The Panel recommended that when the two ingredients are used separately and sequentially, the combination can be classified as Category I (43 FR 38206 at 38235). Each ingredient when used alone cannot be classified as a Category I sunscreen. The submitted data indicated that the two-solution product provides sunscreen protection which varies considerably among individuals, depending on such factors as susceptibility of the skin to fixing of the active ingredients, thickness of the keratin layer where the sunscreen resides, number of daily applications, degree of individual photosensitivity, and amount of UV radiation received (43 FR 38235). The Panel recommended Category I labeling for sunscreen active ingredients and the following warnings: (i) "This is a two lotion product. Do not mix the contents of the two solutions. Use both solutions, for use of one alone will not provide protection." (ii) "Use only on skin free of rash and abrasions." (iii) "May stain clothing when freshly applied."

Canthaxanthin, which has been used in tanning pills, enters the blood stream after ingestion and is partially deposited in skin tissue, giving the skin a tan-like color. Although this compound is approved for use at very low levels as a color additive in some foods and drugs (see 21 CFR 73.75 and 73.1075), it is not approved at any level for use in tanning pills to impart color to the human body. Tanning pills containing canthaxanthin or any other carotenoid additives are considered adulterated cosmetics and, consequently, may not be legally marketed. See, e.g., *U.S.* v. *Eight Unlabeled Cases of an Article of Cosmetic*, 888 F.2d 945 (2nd Cir. 1989). Some reports of adverse reactions associated with "tanning pills" have mentioned aplastic anemia, allergic reactions, stomach cramps, hepatitis, nausea, diarrhea, and deposition of the color in the retina of the eye (Refs. 3, 4, and 5).

In the case of acceleration, the tanning process is supposedly hastened by stimulating the production of melanin by ingredients such as tyrosine or tyrosine derivatives. These derivatives supposedly increase the substrate available for tyrosinase enzyme action. Tyrosinase is a key enzyme in melanogenesis (Ref. 6). The use of tyrosine is based upon the presumption that it penetrates the skin, increases the tyrosine content of the melanocytes, and thus enhances melanin formation. This effect has not been convincingly substantiated in the scientific literature. The agency notes that any product purporting to "accelerate the tanning process" or "stimulate the production of melanin" is claiming to affect the structure and function of the body and, therefore, is a drug. The agency is not aware of any data demonstrating that tyrosine or its derivatives are effective in stimulating the production of melanin. Thus, any product containing tyrosine or its derivatives and claiming to accelerate the tanning process is an unapproved new drug.

The agency is concerned about the health hazards associated with using products labeled for tanning purposes that do not contain sunscreen ingredients. The agency tentatively finds that the majority of consumers expect sunburn protection from suntanning products, whether the product contains a sunscreen ingredient or not. Because of the serious consequences of overexposure to the sun, the agency considers it important for consumers to know whether a suntanning product, including sunless tanning products, contains a sunscreen ingredient or not. Therefore, in conjunction with this tentative final

monograph, the agency is proposing to amend the cosmetic regulations in 21 CFR part 700 by adding § 740.19 as follows: "*Suntanning preparations.* The labeling of suntanning preparations that do not contain a sunscreen ingredient must display the following warning: Warning—This product does not contain a sunscreen and does not protect against sunburn."' This warning also applies to sunless tanning lotions.

References

(1) Memorandum from S. Milstein to J.E. Bailey, dated June 25, 1991, in OTC Vol. 06ATFM, Dockets Management Branch.

(2) "Artificial Suntan Preparations" *in* "Harry's Cosmeticology" in OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

(3) Fenner, L. "The Tanning Pill, a Questionable Inside Dye Job," in OTC Vol. 06ATFM, Docket No. 78N–0038, Dockets Management Branch.

(4) Rousseau, A., et al., "Canthazanthine Deposits in the Eye; *Journal of the American Academy of Dermatology,* 8:123–124, 1983.

(5) Bluhm, R., et al., "Aplastic Anemia Associated with Canthazanthin Ingested for 'Tanning Purposes,'" *Journal of the American Medical Association,* 264:1141–1142, 1990.

(6) Duggan, M., J. Wilmott, and A. Znaiden, Tyrosinase * * * The Enzyme Behind the Tan," *Cosmetics and Toiletries,* 102:97–101, 1987.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act (Pub. L. 96–354). Therefore, this sunscreen proposed rule, which applies only to a single drug category, does not require a regulatory impact analysis or a regulatory flexibility analysis.

The agency recognizes, however, that some products currently marketed by manufacturers as cosmetics would be affected by this rulemaking, e.g., suntanning products, and daily use make-up preparations and skin lotions that contain sunscreens or make drug claims. The presence of a sunscreen ingredient in such products and labeling that includes a drug claim would cause these products to be drugs under the act. While all affected firms are currently subject to general regulatory requirements under the act, some companies would be subject, for the first time, to current good manufacturing practices (CGMP) for drugs, as established in 21 CFR Parts 210 and 211. The agency has limited data but believes that most major manufacturers of sunscreen-containing products already follow these procedures and are familiar with agency regulations for manufacturing drug products. In addition, some states, including California and New York, regulate cosmetic products as drugs and conduct on-site inspections of manufacturing facilities.

Nonetheless, some clear differences exist between cosmetic and drug regulations. For example, current agency regulations allow for the voluntary registration of cosmetic manufacturers, while registration is compulsory for drug manufacturers. The agency attempts to inspect each drug manufacturer every two years, whereas cosmetic inspections are done less frequently. Therefore, many current cosmetic plants can expect more frequent inspection as drug manufacturers.

The agency has attempted to define the possible economic consequences of this proposal but has been hindered by the paucity of data concerning the manufacture of these products. The industry segment that currently manufacturers sunscreen-containing lipsticks, skin lotions, and make-up preparations that would be covered by this regulation would need either to: (1) Reformulate and/or relabel these products to eliminate sunscreen ingredients and omit drug claims, or (2) comply with drug regulations if they do not already do so. The agency will continue to gather economic information and solicit industry comment on the extent of any additional costs of compliance, or other regulatory burdens, that would be associated with this proposed rule.

In addition, the agency specifically invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC sunscreen drug products or on manufacturers who elect to reformulate or relabel their product(s) so that the products' status would continue to be cosmetics. Types of impact may include, but are not limited to, costs associated with product testing, relabeling, repackaging, reformulating, or costs related to conversion to drug manufacturing capabilities to meet CGMPs. Comments regarding the impact of this rulemaking should be accompanied by appropriate documentation. Because the agency has not previously invited specific comment on the economic impact of the OTC drug review on sunscreen drug products, a period of 180 days from the date of publication of this proposed rulemaking in the **Federal Register** will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined under 21 CFR 25.24(c)(6) 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.

Interested persons may, on or before November 8, 1993, submit to the Dockets Management Branch written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before November 8, 1993. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register.**

Interested persons, on or before May 12, 1994, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before July 12, 1994. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets

Management Branch. Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on July 12, 1994. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register**, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

List of Subjects in 21 CFR

Part 352

Labeling, Over-the-counter drugs, Sunscreen drug products.

Part 700

Cosmetics, Packaging and containers.

Part 740

Cosmetic product warning statements.

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 Chapter I be amended as follows:

1. Part 352 is added to read as follows:

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

Subpart A—General Provisions

Sec.

Subpart B—Active Ingredients

Subpart C—Labeling

Subpart D—Testing Procedures

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

Subpart A—General Provisions

§ 352.1 Scope.

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

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

§ 352.3 Definitions.

As used in this part: (a) *Minimal erythema dose (MED).* The smallest dose of ultraviolet (UV) radiation (expressed as Joules per meter squared) that produces redness reaching the borders of the exposure site.

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

(1) *Minimal sun protection product.* A sunscreen product that provides a sun protection factor (SPF) value of 2 to under 4, and offers the least protection, but permits suntanning.

(2) *Moderate sun protection product.* A sunscreen product that provides an SPF value of 4 to under 8, and offers moderate protection from sunburning, but permits some suntanning.

(3) *High sun protection product.* A sunscreen product that provides an SPF value of 8 to under 12, offers high protection from sunburning, and permits limited suntanning.

(4) *Very high sun protection product.* A sunscreen product that provides an SPF value of 12 to under 20, offers very high protection from sunburning, and permits little or no suntanning.

(5) *Ultra high sun protection product.* A sunscreen product that provides an SPF value of 20 to 30, offers the most protection from sunburning, and permits no suntanning.

(c) *Sunscreen active ingredient.* An active ingredient that absorbs at least 85 percent of the radiation in the UV range at wavelengths from 290 to 320 nanometers, but may or may not transmit radiation at wavelengths longer than 320 nanometers.

(d) *Sunscreen opaque sunblock.* An opaque sunscreen active ingredient that reflects or scatters all light in the UV and visible range at wavelengths from 290 to 777 nanometers and thereby prevents or minimizes suntan and sunburn.

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

Subpart B—Active Ingredients

§ 352.10 Sunscreen active ingredients.

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

(a) Aminobenzoic acid up to 15 percent.

(b) Cinoxate up to 3 percent.

(c) Diethanolamine methoxycinnamate up to 10 percent.

(d) Digalloyl trioleate up to 5 percent.

(e) Dioxybenzone up to 3 percent.

(f) Ethyl 4-[bis(hydroxypropyl)] aminobenzoate up to 5 percent.

(g) Glyceryl aminobenzoate up to 3 percent.

(h) Homosalate up to 15 percent.

(i) Lawsone up to 0.25 percent with dihydroxyacetone up to 3 percent.

(j) Menthyl anthranilate up to 5 percent.

(k) Octocrylene up to 10 percent.

(l) Octyl methoxycinnamate up to 7.5 percent.

(m) Octyl salicylate up to 5 percent.

(n) Oxybenzone up to 6 percent.

(o) Padimate 0 up to 8 percent.

(p) Phenylbenzimidazole sulfonic acid up to 4 percent.

(q) Red petrolatum up to 100 percent.

(r) Sulisobenzone up to 10 percent.

(s) Titanium dioxide up to 25 percent.

(t) Trolamine salicylate up to 12 percent.

§ 352.20 Permitted combinations of active ingredients.

(a) *Combinations of sunscreen active ingredients.*

(1) Two or more sunscreen active ingredients identified in § 352.10 may be combined when used in the concentrations established for each

ingredient in paragraph (a)(2) of this section and the finished product has a minimum sun protection factor value of not less than 2 as measured by the testing procedures established in subpart D of this part.

(2) Sunscreen active ingredients shall be used within the following concentrations when used in combination with another sunscreen or when the combination is used with any other permitted active ingredient:

(i) Aminobenzoic acid 5 to 15 percent.

(ii) Cinoxate 1 to 3 percent.

(iii) Diethanolamine methoxycinnamate 8 to 10 percent.

(iv) Digalloyl trioleate 2 to 5 percent.

(v) Dioxybenzone 3 percent.

(vi) Ethyl 4-[bis(hydroxypropyl)] aminobenzoate 1 to 5 percent.

(vii) Glyceryl aminobenzoate 2 to 3 percent.

(viii) Homosalate 4 to 15 percent.

(ix) Lawsone 0.25 percent with dihydroxyacetone 3 percent.

(x) Menthyl anthranilate 3.5 to 5 percent.

(xi) Octocrylene 7 to 10 percent.

(xii) Octyl methoxycinnamate 2.0 to 7.5 percent.

(xiii) Octyl salicylate 3 to 5 percent.

(xiv) Oxybenzone 2 to 6 percent.

(xv) Padimate O 1.4 to 8 percent.

(xvi) Phenylbenzimidazole sulfonic acid 1 to 4 percent.

(xvii) Red petrolatum 30 to 100 percent.

(xviii) Sulisobenzone 5 to 10 percent.

(xix) Titanium dioxide 2 to 25 percent.

(xx) Trolamine salicylate 5 to 12 percent.

(b) *Sunscreen and skin protectant combinations.*

(1) Any single sunscreen active ingredient when used in the concentration established in § 352.10 may be combined with one or more skin protectant active ingredients identified in § 347.10(a), (d), (e), (f), (h), (i), and (j) of this chapter, provided the finished product has a minimum SPF value of not less than 2 as measured by the testing procedures established in Subpart D of this part and provided the product is labeled according to § 352.60.

(2) Two or more sunscreen active ingredients when used in the concentrations established in § 352.20(a)(2) may be combined with one or more skin protectant active ingredients identified in § 347.10(a), (d), (e), (f), (h), (i), and (j) of this chapter, provided the finished product has a minimum SPF value of not less than 2 as measured by the testing procedures established in subpart D of this part and provided the product is labeled according to § 352.60.

(c) *For sunscreen and skin bleaching combinations.* See § 358.50 of this chapter.

Subpart C—Labeling

§ 352.50 Principal display panel of all sunscreen drug products.

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

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

(b) *For products that satisfy the water resistant sunscreen product testing procedures in § 352.76.*

(1) "Water Resistant."

(2) "SPF=(insert SPF value before water resistant testing) before" (select one of the following: "sweating" or "perspiring") "or going into the water. SPF=(insert SPF value resulting from water resistant testing) after 40 minutes of" (select one of the following: "sweating" or "perspiring") "or activity in the water."

(c) *For products that satisfy the very water resistant sunscreen product testing procedures in § 352.76.*

(1) "Very Water Resistant."

(2) "SPF=(insert SPF value before very water resistant testing) before" (select one of the following: "sweating" or "perspiring") "or going into the water. SPF=(insert SPF value resulting from very water resistant testing) after 80 minutes of" (select one of the following: "sweating" or "perspiring") "or activity in the water."

§ 352.52 Labeling of sunscreen drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "sunscreen."

(b) *Indications.* The labeling of the product states, under the heading "Indications" any of the phrases listed in paragraph (b) of this section, as appropriate. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) *For products containing any ingredient identified in § 352.10*—(i) "Sunscreen to help prevent sunburn."

(ii) (Select one of the following: "Filters" or "Screens") "out the sun's" (select one of the following: "burning" or "harsh and often harmful") "rays to prevent sunburn."

(iii) "Allows you to stay in the sun up to (insert SPF of product up to 30) times longer than without sunscreen protection."

(iv) "Provides up to (insert SPF of product up to 30) times your natural protection from sunburn."

(v) (Select one of the following: "Filters" or "Screens") "out the" (select one of the following: "sun's rays," "sun's harsh rays," or "sun's harmful rays") "to help prevent" (select one or more of the following: "lip damage," "skin damage," "freckling," or "uneven coloration").

(vi) (Select one of the following: "Protects from" or "Shields from") (select one of the following: "the harmful rays of the sun" or "the sun") "to help prevent" (select one or more of the following: "lip damage," "skin damage," "freckling," or "uneven coloration").

(2) *Additional indications.* In addition to the indications provided above in § 352.52(b)(1), the following may be used:

(i) *For products containing any ingredient in § 352.10 that provide an SPF of 2 to under 4, any of the following labeling statements may be used*—(A) (Select one of the following: "Provides minimal," "Provides minimum," "Minimal," or "Minimum") "protection against sunburn."

(B) "Prolongs exposure time before sunburn occurs."

(C) "Permits" (select one of the following: "tanning" or "suntanning") "and" (select one of the following: "reduces chance of" or "minimizes") "sunburning."

(D) "Helps prevent sunburn on limited exposure of untanned skin."

(E) "Helps to protect the skin against sunburn while permitting tanning."

(ii) *For products containing any ingredient in § 352.10 that provide an SPF of 4 to under 8, any of the following labeling statements may be used*—(A) (Select one of the following: "Provides moderate" or "Moderate") "protection against sunburn."

(B) "Prolongs exposure time before sunburn occurs."

(C) "Permits" (select one of the following: "tanning" or "suntanning") "and" (select one of the following: "reduces chance of" or "minimizes") "sunburning.

(D) "Helps prevent sunburn on derate exposure of untanned skin."

(iii) *For products containing any ingredient in § 352.10 that provide an SPF of 8 to under 12, any of the following labeling statements may be used*—(A) (Select one of the following: "Provides high" or "High") "protection against sunburn."

(B) "Prolongs exposure time before sunburn occurs."

(C) "Permits" (select one of the following: "tanning" or "suntanning") "and" (select one of the following: "reduces chance of" or "minimizes") "sunburning."

(D) "Helps prevent sunburn."

(E) "For sun-sensitive skin."

(F) "High protection against sunburn for blondes, redheads, and fairskinned persons."

(iv) *For products containing any ingredient in § 352.10 that provide an SPF of 12 to under 20, any of the following labeling statements may be used*—(A) (Select one of the following: "Provides very high" or "Very high") "protection against sunburn."

(B) "Prevents sunburn and limits tanning."

(C) "For sun-sensitive skin."

(D) "Very high protection against sunburn for blondes, redheads, and fairskinned persons."

(v) *For products containing any ingredient in § 352.10 that provide an SPF of 20 to 30, any of the following labeling statements may be used*—(A) (Select one of the following: "Provides the most" or "The most") "protection against sunburn."

(B) "Prevents tanning and sunburn."

(C) "For highly sun-sensitive skin."

(D) "The most protection against sunburn for blondes, redheads, and fairskinned persons."

(E) "Provides the highest degree of" (select one of the following: "sunburn" or "sunscreen") "protection and permits no tanning."

(3) *For products containing the active ingredient identified in § 352.10(s) that provide an SPF of 12 to 30, the following labeling statement may be used.* "Reflects the burning rays of the sun."

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

(1) *For products containing any ingredient in § 352.10*—(i) "For external use only, not to be swallowed."

(ii) "Avoid contact with the eyes. If contact occurs, rinse eyes thoroughly with water."

(iii) "Discontinue use if signs of ritation or rash appear. If irritation or ash persists, consult a doctor."

(2) *For products containing the ingredient identified in § 352.10(i)*—(i) "This product consists of two solutions. Do not mix the contents of the two solutions. Use both solutions; one alone will not provide protection."

(ii) "Use only on skin free of rash and abrasions."

(iii) "May stain clothing when freshly applied."

(3) *For products containing any ingredient identified in § 352.10 formulated as a lip balm or lipstick.* The warning in paragraph (c)(1)(i) of this section is not required.

(4) *For products containing any ingredient identified in § 352.10 formulated as a lipstick.* The warning in paragraph (c)(1)(ii) of this section is not required.

(d) *Directions.* The labeling of the product contains the following information 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 that do not satisfy the water resistant or very water resistant testing procedures in § 352.76.* "Adults and children 6 months of age and over: Apply" (select one or more of the following, as applicable: "liberally," "generously," "smoothly," or "evenly") "before sun exposure. Reapply after swimming, excessive" (select one of the following: "sweating," or "perspiring,") "or anytime after towel drying. Children under 2 years of age should use sunscreen products with a minimum SPF of 4. Children under 6 months of age: consult a doctor."

(2) *For products containing any ingredient in § 352.10 that satisfy the water resistant or very water resistant testing procedures in § 352.76.* "Adults and children 6 months of age and over: Apply" (select one or more of the following, as applicable: "liberally," "generously," "smoothly," or "evenly") "(insert appropriate time interval, if a waiting period is needed) before sun or water exposure. Reapply after" [select one of the following: "40 minutes" (if water resistant) or "80 minutes" (if very water resistant)] "of swimming or excessive" (select one of the following: "sweating" or "perspiring") "or anytime after towel drying. Children under 2 years of age should use sunscreen products with a minimum SPF of 4. Children under 6 months of age: consult a doctor."

(3) *For products containing the ingredient identified in § 352.10(i).* Products are composed of two separate formulations. Solution 1 contains 3 percent dihydroxyacetone and Solution 2 contains 0.25 percent lawsone. "Adults and children 6 months of age and over: Apply liberally before sun exposure as follows: *First application.* The evening prior to sun exposure: Apply Solution 1. Wait 15 minutes then apply Solution 2 to the same areas of skin. Wait until dried. Then repeat application of solutions alternately as before until a total of three applications of both solutions have been applied. Leave on skin without washing. *Repeated application.* After first day, apply one application of each solution. Reapply after swimming or after excessive" (select one of the following "sweating" or "perspiring") "or anytime after towel drying. Children under 2 years of age should use sunscreen products with a minimum SPF of 4. Children under 6 months of age: consult a doctor."

(4) *For products containing any ingredient identified in § 352.10 labeled with only the indications in § 352.52 (b)(1)(v) and/or (b)(1)(vi) and formulated as a make-up preparation or lipstick.* "Apply liberally as often as necessary."

(5) *For products containing any ingredient identified in § 352.10 labeled with only the indications in § 352.52(b)(1)(v) and/or (b)(1)(vi) and formulated as a lip balm or skin preparation.* "Adults and children 6 months of age and over: Apply liberally as often as necessary. Children under 2 years of age should use sunscreen products with a minimum SPF of 4. Children under 6 months of age: consult a doctor."

(e) *Statement on product performance*—(1) *For products containing any ingredient identified in § 352.10, the following PCD labeling claims may be used—(i) For products containing active ingredient(s) that provide an SPF value of 2 to under 4.* "Minimal Sun Protection Product."

(ii) *For products containing active ingredient(s) that provide an SPF value of 4 to under 8.* "Moderate Sun Protection Product."

(iii) *For products containing active ingredient(s) that provide an SPF value of 8 to under 12.* "High Sun Protection Product."

(iv) *For products containing active ingredient(s) that provide an SPF value of 12 to under 20.* "Very High Sun Protection Product."

(v) *For products containing active ingredient(s) that provide an SPF value of 20 to 30.* "Ultra High Sun Protection Product."

(2) *For products containing any ingredient in § 352.10 that satisfy the water resistant testing procedures identified in § 352.76, any of the following labeling statements may be used*—(i) "Retains its sun protection for at least 40 minutes in the water."

(ii) "Resists removal by" (select one of the following: "perspiring" or "sweating".)

(iii) (Select one of the following: "Sweat" or "Perspiration") "resistant."

(3) *For products containing any ingredient in § 352.10 that satisfy the very water resistant testing procedures identified in § 352.76, any of the following labeling statements may be used*—(i) "Retains its sun protection for at least 80 minutes in the water."

(ii) "Resists removal by" (select one of the following: "perspiring" or "sweating.")

(iii) (Select one of the following: "Sweat" or "perspiration") "resistant."

(4) *For products containing any ingredient identified in § 352.10, the following compilation of skin types and SPF's shall be appropriately included in labeling as a guide.*

RECOMMENDED SUNSCREEN PRODUCT GUIDE

Sunburn and tanning history	Recommended sun protection product
Always burns easily; rarely tans.	SPF 20 to 30.
Always burns easily; tans minimally.	SPF 12 to under 20.
Burns moderately; tans gradually.	SPF 8 to under 12.
Burns minimally; always tans well.	SPF 4 to under 8.
Rarely burns; tans profusely.	SPF 2 to under 4.

(5) *For products containing the active ingredient identified in § 352.10(s) that provide an SPF of 12 to 30, the following labeling statement may be used.* "Sunblock."

(6) *For products containing any ingredient identified in § 352.10, the following labeling statement shall be used.* "SUN ALERT: The sun causes skin damage. Regular use of sunscreens over the years may reduce the chance of skin damage, some types of skin cancer, and other harmful effects due to the sun."

(7) *For products containing any ingredient identified in § 352.10.* Any variation of the statement in § 352.52(e)(6) that does not relate skin aging or skin cancer as being "due to the sun" will cause the product to be misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act.

(f) The word physician may be substituted for the word doctor in any of the labeling statements in this part.

§ 352.60 Labeling of permitted combinations of active ingredients.

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

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

(b) *Indications.* The labeling of the product states under the heading "Indications," the indication(s) for each ingredient in the combination as established in the indications sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph. Other truthful and nonmisleading statements, describing only the indications for use that have been established in the applicable OTC drug monographs or listed in this paragraph, may also be used, as provided by § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act. In addition to the required information identified in this paragraph, the labeling of the product may contain any of the "other allowable statements" that are identified in the applicable monographs, provided such statements are neither placed in direct conjunction with information required to appear in the labeling nor occupy labeling space with greater prominence or conspicuousness than the required information.

(1) *For permitted combinations containing a sunscreen and a skin protectant identified in § 352.20(b).* In addition to any or all of the indications for sunscreens in § 352.52(b), the indication for skin protectants in § 347.50(b)(2) of this chapter should be used.

(2) [Reserved]

(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 unless otherwise stated in this paragraph.

(1) *For permitted combinations containing a sunscreen and a skin protectant identified in § 352.20(b).* The warning for skin protectants in § 347.50(c)(3) of this chapter is not required.

(2) [Reserved]

(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.

(1) *For permitted combinations containing a sunscreen and a skin protectant identified in § 352.20(b).* The directions for sunscreens in § 352.52(d) should be used.

(2) [Reserved]

Subpart D—Testing Procedures

§ 352.70 Standard sunscreen.

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

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

OMPOSITION OF PREPARATION A AND PREPARATION B OF THE STANDARD SUNSCREEN

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

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

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

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

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

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

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

(5) *Calculation of the concentration of homosalate.* The concentration of homosalate is determined by the following formula which takes into consideration the absorbance of the sample of the test solution, the dilution of the 1-percent solution (1:50), the weight of the sample of the standard homosalate sunscreen preparation (1 gram), and the standard absorbance value (172) of homosalate as determined by averaging the absorbance of a large number of batches of raw homosalate:

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

§ 352.71 Light source (solar simulator).

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

§ 352.72 General testing procedures.

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

Selection of Fair-skin Subjects

Skin Type and Sunburn and Tanning History (Based on first 30 to 45 minutes sun exposure after a winter season of no sun exposure.)

I—Always burns easily; never tans (sensitive).
II—Always burns easily; tans minimally (sensitive).
III—Burns moderately; tans gradually (light brown) (normal).
IV—Burns minimally; always tans well (moderate brown) (normal).
V—Rarely burns; tans profusely (dark brown) (insensitive).
VI—Never burns; deeply pigmented (insensitive).

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

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

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

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

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

(e) *Application of test materials.* To ensure standardized reporting and to define a product's SPF value, the application of the product shall be expressed on a weight basis per unit area which establishes a standard film. Both the test sunscreen product and the standard sunscreen application shall be 2 milligrams per square centimeter. For oils and most lotions, the viscosity is such that the material can be applied with a volumetric syringe. For creams,

heavy gels, and butters, the product shall be warmed slightly so that it can be applied volumetrically. On heating, care shall be taken so as not to alter the product's physical characteristics, especially separation of the formulations. Pastes and ointments shall be weighed, then applied by spreading on the test site area. A product shall be spread by using a finger cot. If two or more sunscreen drug products are being evaluated at the same time, the test products and the standard sunscreen, as specified in § 352.70, should be applied in a blinded, randomized manner. If only one sunscreen drug product is being tested, the testing subsites should be exposed to the varying doses of UV radiation in a randomized manner.

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

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

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

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

§ 352.73 Determination of SPF value.

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

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

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

$$V_i(\lambda) = 10^{0.015(139-\lambda)} (328 < \lambda < 400 \text{ nm})$$

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

$$E = \sum_{250}^{405} V_i(\lambda) * I(\lambda)$$

where:
E=Erythema Effective Exposure (dose)
V_i=Weighting Factor (Erythema Action Spectrum)
I=Spectral Irradiance (Watts per meter squared per nanometers)

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

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

exposures shall be the MED(US) times 0.64X, 0.80X, 0.90X, 1.00X, 1.10X, 1.25X, and 1.56X, where X equals the expected SPF of the test product. For products with an expected SPF between 8 and 15, the exposures shall be the MED(US) times 0.69X, 0.83X, 0.91X, 1.00X, 1.09X, 1.20X, and 1.44X, where X equals the expected SPF of the test product. For products with an expected SPF greater that 15, the exposures shall be the MED(US) times 0.76X, 0.87X, 0.93X, 1.00X, 1.07X, 1.15X, and 1.32X, where X equals the expected SPF of the test product. The MED is the lowest dose of radiation that produces uniform redness reaching the borders of the exposure site at 22 to 24 hours postexposure. The SPF value of the test sunscreen is then calculated from the dose of UV radiation required to produce the MED of the protected skin and from the dose of UV radiation required to produce the MED of the unprotected skin (control site) as follows:

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

(d) *Determination of the test product's SPF value and PCD.* Use data from at least 20 test subjects with n representing the number of subjects used. First, for each subject, compute the SPF value as stated in § 352.73 (b) and (c). Second, compute the mean SPF value, $\bar{x}$, and the standard deviation, s, for these subjects. Third, obtain the upper 5-percent point from the t distribution table with $n-1$ degrees of freedom. Denote this value by t. Fourth, compute $ts/\sqrt{n}$. Let this quantity be denoted by A (i.e., $A=ts/\sqrt{n}$). Fifth, calculate the SPF value to be used in labeling as follows: the label SPF equals the largest whole number less than $\bar{x}-A$. Sixth and last, the drug product is classified into a PCD as follows: if $20+A<\bar{x}$, the PCD is Ultra High; if $12+A<\bar{x}<20+A$, the PCD is Very High; if $8+A<\bar{x}<12+A$, the PCD is High; if $4+A<\bar{x}<8+A$, the PCD is Moderate; if $2+A<\bar{x}<4+A$, the PCD is Minimal; if $\bar{x}<2+A$, the product shall not be labeled as a sunscreen drug product and may not display an SPF value.

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

The general testing procedures in § 352.72 should 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.* If the sunscreen product retains the same PCD after 40 minutes of water immersion as it had before water immersion, the claim of "water resistant" may be made.

The following procedure shall be used for the water resistance test:

(1) Apply sunscreen product (followed by the waiting period after application of the sunscreen product indicated on the product labeling).

(2) 20 minutes moderate activity in water.

(3) 20-minute rest period.

(4) 20 minutes moderate activity in water.

(5) Conclude water test (air dry test sites without toweling).

(6) Begin solar simulator exposure to test site areas as described in § 352.73.

(b) *Procedure for testing a very water resistant sunscreen product.* If the sunscreen product retains the same PCD after 80 minutes of water immersion as it had before water immersion, the claim of "very water resistant" may be made. The following procedure shall be used for the very water resistant test:

(1) Apply sunscreen product (followed by the waiting period after application of the sunscreen product indicated on the product labeling).

(2) 20 minutes moderate activity in water.

(3) 20-minute rest period.

(4) 20 minutes moderate activity in water.

(5) 20-minute rest period.

(6) 20 minutes moderate activity in water.

(7) 20-minute rest period.

(8) 20 minutes moderate activity in water.

(9) Conclude water test (air dry test sites without toweling).

(10) Begin solar simulator exposure to test site areas as described in § 352.73.

§ 352.77 Test modifications.

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

PART 700—GENERAL

4. The authority citation for 21 CFR Part 700 continues to read as follows:

Authority: Secs. 201, 301, 502, 505, 601, 602, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 352, 355, 361, 362, 371, 374).

5. Section 700.35 is added to subpart B to read as follows:

§ 700.35 Cosmetics containing sunscreens.

(a) A product that includes a sunscreen active ingredient and the term "sunscreen" in its labeling or in any other way represents or suggests that it is intended to prevent, cure, treat, or mitigate disease or to affect a structure or function of the body comes within the definition of a drug in section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act. Sunscreen active ingredients affect the structure or function of the body by screening, reflecting, or scattering the harmful, burning rays of the sun, thereby altering the normal physiological response to solar radiation. These ingredients also help to prevent diseases such as sunburn and reduce the chance of premature skin aging or skin cancer due to the sun. Moreover, when consumers see the term "sunscreen" on the label of a product, they expect the product to protect them in some way from the harmful effects of the sun, irrespective of other labeling statements. Consequently, the use of the term "sunscreen" in a product's labeling normally makes that product a drug. However, sunscreen ingredients may also be used in some cosmetic products for nontherapeutic uses. In order to avoid consumer misunderstanding, if a cosmetic product uses the term "sunscreen" anywhere in its labeling, the term "sunscreen" must be qualified by describing the cosmetic benefit provided by the sunscreen. For example: "This product contains a sunscreen that assists in protecting the hair from damage by the sun."

(b) Any information describing the purpose of the sunscreen in the product shall appear in direct conjunction with the term "sunscreen."

PART 740—COSMETIC PRODUCT WARNING STATEMENTS

6. The authority citation for 21 CFR Part 740 continues to read as follows:

Authority: Secs. 201, 301, 502, 505, 601, 602, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 352, 355, 361, 362, 371, 374).

7. Section 740.19 is added to subpart B to read as follows:

§ 740.19 Suntanning preparations.

The labeling of suntanning preparations that do not contain a sunscreen ingredient must display the following warning:

Warning—This product does not contain a sunscreen and does not protect against sunburn.

Dated: February 3, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

[FR Doc. 93–10888 Filed 5–11–93; 8:45 am]

BILLING CODE 4160–01–P