



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

0910 '00 OCT 18 A10:05

OCT 16 2000

Robert M. Sayre, Ph.D.
P.O. Box 1342
Cordova, TN 38018-0175

Re: 97P-0478

Dear Dr. Sayre:

This letter is in response to the citizen petition that was filed with the Dockets Management Branch on November 18, 1997. FDA has reviewed your petition and has decided to grant the petition in part and to deny the petition in part.

The Photosciences Network, a FDA-wide, inter-Center group of experts on the photosciences, has reviewed your petition. This evaluation has involved the Center for Devices and Radiological Health (CDRH), the Center for Drug Evaluation and Research (CDER), and the Center for Food Safety and Applied Nutrition (CFSAN). A thorough evaluation of the best scientific knowledge was needed to fully address your concerns. In order to evaluate the public health consequences of indoor tanning and the use of tanning products, FDA has cooperated with other federal agencies, the medical community, and the industry in a series of technical workshops and scientific symposia. These meetings explored the many areas associated with the risks from exposure to ultraviolet radiation and the use of tanning products. The first meeting was a Workshop on "UV, Accessory to Melanoma - If so, How?," held in Snowbird, UT on July 11, 1998 (Attachment # 1: program of meeting). The second meeting, held at the National Institute of Standards and Technology (NIST) in Gaithersburg, MD on September 1-3, 1998, was an "International Symposium and Workshop on Measurements of Optical Radiation Hazards" (Attachment # 2: program of meeting). A group of experts discussed typical values of Minimal Erythema Dose (MED) for different skin types at the NIST meeting. The third Workshop was "Risks and Benefits of Exposure to Ultraviolet Radiation and Tanning", held at the Natcher Auditorium, National Institutes of Health (NIH) on September 16-18, 1998 (Attachment # 3: program of meeting). These three meetings provided scientific recommendations from a wide range of government agencies, the medical community, and the industry.

We will address your requests in the same order as they appeared in the original petition.

1. Petitioner requests that FDA relabel all ultraviolet (UV) tanning units to recommend stricter user exposure limits and to warn that exposure to a tanning unit may cause melanoma. Petitioner also requests that user manuals be required to include the current labeling, especially any warnings.

97P-0478

PAV 1

FDA notes that user instructions are currently required to include a reproduction of the warning labels. This requirement appears in the performance standard (21 CFR 1040.20(e)(1)(i)).

FDA agrees that it is possible to acquire more UV, particularly UVA, from sunlamps than from solar exposure as shown in work done by FDA scientists (see Attachment #4), if an unlimited number of sessions are permitted at a tanning parlor. FDA does set recommendations with limits on the number of tanning sessions at an indoor salon. The FDA performance standard (21 CFR 1040.20(e)(1)(iv)) (Attachment # 5) requires that sunlamp product manufacturers provide a recommended exposure schedule, and a FDA policy letter dated August 21, 1986 (Attachment # 6) provides recommended exposure guidelines, which effectively recommend a limit for the total daily, weekly, and yearly amounts of ultraviolet radiation. These recommendations may not be strictly followed by and may not be known to some salon operators or tanners. FDA has published an Advanced Notice of Proposed Rulemaking (64 FR 6288, February 9, 1999) that solicits comments and information about possible changes to its sunlamp performance standard. Among the changes FDA is considering are expanding applicability of the rule to reach certain individuals who modify sunlamp products, developing new values for recommended doses or intervals that reflect recent findings concerning UVA and UVB exposure, and revising labeling requirements to highlight risks.

2. Petitioner requests that FDA require the warning label "For Indoor Use Only, Not to Be Used Outdoors," on tanning products that are not intended to be used outdoors.

FDA denies this request. Labeling of sunscreen drug products and suntanning preparations was addressed in the rulemaking for OTC sunscreen drug products, published on May 21, 1999 (64 FR 27666). Labeling requirements for OTC sunscreen drug products are set forth at 21 CFR Part 352, Subpart C. Labeling of sun tanning preparations that do not contain a sunscreen ingredient, must contain the statement: "Warning—This product does not contain a sunscreen and does not protect against sunburn. Repeated exposure of unprotected skin while tanning may increase the risk of skin aging, skin cancer, and other harmful effects to the skin even if you do not burn" in accordance with the requirements of 21 CFR 740.19. FDA believes that these labeling requirements provide consumers with the necessary information and warnings.

3. Petitioner requests that FDA require all products marketed as "tan accelerators," "tan enhancers," or "tan optimizers" be supported by an approved New Drug Application (NDA).

The FDA denies this request because some of these products may, depending on the particular circumstances, be regulated as cosmetics that do not require NDAs.

FDA reviews products marketed to enhance or permit tanning that do not contain a sunscreen ingredient on a case-by-case basis to determine whether the products are intended solely to provide a cosmetic benefit (such as moisturizing) or whether they are intended to enhance or permit tanning by some other mechanism of action (i.e. intended to affect the structure or any function of the body). (64 FR 27666 at 27669) (Attachment # 7)

4. The petitioner requests that FDA require that all products sold as tanning products be manufactured and labeled according to the Tentative Final Monograph (TFM). The petitioner further requests that products labeled "SPF 0" and "SPF 1" be removed from the market.

FDA grants this request in part. A final monograph completing the TFM except for certain testing and UVA labeling issues was issued on May 21, 1999 (64 FR 27666). Products that fall within the scope of the OTC sunscreen drug product final monograph must comply with its provisions upon the effective date. These provisions include the requirement that a finished OTC Sunscreen Drug Product provides a minimum sun protection factor (SPF) of not less than 2. (21 CFR 352.10 (64 FR 27666 at 27687)) Such a product providing a minimum SPF of less than 2 would fail to conform to the Final Monograph and therefore be liable to regulatory action. See 21 CFR 330.1. A label such as "SPF 0" or "SPF 1" on a drug tanning preparation that contains no sunscreen ingredient would be false and misleading in that it could cause consumers to expect the product to provide some protection against the adverse effects of the sun when, in fact, it does not and may cause the product to be misbranded under Section 602 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 362) (Attachment # 8) See 58 FR 28194 at 28207.

FDA denies your request to the extent that it requests cosmetic tanning products to meet OTC drug manufacturing and labeling requirements of the Final Monograph. While the agency believes that all suntanning preparations should be labeled so that the consumer can use them safely, the Act does not provide the legal authority for FDA to require that cosmetic tanning products meet the manufacturing and labeling requirements that apply to products that are OTC drugs. Cosmetic suntanning preparations are subject to separate labeling requirements set forth at 21 CFR 740.19. A label such as "SPF 0" or "SPF 1" on a cosmetic tanning preparation that contains no sunscreen ingredient would be false and misleading in that it could cause consumers to expect the product to provide some protection against the adverse effects of the sun when, in fact, it does not and may cause the product to be misbranded under Section 602 of the Act (21 U.S.C. 362).

5. Petitioner requests that FDA not allow any oral or vitamin therapy products to claim to enhance tanning or to treat or prevent UV injury without an approved NDA or to remove products with such claims from the market.

FDA denies your request to "not allow" oral or vitamin therapy products with claims only to enhance tanning "without an approved NDA." Such products could possibly be regulated as dietary supplements or cosmetics that do not require NDAs.

Ingested vitamin-containing products are dietary supplements if they meet the statutory requirements in 21 U.S.C. 321(ff). A statement describing the role of a dietary ingredient intended to affect the structure or function of the body may be permitted to be made for dietary supplements in accordance with 21 U.S.C. 343(r)(6). Such statements do not make the dietary supplement for which they are made a drug, for which an NDA would be required.

Oral products with the effect of producing a tanned appearance by deposition of an ingested ingredient may be regulated as cosmetics. The ingredient that imparts color must be the subject

of an approved color additive petition. See United States v. Eight Unlabeled Cases, 888 F 2d 945 (2nd Cir. 1989).

As noted in our response to number three above, certain products labeled with claims to "enhance tanning" may be regulated as cosmetics, depending on the intended use of the product, including product formulation or other label and labeling claims being made for the product.

Tanning products claiming to "prevent UV injury" are subject to regulation as drug products (see 64 FR 27666 at 27668). Products claiming to "treat UV injury" must be reviewed on a case-by-case basis to determine whether they are intended to provide a cosmetic benefit or are subject to regulation as drug products. However, any OTC drug product subject to a final monograph may not contain a nonmonograph condition (such as a use that has not been determined to be generally recognized as safe and effective) unless it is the subject of an approved NDA or abbreviated NDA.

Petitioner requests that FDA not allow tanning products to claim that a product "tans faster," "tans darker," "optimizes the tan," "enhances the tan" or other category II sunscreen drug product claims on its label, advertising or promotional material.

FDA grants this request to the extent that it refers to tanning products regulated as OTC drugs. The OTC sunscreen drug product Final Monograph establishes uses that can be included on OTC sunscreen drug product labeling. These uses do not include the "Category II" claims referenced in your petition. OTC products falling within the scope of the Final Monograph using the claims referenced in your petition would be subject to regulatory action. See 21 CFR 330.1.

Advertising and promotion of OTC drug products is regulated by the Federal Trade Commission. However, the inclusion of promotional statements in the labeling of a drug product is reviewed by FDA on a case-by-case basis to determine if the statements render the product misbranded under Section 502 of the Act or an unapproved new drug under section 505 of the Act. Furthermore, the advertising of OTC drug products subject to a final monograph must prescribe, recommend, or suggest its use only under the conditions stated in the labeling of the product (21 CFR 330.1(d)).

6. Petitioner requests that FDA carefully review all manufacturers of cosmetic-drug products and their facilities that manufacture tan accelerators or other indoor tanning products and close those manufacturers that do not meet acceptable standards.

Manufacturers of drugs and cosmetics continue to be subject to periodic factory inspection in accordance with Section 704(a)(1) of the Act (21 U.S.C. 374(a)(1))(Attachment # 9). Furthermore, manufacturers of drug products, including OTC sunscreen products, are required to comply with current Good Manufacturing Practice under Section 501(a)(2)(B) of the Act (21 U.S.C. 351(a)(2)(B))(Attachment # 10) and regulations at 21 CFR Part 211 (Attachment # 11). All drug and cosmetic manufacturers also must assure that their products are properly labeled in accordance with the requirements of the Act and regulations. FDA intends to continue to pursue

regulatory action against tanning accelerators or other indoor tanning products that do not comply with the requirements of the applicable laws and regulations as resources permit.

7. Petitioner requests that FDA require each user of a tanning salon be provided with a graphic warning pamphlet prepared by the American Academy of Dermatology (AAD) and American Academy of Ophthalmology.

FDA denies this request. In conjunction with other federal and private agencies, FDA has recently issued such a pamphlet. Over the course of the last few decades, FDA has worked with the Centers for Disease Control and Prevention (CDC), and others to periodically issue a pamphlet warning consumers of the dangers of overexposure to ultraviolet radiation. Recently FDA worked with CDC and the AAD to re-issue a revised version of the pamphlet: "The Darker Side of Tanning" (Attachment # 12). In addition, numerous other pamphlets are available from the AAD and other organizations. FDA's performance standard (21 CFR 1040.20(e)) requires user instructions to include warnings, proper operation of equipment, and "correct exposure time and schedule for persons according to skin type".

FDA further recommends that tanning salons use informed consent statements. As with all medical procedures and for all medical products, informed consent statements are a valuable part of delivering needed information to the consumer. In conjunction with the states, FDA has developed a model standard for regulating tanning salons and has urged the operators of all tanning salons to incorporate an informed consent statement into their contracts with clients. FDA has drafted a recommended informed consent statement for use by salon operators. This model regulation is identified as "Part BB" of the Suggested State Regulations for the Control of Radiation (Attachment # 13)

8. Petitioner requests that FDA to outlaw selling unlimited tanning or monthly or yearly tanning memberships to tanning salons.

FDA denies this request. Although FDA has a range of authorities that empower the agency to regulate tanning products, FDA has limited authority to regulate the day-to-day operations of tanning salons. The regulation of individual salons is a state and/or local matter. The recommended exposure schedules, described in Item 1 above, and developed as a model regulation for states (Attachment # 13) has served as a model for state and local enforcement.

9. Petitioner requests that FDA establish guidelines for certification of tanning salon operators and workers.

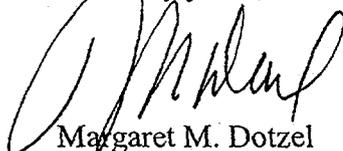
FDA denies this request. FDA does not have the authority to establish guidelines for certification of tanning salon operators and workers. State and local government agencies have authority to establish standards for tanning salon personnel. Model state regulations (Attachment # 14) have been developed, in cooperation with the FDA, to be used by State and local authorities in carrying out a regulatory program for commercial sunlamp product users. Some states have adopted this model regulation, in some cases with modifications.

This model regulation is identified as "Part BB" of the Suggested State Regulations for the Control of Radiation (Attachment # 13). The latest version contains a requirement for training. However, the training does not specify that salon operators and workers be required to provide warnings concerning risk of exposure. The model requires salons to maintain records of training for salon personnel. The model is available from the Conference of Radiation Control Program Directors (CRCPD). As the need is identified, this model regulation can be updated, as directed by the CRCPD Board of Directors.

10. Petitioner requests FDA, with the help of the American Academy of Dermatology, to examine the list of possible phototoxic drugs and shorten it to a more workable length in order to provide more useful information to tanners.

FDA denies this request. FDA evaluates the safety of individual drug products. Persons concerned with photosensitivity effects of particular drug products should consult their health care practitioner, the product's package insert, or information sources such as the Physician's Desk Reference or MEDLINE. FDA no longer publishes a list of photosensitive drugs. FDA published this list once in 1990. The list made no distinction between those drugs with rarely observed and frequently observed photosensitivity events, or the severity of photosensitivity effects. FDA cannot control persons publishing lists of phototoxic drugs based on data gleaned from the open literature or obtained by FOI requests. Since the UV dose from tanning beds may cause greater sensitization than sunlight, it may be unwise to shorten the list of photosensitizing drugs. With current computer search capability, the length of the list of photosensitizing drugs should not pose a problem.

Sincerely yours,



Margaret M. Dotzel
Associate Commissioner
for Policy

cc:

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Enclosures:

Attachment # 1: Program - Workshop on "UV, Accessory to Melanoma – If so, How?", held in Snowbird, UT on July 11, 1998.

Attachment # 2: Program of "International Symposium and Workshop on Measurements of Optical Radiation Hazards" NIST in Gaithersburg, MD on September 1-3, 1998.

Attachment # 3: Program "Risks and Benefits of Exposure to Ultraviolet Radiation and Tanning", to be held at the Natcher Auditorium, NIH on September 16-18, 1998.

Attachment # 4: paper by Miller et. al.

Attachment # 5: The FDA performance standard (21CFR1040.20).

Attachment # 6: FDA policy letter dated August 21, 1986 (Attachment # 6).

Attachment # 7: 64 FR 27666 at 27669.

Attachment # 8: Section 602 of the Act (21 U.S.C. 362).

Attachment # 9: Section 704(a)(1) of the Act.

Attachment # 10: Good Manufacturing Practice under 21 U.S.C. 351(a)(2)(B).

Attachment # 11: 21 CFR Part 211.

Attachment # 12: "The Darker Side of Tanning"

Attachment # 13: Part BB" of the Suggested State Regulations for the Control of Radiation

AMERICAN SOCIETY FOR PHOTOBIOLOGY TWENTY SIXTH ANNUAL MEETING

JULY 11-15, 1998

SNOWBIRD SKI AND SUMMER RESORT
SNOWBIRD, UTAH

SATURDAY, JULY 11

8:00 - 9:00 AM EXECUTIVE COMMITTEE MEETING

Maybird

9:00 AM - 2:00 PM COUNCIL MEETING

Maybird

1:30 - 5:30 PM

Ballroom 1

StPM-A

WORKSHOP I: UV, Accessory to Melanoma - If So, How?

Chairs: Janusz Z. Beer, Food and Drug Administration, Rockville, Maryland and
Frank de Gruijl, University Hospital, Utrecht, The Netherlands

The purpose of the workshop is to review our knowledge on the relationships between UV exposure and melanoma induction. This issue will be addressed at the workshop from perspectives ranging from the epidemiological to the molecular. Human UV exposure will be also be presented from the viewpoint of melanoma induction. The contributors are asked to provide the background information and refer to important published data in addition to the presentation of their own work. A targeted discussion on two theses will conclude the workshop.

1:30 pm

Opening Remarks

J.Z. Beer and F.R. DeGruijl

1:40 pm

StPM-A1

Cutaneous Melanoma and UV Radiation - How Strong is the Connection?

R.P. Gallagher

British Columbia Cancer Agency, Vancouver, Canada

2:00 pm

StPM-A2

Melanoma Incidences and UVB/UVA Exposures

J. Moan and H. Bårnrud

Institute for Cancer Research, Oslo, Norway

2:20 pm

StPM-A3

UV and Melanoma Induction: Insights from Studies of Xeroderma Pigmentosum

K.H. Kraemer

National Institutes of Health, Bethesda, MD

2:35 pm

StPM-A4

UV and Melanoma: The Sunscreen Perspective

M. Berwick

Memorial Sloan-Kettering Cancer Center, New York

2:50 pm

StPm-A5

Comparison of UV Emissions from Sunlamps and from Solar Exposure Through Sunscreens: The Potential Importance for Melanoma

S.A. Miller¹, R.M. Sayre² and W. H. Cyr¹

¹Food and Drug Administration, Rockville, MD and ²Rapid Precision Testing Laboratory, Cordova, TN

3:05 pm

Discussion

3:25 pm

Break

3:45 pm

StPM-A6

Melanocortin 1 Receptor (MC1R) Variant ARG151CYS and Fair Skin Modify Melanoma Risk in Dutch Melanoma Families

N.A. Gruis, P.A. van der Velden, S. Pavel, L.A. Sandkuijl, W. Bergman and R.R. Frants

Leiden University, The Netherlands

Saturday, July 11

- 4:05 pm StPM-A7 **Induction of Both Pheomelanin and Eumelanin Decreases Killing of Melanoma Cells by Reactive Oxygen Species**
G. Ghanem, E. Kinnaert and H.Z. Hill
Institut Jules Bordet, Bruxelles, Belgium and New Jersey Medical School, Newark
- 4:25 pm StPM-A8 **UV and Melanoma: The Experimental Animal Perspective**
R.D. Ley
University of New Mexico School of Medicine, Albuquerque
- 4:45 pm StPM-A9 **Accelerated UV Carcinogenesis in Hepatocyte Growth Factor/Scatter Factor Transgenic Mice (WAM-E2)**
F.P. Noonan, T. Otsuka, S. Bang, M. Anver and G. Merlino
The George Washington University Medical Center, Washington, DC, National Cancer Institute, Bethesda, MD and Frederick Cancer Research and Development Center, Frederick, MD
- 4:55 pm StPM-A10 **Induction of Melanoma in p53 Knockout Mice by UV Radiation**
W. Jiang, H.K. Muller and M.L. Kripke
The University of Texas M.D. Anderson Cancer Center, Houston
- 5:05 pm Discussion to be focused on two theses:

1. UV exposure causes melanoma in humans: the public must be regularly warned about particular risks of (a) exposure of children and (b) overexposure
2. UVA plays a dominant role in UV-induced human melanoma
 - 2.1. Use of (UVB blocking) sunscreens and UVA tanning devices should therefore be discouraged.
 - 2.2. It would be safer to tan using solar emission sunlamps rather than "UVA" sunlamps.

2:00 - 5:00 PM
Ballroom 2

StPM-B **WORKSHOP II: Undergraduate Teaching and Research in Photobiology and Photochemistry**
Chairs: Thomas M. Brennan, Dickinson College, Carlisle, Pennsylvania,
Christopher Lambert, Connecticut College, New London, Connecticut and
Kevin O'Shea, Florida International University, Miami, Florida

This workshop is intended to bring together photobiologists and photochemists who are engaged in teaching at the undergraduate level and who involve undergraduate students in their research. Topics will include the appropriate scope of such courses, examples of successful laboratory exercises and student research projects, and means of interesting both students and the general public in photobiology and photochemistry. The workshop will conclude with a period of open discussion.

- 2:00 pm **Opening Comments**
T. Brennan, C. Lambert and K. O'Shea
- 2:05 pm StPM-B1 **Basics of Photochemistry, Photophysics and Photobiology**
C.S. Foote
University of California, Los Angeles
- 2:30 pm StPM-B2 **Photobiology as an Integrated Part of the Undergraduate Curriculum**
P.C. Beaumont and P.F. Heelis
North East Wales Institute, Wrexham, Wales, United Kingdom
- 2:45 pm StPM-B3 **Case Study of UV Effects in an Undergraduate Problem-Based Physics Course**
L.R. Jones
College of Charleston, Charleston, SC

International Symposium on Measurements of Optical Radiation Hazards

at the

National Institute of Standards and Technology

September 1 – 3, 1998

**Final Symposium Program
and
Book of Abstracts**

Cosponsoring Organizations:

Commission Internationale de l'Éclairage

International Commission on Non-Ionizing Radiation Protection

National Institute of Standards and Technology, Optical Technology Division

**US Army Center for Health Promotion and Preventive Medicine, Laser/Optical Radiation
Program**

Center for Devices and Radiological Health, Food and Drug Administration

Tuesday September 1, 1998

8:00-8:30 *Registration*

8:30-9:00 *Introduction and Opening Remarks*

Albert C. Parr, Chief, NIST Optical Technology Division
 Jack J. Hsia, President, International Commission on Illumination (CIE)
 David H. Sliney, Director, CIE Division 6 on Photobiology and
 Photochemistry
 Rudiger Matthes, ICNIRP Scientific Secretariat
 Elizabeth Jacobsen, Associate Director, Center for Devices and
 Radiological Health, Food and Drug Administration

SESSION I: The Photobiological Basis for Risk Assessment – Action Spectra

Moderators: AM John Mellerio, University of Westminster GB
 PM Frederick Urbach, Temple University Medical Practices, US

9:00-9:30 *The Meaning of Action Spectra*

(I-1) Thomas Coohill, Ultraviolet Consultants, US

9:30-9:50 *Photobiological Action Spectra – Limits on Resolution*

(I-2) David H. Sliney, US Army Center for Health Promotion and Preventive
 Medicine, US

9:50-10:10 *Ultraviolet Action Spectrum for Erythema – History*

(I-3) Frederick Urbach, Temple University Medical Practices, US

10:10-10:30 *CIE Ultraviolet Action Spectrum for Erythema*

(I-4) Brian L. Diffey, Regional Medical Physics Department, Newcastle General
 Hospital, GB

10:30-10:50 Coffee Break

10:50-11:10 *Ultraviolet Action Spectrum for Erythema – High Resolution from Lasers*

(I-5) Angelika Anders, Institute of Biophysics, University of Hanover, DE

11:10-11:30 *Ultraviolet Action Spectra for Photosensitization*

(I-6) Jean-Pierre Cesarini, Rothschild Foundation, FR

11:30-11:50 *Ultraviolet Action Spectra for Skin Carcinogenesis*

(I-7) Frank de Gruijl, Department of Dermatology, University Hospital AZU, NL

11:50-12:10 *A Standard UVR Action Spectrum for Non-Melanoma Skin Cancer*

(I-8) P. Donald Forbes, Primedica Corporation, Argus Research Lab, Inc., US

12:10-12:30 *UV-Induced Immunosuppression: Wavelength Dependency and its Implications*

(I-9) Edward C. de Fabo, George Washington University Medical Center, US

Tuesday September 1, 1998

- 12:30-12:50 (I-10) *The Effects of UVB and UVA on the Photoaging of Dermal Connective Tissue*
Lorraine H. Kligman, School of Medicine, University of Pennsylvania, US
- 12:50-1:50 Lunch
- 1:50-2:10 (I-11) *Neuroendocrine and Circadian Regulation by Visible and Ultraviolet Radiation*
George Brainard, Department of Neurology, Jefferson Medical College, US
- 2:10-2:30 (I-12) *The Cornea – Ultraviolet Action Spectrum for Photokeratitis*
Joseph Zuclich, TASC Inc., US
- 2:30-2:50 (I-13) *The Lens – Ultraviolet and Infrared Action Spectra for Cataract Acute In Vivo Studies*
Anthony Cullen, School of Optometry, University of Waterloo, CA
- 2:50-3:10 (I-14) *The Lens – Infrared Action Spectrum for Cataract - A Study Based on a Thermal Model*
Tsutomu Okuno, National Institute of Industrial Health, JP
- 3:10-3:30 (I-15) *The Lens – Human Data from Chronic Exposure*
Kazuyuki Sasaki, Department of Ophthalmology, Kanazawa Medical University, JP
- 3:30-3:50 Coffee Break
- 3:50-4:10 (I-16) *The Retina and Action Spectrum for Photoretinitis ("Blue-Light Hazard")*
Bruce Stuck, US Army Medical Research Detachment, US
- 4:10-4:30 (I-17) *Action Spectrum for Retinal Thermal Injury*
David J. Lund, US Army Medical Research Detachment, US
- 4:30-5:15 *Discussion on Action Spectra*
Panel Chair: Dianne Godar, Center for Devices and Radiological Health, Food and Drug Administration, US
- 5:30 *Meeting adjourns*
- 6:00 *Reception/Exhibition at Gaithersburg Hilton*

Wednesday September 2, 1998

SESSION II: Photobiological Guidelines and Standards for Health Protection and Product Safety

Moderators: AM P. Donald Forbes, Primedica Corporation Inc., US
PM Jean-Pierre Cesarini, Rothchild Foundation, FR

- 8:20-8:50 (II-1) *ACGIH Action Spectra for Threshold Limit Values and Health Hazard Assessment*
David H. Sliney, US Army Center for Health Promotion and Preventive Medicine, US
Maurice Bitran, Ontario Ministry of Labor, Non-Ionizing Radiation Section, CA
- 8:50-9:10 (II-2) *ICNIRP Action Spectra and Guidelines*
Patrick von Nandelstadh, Institute of Occupational Health, Vantaa, FI
- 9:10-9:30 (II-3) *CIE Efforts in Standardization of Action Spectra*
Jean-Pierre Cesarini, Rothchild Foundation, FR
- 9:30-9:50 (II-4) *ANSI/IESNA Photobiological Lamp Safety Standards*
Robert Landry, Electro-Optics Branch, Center for Devices and Radiological Health,
Food and Drug Administration, US
- 9:50-10:10 (II-5) *CIE Photobiological Safety of Lamps – Standardization Effort*
Robert Levin, Osram Sylvania, US
- 10:10-10:30 Coffee Break
- 10:30-10:50 (II-6) *Optical Radiation Hazards and International Standards for Lighting Products*
Peter Drop, Philips Lighting, NL
- 10:50-11:10 (II-7) *Center for Devices and Radiological Health, Food and Drug Administration Activities in Lamp Evaluation*
Sharon A. Miller and Robert H. James, Electro-Optics Branch, Center for Devices and Radiological Health, Food and Drug Administration, US
- 11:10-11:30 (II-8) *Visual Impact of Effective Ocular Protection*
John Mellerio, University of Westminster, GB
- 11:30-11:50 (II-9) *Maximum Permissible Exposure to Incoherent Radiation - Activities in IEC / TC / 76*
Ernst Sutter, Federal Institute for Physical Technology, DE
- 11:50-12:10 (II-10) *Action Spectra for Treatment of Hyperbilirubinemia – Monitoring Meters*
Myron L. Wolbarsht, Department of Psychology, Duke University, US
- 12:10-12:30 (II-11) *UV Monitoring – Meeting the Challenge of Accuracy*
John DeLuisi, National Oceanic and Atmospheric Administration, US
- 12:30-12:50 (II-12) *UV Indices – Communicating UV Levels to the Public*
Elizabeth Weatherhead, National Oceanic and Atmospheric Administration, US

Wednesday September 2, 1998

12:50-1:50 Lunch

1:50-2:10 *Discussion on Action Spectra Used in Standards*
(II-13) Colin Roy, Australian Radiation Laboratory, AU

2:10-2:30 *Germicidal Action Spectra and UV Disinfection Monitoring Meters*
(II-14) Richard Vincent, EPRI Northeast Regional Community Environmental Center, US

2:30-2:50 *Hazards from Ophthalmic Instruments - ISO Safety Standards*
(II-15) Michael Wolffe, Ophthalmic Consultant, GB

2:50-3:10 *Real Life Measurement for Hazard Assessment - Measurement*
(II-16) *Requirements to Gain FDA Clearance for an Ophthalmic Instrument*
Ray Lambe, National Physical Laboratory, GB

3:10-3:30 Coffee Break

3:30-3:50 *Discussion - Impact of Standards on Product Safety*
Panel Chair: Charles Campbell, Humphrey Systems, US
Members: Peter Drop, Philips Lighting, NL
Robert Levin, Osram Sylvania, US
Michael Wolffe, Ophthalmic Consultant, GB

3:50-4:10 *Sunscreens - In Vivo Versus in Vitro Testing: Pros and Cons*
(II-17) Serge Forestier, Department of Biology, L'Oreal Research Lab, FR

4:10-4:30 *Protective Qualities of UV Shading Materials*
(II-18) Natasha van Tonder, CSIR, ZA

4:30-4:50 *UV Index and Communicating UV Information to the Public*
(II-19) Pierre Cesarini, Securite Solaire, FR

4:50-5:10 *Discussion - Problems in Standards - Future Needs*
Panel Chair: Prof. Jan Stolwijk Yale University, US
Members: Robert Landry, CDRH/FDA, US
Rudiger Matthes, ICNIRP Scientific Secretariat, DE
David H. Sliney, US Army CHPPM, US
Ernst Sutter, Physikalisch-Technische Bundesanstalt, DE

5:10-5:30 *Photometry - The CIE $V(\lambda)$ Function and What Can Be Learned from*
(II-20) *Photometry*
Yoshi Ohno, National Institute of Standards and Technology, US

5:30-5:45 *Measuring The Radiance Of Conventional Lamps And Leds*
(II-21) Terry L. Lyon, US Army Center for Health Promotion and Preventive Medicine, US

5:50 *Meeting adjourns*

Thursday September 3, 1998

SESSION III: Measurements Needed to Apply Photobiological Guidelines and Standards

Moderators: AM Edward A. Early, NIST Optical Technology Division US.
 PM Ambler Thompson, NIST Optical Technology Division US

- 8:20-8:50 *Broad-Band Radiometers – Uses and Limitations*
 (III-1) Wesley J. Marshall, US Army Center for Health Promotion and Preventive Medicine, US
- 8:50-9:10 *Spectroradiometric Basis for Calibration*
 (III-2) Robert Saunders, National Institute for Standards and Technology, US
- 9:10-9:30 *Assessing UV Hazard with Magnesium-Tungstate Meters*
 (III-3) Daniel Berger, Solar Light Company Inc., US
- 9:30-9:50 *Interference-filter Radiometry*
 (III-4) Alex Ryer, International Light Inc., US
- 9:50-10:10 *Field Portable Acousto-Optic Spectrometers*
 (III-5) Neelam Gupta, Army Research Lab, US
- 10:10-10:30 Coffee Break
- 10:30-10:50 *Filter Detector for Studying the Blue Light Hazard*
 (III-6) Kohtaro Kohmoto, Toshiba Lighting and Technology Corporation, JP
- 10:50-11:10 *Experiences of Measurements in the Workplace*
 (III-7) Harald Siekmann, Institute for Occupational Safety, DE
- 11:10-11:30 *Polysulfone Films as Actinic UV Dosimeters – A Physical Description*
 (III-8) Andreas Krins, University of Dresden, Clinic for Dermatology, DE
- 11:30-11:50 *Problems in Outdoor Field Measurements of Light Sources*
 (III-9) James Franks, US Army Center for Health Promotion and Preventive Medicine, US
- 11:50-12:10 *Measurements of Welding Arcs*
 (III-10) Patrick von Nandelstadh, Institute of Occupational Health, FI
- 12:10-12:30 *Solar UV Monitoring by Spectroradiometry Versus Broad-Band Monitors*
 (III-11) Kirsti Leszczynski, Danish National Meteorological Institute, DK
- 12:30-12:50 *Multi-Band Radiometers – A Class of UV Radiometers Used for Dose, Cloud and Ozone Determinations*
 (III-12) Charles R. Booth, Biospherical Instruments, Inc., US
- 12:50-1:50 Lunch
- 1:50-2:10 *Critical Fields-of-View and Entrance Aperture in Hazard Evaluations*
 (III-13) Karl Schulmeister, Institute for Radiation Protection, AT

Thursday September 3, 1998

- 2:10-2:30 (III-14) *Using Broad Band Radiometers for Measurements on Sources*
Teresa Goodman, National Physical Laboratory, GB
- 2:30-2:50 (III-15) *Quality Control and Calibration of Broad-Band Solar UV Monitoring Networks*
Andrew J. Pearson, Optical Radiation Group, Oxon, GB
- 2:50-3:10 (III-16) *The Swedish Radiation Protection Institute's Criteria for Sunbed Lamp Measurements – A Proposed New Legislation on Sunbeds in Sweden Specifies Criteria for Fluorescent Tube Replacement Lamps in "UV-type 3" Solaria*
Ulf Wester, Swedish Radiation Protection Institute, SE
- 3:10-3:30 Coffee Break
- 3:30-3:50 (III-17) *Solar Simulators for Sunscreen Testing*
Frank Wilkinson, Division of Applied Optics, CSIRO, AU
- 3:50-4:10 (III-18) *Solar Simulators - Used in Drug and Cosmetic Testing*
Robert M. Sayre, Rapid Precision Testing Laboratories, US
- 4:10-4:40 *Contributed Posters and Abstracts*
Janusz Beer, Center for Devices and Radiological Health, Food and Drug Administration, US
- 4:40-5:20 *CIE Activities and Requirements for Standards*
Panel Chair: Colin Roy, Australian Radiation Laboratory, AU
- 5:20 *Closing Remarks*
David H. Sliney, US Army Center for Health Promotion and Preventive Medicine, US
- 5:30 *Meeting adjourns*

RESEARCH WORKSHOP ON RISKS AND BENEFITS
OF EXPOSURE TO ULTRAVIOLET
RADIATION AND TANNING

PRELIMINARY AGENDA

WEDNESDAY, SEPTEMBER 16, 1998
NATCHER CONFERENCE CENTER
7:00-9:30 P.M.

5:30-7:00 REGISTRATION

7:00-7:10 WELCOME

Stephen I. Katz, M.D., Ph.D.
Alan N. Moshell, M.D.
Vincent De Leo, M.D.
Workshop Chair

SESSION A Ultraviolet Radiation: Sources and Measurement

7:10-7:15 Overview

David H. Sliney, Ph.D.
Session Chair

7:15-7:30 Measurement of UVA and UVB

David H. Sliney, Ph.D.

7:30-7:45 Broadband and Narrow-Band
UV Sources

Edward C. De Fabo, Ph.D.

7:45-8:00 Artificial UV Sources Intended
for Human Skin Exposure

Robert M. Sayre, Ph.D.

8:00-8:15 Sources of Inadvertent Skin
UVL Exposure

Gene Moss, M.S., MPH

8:15-9:30 Session A Discussion

Panel Members

Donald Forbes, Ph.D., ATS
Robert James
Joseph Stanfield, M.S.

9:30 ADJOURNMENT

THURSDAY, SEPTEMBER 17, 1998
NATCHER CONFERENCE CENTER
8:00 A.M.-7:30 P.M.

SESSION B Ultraviolet Interactions With and Effects on the Skin

8:00-8:05	Overview	Irene E. Kochevar, Ph.D. Session Chair
8:05-9:05	Mutagenesis and Carcinogenesis	
8:05-8:20	Molecular/DNA	Frank deGruijl, Ph.D.
8:20-8:35	Molecular/Non-DNA	Vincent A. De Leo, M.D.
8:35-9:05	Epidemiologic Aspects	Margaret A. Tucker, M.D. Richard P. Gallagher, M.A.
9:05-9:20	Photoimmunology	Paul R. Bergstresser, M.D.
9:20-9:35	Aging in Skin	Gary J. Fisher, Ph.D.
9:35-11:00	Session B Discussion	
	Panel Members	Janusz Z. Beer, Ph.D. Kenneth H. Kraemer, M.D. Frances Noonan, Ph.D. Joseph Stanfield, M.S. Jan C. van der Leun, Ph.D.

11:00-11:15 BREAK

SESSION C Beneficial Effects of UV Exposure

11:15-11:20	Overview	Jan C. van der Leun, Ph.D. Session Chair
11:20-12:00	Epidemiologic Evidence: Natural and Acquired Pigmentation	Martin A. Weinstock, M.D., Ph.D. Michael F. Holick, M.D., Ph.D. George Studzinski, M.D., Ph.D. Cedric F. Garland, Dr.PH

12:00-12:15	Seasonal Affective Disorder	Norman E. Rosenthal, M.D.
12:15-1:15	LUNCH BREAK	
1:15-2:55	Session C Discussion	
	Panel Members	W. Howard Cyr, Ph.D. Alan B. Fleischer, M.D. Robin L. Hornung, M.D., MPH Kenneth H. Kraemer, M.D. Joseph Schuster James M. Spencer, M.D. Antony R. Young, Ph.D.
SESSION D	<u>Methods of Producing/Enhancing the Tanning Process</u>	
2:55-3:00	Overview	Barbara A. Gilchrest, M.D. Session Chair
3:00-3:30	Tanning Process	
3:00-3:15	Molecular/Enzymatic Events	Vincent J. Hearing, Jr., Ph.D.
3:15-3:30	Biologic/Cellular Events in Human Skin	R. Rox Anderson, M.D.
3:30-3:45	BREAK	
3:45-4:15	UVA Tanning	Jan C. van der Leun, Ph.D. Gordon Ainsleigh, D.C.
4:15-4:30	UVA and Psoralen	Robert S. Stern, M.D.
4:30-4:45	DNA Fragments or Other Methods To Turn On the Cellular Tanning Process	Barbara A. Gilchrest, M.D.
4:45-5:00	Induction of Melanogenesis by Diols	David A. Brown, Ph.D.
5:00-5:30	BREAK	

5:30-5:40 Comments From Australia:
Bruce Armstrong, M.D., Ph.D. Martin A. Weinstock, M.D., Ph.D.
Richard P. Gallagher, M.A.

5:40-7:30 Session D Discussion

Panel Members

Patricia Agin, Ph.D.
David A. Brown, Ph.D.
Andrija Kornhauser, Ph.D.
Joseph Levy
Robert Wagner

FRIDAY, SEPTEMBER 18, 1998
NATCHER CONFERENCE CENTER
8:30 A.M. - 2:30 P.M.

SESSION E Sunburn as a Surrogate Marker
of Later Biologic Events

8:30-8:35 Overview

Francis P. Gasparro, Ph.D.
Session Chair

8:35-8:50 Measurement of Photoprotection
from UVB and/or UVA

Kays Kaidbey, M.D.

8:50-9:50 Correlation of Protection From Sunburn
With Prevention of

8:50-9:20 Carcinogenesis and
Photoimmunologic
Events

Margaret Kripke, Ph.D.
Marianne Berwick, Ph.D., MPH

9:20-9:35 Photoaging

Lorraine Kligman, Ph.D.

9:35-9:50 Other Surrogate Markers

Douglas Brash, Ph.D.

9:50-10:05 **BREAK**

10:05-11:30 Session E Discussion

Panel Members

Colin F. Chignell, Ph.D.
Lynne Drake, M.D.
Richard P. Gallagher, M.A.
C. Lee Peeler
Margaret A. Tucker, M.D.
Antony R. Young, Ph.D.

SESSION F

11:30-12:30 Open Discussion of All Topics

Vincent De Leo, M.D.

12:30-1:30 LUNCH BREAK

SESSION G

1:30-2:30 Workshop Summations

David H. Sliney, Ph.D.
Irene E. Kochevar, Ph.D.
Jan C. van der Leun, Ph.D.
Barbara A. Gilchrest, M.D.
Francis P. Gasparro, Ph.D.
Vincent A. De Leo, M.D.

2:30 ADJOURNMENT

RESEARCH WORKSHOP ON RISKS AND BENEFITS OF EXPOSURE TO ULTRAVIOLET RADIATION AND TANNING

A workshop focusing on the effects that ultraviolet A and ultraviolet B radiation have on the skin will be held at the Natcher Conference Center, National Institutes of Health, Bethesda, Maryland. The workshop will begin at 7 p.m. on Wednesday, September 16, and adjourn at 2:30 p.m. on Friday, September 18, 1998.

The workshop is being cosponsored by:

- National Institutes of Health: the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Cancer Institute, the National Institute of Environmental Health Sciences, and the National Institute on Aging
- Centers for Disease Control and Prevention: the National Institute for Occupational Safety and Health and the National Center for Chronic Disease Prevention and Health Promotion
- Food and Drug Administration.

The purpose of the workshop is to review the state of the science regarding ultraviolet A and ultraviolet B radiation, and to address the health effects of various methods of inducing a tan and using sunscreens agents.

This meeting has important public health implications, and recommendations resulting from it will guide future research directions in this area.

The workshop format will consist of formal presentations followed by panel discussions, which will be open to attendees. At least one-half of the time allotted to each session will be devoted to discussion.

The preliminary agenda is posted at [Agenda](#)

Attendees should include basic and clinical researchers, members of the medical community, and representatives from government, industry, and the public.

The registration fee is \$150 for non-government registrants. The fee is waived for Federal Government employees. To register, please access the registration form

[Agenda](#)

[Registration Form](#)

An Analysis of UVA Emissions from Sunlamps and the Potential Importance for Melanoma

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³Swedish Radiation Protection Institute, Stockholm, Sweden

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ABSTRACT

Exposure to solar UV radiation is a risk factor for cutaneous malignant melanoma (CMM). Epidemiologic studies have also considered the use of sunlamps as a possible contributor to CMM. We measured and analyzed the emission spectra of six different currently marketed sunlamps and a historical sunlamp, the UVB-emitting FS lamp, and compared the results to solar exposure. For a typical tanner (20 sessions @ 2 minimal erythema doses (MED)/session), the annual UVA doses from commonly used fluorescent sunlamps were 0.3–1.2 times that received from the sun. For a frequent tanner (100 sessions @ 4 MED/session), the annual UVA doses from fluorescent sunlamps were 1.2–4.7 times that received from the sun and 12 times for recently available, high-pressure sunlamps. To determine biologically effective doses, action spectra for squamous cell carcinoma (SCC) in humans and for melanoma in the *Xiphophorus* fish (XFM) were applied to the sunlamps' emission spectra. The results for the effective doses using the SCC action spectrum tracked the UVB doses, while the results using the XFM action spectrum tracked the UVA doses. When combined with UV exposure received from the sun, typical sunlamp use results in an approximate doubling of annual effective dose, if the XFM action spectrum is applied. Frequent use, however, can increase the annual effective XFM dose by as much as 6 times what would be received from the sun alone for fluorescent sunlamps and as much as 12 times for newer, high-pressure sunlamps.

INTRODUCTION

The incidence of cutaneous malignant melanoma (CMM)[†] has been increasing at rates of 4–5% per annum over the

past several decades among the Caucasian population (1). It is well established that solar exposure is a significant risk factor in the development of this disease (1–3). Melanoma incidence demonstrates an inverse dependence on latitude, though this relationship is not as pronounced as it is for nonmelanoma skin cancer (NMSC) (1).

Several epidemiologic studies have concluded that exposure to UV radiation from sunlamps appears to be a risk factor for melanoma (4–7). An epidemiologic study performed in Sweden (5) found a significant association (odds ratio [OR] = 4.2, 95% confidence interval [CI] = 1.6–11.0) for melanomas of the trunk with >10 sunlamp exposures per year. Previous epidemiologic studies from Canada and Europe have reported odds ratios in the range of 1.1–2.9 for individuals who ever used sunlamps *versus* no use (4,6–8). The strength of association tended to increase as sunlamp usage increased (4–6), indicating that cumulative, intense doses, such as those received from sunlamps, may play a role in melanoma etiology.

To assess the wavelength-dependence of UV-induced melanoma, an action spectrum for induction of melanoma (hereafter referred to as XFM) has been determined in the *Xiphophorus* fish (9). In this action spectrum the UVA (320–400 nm) wavelengths are only 5–50 times less effective than UVB (290–320 nm) in inducing melanoma. Also, a recent study using *Monodelphis domestica*, a South American opossum, found that UVA exposures of 25 kJ/m² were as effective as UVB exposures of 250 J/m² (*i.e.* a factor of 100 difference) in inducing precursors of melanoma (10). These results are significantly different from induction of erythema in humans (11) or squamous cell carcinoma (SCC) in mice (12) where the UVA wavelengths are about 1000 times less effective than the UVB wavelengths.

Because the emission spectra from most sunlamps is significantly different than that from the sun, we examined the differences in UVB and UVA outputs from various sunlamps and compared them with solar exposures. In addition, the sunlamps' emission spectra were weighted with two different action spectra to determine the difference in biological effectiveness between sunlamp and solar exposure. Spectral irradiance data were obtained from sunlamps typical of those sold in the U.S. over the past two decades and from two newly marketed sunbeds. Spectra were also obtained from

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†Abbreviations: CMM, cutaneous malignant melanoma; FDA, Food and Drug Administration; MED, minimal erythema dose; NIST, National Institute of Standards and Technology; NMSC, nonmelanoma skin cancer; SCC, squamous cell carcinoma; UVA, 320–400 nm; UVB, 290–320 nm; WEAC, Winchester Engineering and Analytical Center; XFM, *Xiphophorus* fish melanoma.

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the two most commonly sold sunlamps in Sweden to determine if there were any significant spectral differences that might account for the epidemiologic findings from the Swedish study (5). These lamps are likely to be typical of sunlamps used in that country for the last 10–20 years. The relative risk from sunlamp exposure *versus* solar exposure was determined using both the XFM action spectrum (9) and the SCC action spectrum (determined in the hairless mouse, corrected for human skin transmittance) (12). The SCC action spectrum was used because it is more similar to action spectra for erythema in humans and DNA damage, and it was developed for a mammalian model. It has yet to be shown that the XFM action spectrum is applicable to humans. Significant modifications may be required to account for differences in skin transmittance and possible differences in the underlying processes that lead to melanoma between the two species.

A survey of sunlamp users in the UK reports that the typical use pattern is 20 visits per year, but 7% of patrons use sunlamps 100 times per year or more (13). Therefore, the following two patterns of sunlamp exposure were considered in this evaluation: (1) a typical use pattern of 20 sunlamp sessions per year, at 2 minimal erythema doses (MED)/session and (2) a frequent use pattern of 100 sunlamp sessions per year at 4 MED/session.

MATERIALS AND METHODS

UVR sources. Spectral irradiance measurements from over 100 UVA sunlamps (single, bare lamps) sold in the US were performed at the Food and Drug Administration's (FDA's) Winchester Engineering and Analytical Center (WEAC). The spectra generally fell into one of three categories, matching the three different UVA phosphors used in sunlamp manufacture that produce emission spectra that peak at approximately 340 nm, 350 nm or 366 nm as demonstrated in Fig. 1A and B. From these data, two lamps, representing the 340 nm and 366 nm groups, were chosen for this study. In addition, two lamps commonly used in Sweden were also included; they were of European manufacture and were evaluated at the Swedish Radiation Protection Institute.

A total of seven tanning devices were evaluated in this study. In the cases in which the output from only a single lamp was measured, the output was adjusted to simulate the radiation levels received in a typical tanning situation, consisting of a bank of closely spaced sunlamps in a sunbed or tanning booth. Six currently used tanning devices were included: two 100 W UVA fluorescent lamps selected from lamps commonly used in sunbeds in the US identified as lamps 1 and 2; two 100 W UVA fluorescent lamps selected from lamps commonly used in sunbeds in Sweden identified as lamps 3 and 4; a high-speed sunbed unit consisting of 24–160 W fluorescent lamps that contain significantly more UVB than most UVA sunlamps and 4–400 W filtered high-pressure arc lamps in the facial area; and a UVA sunbed consisting of an array of 18–1600 W high-pressure arc lamps filtered to emit radiation primarily at wavelengths longer than 330 nm and a historical tanning device: a UVB fluorescent FS lamp (used >20 years ago for tanning).

Spectral irradiance data for the sun (including direct and diffuse radiation) equivalent to a clear day, at noon, in July in Washington, DC (latitude 38.9°N, zenith angle of 15°, 3.2 mm atmospheric ozone) (14) was also included in this analysis for comparison. These solar irradiance data were generated from an empirical equation developed by Diffey (15) based upon the measurements of Bener (16) that were performed over a period of years for different atmospheric ozone concentrations.

Measurements. The two lamps that were evaluated in Sweden were measured with an Optronics model 742 (Optronics Laboratories, Orlando, FL). This double-grating spectroradiometer has a teflon diffuser input with cosine angular response. The spectral irradiance was measured at 1 nm intervals (instrument bandwidth was

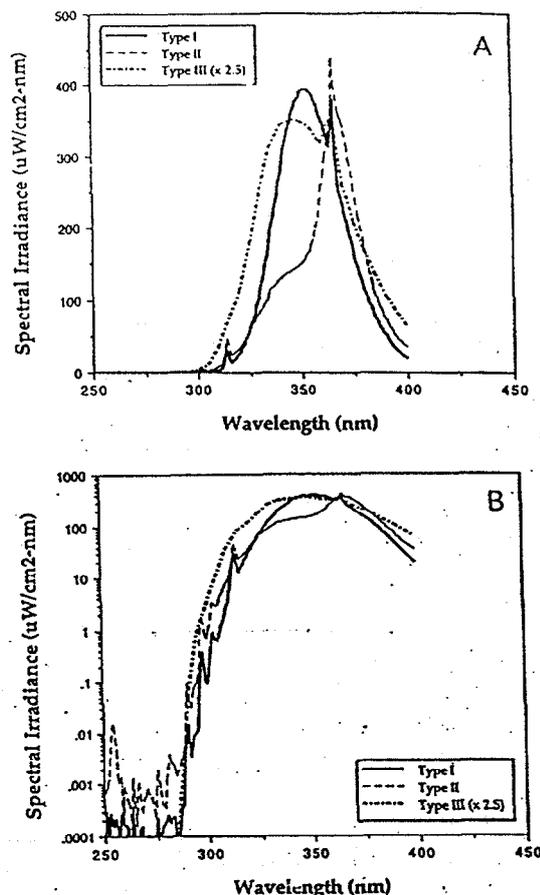


Figure 1. Spectral irradiance *versus* wavelength for three different phosphor combinations that are used in sunlamps. The linear plot A more readily demonstrates the spectral differences between the lamps, whereas the logarithmic plot B allows the output in the UVB and UVC regions to be represented also. The absolute output of the lamp with spectrum of type III was scaled upward by a factor of 2.5 to allow for easier comparison of the three types of phosphors. In these figures the lamp output was not corrected with the spectral transmittance of any acrylic filter.

1.6 nm with a wavelength accuracy of ± 0.5 nm). The calibration of the Optronics 742 is traceable to the National Institute of Standards and Technology (NIST) through the Swedish National Testing and Research Institute, Borås. The overall uncertainty associated with the measurement process is estimated at 15%.

The two sunlamps from Sweden (single bare lamp, no reflector) were measured at a distance of 1 mm. At this close distance, the input aperture of the detector "sees" an apparently infinite field of radiation. This radiation field is similar to the radiation from a sunbed consisting of a closely spaced bank of lamps in front of a reflector at a use distance of 2–3 cm. This relationship was verified by comparing the output of a single lamp at 1 mm to measurements of the output of the lower half of a sunbed, both measured with a handheld photometer (Digiphot, United Detector Technologies, Hawthorne, CA). These measurements indicated that the irradiance from an approximately flat field of radiation (*i.e.* the lower half of the sunbed) does not decrease significantly ($\pm 5\%$) with distance until the detector distance approaches 25 cm (approximately one-third the smallest dimension of the field).

The two US sunlamps (single bare lamp, no reflector) were measured at a distance of 50 cm with a double-grating spectroradiometer (Optronics model 747). The input of the spectroradiometer was a 7.6 cm-diameter integrating sphere with a 4 cm² entrance aperture. Spectral irradiance was measured at 5 nm intervals (instrument bandwidth was 5 nm, with a wavelength accuracy of ± 0.2 nm). The spectroradiometer system was calibrated by measuring a 1000 W

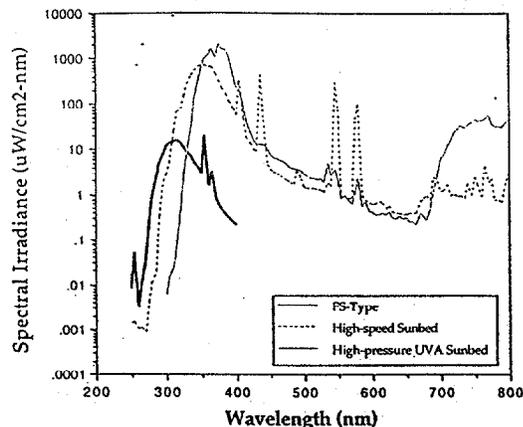


Figure 2. Spectral irradiance versus wavelength for the FS-type UVB sunlamp and for the two sunbeds: the high-pressure UVA sunbed consisting of 18–1600 W filtered high-pressure lamps and the new high-speed sunbed consisting of 24–160 W fluorescent lamps combined with 4–400 W filtered high-pressure lamps in the facial area. The absolute output indicated represents exposure levels under typical use conditions.

quartz halogen standard lamp that was calibrated by NIST. Assuming sunlamp instability of $\pm 10\%$, the total uncertainty (determined as a combination in quadrature of random errors and source instability) is estimated at 12.5%.

The measured spectral irradiance from the single US lamps was adjusted to the intensity level of an entire sunbed at a distance of 2–3 cm, again with the assistance of a handheld photometer. To account for geometrical differences in source size as “seen” by the detector, an additional uncertainty of an estimated 10% should be added to the previous uncertainty value of 12.5%, bringing the total uncertainty to 16%.

The adjusted emission spectra of lamps 1–4 were weighted with the spectral transmittance of a typical 5 mm-thick acrylic panel commonly used in sunbeds (data obtained from Steve Rothenberg at Interlectric, Warren, PA). This result simulated the spectral intensity that a sunbed user would receive at a distance of 2–3 cm, from a bed consisting of 18–24 closely spaced lamps in front of a reflector, behind an acrylic panel.

The UVB/FS lamp, the high-speed sunbed and the high-pressure UVA sunbed measurements were performed with a portable spectroradiometer system (Optronics model 752). The spectral outputs of these lamps are shown in Fig. 2. The input of the spectroradiometer was a 10.2 cm-diameter integrating sphere with a 9.6 cm² entrance aperture. Spectral irradiance was measured at 5 nm intervals (instrument bandwidth was 5 nm, with a wavelength accuracy of ± 0.2 nm). The spectroradiometer system was calibrated by measuring a 1000 W quartz halogen standard lamp that was calibrated by NIST. Assuming source instability of $\pm 10\%$, the total uncertainty (determined as a combination in quadrature of random errors and source instability) is estimated at 12.5% for the sunbed measurements. The spectral irradiance of the single UVB/FS lamp was measured and adjusted to a radiation level equivalent to what one would receive in an older style UVB lamp-equipped tanning booth by comparison with data from actual tanning booth measurements provided by Dr. Robert M. Sayre (Rapid Precision Testing Laboratories, Cordova, TN, personal communication). As before, an additional uncertainty of an estimated 10% should be added to the uncertainty value of 12.5% to account for geometrical differences, bringing the total uncertainty to 16%.

The measurements of both sunbeds were performed with the input aperture of the integrating sphere centered (facing up) under the top, curved canopy of the bed. To simulate actual exposure conditions, the integrating sphere was positioned at 20 cm above the lower bed surface, at approximately the position of a user's midabdomen, with the upper canopy closed.

Action spectra weighting. The CIE-adopted action spectrum for erythema (11) was used so that effective doses could be compared on

the basis of a biologically relevant exposure, the MED. The SCUHP action spectrum for human SCC (12) and the XFM action spectrum for melanoma in *Xiphophorus* (arithmetically derived through straight-line interpolation from data published in Setlow *et al.* (9)) were used to weight doses for cancer effectiveness. The SCC action spectrum was derived from a carcinogenesis action spectrum for hairless mice, adjusted to account for differences between mouse and human epidermal transmittance and normalized to one at 299 nm (12). The XFM action spectrum has not been adjusted to account for differences between *Xiphophorus* and human skin transmittance or other possible differences that may exist in the melanoma development process between the two species. As published, the XFM action spectrum begins and is normalized to one at 302 nm but has been extrapolated to 295 nm (at a value of one) for the purposes of this analysis.

The spectral irradiance at 5 nm intervals (1 nm for the lamps measured in Sweden) emitted by each tanning device was weighted with each of three different action spectra and integrated over the relevant UV wavelength region to give the effective spectral irradiance, E_{eff} :

$$E_{\text{eff}} = \int_{295}^{400} E_{\lambda} S_{\lambda} d\lambda \quad (1)$$

where E_{λ} is the spectral irradiance ($\text{W}/[\text{m}^2 \text{nm}]$) and S_{λ} is the action spectrum of interest.

UVB, UVA and effective doses per MED. The integrated irradiance values were converted to the UVB, UVA and effective doses that one would receive in the time required to reach 1 MED. The calculated “time to 1 MED” was determined by taking the erythemally effective irradiance for each source and dividing it into a standard MED for a person with skin type II of 200 J/m^2 (17):

$$t_{\text{MED}} = \frac{200 \text{ J}/\text{m}^2}{\int_{295}^{400} E_{\lambda} S_{\lambda} d\lambda} \quad (2)$$

where S_{λ} is the CIE erythemal action spectrum in this calculation.

The UVB and UVA doses received per MED were determined by multiplying the UVB and UVA dose rates (W/m^2) by the time to 1 MED (s). The effective doses received per MED were determined by multiplying the SCC-weighted effective irradiances (W/m^2) and the XFM-weighted effective irradiances (W/m^2) by the time to 1 MED (s). These values were then divided by the analogous results from the solar irradiance data, so that all further results are relative to the sample solar spectrum.

RESULTS

Emission spectra

The three types of spectra; types I, II and III, found by examining the output of the many sunlamps evaluated by WEAC over the past few years are shown by the three different lamp output spectra in Fig. 1A and B. The two lamps from the US market have emission spectra similar to lamps type II and III, while the two lamps from the Swedish market have emission spectra similar to lamps type I and II.

The integrated UV spectral irradiances (below 320 nm [UVC plus UVB] and above 320 nm [UVA]) for each sunlamp and for the sun are presented in Table 1. The output levels below 295 nm from lamps 1–4 were insignificant after filtration through the acrylic panel. The values in Table 1 demonstrate that all of the currently used sunlamps emit more UVA radiation than UVB radiation. The proportion of UVA emitted by lamp 2 (95.7%) was most similar to that of the sun (94.7%), whereas the emission spectra of lamps 1, 3 and 4 contained more than 97% UVA radiation.

UVB and UVA dose rates

The UVB dose rate from lamps 1–4 was 0.21–1.34 times that from noontime summer sun, while the UVA dose rate

Table 1. Integrated irradiance for the UVB and the UVA regions for sunlamps and the sun

Source	UVB (<320 nm) (W/m ²)	UVA (320-400 nm) (W/m ²)	%UVA/ total UV
Lamp 1 (US)—100 W fluorescent	0.58	89	99.0
Lamp 2 (US)—100 W fluorescent	3.56	80	95.7
Lamp 3 (Sweden)—100 W fluorescent	1.55	146	98.9
Lamp 4 (Sweden)—100 W fluorescent	2.59	117	97.8
Sunbeds			
High-speed—160 W fluorescent, with 4 400 W filtered arc lamps in facial area	6.8	310	97.8
UVB/FS-type—40 W fluorescent	4	3.8	48.7
High-pressure UVA with 18 1600 W filtered arc lamps	0.02	620	99.9
Solar—noon, July, Washington, DC (38.9°N)	2.65	48	94.7

was approximately 2–3 times that from the sun. The high-speed sunbed emitted approximately 2.5 times the UVB dose rate and 6 times the UVA dose rate of the sun. The high-pressure UVA sunbed emitted 13 times the UVA dose rate of the sun.

Effective dose rates

The effective dose rates for the tanning devices and the sun are shown in Table 2. For lamps 1–4, there was approximately a factor of 3 difference between the least and most effective lamp, in terms of erythema and SCC-effective dose rate. These two effective dose rates for lamps 1–4 and the sun are very similar, but they are approximately 3 and 8 times higher for the high-speed sunbed and the FS lamp, respectively. The XFM dose rates are 2–4 times higher than that from the sun in the case of lamps 1–4 and 8 and 12 times higher than that from the sun for the high-speed sunbed and the high-pressure UVA sunbed, respectively.

Table 2. Effective dose rate for erythema, SCC and melanoma calculated for the different sunlamps and the sun under typical use conditions*

Source	Erythema (W/m ² -eff)	SCC (W/m ² -eff)	XFM (W/m ² -eff)
Lamp 1 (US)	0.08	0.13	21
Lamp 2 (US)	0.27	0.52	20
Lamp 3 (Sweden)	0.16	0.22	38
Lamp 4 (Sweden)	0.22	0.40	28
Sunbeds			
High-speed	0.66	1.1	82
High-pressure UVA	0.22	0.33	120
UVB/FS-type	1.4	3.2	1.7
Solar—noon, July, Washington, DC	0.18	0.39	9.7

*All values, in effective W/m², represent the integrated effective irradiance from 295 to 400 nm for each action spectrum.

UVB, UVA and effective doses/MED

Effective dose rates were normalized to a biological exposure unit, 1 MED, and are presented as relative values to the output from the sun (Table 3). The last row in this table lists the absolute solar doses from which the absolute values for the sunlamps can be determined. On a per-MED basis, the UVB doses from lamps 1–4 are 0.48–0.85 times that of the sun, while the UVA doses are 1.1–4.1 times that of the sun. The UVA dose per MED from the high-pressure UVA sunbed is 10 times that of the sun.

The effective dose at 1 MED was determined from both the SCC dose rates and the XFM dose rates. The SCC dose per MED for all the UVA sunlamps and sunbeds was 0.64–0.87 times that of the sun, while for the FS lamp it was equal to that of the sun. However, the XFM dose per MED of lamps 1–4 and the high-pressure UVA sunbed was 1.3–4.5 and 9.8 times that of the sun, respectively. The XFM dose per MED for the FS lamp was only 0.02 times that of the sun.

Annual dose (MED) from the sun

Next the annual cumulative doses were compared for both sunlamp exposure and solar exposure. This analysis was based on the annual solar exposure of two types of indoor workers, typical and frequent tanners. Previous studies have shown that typical indoor workers receive approximately 2–4% of the available ambient solar UV during nonvacation time (18,19). The available annual solar UV in the Washington, DC area has been determined to be approximately 3500 MED (20). If we choose a median value of 3% of the total for a typical indoor worker and add an additional 1% for vacations (21), this translates to a total annual solar dose of 140 MED. For frequent tanners, the annual solar exposure has been found to be up to 10% of the available dose (22). This would translate to an annual solar dose of 350 MED in the Washington, DC area.

Annual dose (MED) from sunlamps

This analysis assumes one of two different sunlamp/solar exposure patterns: typical and frequent, of 20 and 100 ses-

Table 3. The UVB, UVA and effective (SCC and XFM) doses per MED from sunlamps relative to that of the sun

Source	Time to 1 MED (min)	Relative doses at 1 MED			
		UVB	UVA	Effective dose	
				SCC	XFM
Lamp 1 (US)	42	0.48	4.1	0.71	4.5
Lamp 2 (US)	12	0.85	1.1	0.87	1.3
Lamp 3 (Sweden)	21	0.65	3.4	0.64	4.3
Lamp 4 (Sweden)	15	0.77	2.0	0.83	2.2
Sunbeds					
High-speed	5	0.67	1.7	0.71	2.2
High-pressure UVA	15	0.006	10	0.66	9.8
UVB/FS-type	2	0.16	0.02	1.02	0.02
Solar—noon, July, Washington, DC	19	1.0	1.0	1.0	1.0
Solar, absolute dose (kJ/m ²)		(3)	(55)	(0.44)	(11)

sions per year and 140 and 350 MED from the sun per year, respectively. During a tanning session, a patron can receive from 0.8 MED (13) to the maximum of 4 MED, which is specified by the US FDA policy on timer limits (23). We assumed an average exposure of 2 MED per session or 40 MED/year from 20 sessions for the typical tanner/sunlamp user. For the frequent tanner/sunlamp user, we assumed the maximum of 4 MED/session or 400 MED/year from 100 sessions. The results in Tables 4 and 5 have been based on these two exposure patterns.

Annual UVA doses

The annual available UVA from the sun was estimated to be 192 500 kJ/m² based on 3500 MED/year multiplied by 55 kJ/m²/MED (Table 3). For a typical tanner, with an annual exposure of 140 MED, this translates to an annual UVA dose of 7700 kJ/m². For a frequent tanner with an annual exposure of 350 MED, this translates to an annual UVA dose of 19 250 kJ/m². It should be mentioned that if the majority of an individual's exposure occurs at times before 10:00 A.M.

or after 3:00 P.M., their annual solar UVA dose could be significantly higher, as the proportion of UVA to erythema-effective radiation is much larger at these times of day.

The annual UVA doses from the sunlamps and the sun were calculated based on the annual number of MED for the two exposure patterns and are shown in Table 4. The UVA dose received from 20 sessions at 2 MED per session and during 100 sessions at 4 MED per session was calculated for each sunlamp. When compared to solar exposure, 20 visits to a tanning salon at 2 MED per session can contribute an additional 0.31–1.2 times an individual's annual solar UVA dose for lamps 1–4 and as much as 2.9 times for a high-pressure UVA sunbed. In the case of a frequent tanner, 100 visits to a tanning salon at 4 MED per session can contribute 1.2–4.7 times an individual's annual solar dose for lamps 1–4 and as much as 12 times for 100 sessions under a high-pressure UVA sunbed.

Effective annual doses from sunlamps versus the sun

A similar analysis can be performed to compare the effective doses. In Table 5 the annual effective doses from the sun

Table 4. Assessment of the relative annual UVA dose due to sunlamp exposure relative to solar exposure for two types of sunlamp users: a typical user with 20 sessions/year @ 2 MED/session and a frequent user with 100 sessions/year @ 4 MED/session

Source	Relative annual UVA dose	
	Typical tanner with annual solar exposure of 140 MED	Frequent tanner with annual solar exposure of 350 MED
Lamp 1 (US)	1.2	4.7
Lamp 2 (US)	0.31	1.2
Lamp 3 (Sweden)	0.97	3.9
Lamp 4 (Sweden)	0.57	2.3
Sunbeds		
High-speed	0.48	1.9
High-pressure UVA	2.9	12
UVB/FS-type	0.005	0.02
Solar—noon, July, Washington, DC	1.0	1.0
Solar, absolute dose (kJ/m ²)	(7700)	(19 250)

Table 5. Assessment of the relative annual effective (SCC and XFM) dose due to sunlamp exposure relative to solar exposure for two types of sunlamp users: a typical user with 20 sessions/year @ 2 MED/session and a frequent user with 100 sessions/year @ 4 MED/session

Source	Relative annual effective dose			
	Typical tanner with annual solar exposure of 140 MED		Frequent tanner with annual solar exposure of 350 MED	
	SCC	XFM	SCC	XFM
Lamp 1 (US)	0.21	1.3	0.84	5.2
Lamp 2 (US)	0.24	0.38	0.97	1.6
Lamp 3 (Sweden)	0.17	1.2	0.71	5.0
Lamp 4 (Sweden)	0.22	0.67	0.91	2.7
Sunbeds				
High-speed	0.21	0.63	0.82	2.5
High-pressure UVA	0.19	2.8	0.77	11
UVB/FS-type	0.24	0.006	0.97	0.02
Solar—noon, July, Washington, DC	1.0	1.0	1.0	1.0
Solar, absolute dose (kJ/m ²)	(62)	(1500)	(150)	(3900)

were determined by multiplying the respective effective dose per MED times the number of annual MED for each type of tanner, typical or frequent. Then, the relative annual effective dose from sunlamp exposure was compared to the total annual effective dose from the sun, for both a typical tanner/sunlamp user and for the frequent tanner/sunlamp user. Applying the SCC action spectrum results in sunlamp exposure contributing approximately 0.20 times the annual solar effective dose for the typical user. For the frequent user the SCC-effective dose from sunlamp exposure is approximately equal to that from solar exposure for all of the sunlamps.

If the calculations are performed using the XFM action spectrum, the results are very similar to the analysis of UVA exposure. For the typical tanner/sunlamp user receiving 140 MED/year from the sun the XFM dose from solar exposure is approximately 1500 kJ/m². Thus 20 visits to a tanning salon at 2 MED per session can contribute 0.38–1.3 times an individual's annual solar dose for lamps 1–4 and as much as 2.8 times for 20 sessions under a high-pressure UVA sunbed. In the case of a frequent tanner/sunlamp user, 100 visits to a tanning salon at 4 MED per session can potentially contribute 1.6–5.2 times an individual's annual solar dose for lamps 1–4 and as much as 11 times for 100 sessions under a high-pressure UVA sunbed.

DISCUSSION

Our measurements indicate that the UVB dose rates from typical UVA fluorescent sunlamps, such as lamps 1–4, are similar to that of noontime, summer sun (latitude 38.9°N), while the UVA dose rates are two to three times higher. The two US sunlamps chosen for this study have significantly different emission spectra, with lamp 1 emitting 99% UVA and lamp 2 emitting 95.7% UVA, which is more similar to the sun. A recently available high-speed sunbed allows tanning in a much shorter period of time, with a UVB dose rate of two times and a UVA dose rate six times that of summer sun. The high-pressure UVA sunbed emits the highest UVA dose rate of 13 times that of summer sun. These last two are

examples of newer technology in the sunlamp industry that, although not widely used today, may represent a trend to lamps of higher dose rate.

The effective dose rates for typical UVA sunlamps (lamps 1–4) are similar to that of the sun when both the erythema and the SCC action spectra are used (Table 2). As expected, these effective dose rates from both the higher UVB-emitting high-speed sunbed and FS lamp exceed that of the sun. Although the high-pressure UVA sunbed emits less than 0.1% UVB, the large quantity of UVA radiation present contributes significantly to the weighted integral and the resultant effective dose rate is very similar to that of the sun when both the erythema and SCC action spectra are used. The absolute magnitude of the effective XFM dose rate is much larger than the erythema or SCC dose rate because the weighting factors in the UVA region of the XFM action spectrum are two to three orders of magnitude higher than in the other two action spectra. This fact renders all but the FS lamp significantly more effective than the sun when the XFM action spectrum is used, especially the high-pressure UVA sunbed that has an XFM dose rate over 12 times that of the sun.

Once the results are normalized to 1 MED (Table 3), both the UVB doses and the SCC doses from sunlamps are lower than the solar doses, while the UVA and XFM doses are significantly higher. Lamp 2 from the US market is the exception to this, as it appears to be most similar to the sun in its UV spectral content. For the high-speed sunbed, the SCC-effective dose is now less than that from the sun, while the XFM-effective dose is only twice that of the sun. However, the high-pressure UVA sunbed still stands out from the rest of the sunlamps with its UVA and XFM dose at 10 times and 9.8 times that of the sun, respectively. As expected, the SCC doses track the UVB doses and the XFM doses track the UVA doses. Thus, the unweighted doses could be used as a surrogate for the effective doses in an analysis of sources with emission spectra similar to the sources evaluated in this study.

Although the UVA dose rates from lamps 3 and 4 are

higher than the UVA dose rates from lamps 1 and 2, the UVA doses per MED and the effective doses per MED fall within the same range. Thus, there appear to be no significant differences between sunlamps marketed in the US and those marketed in Sweden that would account for the high odds ratios reported in the Swedish epidemiologic study (5). However, the available annual erythemally effective solar dose in Stockholm (59°N) is less than 0.60 of what is available in Washington, DC (24). Thus, although the UVA dose rates are not that different in the two locations (25), an examination of annual cumulative doses would demonstrate that sunlamp exposure contributes a significantly larger proportion of an individual's annual UV dose in Sweden compared to Washington, DC, assuming similar solar exposure patterns. Thus if cumulative, intense exposures are important to melanoma induction, the high odds ratios reported in the Swedish epidemiologic study (5) could be explained by this difference between sunlamp exposure and environmental exposure. In other words, for individuals residing in geographical areas of low solar exposure, sunlamp exposure could constitute a greater relative risk than for individuals residing in geographical areas of high solar exposure.

The results in Table 4 point to the fact that exposure to sunlamps can significantly increase an individual's total annual UVA dose, but this is highly dependent on exposure frequency. For lamps 1 and 3, the typical user is effectively doubling their annual UVA dose by adding 20 sunlamp sessions to their typical yearly solar exposure. Using lamp 2 will increase the yearly UVA dose by only a factor of 0.30, whereas using a high-pressure UVA sunbed will increase the yearly UVA dose to nearly four times what it would have been from solar exposure alone. For the frequent user, the situation looks significantly worse, even though a base solar dose of 2.5 times that of the typical tanner is assumed. In this case, the annual UVA dose can be increased by almost a factor of 6 for a 99.0% UVA sunlamp and by as much as a factor of 13 for the high-pressure UVA sunbed. Considering that the base solar UVA dose assumed is 19 250 kJ/m², a frequent user could receive up to 250 000 kJ/m² of UVA per year (eight times the dose for a typical user) if a high-pressure UVA sunbed were used 100 times/year at 4 MED/session in addition to the solar dose of 350 MEDs.

The results in Table 5 indicate that the magnitude of relative contribution of sunlamp exposure to total annual exposure is highly dependent on which action spectrum is chosen. If the SCC action spectrum is applied, the annual effective doses are increased by only a factor of approximately 0.20 over what would be received from the sun alone for a typical sunlamp use of 20 sessions/year. For the frequent user, this increases to approximately 0.8. If the XFM action spectrum is applied, the contribution from lamps 1-4 ranges from 0.38 to 5.2 times the solar dose, depending on the pattern of use. This relative increased dose goes up to 11 times for the high-pressure UVA sunbed for the frequent user. Thus, the choice of action spectrum is critical in determining the relative risk of sunlamp use.

If the XFM action spectrum proves to be accurate for humans, then exposure to UVA sunlamps could contribute a significantly higher risk for melanoma development than does exposure to the sun or exposure to the older UVB-type of sunlamp. However, in reality, a sunlamp user may be

more likely to get a burn from a UVB sunlamp because the time to reach an MED with a UVB sunlamp is much shorter and therefore more likely to be exceeded inadvertently during a tanning session. This potential could be reduced by lowering the dose rate and thereby increasing the time to erythema. In addition, there are remaining controversies regarding the importance of burns to the etiology of melanoma. Some researchers have suggested that only those exposures that result in a burn may be important (8,26). However, there is evidence, particularly from Australia, indicating that total cumulative overexposure of sunlight—not necessarily resulting in burns—is also important (27). If more data become available regarding the correct action spectrum and dose response model for melanoma, the comparative risk levels from exposure to sunlamps of differing spectral output can be quantified.

In generating the relative effective dose in Table 5, it was assumed that all exposure contributes equally to the total effective dose. However, a comparison of total cumulative dose received annually from sunlamps and especially the sun may not be a valid method of risk analysis for melanoma. One might argue that frequent users of sunlamps are similar to outdoor workers who do not demonstrate a significantly increased risk of melanoma over indoor workers (28-30). However, the emission spectrum, UV dose rate and exposure pattern of sunlamps are different from that of the sun, so the experience with outdoor workers cannot be directly extrapolated to the situation with indoor workers who use sunlamps. The etiology of melanoma depends strongly on genetic factors that may influence an individual's exposure pattern as well. In fact, in studies showing indoor workers to be at higher risk than outdoor workers, this difference in risk is reduced once host factors like skin color are taken into account (27). In addition, there may be a protective effect afforded by regular exposure to full-spectrum solar radiation, such as vitamin D production (29).

The data reported here indicate that modest exposures to commonly used sunlamps would increase an individual's annual UVA dose by 0.31-1.2 times. However, quite significant (>10 times higher) UV exposures can be obtained for frequent use of newly marketed sunlamps like the high-pressure UVA sunbed. The resulting annual effective doses exhibit an even larger variation than the annual UVA doses. Depending on which action spectrum is chosen—SCC or XFM—and which exposure pattern—typical or frequent—the range in annual effective doses can fall anywhere between a 0.17 increase to a 11-fold increase over what would be received from the sun. Until more information is available regarding the correct action spectrum and dose response for melanoma in humans, limiting one's exposure to both sunlamps and the sun would appear to be the most effective way to reduce one's risk.

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sequential exposures and maximum exposure time(s) in minutes.

(v) A statement of the time it may take before the expected results appear.

(vi) Designation of the ultraviolet lamp type to be used in the product.

(2) *Labels for ultraviolet lamps.* Each ultraviolet lamp shall have a label which contains:

(i) The words "Sunlamp—DANGER—Ultraviolet radiation. Follow instructions."

(ii) The model identification.

(iii) The words "Use ONLY in fixture equipped with a timer."

(3) *Label specifications.* (1) Any label prescribed in this paragraph for sunlamp products shall be permanently affixed or inscribed on an exterior surface of the product when fully assembled for use so as to be legible and readily accessible to view by the person being exposed immediately before the use of the product.

(i) Any label prescribed in this paragraph for ultraviolet lamps shall be permanently affixed or inscribed on the product so as to be legible and readily accessible to view.

(ii) If the size, configuration, design, or function of the sunlamp product or ultraviolet lamp would preclude compliance with the requirements for any required label or would render the required wording of such label inappropriate or ineffective, or would render the required label unnecessary, the Director, Office of Compliance (HFZ-300), Center for Devices and Radiological Health, on the Center's own initiative or upon written application by the manufacturer, may approve alternate means of providing such label(s), alternate wording for such label(s), or deletion, as applicable.

(iv) In lieu of permanently affixing or inscribing tags or labels on the ultraviolet lamp as required by §§ 1010.2(b) and 1010.3(a), the manufacturer of the ultraviolet lamp may permanently affix or inscribe such required tags or labels on the lamp packaging uniquely associated with the lamp, if the name of the manufacturer and month and year of manufacture are permanently affixed or inscribed on the exterior surface of the ultraviolet lamp so as to be legible and readily accessible to view. The

name of the manufacturer and month and year of manufacture affixed or inscribed on the exterior surface of the lamp may be expressed in code or symbols, if the manufacturer has previously supplied the Director, Office of Compliance (HFZ-300), Center for Devices and Radiological Health, with the key to such code or symbols and the location of the coded information or symbols on the ultraviolet lamp. The label or tag affixed or inscribed on the lamp packaging may provide either the month and year of manufacture without abbreviation, or information to allow the date to be readily decoded.

(v) A label may contain statements or illustrations in addition to those required by this paragraph if the additional statements are not false or misleading in any particular; e.g., if they do not diminish the impact of the required statements; and are not prohibited by this chapter.

(e) *Instructions to be provided to users.* Each manufacturer of a sunlamp product and ultraviolet lamp shall provide or cause to be provided to purchasers and, upon request, to others at a cost not to exceed the cost of publication and distribution, adequate instructions for use to avoid or to minimize potential injury to the user, including the following technical and safety information as applicable:

(1) *Sunlamp products.* The users' instructions for a sunlamp product shall contain:

(i) A reproduction of the label(s) required in paragraph (d)(1) of this section prominently displayed at the beginning of the instructions.

(ii) A statement of the maximum number of people who may be exposed to the product at the same time and a warning that only that number of protective eyewear has been provided.

(iii) Instructions for the proper operation of the product including the function, use, and setting of the timer and other controls, and the use of protective eyewear.

(iv) Instructions for determining the correct exposure time and schedule for persons according to skin type.

(v) Instructions for obtaining repairs and recommended replacement components and accessories which are compatible with the product, including

compatible protective eyewear, ultraviolet lamps, timers, reflectors, and filters, and which will, if installed or used as instructed, result in continued compliance with the standard.

(2) *Ultraviolet lamps.* The users' instructions for an ultraviolet lamp not accompanying a sunlamp product shall contain:

(i) A reproduction of the label(s) required in paragraphs (d)(1)(i) and (2) of this section, prominently displayed at the beginning of the instructions.

(ii) A warning that the instructions accompanying the sunlamp product should always be followed to avoid or to minimize potential injury.

(iii) A clear identification by brand and model designation of all lamp models for which replacement lamps are promoted, if applicable.

(f) *Test for determination of compliance.* Tests on which certification pursuant to § 1010.2 is based shall account for all errors and statistical uncertainties in the process and, wherever applicable, for changes in radiation emission or degradation in radiation safety with age of the product. Measurements for certification purposes shall be made under those operational conditions, lamp voltage, current, and position as recommended by the manufacturer. For these measurements, the measuring instrument shall be positioned at the recommended exposure position and so oriented as to result in the maximum detection of the radiation by the instrument.

(The information collection requirements contained in paragraphs (d) and (e) were approved by the Office of Management and Budget under control number 0910-0195)

[50 FR 36550, Sept. 6, 1985]

§ 1040.30 High-intensity mercury vapor discharge lamps.

(a) *Applicability.* The provisions of this section apply to any high-intensity mercury vapor discharge lamp that is designed, intended, or promoted for illumination purposes and is manufactured or assembled after March 7, 1980, except as described in paragraph (d)(1)(ii) of this section.

(b) *Definitions.* (1) *High-intensity mercury vapor discharge lamp* means any lamp including any "mercury vapor" and "metal halide" lamp, with the ex-

ception of the tungsten filament self-ballasted mercury vapor lamp, incorporating a high-pressure arc discharge tube that has a fill consisting primarily of mercury and that is contained within an outer envelope.

(2) *Advertisement* means any catalog, specification sheet, price list, and any other descriptive or commercial brochure and literature, including videotape and film, pertaining to high-intensity mercury vapor discharge lamps.

(3) *Packaging* means any lamp carton, outer wrapping, or other means of containment that is intended for the storage, shipment, or display of a high-intensity mercury vapor lamp and is intended to identify the contents or recommend its use.

(4) *Outer envelope* means the lamp element, usually glass, surrounding a high-pressure arc discharge tube, that, when intact, attenuates the emission of shortwave ultraviolet radiation.

(5) *Shortwave ultraviolet radiation* means ultraviolet radiation with wavelengths shorter than 320 nanometers.

(6) *Cumulative operating time* means the sum of the times during which electric current passes through the high-pressure arc discharge.

(7) *Self-extinguishing lamp* means a high-intensity mercury vapor discharge lamp that is intended to comply with the requirements of paragraph (d)(1) of this section as applicable.

(8) *Reference ballast* is an inductive reactor designed to have the operating characteristics as listed in Section 7 in the American National Standard Specifications for High-Intensity Discharge Lamp Reference Ballasts (ANSI C82.5-1977)¹ or its equivalent.

(c) *General requirements for all lamps.*

(1) Each high-intensity mercury vapor discharge lamp shall:

(i) Meet the requirements of either paragraph (d) or paragraph (e) of this section; and

(ii) Be permanently labeled or marked in such a manner that the name of the manufacturer and the month and year of manufacture of the lamp can be determined on an intact lamp and after the outer envelope of

¹ Copies are available from American National Standards Institute, 1430 Broadway, New York, NY 10018.

D-U
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

AUG 21 1985

Food and Drug Administration
8757 Georgia Avenue
Silver Spring MD 20910

TO: ALL MANUFACTURERS, IMPORTERS AND POTENTIAL MANUFACTURERS OF
SUNLAMP PRODUCTS.

SUBJECT: POLICY ON MAXIMUM TIMER INTERVAL AND EXPOSURE SCHEDULE FOR
SUNLAMP PRODUCTS.

BACKGROUND:

The amended performance standard for sunlamp products (21 CFR 1040.20) was published in the September 6, 1985 issue of the Federal Register and will become effective September 8, 1986. Any sunlamp product manufactured on or after that date must comply with the amended standard.

The ten (10) minute maximum timer interval requirement was removed from the original performance standard since there are newer sunlamp products on the market for which ten (10) minutes is not appropriate. The maximum timer interval now depends on the intensity and spectral distribution of ultraviolet (UV) radiation emission of each individual model of sunlamp product and must not exceed the maximum recommended exposure time provided on the required product warning label. Therefore, sunlamp product manufacturers must develop an exposure schedule and establish the maximum recommended exposure time (and therefore the maximum timer interval) based on the characteristics of their particular products.

The intended purposes of a sunlamp product timer are to provide for reliable control of exposures and to limit acute (and delayed) damage from unintentionally long exposures. However, the maximum timer setting should also allow for selection of exposure times needed to build up and maintain a tan. The maximum timer interval is in no way to be considered as a safe limit; all ultraviolet radiation is potentially hazardous.

The standard requires the manufacturer to provide an exposure schedule in the product warning label. The purpose of the exposure schedule is to allow a person to gradually build-up skin pigmentation and to maintain a tan while controlling the risk of acute injury and delayed adverse effects. Since the UV radiation dose that causes a barely discernible pink coloration (minimal erythema dose or MED) is not the same for different skin types, the exposure schedule for first time users will depend on the skin type of the user. Furthermore, suberythemogenic doses of UV radiation received at 24 hours intervals initially lead to lowering of the erythema and tanning thresholds. Therefore, the exposure schedule and maximum recommended exposure time should be constrained by the potential for erythema as well as the quantity of radiation necessary to achieve and maintain a tan.

POLICY:

The Center for Devices and Radiological Control (CDRC) will use the following criteria to evaluate the adequacy of the exposure schedule and the recommended maximum exposure time (and therefore the maximum timer

Page 2

1) The maximum recommended exposure time (and maximum timer interval) must not exceed a value which will result in an exposure of four (4) times the minimal erythema dose (MED) for untanned Type II skin (always burns, then tans slightly). This is based on the CDRH Erythema Action Spectrum [proposed action spectrum of Commission Internationale de L'Eclairage (CIE) modified by CDRH]. See Appendix A for the action spectrum and weighting factors and equations needed to derive it.

The formula for determining the recommended maximum exposure time, T_e in seconds is:

$$T_e = \frac{624J/M^2}{\sum V_i R_i} \quad \text{where Standard MED} = 156J/M^2 \text{ at } 296nm$$

V_i = weighting factor
 R_i = irradiance in W/M^2

2) The recommended maximum exposure time must not exceed a value which will result in an exposure of four (4) times the minimal melanogenic dose (MMD) for untanned Type II skin. This is based on the melanogenic action spectrum developed by Parrish et al (1982). See Appendix B for this action spectrum.

The formula for determining the recommended maximum exposure time, T_m in seconds is:

$$T_m = \frac{1836J/M^2}{\sum J_i R_i} \quad \text{where standard MMD} = 459J/M^2 \text{ at } 296nm$$

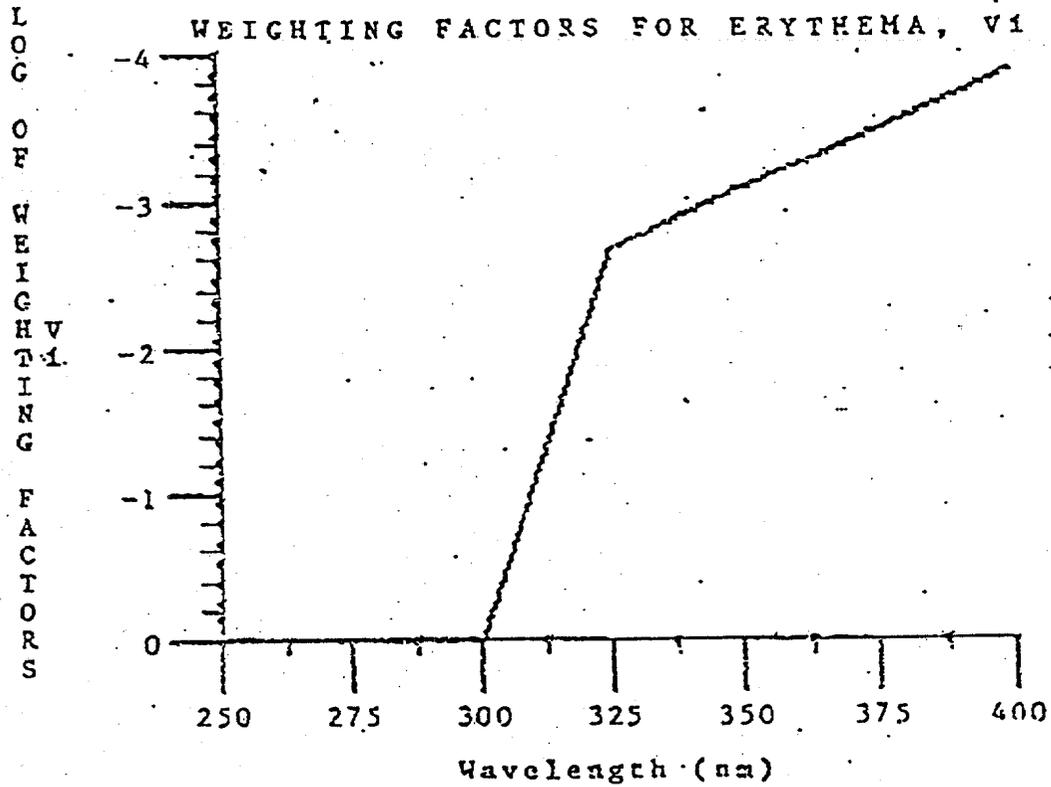
J_i = weighting factor
 R_i = irradiance in W/M^2

3) The recommended exposure schedule should provide for exposures of no more than 0.75 MED three times the first week, gradually increasing the exposure the following weeks until maximum tanning has occurred (approximately four weeks total) and then provide for maintenance of a tan by biweekly or weekly exposures of up to four(4) MEDs or four(4) MMDs, whichever is less.

CDRH believes that the above criteria balances the need to limit acute (and delayed) damages from unintentionally long exposure and the need to provide for single exposure durations adequate to achieve and maintain a tan.

Walter E. Gundaker
for Walter E. Gundaker, Director
Office of Compliance
Center for Devices and
Radiological Health

Appendix A
(page 1)

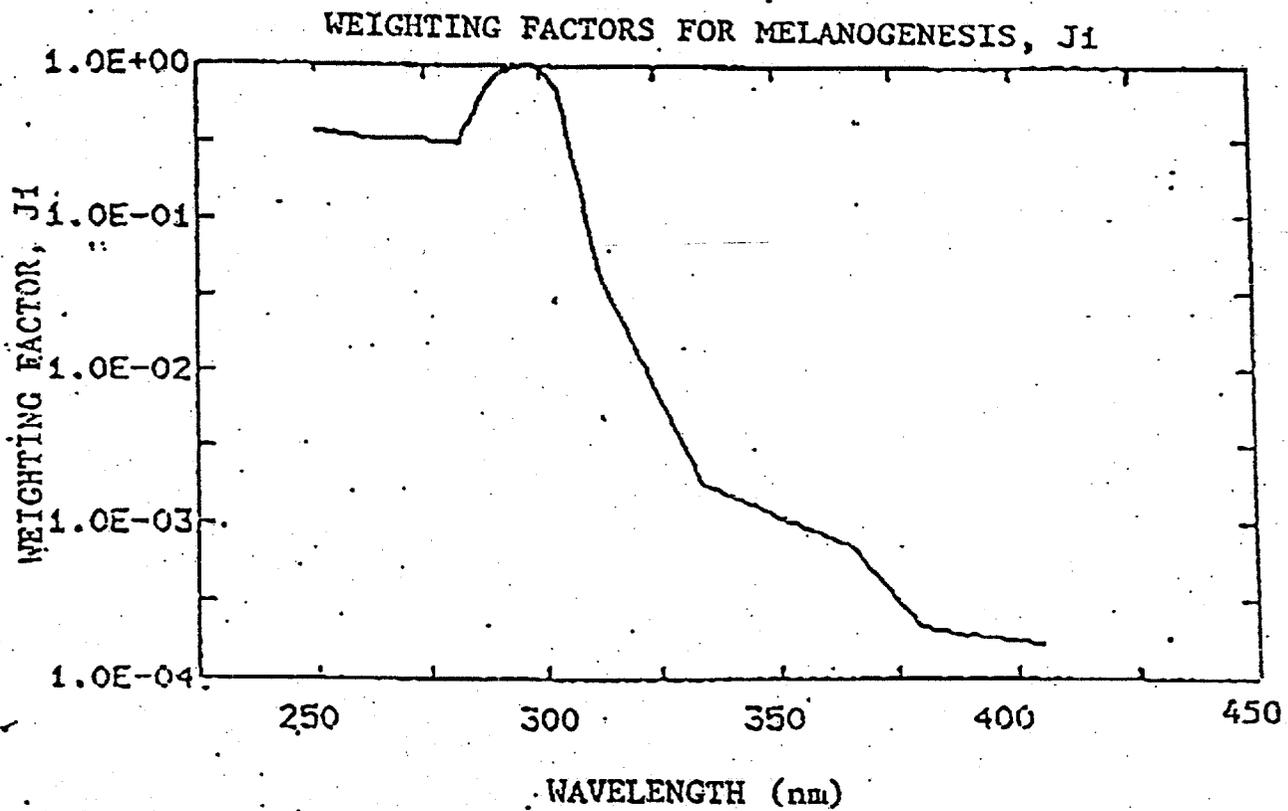


The equations describing the curve are:

$$V_1(\lambda) = 1.0 \quad (250 < \lambda < 302 \text{ nm})$$

$$V_2(\lambda) = 10^{0.114(302-\lambda)} \quad (302 < \lambda < 325 \text{ nm})$$

$$V_2(\lambda) = 10^{0.0161(159-\lambda)} \quad (325 < \lambda < 405 \text{ nm})$$

Appendix B
(page 1)

The MMD as function of wavelength has been interpolated (using log MMD) from the action spectrum for melanogenesis of type II skin (Parrish et al 1982)

Appendix B
(page 2)

PARRISH MELANOGENSIS TYPE II SKIN 1982 NORMALIZED TO 296 NM

WAVELENGTH (nm)	Ji				
250	.378409	302	.815392	354	.100202E-02
251	.374828	303	.750391	355	.972644E-03
252	.371248	304	.690261	356	.944186E-03
253	.367714	305	.502296	357	.916645E-03
254	.364225	306	.36551	358	.890022E-03
255	.360783	307	.265997	359	.863859E-03
256	.35734	308	.193565	360	.838613E-03
257	.353943	309	.14087	361	.813826E-03
258	.350547	310	.102497	362	.789958E-03
259	.347196	311	.745893E-01	363	.767007E-03
260	.343891	312	.054301	364	.747729E-03
261	.340632	313	.395016E-01	365	.722942E-03
262	.337419	314	.341137E-01	366	.666943E-03
263	.334206	315	.294593E-01	367	.615075E-03
264	.331039	316	.254384E-01	368	.567338E-03
265	.327672	317	.219683E-01	369	.523272E-03
266	.324413	318	.189709E-01	370	.48288E-03
267	.326954	319	.163921E-01	371	.44547E-03
268	.326449	320	.141467E-01	372	.410953E-03
269	.32599	321	.122143E-01	373	.379097E-03
270	.325531	322	.105481E-01	374	.34972E-03
271	.325072	323	.911137E-02	375	.322593E-03
272	.324613	324	.786745E-02	376	.297577E-03
273	.324154	325	.679336E-02	377	.274534E-03
274	.323695	326	.586616E-02	378	.253236E-03
275	.323236	327	.506748E-02	379	.233591E-03
276	.321445	328	.437483E-02	380	.215505E-03
277	.319609	329	.377812E-02	381	.213532E-03
278	.317865	330	.326255E-02	382	.211558E-03
279	.316075	331	.281741E-02	383	.209963E-03
280	.314285	332	.243276E-02	384	.207702E-03
281	.312541	333	.210089E-02	385	.205921E-03
282	.31075	334	.181447E-02	386	.203939E-03
283	.351694	335	.176123E-02	387	.202057E-03
284	.398008	336	.170982E-02	388	.200221E-03
285	.450427	337	.165978E-02	389	.189296E-03
286	.509732	338	.161113E-02	390	.196594E-03
287	.576885	339	.156385E-02	391	.194804E-03
288	.652851	340	.151841E-02	392	.193014E-03
289	.738778	341	.147388E-02	393	.191224E-03
290	.836088	342	.143074E-02	394	.18948E-03
291	.861518	343	.138897E-02	395	.187735E-03
292	.887498	344	.134812E-02	396	.186037E-03
293	.91435	345	.130864E-02	397	.184339E-03
294	.94212	346	.127054E-02	398	.18264E-03
295	.970625	347	.123335E-02	399	.180989E-03
296	1	348	.11971E-02	400	.179336E-03
297	.990959	349	.116222E-02	401	.177683E-03
298	.982054	350	.112825E-02	402	.176077E-03
299	.973287	351	.109525E-02	403	.17447E-03
300	.96429	352	.106307E-02	404	.172864E-03
301	.886993	353	.103123E-02	405	.171257E-03

* * * EFFECTIVE UPON PUBLICATION

FDC date	State	City	Airport	FDC No.	SIAP
04/29/99	PA	STATE COLLEGE	UNIVERSITY PARK	9/2846	VOR/DME RNAV or GPS RWY 6 AMDT 6
04/29/99	PA	STATE COLLEGE	UNIVERSITY PARK	9/2847	VOR or GPS-B AMDT 9
04/29/99	WI	APPLETON	OUTAGAMIE COUNTY REGIONAL	9/2851	ILS RWY 3, AMDT 16C
04/30/99	MO	BUTLER	BUTLER MEMORIAL	9/2875	GPS RWY 18, ORIG
04/30/99	TX	AUSTIN	AUSTIN-BERGSTROM INTL	9/2879	ILS RWY 35L, AMDT 1
04/30/99	TX	AUSTIN	AUSTIN-BERGSTROM INTL	9/2880	GPS RWY 35L, AMDT 1
04/30/99	TX	AUSTIN	AUSTIN-BERGSTROM INTL	9/2881	GPS RWY 17R, AMDT 1
04/30/99	TX	AUSTIN	AUSTIN-BERGSTROM INTL	9/2882	ILS RWY 17R, AMDT 1
05/1/99	NH	MANCHESTER	MANCHESTER	9/3102	ILS RWY 2, AMDT 2
05/1/99	NH	MANCHESTER	MANCHESTER	9/3103	ILS RWY 35, AMDT 19
05/04/99	IL	CHICAGO/AURORA	AURORA MUNI	9/2970	VOR or GPS-A AMDT 1A
05/05/99	IL	CHICAGO/AURORA	AURORA MUNI	9/2983	ILS RWY 9, AMDT 1A
05/06/99	OH	MIDDLETOWN	HOOK FIELD MUNI	9/3009	LOC RWY 23, AMDT 7B
05/06/99	OH	MIDDLETOWN	HOOK FIELD MUNI	9/3010	NDB or GPS RWY 23, AMDT 8A
05/06/99	OH	MIDDLETOWN	HOOK FIELD MUNI	9/3011	NDB or GPS-A, AMDT 2A
05/10/99	MN	WORTHINGTON	WORTHINGTON MUNI	9/3086	NDB or GPS RWY 29, ORIG
05/10/99	MN	WORTHINGTON	WORTHINGTON MUNI	9/3088	ILS RWY 29, ORIG
05/10/99	VA	RICHMOND	CHESTERFIELD COUNTY	9/3074	NDB or GPS RWY 33, AMDT 7A
05/10/99	VA	RICHMOND	CHESTERFIELD COUNTY	9/3075	VOR/DME or GPS RWY 15, ORIG
05/10/99	VA	RICHMOND	CHESTERFIELD COUNTY	9/3082	ILS RWY 33, ORIG

[FR Doc. 99-12949 Filed 5-20-99; 8:45 am]
BILLING CODE 4910-13-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310, 352, 700, and 740

[Docket No. 78N-0038]

RIN 0910-AA01

Sunscreen Drug Products For Over-The-Counter Human Use; Final Monograph

AGENCY: Food and Drug Administration, HHS,

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing conditions under which over-the-counter (OTC) sunscreen drug products are generally recognized as safe and effective and not misbranded as part of FDA's ongoing review of OTC drug products. FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and new data and information on sunscreen drug products that have come to the agency's attention. FDA is also issuing final rules regarding the labeling of certain cosmetic products to inform consumers that these products do not provide protection from the sun.

EFFECTIVE DATES: This regulation is effective May 21, 2001 for parts 310, 352, and 700 and is effective May 22, 2000 for part 740.

FOR FURTHER INFORMATION CONTACT: John D. Lipnicki, Center for Drug Evaluation and Research (HFD-560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-2222.

SUPPLEMENTARY INFORMATION:

I. Introduction

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 (ANPRM) 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 Drug Products (the Panel), which was the advisory review panel that evaluated data on the active ingredients in this drug class. The agency's proposed regulation for OTC sunscreen drug products, in the form of a tentative final monograph, was published in the Federal Register of May 12, 1993 (58 FR 28194).

In the Federal Register of June 8, 1994 (59 FR 29706), the agency proposed to amend the tentative final monograph (and reopened the comment period until August 22, 1994) to remove five sunscreen ingredients because of a lack of interest in establishing United States Pharmacopeia (USP) monographs: Digalloyl trioleate, ethyl 4-[bis(hydroxypropyl)] aminobenzoate,

glyceryl aminobenzoate, lawsone with dihydroxyacetone (interest was subsequently shown in developing a monograph for lawsone and dihydroxyacetone), and red petrolatum. The agency also reiterated that all sunscreen ingredients must have a USP monograph before being included in the final monograph for OTC sunscreen drug products. This final rule includes those sunscreen ingredients that have USP monographs.

In the Federal Register of September 16, 1996 (61 FR 48645), the agency amended the proposed rule to include avobenzene as a single ingredient and in combination with certain other sunscreen ingredients (interim marketing was allowed in the Federal Register of April 30, 1997 (62 FR 23350)). In the Federal Register of October 22, 1998 (63 FR 56584), the agency proposed to amend the tentative final monograph to include zinc oxide as a single ingredient and in combination with any proposed Category I sunscreen active ingredient except avobenzene.

In the Federal Register of April 5, 1994 (59 FR 16042), the agency reopened the administrative record and announced a public meeting to discuss ultraviolet A (UVA) radiation claims and testing procedures. In the Federal Register of August 15, 1996 (61 FR 42398), the agency reopened the administrative record and announced a public meeting to discuss the photochemistry and photobiology of sunscreens.

This final monograph completes the tentative final monograph except for

certain testing issues and UVA labeling, which the agency will discuss in future issues of the Federal Register. Until then, UVA labeling may continue in accord with the tentative final monograph and its amendments. The agency advises that on or after May 21, 2001, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved new drug application or abbreviated new drug 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 as soon as possible.

In response to the proposed rule on OTC sunscreen drug products and subsequent reopenings of the administrative record, the agency received 433 comments. The comments included four petitions (Refs. 1 through 4) requesting consideration of sunscreen ingredients that have been marketed in Europe but not in the United States. The status of these petitions is discussed in section II.C, comment 13 of this document. One manufacturer requested an oral hearing before the Commissioner of Food and Drugs if the agency mandated a limit on sun protection factor (SPF) values in this final rule. Copies of the information considered by the Panel, the comments and petitions, and the hearing request are on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All "OTC Volumes" cited throughout this document refer to information on public display.

A number of comments were filed in the Dockets Management Branch after the dates the administrative record had officially closed. The agency has considered these comments as "feedback" communications under the OTC drug review procedures, as discussed in the Federal Register of September 29, 1981 (46 FR 47740), and clarified in the Federal Register of April 1, 1983 (48 FR 14050). When "feedback" material submitted after an administrative record has officially closed directly influences or forms one of the bases for the agency's decision on a matter in an OTC drug rulemaking proceeding, the agency adds it to the administrative record without

submission of a formal petition by an interested party.

The agency has included these data and information in the administrative record and addressed them in this document. The agency has considered the request for an oral hearing in its response to the comment and believes it has adequately responded to the manufacturer and that a hearing is not needed. As discussed in section II.G, comment 29 of this document, the agency is allowing the marketing of OTC sunscreen drug products with SPF values above 30 under one collective term (i.e., "30 plus" or "30 +"). The agency will also consider including labeling in the monograph with actual label SPF values on products with SPF values over 30 when adequate data are submitted to substantiate a testing procedure applicable to SPF values over 30.

II. The Agency's Conclusions on the Comments

A. General Comments on OTC Sunscreen Drug Products

1. Several comments asked that the agency either exempt currently marketed sunscreen products from the requirement for redetermining the SPF or provide a 2-year implementation period. One comment requested a 3-year implementation period. The comments contended that the proposed 12-month implementation period would result in lost business and a serious economic hardship for manufacturers, estimated to be 35 million dollars for reformulating, retesting, and relabeling sunscreen products.

The agency agrees with the comments that the proposed 12-month implementation period may cause undue economic burden on some manufacturers of these products without a corresponding benefit to consumers (see section VII of this document). As discussed in section VII, a 24-month effective date would allow most firms to relabel products during a normal relabeling cycle without incurring additional costs. Accordingly, the final rule will be effective 24 months from the date of this publication. Because this final rule provides testing procedures that were proposed in the tentative final monograph, currently marketed products that have already been tested by those procedures will not need to be retested. However, sunscreen products that have not been tested will need to be tested using the methods described in this document. The agency intends to propose modified test procedures in a future issue of the Federal Register and any necessary retesting time will be

specified when the final rule for testing procedures publishes.

2. Several comments recommended modifications to the definition of minimal erythema dose (MED) in proposed § 352.3(a). Some comments objected to the presumption that erythema is a "diffusing" reaction that starts from within the exposed site and moves outward in a dose dependent manner, i.e., "redness reaching the borders of the exposure site." Other comments asserted that the definition is too limiting because it may not be appropriate for all solar simulator configurations (e.g., no template). Many comments recommended the definition of MED used by the European Trade Association COLIPA (Ref. 5): "The quantity of radiant energy required to produce the first perceptible, unambiguous redness reaction with clearly defined borders." Another comment recommended "erythema-effective ultraviolet radiation" in place of "radiant energy."

The agency agrees that the proposed definition of MED should be modified for the reasons discussed by the comments and is revising § 352.3(a) in this final rule, as follows: "*Minimal erythema dose (MED)*. The quantity of erythema-effective energy (expressed in Joules per square meter) required to produce the first perceptible redness reaction with clearly defined borders." The agency considers this definition broad enough to encompass tests conducted with solar simulator configurations with no template and consistent with COLIPA's definition.

3. One comment noted that the wavelength ranges for UVA, UVB, and UVC radiation in the tentative final monograph differed from the official ranges of the Commission International de L'Eclairage (CIE), which are: (1) UVC—radiation of less than 280 nanometers (nm), (2) UVB—280 to 315 nm, and (3) UVA—315 to 400 nm. The comment mentioned the agreement reached at the 11th International Congress on Photobiology (Ref. 6) on the short wavelength end of UVB radiation (280 or 290 nm) and suggested that the scientific evidence supports 320 nm as the long-wavelength boundary of UVB radiation.

The agency agrees with the comment that the scientific evidence supports 320 nm as the long-wavelength boundary of UVB radiation. However, the short-wavelength boundary for UVB radiation has been accepted as either 280 or 290 nm. Given that the comment did not provide a compelling reason to change the proposed definition of UVB radiation, the agency will continue to

define the boundaries of UVB radiation as 290 to 320 nm.

4. Comments requested the agency to amend the definition of a sunscreen active ingredient in proposed § 352.3(c) to include mechanisms other than absorption, to expand the UV range to include UVA radiation, and to provide a minimum SPF value requirement. The comments added that some proposed Category I active ingredients (e.g., menthyl anthranilate and titanium dioxide) do not meet the proposed definition, and that the definition is not interpretable without specifications for measuring 85 percent absorbance.

The agency discussed the need to modify the definition in a 1996 proposed amendment of the tentative final monograph (61 FR 48645 at 48646). The agency agrees that modifications should be to: (1) Include mechanisms other than absorption, (2) redefine wavelengths, and (3) remove the percent absorbance requirement. The agency does not agree that a minimum SPF value should be included in the definition because this information is more appropriately a characteristic of the final formulation. Therefore, the agency has revised proposed § 352.3(c) in this document, to read: "*Sunscreen active ingredient.* An ingredient listed in § 352.10 that absorbs, reflects, or scatters radiation in the ultraviolet range at wavelengths of 290 to 400 nanometers."

5. One comment recommended that the agency reevaluate statements in the tentative final monograph on the harmful nature of tanning. The agency discussed the harmful effects of UV radiation-induced tanning in the tentative final monograph (58 FR 28194 at 28238 to 28239). The comment suggested that a natural tan reduces cumulative sun exposure and may potentiate sunscreen effectiveness. The comment did not, however, provide data or references to support this claim or to otherwise cause the agency to change its position.

6. One comment requested that the final monograph require expiration dating and storage information in the labeling of OTC sunscreen drug products. The comment noted that under 21 CFR 211.137, OTC drug products with data demonstrating stability for 3 years and without labeled dosage limitations are not required to include an expiration date in their labeling. The comment stated that it was aware of numerous cases that suggest these products may not be stable for 3 years.

The agency requested the comment to provide data and information about the specific products it was aware of (Ref.

7), but none were subsequently provided. The agency is not currently aware of stability problems that would require expiration dating for OTC sunscreen drug products but will address such a requirement if data become available. All sunscreen active ingredients included in the final monograph also have a USP monograph that contains packaging and storage requirements and standards for products containing these ingredients.

7. Comments recommended that the agency establish procedures for ensuring batch-to-batch SPF test results, and that it approve testing laboratories and regulate their performance.

Regulations already exist to assure that each batch of drug product meets established specifications for the identity and strength of each active ingredient. Specifically, 21 CFR 211.160 requires that product specifications and laboratory controls be established and performed. Although the agency would not require SPF testing on human subjects for every batch produced, manufacturers need to assure conformance to their finished product specifications. Further, any changes to the batch formula would, at a minimum, require review and documentation by the manufacturer's quality control unit to determine if SPF retesting is necessary. Finally, 21 CFR 211.180 provides for the inspection of records pertaining to production, control, and distribution of batches of drug products. Thus, testing laboratories are subject to these regulations.

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

8. One comment questioned whether sunscreen products should be regulated as drugs. The comment asserted that such products are not active in the mitigation or elimination of a disease condition, and that sunscreen products have no more effect on the structure and function of the body than "being in physical shade."

The basis for the agency's determination that products intended for use as sunscreens are subject to regulation as drugs under section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(g)(1)) is set forth at length in the tentative final monograph (58 FR 28194 at 28203 to 28206). Essentially, sunscreen active ingredients affect the structure and function of the body by absorbing, reflecting, or scattering the harmful, burning rays of the sun, thereby altering the normal physiological response to solar radiation. Proper use of sunscreen ingredients (see section II.L, comment

51 of this document) may help to prevent skin damage and may help reduce the risk of skin lesions, skin cancer, and other disease conditions. Products that are marketed to achieve these important health benefits meet the definition of a drug under section 201(g)(1)(B) and (g)(1)(C) of the act.

9. One comment disagreed with the agency's tentative conclusion that products containing a sunscreen ingredient, but labeled for the purpose of obtaining an "even tan," are subject to regulation as drugs. According to the comment, such a product is subject to regulation as a drug only if it bears a claim to treat or prevent sunburn. The comment asserts that this has been the agency's consistent approach since 1940.

Another comment stated that sunless tanning products, used to impart color without exposure to the sun, could be improved by adding a sunscreen to provide users protection during their normal outside activities. The comment requested that such products should be regarded as cosmetics, because they would be used primarily for a cosmetic effect, with the sunscreen protection serving only a secondary purpose.

The agency thoroughly discussed the regulatory status of "tanning" products, including the basis for withdrawing its 1940 advisory opinion on sunburn and suntan preparations, in the tentative final monograph (58 FR 28194 at 28203 to 28207, 28293 to 28294). As discussed in the tentative final monograph, the presence of a sunscreen active ingredient, in conjunction with labeling claims that the product may be used, e.g., to permit tanning or to acquire an even tan, generally establishes that the product's intended use is that of a drug. Such products suggest, among other things, that the ingredients in the product will allow the consumer to stay in the sun longer without suffering skin damage (58 FR 28194 at 28204). Likewise, products that claim to accelerate or stimulate the tanning process are claiming, either expressly or impliedly, to stimulate the production of melanin in the body. Such a claim to affect the structure or function of the body renders the product subject to regulation as a drug under section 201(g)(1) of the act (see 58 FR 28194 at 28293). Finally, a sunless tanning product that contains a sunscreen ingredient, to provide protection to the consumer, is subject to regulation as a drug. The idea that the sunburn protection offered by the product may only be a "secondary" feature for the consumer is not relevant. If an intended use of the product is to provide users with sun protection when they go

outside (as the comment suggests), then the product is subject to regulation as a drug.

On the other hand, products that do not make express or implied sun protection claims, and do not contain sunscreen ingredients, may be regarded as cosmetics under section 201(i) of the act. If the product is intended solely to provide cosmetic effects on the skin (e.g., to moisturize the skin while sunbathing), or solely to impart color to the skin without exposure to the sun or other sources of light (i.e., sunless tanning), then the product may be marketed as a cosmetic. Such products, however, must include a warning statement (discussed in this section, comment 10 of this document) to inform the consumer that the product does not provide any protection against sunburn. Products marketed to enhance or permit tanning that do not contain a sunscreen ingredient must be reviewed on a case-by-case basis to determine whether the product is intended solely to provide a cosmetic benefit (such as moisturizing) or whether the product is intended to enhance or permit tanning by some other mechanism of action.

The comments offered no other reasoning and no data to the contrary, other than to suggest that the agency's approach would encourage manufacturers to remove sunscreen ingredients from suntan products and, thereby, expose consumers to even higher levels of harmful ultraviolet rays. The agency is not persuaded that a significant number of manufacturers will choose to reformulate their products, to make them less safe for consumers, as a result of this final rule. Moreover, consumers will continue to have an array of sunscreen-containing products from which to choose. Finally, as discussed below, certain tanning products (including sunless tanning products) that do not contain sunscreen ingredients must bear a prominent warning to the consumer. This will ensure that the consumer is fully informed as to which products offer sun protection and which do not.

10. One comment requested that the signal word "Caution" replace the signal word "Warning" preceding the following statement for suntanning preparations: "Warning—This product does not contain a sunscreen and does not protect against sunburn." The comment stated that the word "Warning" suggests safety hazards associated with these products that are unrelated to sunburn. Another comment petitioned to add a second sentence to the warning: "Tanning in sunlight or under tanning lamps can cause skin cancer and premature skin aging—even if

you don't burn." The comment concluded that the availability of tanning products without a protective sunscreen ingredient is a serious health issue and detrimental to public health. A third comment objected to any such warnings on tanning products.

The agency considers it an important public health issue that users of suntanning products be alerted when these products do not contain a sunscreen and do not protect against sunburn or other harmful effects to the skin. Because suntanning products are intended for repeated use under the sun or suntanning lamps while acquiring a tan, the agency considers failure to provide information on hazards associated with repeated, unprotected exposure to UV radiation to be a failure to reveal material facts (see sections 201(n), 502(a), and 602(a) of the act (21 U.S.C. 352(a) and 362(a))), especially in light of the representations that are made for the product (e.g., suntanning). Therefore, the agency is requiring the labeling of suntanning preparations that do not contain a sunscreen ingredient (§ 740.19 (21 CFR 740.19)) to bear the following: "Warning—This product does not contain a sunscreen and does not protect against sunburn. Repeated exposure of unprotected skin while tanning may increase the risk of skin aging, skin cancer, and other harmful effects to the skin even if you do not burn." The agency considers this information to be sufficiently important, for safety reasons, to require a 12-month effective date (as opposed to 24 months, for the balance of the rule) and to require the strongest possible signal word, i.e., "Warning."

11. One comment disagreed with the proposal that hair care and nail products that contain a sunscreen ingredient for a nontherapeutic use (e.g., to protect the color of the product), and that use the term "sunscreen" in the labeling, must describe in the labeling the functional role of the sunscreen. According to the comment, it is highly unlikely that consumers would think that these products are intended to protect the skin. If this requirement were finalized, the comment requested that the agency permit the term "sunscreen" to appear once anywhere in the labeling, with the purpose of the sunscreen explained elsewhere in the labeling.

The agency disagrees with the premise of this comment. The use of the term "sunscreen" in labeling suggests that the product in some way will protect the consumer from the harmful effects of the sun. The health risks associated with relying on a product for protection from the sun, when in fact

the product does not provide such protection, are sufficiently serious to require the type of disclosure outlined in the proposed rule. Information about the purpose of a sunscreen ingredient in a hair care or nail product will be useful to consumers to inform them that the ingredient protects only the hair or only the color of the product.

This information need appear only once and can appear anywhere in the labeling, provided the qualifying purpose appears prominently and conspicuously and in conjunction with the word "sunscreen." The information may, e.g., be combined in a single statement, e.g., "Contains a sunscreen—to protect product color." This will ensure that consumers will see and readily associate the two pieces of information.

12. Two comments objected to the use of an OTC drug rulemaking process to change cosmetic labeling requirements, i.e., the addition of a warning on certain tanning products and the labeling requirements for hair care or nail products that contain a sunscreen for a nontherapeutic use.

The agency addressed this procedural concern, which was also raised in response to the ANPRM, at length in the tentative final monograph (58 FR 28194 at 28201 to 28202). The industry and consumers have had ample notice of the fact that this proceeding included several cosmetic labeling issues that arise out of the same facts and findings at issue in developing the OTC drug monograph. It is not uncommon for the agency to address in an OTC rulemaking document the status of, or the regulation of, products that fall outside of the monograph. In this instance, the cosmetic labeling issues were so closely related to the OTC drug issues that a separate proceeding would have been overly duplicative and inefficient.

C. Comments on Specific Sunscreen Active Ingredients

13. Several comments noted that FDA had deferred a decision on the citizen petitions requesting that sunscreen active ingredients marketed solely in foreign countries be included in the OTC sunscreen monograph. The comments urged FDA answer these petitions and establish a policy concerning the inclusion of OTC sunscreens based solely on foreign data and marketing experience.

In the Federal Register of October 3, 1996 (61 FR 51625), the agency published an ANPRM that addressed establishing eligibility criteria for considering additional OTC conditions (i.e., OTC drug active ingredients, indications, dosage forms, dosage

strengths, routes of administration, and active ingredient combinations) in the OTC drug monograph system. These proposed criteria would address how foreign or domestic OTC marketing experience could be used to support the inclusion of an ingredient in an OTC drug monograph. Specifically, the criteria would address how OTC marketing experience in the United States or abroad could be used to meet the statutory requirement under section 201(p) of the act of marketing "to a material extent" and "for a material time." "Material extent" and "material time" are needed to qualify a specific OTC drug condition for consideration under the OTC drug monograph system.

The decision on whether to proceed with a final rulemaking on this subject will be based, in part, on the information and comments submitted in response to the notice of proposed rulemaking that the agency is preparing for publication in a future issue of the Federal Register. Resolution of the pending sunscreen petitions must await the outcome of any final rulemaking on this subject.

14. One comment requested that the agency adopt simpler, more user-friendly, names for several sunscreen ingredients: (1) Roxadimate for ethyl-[bis(hydroxypropyl)] aminobenzoate, (2) lisadimate for glyceryl aminobenzoate, and (3) diolamine methoxycinnamate for diethanolamine methoxycinnamate. The comment claimed that these names had been adopted or designated by the United States Adopted Names (USAN) Council. The comment also requested that if USAN adopts a name for phenylbenzimidazole sulfonic acid, FDA adopt this name as well. The comment also suggested the use of the acronyms "TEA" and "DEA" for triethanolamine and diethanolamine, respectively.

The agency is including in this final monograph only those active ingredients that are the subject of an official USP compendial monograph that sets forth its standards of identity, strength, quality, and purity (see section I of this document). In the Federal Register of June 8, 1994, FDA deleted ethyl-[bis(hydroxypropyl)] aminobenzoate and glyceryl aminobenzoate from the tentative final monograph due to the lack of interest in establishing USP monographs for these ingredients. Moreover, two sunscreen ingredients (including diethanolamine methoxycinnamate) have been deferred from the final monograph due to the lack of a current or proposed compendial monograph. Therefore, the issue of whether a "user-friendly" name for these ingredients should be

developed or adopted need not be resolved in this proceeding at this time. Similarly, TEA and DEA need not be addressed in this proceeding, as triethanolamine is not a sunscreen active ingredient, and diethanolamine is only used in the ingredient diethanolamine methoxycinnamate which, as discussed, is not a monograph ingredient at this time.

With respect to the comment on the monograph ingredient phenylbenzimidazole sulfonic acid, the agency agrees that if USAN or the USP were to adopt a different or alternative name for this ingredient, such a name could be used in the labeling of a product that contains this ingredient. As discussed in comment 30 of the tentative final monograph (58 FR 28194 at 28207 to 28209), the agency is using the compendial name as the established name for each active ingredient.

15. Two comments requested that the term "PABA" continue to be allowed in labeling. The comments stated that the name aminobenzoic acid is meaningless to consumers and physicians, who over the years have learned to recognize this ingredient on the label as PABA. One comment recommended the use of aminobenzoic acid in the ingredient list and the use of PABA in other communications about the product. The comment added that the term "PABA-free" should be allowed on products that do not contain aminobenzoic acid. The other comment proposed either to permit the listing of the ingredient as PABA or, if that is unacceptable, as PABA (aminobenzoic acid).

In comment 30 of the tentative final monograph (58 FR 28194 at 28207 to 28209), the agency discussed the issue of the appropriate established name for this and other sunscreen ingredients. As the agency stated in that discussion, the recognized compendial name for aminobenzoic acid no longer includes the term PABA.

The agency acknowledges, however, that the term PABA formerly was part of the established name for this ingredient and that the use of the term in consumer labeling has continued despite the change in the compendial name. In addition, the agency agrees with the comment that many consumers have learned to recognize this ingredient as, and only as, PABA. The agency also recognizes that consumers seeking to avoid the use of this ingredient for health-related reasons (e.g., allergy) may, in this case, be misled if the term PABA were no longer permitted. Some consumers may believe that a product that lists aminobenzoic acid as an ingredient, but does not list PABA, is PABA-free. If such a consumer

has an allergy to aminobenzoic acid, the individual may suffer adverse health consequences.

For these reasons, and especially in light of the potential safety concerns for certain consumers, the agency concludes that wherever the ingredient aminobenzoic acid appears in the labeling of an OTC sunscreen drug product, including labeling that notes the absence of this ingredient, the descriptive term PABA must immediately follow the established name, i.e., "Aminobenzoic acid (PABA)." Thus, e.g., a product that is currently marketed as "PABA-free" would now be required to state that the product is "Aminobenzoic acid (PABA)-free." This convention will allow consumers to begin to recognize that the ingredient they may wish to avoid is "aminobenzoic acid." After a sufficient period of time, the agency will revisit the need for consumer labeling to continue to bear the descriptive term PABA.

16. One comment stated that claims of protection by artificial melanin, melanin-containing products, and antioxidants should be enumerated, well regulated, and defined.

The agency agrees with the comment, but these claims are not covered by this final monograph. Melanin and artificial melanins are not recognized sunscreen active ingredients. Any product containing melanin or artificial melanins as active ingredients and making sun protection claims would have to seek marketing approval under a new drug application (NDA).

The agency is aware that claims of protection from antioxidants are used in the labeling of some cosmetic products with or without a sunscreen. The agency will ascertain the nature of any such claims (drug or cosmetic) on a case-by-case basis.

17. Several comments objected to the agency's proposal that OTC sunscreen drug products must contain less than 500 parts per billion (ppb) of N-methyl-N-nitrosoaminobenzoate octyl ester (NMPABAO) for several reasons: (1) Toxicological studies indicate that NMPABAO does not have mutagenic or suspected carcinogenic potential (Ref. 8), (2) NMPABAO may be present in sunscreens containing padimate O only in small amounts (ppb range) and the risks associated with NMPABAO are very low, (3) NMPABAO decomposes quickly when exposed to UV radiation, and (4) industry is aware not to formulate with known nitrosating agents in the presence of amines in order to avoid nitrosamine contamination of its products. Some comments stated that FDA's own conclusions in the tentative

final monograph concerning the safety of both NMPABAO and padimate O do not support the imposition of concentration limits for NMPABAO in sunscreens nor do they justify the high cost of analyzing each batch of sunscreen product for NMPABAO. One comment contended that any proposed limit should apply to all nitrosamines and not just NMPABAO. The comment stated that nitrosamines can be formed from any secondary or tertiary amine. Several sunscreen active ingredients contain this moiety in their chemical structure and many inactive ingredients are secondary or tertiary amines. The comment concluded that targeting NMPABAO falsely conveys that padimate O is a unique concern, resulting in manufacturers using other ingredients to avoid costly testing and negative implications.

In the tentative final monograph, the agency did not propose a concentration limit on NMPABAO. Rather, based on concerns that had been raised, the agency asked for comment on whether it should consider proposing a fixed limit. As discussed in the tentative final monograph (58 FR 28194 at 28288 to 28293), toxicological studies support the agency's belief that the risk associated with NMPABAO contamination of sunscreen drug products is very low due to NMPABAO's low mutagenicity and carcinogenicity potential and rapid decomposition in the presence of UV radiation. The agency has not become aware of any new data or information since the publication of the tentative final monograph suggesting a safety concern with NMPABAO in sunscreen drug products. Therefore, the agency has decided not to propose or otherwise include in this final monograph a requirement that OTC sunscreen drug products must contain less than 500 ppb of NMPABAO.

In the tentative final monograph (58 FR 28194 at 28292), the agency discussed its analysis for NMPABAO in 25 commercially available sunscreen products. Of the 11 samples found to be contaminated with NMPABAO, the four highest contained 2-bromo-2-nitro-1,3-propanediol, an indirect nitrosating agent. The agency concluded that there would be no nitrosamine contamination if these products were formulated without the nitrosating agent. As noted by several of the comments, the industry is aware not to formulate with known nitrosating agents in the presence of amines in order to avoid nitrosamine contamination of its products.

18. One comment submitted a reference to a subchronic oral toxicity study in rats conducted with padimate O which a chemical manufacturer had

submitted to the Toxic Substance Control Act 8(e) coordinator of the United States Environmental Protection Agency for consideration. The study was a 4-week repeated dose study at doses of 0, 100, 300, and 1,000 milligrams (mg)/kilogram (kg)/day of padimate O administered by gavage in a corn oil vehicle (10 to 15 rats/group/sex). The study included a 4-week recovery period to assess the persistence or reversibility of any toxic effects. At the end of the 4-week treatment period, toxic effects were seen in four target organs: Testes, epididymis, spleen, and liver. The no-observed-effect-level in this study was 100 mg/kg/day for both males and females. Toxic effects appeared reversible in the animals necropsied after the 4-week recovery period with the exception of marked epididymal hypospermia at the 1,000 mg/kg/day dose (5/5 animals).

The clinical relevance of this animal toxicity study is difficult to assess. Padimate O was administered chronically and at very high oral doses. Under normal use conditions, sunscreen drug products containing padimate O are applied topically and used intermittently. In addition, pharmacokinetic parameters were not calculated and the different routes of administration (oral in this study versus topical for sunscreen products) preclude calculation of a "safety margin" on the basis of dose per unit of body weight or surface area. Similarly, kinetic data are not available for a comparison of serum levels of drug or metabolites. Literature searches indicate no published information on the kinetics of padimate O with topical application in man. If percutaneous absorption of padimate O does occur in man, it seems likely that the peak and/or cumulative levels achieved with sunscreen usage would be quite low compared to the systemic exposure achieved in this animal toxicity study. Further, it is not known whether the irreversible epididymal hypospermia found in the 1,000 mg/kg/day group would also be reversible with more time.

The agency has determined that this study does not present sufficient data to exclude padimate O from the final monograph and that an adequate safety margin exists for its use as an OTC sunscreen ingredient.

19. Two comments submitted safety and/or efficacy data to support Category I status for micronized titanium dioxide (Refs. 9 and 10). One comment stated that micronized titanium dioxide is not a new material but is a selected distribution of existing material that provides higher SPF values while being transparent and esthetically pleasing on

the skin. The comments added that micronized titanium dioxide meets all safety and efficacy criteria and also meets the USP specifications for purity except pure water content.

Another comment asserted for the following reasons that micronized titanium dioxide is a new ingredient with several unresolved safety and efficacy issues: (1) It does not meet the definition of a sunscreen opaque sunblock, (2) there is no control of particles to agglomerate, which is critical to effectiveness, (3) no standards exist to ensure integrity of coatings, (4) there are no performance-based standards of identity; micronized titanium dioxide is not included in the USP, (5) its photocatalyst potential, and (6) the potential for the smaller particle size to accumulate under the skin.

The agency finds the data with the comments supportive of monograph status for micronized titanium dioxide. Acute animal toxicity, irritation, sensitization, photoirritation, photosensitization, and human repeat insult patch and skin penetration studies revealed no deleterious effects. SPF values for four product formulations containing from 4.4 to 10 percent micronized titanium dioxide were from 9 to 24 and support effectiveness as a sunscreen ingredient.

The agency is aware that sunscreen manufacturers are using micronized titanium dioxide to create high SPF products that are transparent and esthetically pleasing on the skin. The agency does not consider micronized titanium dioxide to be a new ingredient but considers it a specific grade of the titanium dioxide originally reviewed by the Panel. Fairhurst and Mitchnick (Ref. 11) note that "fines" have been part of commercially used titanium dioxide powders for decades, and that a micronized product simply refers to a refinement of particle size distribution. Based on data and information presented at the September 19 and 20, 1996, public meeting on the photobiology and photochemistry of sunscreens (Ref. 12), the agency is not aware of any evidence at this time that demonstrates a safety concern from the use of micronized titanium dioxide in sunscreen products. While micronized titanium dioxide does not meet the proposed definition of a sunscreen opaque sunblock, the agency has not included the use of this term in the final monograph (see section II.L, comment 52 of this document). The potential for titanium dioxide particles to agglomerate in formulation, which could result in lower SPF values, is addressed by the final product SPF test.

The SPF data that the agency reviewed (Ref. 9) did not indicate such a problem.

Micronized titanium dioxide meets current USP monograph specifications for titanium dioxide with the exception that the material contains more associated water. In both the July through August 1996 and 1998 issues of the *Pharmacopeial Forum* (Refs. 13 and 14), the United States Pharmacopeial Convention published in-process revision proposals to make the monograph for titanium dioxide more applicable to ingredients used in sunscreen drug products. The agency will work with the USP in the future to update this monograph as necessary.

20. One comment stated that it is unnecessary to set the maximum limit of titanium dioxide at 25 percent.

The Panel discussed the safety and effectiveness of 2 to 25 percent titanium dioxide in the ANPRM (43 FR 38206 at 38250) and the agency concurred with the Panel's findings in the tentative final monograph (58 FR 28194 at 28295). The comment submitted no data and the agency has no data to support the use of titanium dioxide in sunscreen drug products at concentrations higher than 25 percent.

D. Comments on Dosages for Sunscreen Drug Products

21. Several comments objected to the minimum concentration requirements for sunscreen active ingredients when used in combination because they: (1) Are a less effective measurement of effectiveness than a performance-based SPF test, (2) impact on creativity and innovation of new formulations (technological advances since publication of the 1978 ANPRM have resulted in higher SPF values using lower concentrations of active ingredients), (3) increase potential for irritation and allergic reactions due to unnecessarily high concentration levels of active ingredients, (4) contradict FDA's position that the lowest effective dose of an active ingredient be used to produce the desired treatment effect, (5) result in higher manufacturing and consumer costs due to unnecessary levels of active ingredients, and (6) affect international harmonization because Canada, Australia, and the European Union have no concentration minimums for active ingredients when used in combination.

One comment petitioned the agency to amend proposed § 352.20 of the tentative final monograph to include a provision for formulating combination sunscreen products at lower minimum concentrations. Two comments submitted efficacy data to support lower concentrations of sunscreen active

ingredients when used in combination. One comment (Ref. 15) submitted in vitro SPF testing data for several different combinations. Although these data showed a statistically significant increased efficacy for lower than minimum concentrations, they were not predictive of the SPF values that would be obtained with human testing and, therefore, were not used to support lower concentrations of sunscreen active ingredients when used in combination. The other comment (Ref. 16) submitted in vivo SPF testing data conducted according to the procedure proposed in the tentative final monograph (58 FR 28194 at 28298 to 28301) in which a selected cross section of active ingredients were tested in pairs by substituting water or the solvent system for the active ingredients. The data were evaluated using a matched pairs comparison statistical hypothesis test procedure and demonstrated that concentrations of sunscreen active ingredients lower than the minimum concentrations proposed in § 352.20(a)(2) for combination products can provide a significant contribution to product effectiveness.

The agency recognizes that technological advances in sunscreen formulation technology since 1978 have resulted in the ability to formulate products with lower concentrations of active ingredients and higher SPF values. The agency also recognizes that final product testing, and not the concentration of the active ingredients in the combination, ensures product effectiveness.

Due to the recent advances in sunscreen formulation and the data referenced previously, the agency is concerned that setting minimum concentration requirements for active ingredients in sunscreen combination drug products could subject consumers to unnecessary levels of active ingredients. Therefore, the agency is only requiring the maximum concentration limits in § 352.10 for sunscreen active ingredients when used in combination with another sunscreen or when the combination is used with any other permitted active ingredient. However, any such ingredient used in combination with one or more sunscreen active ingredients must be consistent with the regulations in § 330.10(a)(4)(iv), i.e., each of the combined active ingredients must make a contribution to the claimed effect, the combining of active ingredients must not decrease the safety or effectiveness of any individual active ingredient, and the combination must provide rational concurrent therapy for a significant proportion of the target population.

Although the agency needs assurance that each ingredient is contributing to the effectiveness of the product, it does not want to impose unnecessary testing requirements on sunscreen product manufacturers. Therefore, the agency is removing the minimum concentration requirement for sunscreen active ingredients proposed in § 352.20 and is adding the requirement that: (1) The concentration of each active sunscreen ingredient used in a combination product must be sufficient to contribute a minimum SPF of not less than 2 to the finished product, and (2) the finished product must have a minimum SPF of not less than the number of the sunscreen active ingredients used in combination multiplied by 2.

E. Comments on Labeling and Testing Procedures for UVA Sunscreen Drug Products

22. In the sunscreen tentative final monograph (58 FR 28194 at 28232 and 28233), the agency proposed to allow claims relating to "broad spectrum protection" or "UVA radiation protection" for sunscreen products: (1) Containing sunscreen active ingredients with absorption spectra extending to 360 nm or above, and (2) that demonstrate meaningful UVA radiation protection using appropriate testing procedures to be developed. The agency received numerous comments concerning such claims and current scientific evidence implicates UVA radiation as a major cause of, among other things, photoaging of the skin (Refs. 17 through 20).

In the Federal Register of September 16, 1996, and October 22, 1998, the agency proposed a specific skin damage and premature skin aging claim for sunscreen products containing specific concentrations of avobenzone or zinc oxide based upon the submission of data to support claims of UVA radiation protection in such products. The agency will address comments pertaining to measurement of UVA radiation protection in sunscreen products and related UVA radiation protection claims in a future issue of the Federal Register. Until then, UVA labeling may continue in accord with the tentative final monograph and its amendments.

F. General Comments on the Labeling of Sunscreen Drug Products

23. Several comments requested that products containing sunscreen ingredients as an adjunct to their main purpose (e.g., a daily moisturizer or a lipstick with a sunscreen) be considered "secondary sunscreens" (intended only for incidental or casual sun exposure) and should be subject to different

labeling requirements from "primary" sunscreen products. A number of comments likewise contended that some of the labeling requirements for "beach" or "primary" sunscreen products are not appropriate for "non-beach" or "secondary" sunscreen products.

For example, the comments stated that neither the proposed "Recommended Sunscreen Product Guide" nor any other references to sunburn or sunburn protection should be required for secondary sunscreens. Some suggested that the warnings be reduced for secondary sunscreens to a statement such as "For external use only, keep out of eyes. Discontinue use if signs of irritation appear." One comment recommended that the statement of identity for a secondary sunscreen should be its cosmetic function, e.g., "moisturizer." Another recommended stating the primary (cosmetic) function first, then the secondary (drug) function, e.g., "moisturizing face cream with sunscreen (or with SPF _____ sunscreen)."

The comments also suggested that secondary products be permitted to bear certain labeling claims relating to aging, such as "Helps reduce the chance of skin aging caused by incidental (or casual) exposure to the sun," or "Helps reduce premature aging from incidental (or casual) exposure to the sun." Some also requested the option of being allowed to relate skin aging claims directly to sun exposure, to inform consumers more clearly that sun protection is not the primary attribute of the product, e.g., "Provides moisture to facial skin throughout the day while protecting facial skin from skin aging due to exposure to sun." Other comments recommended that the proposed "Sun alert" statement or other references to "skin cancer" or other cancers should not be required for secondary products.

On the other hand, the agency also received comments opposing the idea of recognizing "primary" and "secondary" or "beach" and "non-beach" categories of sunscreen products. One comment stated that any product containing a sunscreen for the purpose of protection from the sun's harmful effects should be held to the same standards as other sunscreen products. Another comment disagreed with the idea of allowing different sets of claims for "primary" and "secondary" products. According to this comment, claims such as "Helps reduce the chance of skin aging" are drug claims and should be regulated as such. Finally, one comment stated that any sunscreen product (primary or secondary) must have an SPF of 15 to

30 or higher to provide adequate protection, whether for continuous beach exposure or everyday (incidental) sun exposure.

The agency agrees that all sunscreen products (whether drug only or drug-cosmetic) should be held to the same standards (e.g., active ingredient(s), testing requirements, and labeling). Regardless of what type of product a consumer chooses for sun protection, the essential information relevant to sun protection is the same. Thus, to ensure that consumers are adequately protected from overexposure to the sun, all products intended for use as sunscreens should have similar labeling requirements, irrespective of their method of use and irrespective of whether the sunscreen use is considered primary or secondary to the product. Consistent with this approach, the agency has developed uniform, streamlined labeling for all sunscreen products (see sections II.I through II.L of this document).

The agency also notes, however, that a number of the labeling issues raised in these comments, including the issue of the "Recommended Sunscreen Product Guide," are addressed elsewhere in this document. In addressing these issues, the agency gave careful consideration to the wide variety of products marketed for sunscreen uses.

Finally, the agency notes that under the recently issued standardized OTC drug product labeling format (§ 201.66 (21 CFR 201.66)), manufacturers will not be allowed to commingle drug and cosmetic claims within the "Drug Facts" portion of the labeling.

24. One comment requested clarification of the agency's discussion of the term "anti-aging" as a claim or as part of a trade name (58 FR 28194 at 28287). The comment was concerned that products containing no sunscreen active ingredients and no sunscreen claims, but which are sold under "anti-aging" trade names, would be subject to regulation under the OTC drug sunscreen monograph.

The use of "anti-aging" language in a product that made no sunscreen claims and contained no sunscreen active ingredients would not, as the comment asked, cause the product to fall within the scope of the OTC sunscreen drug monograph. Such a product may, however, be subject to regulation as a drug and as a new drug, under section 201(g)(1) and (p) of the act, or as a cosmetic under section 201(i), or as both a drug and a cosmetic, depending upon all of the circumstances surrounding its distribution. A product that is marketed under the final OTC sunscreen drug monograph, but which uses anti-aging

language in the labeling to suggest or imply an unapproved therapeutic or physiologic effect, would likely be subject to regulatory action as an unapproved new drug (58 FR 28194 at 28286 to 28287; see comments 37 and 38 in section II.I of this document).

25. Three comments contended that the terms "natural," "non-chemical," and "chemical free" are false and misleading in the labeling of OTC sunscreen drug products. The comments requested the agency to restrict the use of these terms, especially for sunscreen products containing titanium dioxide and zinc oxide.

Generally, the appropriateness of these terms requires case-specific analysis to determine whether their use would render the product false or misleading in any particular (see sections 502(a) and 602(a) of the act). The agency notes, however, that the use of the terms "non-chemical" and "chemical-free" in the labeling of an OTC sunscreen drug product, to describe the ingredients contained in the product, is likely to be considered unacceptable. Sunscreen drug products contain active (and often inactive) ingredients that have been obtained through a chemical process, or that have been formulated into the finished product through a chemical process. The term "natural" is more likely to require context-specific analysis, particularly when used in labeling to describe certain cosmetic aspects or uses of a sunscreen product. The term "natural," however, would not be permitted to appear within the required OTC drug labeling of a sunscreen product and is not considered to be interchangeable with any of the final sunscreen monograph language.

26. Four comments opposed any labeling that a sunscreen product "does not provide UVA protection," contending that FDA's policy does not require disclaimers of broader purposes for which products are not useful. One comment added that an SPF 15 product must block UVA radiation to be effective in preventing sunburn.

Two comments argued that a "negative warning" would be useful and necessary to warn and protect consumers and suggested "Does not provide broad spectrum UVA protection," or "Caution: This product does not provide protection from the recognized dangers of UVA rays which may contribute to skin cancer and other chronic skin disease."

Labeling should primarily direct consumers towards the purposes for which a product is considered useful. However, in establishing the conditions for the safe and effective use of an OTC

drug product, the agency also must take into account, among other things, the context in which a product is customarily marketed and the potential that consumers may use the product for a use for which it may not be beneficial (see sections 201(n) and 502(a) of the act; § 330.10(a)(3)).

With these factors in mind, the agency will further evaluate whether "negative warnings" or disclosure statements are needed when it completes the UVA portion of the sunscreen monograph in a future issue of the Federal Register.

27. Four comments contended that the signal words "Indications" and "Directions" are not needed, take up valuable label space, and should either not be required or be optional, especially for sunscreen-containing drug products that have some "traditional" cosmetic uses (e.g., lipsticks).

The agency allows the signal word "Use" or "Uses" in place of "Indication" or "Indications." This short signal word is useful for consumers, appropriate for dual use products, and does not clutter label space. Likewise, the agency concludes that the signal word "Directions" is useful for consumers and does not clutter label space (64 FR 13254 at 13264 to 13268, March 17, 1999). The agency is including § 352.52(f) in this final monograph to provide labeling modifications for sunscreen products that meet the small package specifications in § 201.66(d)(10) and are labeled for use on specific small areas of the face (e.g., lips, nose, ears, and/or around eyes). These products include many traditional cosmetics (e.g., lipstick or eye makeup) that may contain sunscreens. These products will be allowed to present a condensed "Uses" section and may omit directions for use if they are marketed in a lipstick form.

28. One comment requested that the monograph include professional labeling for both UVB and UVA radiation protection to assist health professionals to select appropriate products. The comment recommended inclusion of the absorption spectrum of each sunscreen in the product and suggested that the labeling include information that the product: (1) Protects against drug-induced photosensitization reactions induced by UV radiation in the ranges ___ nm to ___ nm, and (2) other truthful and nonmisleading statements describing both UVB and UVA radiation protection against photosensitization reactions.

The agency did not propose professional labeling in the tentative final monograph, but did ask for data to be submitted (58 FR 28194 at 28210 and 28245). No data were received. The

agency will consider including this type of professional labeling in the monograph in the future when specific supportive data are provided.

G. Comments on Sunscreen Drug Products With High SPF Values

29. Numerous comments objected to the proposed maximum SPF value of 30 for OTC sunscreen drug products. The comments requested either that the agency adopt no limit or a limit of SPF 50, for the following reasons: (1) UV radiation exposure is increasing due to both lifestyle changes and depletion of the atmospheric ozone layer, (2) skin cancer rates are increasing and there is no safe threshold to prevent cancer, (3) people using an SPF 30 sunscreen will have slight sunburn after receiving their 30 MED and therefore should have available sunscreens with higher SPF values, (4) high SPF sunscreens are needed for extremely sun-sensitive people during periods of unavoidable, intense or lengthy sun exposure, and because of less than ideal usage by consumers due to misjudging of their skin type and/or inadequate/infrequent application, (5) there is a significant variation of skin types, sensitivities, and UV radiation exposures among people, (6) formulation techniques can increase SPF values without necessarily increasing ingredient concentrations, (7) current information does not support an association between high SPF products and safety concerns, and (8) high SPF products provide for greater relative exposure times and decreased UV radiation transmission. Three comments (Refs. 21, 22, and 23) submitted supporting data.

Some comments stated that "High SPF" (i.e., above SPF 30) products are on the market and used by consumers, and that limiting SPF values would stifle sunscreen product development and preventative health benefits. Other comments argued that sunscreens with high SPF values provide increased protection from ultraviolet radiation effects such as photoimmunosuppression and are needed by those with "dermatological problems."

In contrast, some comments supported the agency's proposal to limit SPF values to 30 to stop the promotional "bidding war" or "horsepower race." Another comment contended that real consumer benefit is achieved through appropriate balance of SPF, substantivity, UVA radiation protection, irritation potential, and cost, whereas SPF values above 30 provide only "incremental benefit" and an unnecessary increase in drug exposure.

The data provided by the comments in support of allowing numerical values above 30 were of only limited use. Data from a field survey of 62 sunbathers on Miami's South Beach during July 1993 (Ref. 21) did not provide any reliable conclusions on the frequency or extent of solar overexposure by light-skinned individuals or a benefit provided by sunscreen products with an SPF value above 30 as: (1) The sample size was small and the survey population did not represent a random sample, (2) the MED was not determined under controlled conditions or standardized procedure, and (3) full-day UVB radiation exposure was based on crude extrapolation of weather data.

Data from MED determinations on 1,332 people with skin types I, II, and III, and UV radiation data for the month of June 1974 in 5 cities in the United States (Ref. 22), support the contention that a sizeable population may exist that is at risk to more than 30 MED's of UV radiation per day. However, the data are insufficient for extrapolation to the general population. The small sample size in this study limits the sensitivity of the study and the study population did not represent a random sample.

Finally, data from animal studies (Ref. 23) showed that: (1) Limiting sunscreen protection to SPF 30 may not be prudent if UV radiation damage is not related to SPF; (2) a greater amount of sunscreen is needed to completely inhibit some of the nonerythemogenic damage caused by UV radiation, and (3) nonerythemogenic effects (e.g., photoimmunosuppression) occur with suberythemal doses of UV radiation (as can be obtained with the use of low or high SPF sunscreens). While the agency agrees that higher SPF values may provide for greater relative exposure times, the SPF test is not the appropriate measurement of protection from nonerythemogenic damage because SPF is only a measure of erythema. The agency finds that the data from these studies were not sufficient to either support or dismiss limiting the maximum SPF value in this final rule.

The agency continues to agree with the comments about overall increases in both UV radiation exposure (58 FR 28194 at 28223), skin cancer rates (58 FR 28194 at 28227), and the variation of skin types, sensitivities, and UV radiation exposures among people (58 FR 28194 at 28222). The agency also agrees with the comment that a person using an SPF 30 sunscreen could have a slight sunburn after being exposed to their 30 MED (i.e., after their skin receives a MED). However, the agency continues to believe that an SPF 30 sunscreen product provides adequate

protection for the majority of consumers even under extreme conditions, less than ideal usage, or in varying weather conditions (58 FR 28194 at 28225).

On the other hand, the agency is also aware that many OTC sunscreen products with SPF values above 30 are currently marketed and are increasingly used by consumers. Numerous comments from health professionals, consumers, and industry provide actual use information in support of SPF values above 30 for what may be a substantial number of sun-sensitive people in this country. Further, as numerous comments noted: (1) There is a lack of data to correlate higher than SPF 30 sunscreen products with corresponding safety problems, and (2) modern formulation techniques have resulted in higher SPF values using lower active ingredient concentrations.

Because of the numerous concerns from health professionals, new data to support the need for SPF values above 30, and the lack of data concerning safety problems with such SPF values, the agency concludes that OTC sunscreen drug products with SPF values above 30 should be available for those sun-sensitive consumers who require such products based upon personal knowledge of their skin's susceptibility to sunburn, experience with specific products, planned sun exposure, or the recommendation of a health professional. The agency agrees with the comments that higher SPF values generally can provide for greater relative exposure times and decreased UV radiation transmission. However, the agency continues to believe that the additional sunburn protection provided by an SPF 30 sunscreen and, e.g., an SPF 50 sunscreen (i.e., about a 1.3 percent increase in absorption of erythema UV radiation) is extremely small for most people. The agency is also concerned about the ability of current testing methods to accurately and reproducibly determine SPF values for high SPF products (see section II.M, comment 53 of this document). In addition, nonlinearity of the SPF rating system is a concept difficult to explain in the limited space on a product label. Therefore, the agency concludes that the label SPF declaration for sunscreens with SPF values above 30 should be limited to one collective term, which appears in § 352.50(a) of this document as follows: "For products with SPF values over 30, 'SPF 30' (select one of the following: 'plus' or '+'). Any statement accompanying the marketed product that states a specific SPF value above 30 or similar language indicating a person can stay in the sun more than 30 times longer than without sunscreen

will cause the product to be misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (the act)."

Numerous comments from dermatologists asked that a specific SPF 50 product be allowed to remain on the market because it is needed for the "ultrasensitive patient" and for patients with "dermatological problems." The agency has previously discussed the use of high SPF sunscreen drug products to protect consumers with photosensitivity diseases (58 FR 28194 28225) and the need to provide data for such uses (see section II.F, comment 28 of this document) as the absorption spectrum of a specific product, not necessarily the SPF, may be the more clinically significant factor for such people.

As discussed previously in this comment 29 of section II.G of this document, the agency has concluded that the use of SPF label values above 30 in OTC drug products is not supported at this time. The agency, however, invites interested persons to continue developing the test methods needed to measure high SPF values, and to submit the data in support of such methods to FDA. If test methods are developed, the agency also invites interested persons to consider proposed methods for communicating in labeling the level of protection associated with high SPF values (given the nonlinear nature of the SPF rating system). These and other well-supported improvements to the methodology for accurately and reproducibly measuring SPF values will be addressed, as appropriate, in future issues of the Federal Register. Until then, OTC sunscreen drug products are permitted to be labeled with SPF values no higher than "30+" or "30 plus."

Finally, the agency does not agree with the argument that limiting SPF values would stifle sunscreen product development and preventative health benefits. Undue emphasis for sunburn protection should not be placed upon SPF value alone (i.e., "single focus products"). As noted by another comment, consumer benefit is achieved through appropriate balance of several factors, including substantivity, UVA radiation protection, and irritation potential.

H. Comments on Water Resistant Labeling and Testing for Sunscreen Drug Products

30. One comment agreed and several disagreed with proposed § 352.52(e)(2)(iii) and (e)(3)(iii) concerning sweat resistant claims based upon water resistance testing instead of a specific sweat resistance test. One comment submitted data from two sweat resistance studies and two water

resistance studies (Ref. 24) utilizing methods proposed by the Panel in the ANPRM (43 FR 38206) and involving a total of 117 subjects. The comment concluded that the water resistance test is less stressful than the sweat resistance test.

The agency does not find the data submitted in the studies sufficient to support the comment's contention. The studies each comprised distinct subject populations and addressed a single variable, i.e., the effect of water exposure or induced sweating on a product's SPF. Therefore, a comparison of mean SPF values across studies is not the appropriate measure of relative "stress" associated with these variables. The agency believes that a randomized, two-period crossover study design in a single patient population would better have addressed the comment's contention. Further, the Panel's sweat and water resistance protocols provide qualitative information and were not designed to provide comparative assertions requiring valid statistical inferences. Thus, the agency is allowing water and sweat resistant claims based upon the water resistance test procedures in § 352.76 of this document.

31. One comment contended that the "water resistant" labeling proposed in § 352.50(b)(1) and (c)(1) should not be required for products labeled or purchased for uses other than swimming or bathing.

The agency notes that the water resistance statements referenced by the comment were not required unless the manufacturer wished to make water resistant claims in the labeling of its sunscreen products. This final rule also will not require a manufacturer to make a water resistance claim for its sunscreen product, even if the product is determined to be water resistant. However, a manufacturer wishing to make water resistance claims must comply with §§ 352.50(b) or (c) and 352.52(b)(1)(ii) or (b)(1)(iii) of this document, as applicable for "water resistant" or "very water resistant" products.

32. Several comments urged the agency to return to the "waterproof" and "water resistant" label claims proposed by the Panel and to limit the labeled SPF value to only the SPF after water resistance testing. Another comment requested only general guidelines for claims such as "water resistant" or "sweat resistant" on the basis that such claims reflect the inherent characteristics of specific formulations and not sunscreen ingredients.

The agency thoroughly discussed use of the terms "waterproof" and "water resistant" in the tentative final monograph (58 FR 28194 at 28228). The comments did not present any arguments or data that the agency did not previously consider. In addition, the agency points out that performance claims such as these for OTC sunscreen drug products are based on final product formulation.

The agency agrees with the comments that the more relevant SPF value for products labeled "water resistant" or "very water resistant" is the SPF value of the final product formulation following water resistance testing. Therefore, in this document the agency is limiting the SPF label declaration to the SPF after water resistance testing and is modifying the testing procedures in § 352.76 to reflect deletion of the proposed dual SPF testing requirement for sunscreen products with water resistant claims.

33. Two comments suggested that "water resistant" labeling be permitted for drug products retaining at least 80 percent of their SPF value after static testing in pools and that any product meeting this criterion could also be labeled "sweat proof." The comments further suggested that the term "very water resistant" should be permitted for products retaining 90 to 98 percent of their SPF after testing.

The agency disagrees with the comments. Simple immersion provides neither an aqueous shear stress nor thermal challenge, and thus is an inadequate assessment of water resistance. In addition, no justification was offered for the respective threshold values of 80 percent and 90 to 98 percent.

34. Several comments contended that the water resistance testing procedures in § 352.76 should be amended to allow for continuation of the water exposure regimen beyond the 80 minute total and suggested that the "very water resistant" claim be expanded beyond 80 minutes for products meeting such testing requirements. One comment provided data (Ref. 24) to support extended water resistance claims. Another comment also proposed a testing protocol (Ref. 25) for an additional claim of "rubproof" or "abrasion proof."

The agency does not concur with an expansion of the "very water resistant" claim. Although data submitted by the comment (Ref. 24) show that under testing conditions products may retain their SPF values for up to 270 minutes of water exposure, no usage data were presented to refute the Panel's determination of an 80 minute upper exposure limit (58 FR 28194 at 28277).

In addition, the agency believes that for consumers to compare products with multiple performance characteristics, a labeling claim of "very water resistant" is best supported by a uniform testing standard. Should the agency receive data in the future indicating customary usage patterns in excess of 80 minutes of water exposure, it will reconsider this limit.

35. One comment disagreed with the agency's proposal in the tentative final monograph (58 FR 28194 at 28278) that manufacturers determine the waiting periods for the most effective use of their sunscreen products (i.e., the time between application and exposure to the sun or water, if applicable). This information would then be included in the directions for the product. The comment asserted there is no reason to require a "time versus efficacy" study for every sunscreen formula because studies show that products maintain their efficacy for up to 8 hours.

In the tentative final monograph, the agency did not propose a specific method or testing procedure for the determination of a proper waiting period because of the variation in sunscreen product dosage forms and formulations. Instead, the agency allowed manufacturers to make this determination. However, the agency did propose in § 352.52(d)(2) that a waiting period before sun or water exposure, if applicable, be included in the labeling of sunscreen products for their most effective use. In this final rule, the agency has included the requirement for a waiting period in the sunscreen product application statement in proposed § 352.52(d)(1) for the reasons stated in the tentative final monograph (58 FR 28278). The agency continues to allow the manufacturer to determine both the necessity for this statement (based on the product's formulation and dosage form) and how the waiting period, if applicable, is determined.

I. Comments on Indications for Sunscreen Drug Products

36. One comment urged the agency to more strongly state the effectiveness of sunscreens (a specific claim was not suggested). The comment cited a controlled study of a broad spectrum, SPF 17 sunscreen on 431 Caucasian subjects over one summer in Australia (Ref. 26). The study showed that the group using the sunscreen had significantly fewer solar keratoses and more remissions than the control group. Another comment expressed concern that use of the term "help prevent skin damage" may mislead consumers to think that these products prevent skin cancer and premature skin aging.

The agency agrees that solar keratoses are a clinical sign of skin damage. However, although sunscreens are associated with a statistically significant decrease in solar keratoses after 1 or 2 years, the solar keratoses reduction in this study was small and neither the clinical nor biological significance of this reduction has been established. Most solar keratoses never become skin cancers and typically resolve spontaneously (Refs. 27 and 28).

Because of the wide variability possible in the formulation of sunscreen products, not all sunscreen products are identical in their UV radiation absorption characteristics. Sunscreen products may contain active ingredients that absorb in different regions of the UVB radiation spectrum (the primary cause of sunburn) or absorb in both the UVB and different regions of the UVA radiation spectrum. Therefore, even the degree/type of UV radiation protection reported in one study using a specific sunscreen formulation may not be relevant to all possible sunscreen products within the scope of this final monograph. Further, the agency does not believe that it is prudent to extrapolate claims for skin cancer or skin aging based upon a test designed to only measure erythema (i.e., the SPF test).

The agency has reviewed information concerning the mechanisms of skin cancers and photoaging. UV radiation appears to have a dual role in the induction of skin cancers as it can cause several varieties of direct DNA damage (Refs. 23 and 29 through 32) plus suppress the immune response to developing skin cancers (Refs. 33 through 37). This immune suppression may be a critical variable as skin cancers, unlike other cancer types, evoke a strong immune response (especially by Langerhans cells and T-lymphocytes) (Ref. 38). In photoaging, there are multiple sites in the skin that can be damaged by UV radiation (Ref. 17). For example, recent studies support the concept that specific UV radiation-induced enzymes (i.e., matrix metalloproteinases) can mediate connective tissue damage and result in the premature aging effects seen in skin exposed to UV radiation (Refs. 19 and 20). These data also suggest that these mechanisms of carcinogenesis and photoaging can occur from doses of UV radiation below that required to produce sunburn (i.e., suberythemal doses). Thus, even if no sunburn has occurred with the use of a sunscreen, the consumer cannot assume that sun-induced skin damage that might contribute to the eventual development

of skin cancer or signs of photoaging has not occurred.

The agency agrees with the comment that terms such as "help prevent skin damage" may mislead consumers to think that sunscreen use alone will prevent skin cancer and premature skin aging. However, the agency believes that an appropriate statement can be used to inform consumers that sunscreens may reduce the risks of skin aging, skin cancer, and other harmful effects from the sun when used in a regular program that includes limiting sun exposure and wearing protective clothing (see section II.L, comment 51 of this document).

37. Several comments expressed concern that the statements "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" in proposed § 352.52(b)(1)(iii) and (b)(1)(iv) may mislead consumers as to the amount and degree of protection sunscreen products provide. The comments were concerned that this message will convey a more expansive meaning than intended and that consumers might be misled about how long they can stay in the sun without risking any sun-induced skin injury. One comment expressed additional concern because the SPF value is only a laboratory test of a few minutes' duration.

One comment also objected to the unqualified use of terms such as "shields from," "protects from," "filters" or "screens out" the "sun's rays," "sun's harsh rays," or "sun's harmful rays" to "help prevent skin damage" proposed in § 352.52(b)(1)(v) and (b)(1)(vi). The comment expressed concern that these unqualified terms could imply complete protection from the sun's harmful rays and may mislead consumers by inducing a false sense of security when using sunscreen products.

As discussed in section II.L, comment 36 of this document, the agency believes that sunscreen use alone will not prevent all of the possible harmful effects due to the sun. Variation between individuals, UV radiation absorption and substantivity of sunscreen products, exposure conditions, and conditions of use cannot promise a precise result for each individual. Thus, the agency agrees that these statements could provide the wrong message and a false sense of security to some consumers. The agency therefore is not including proposed § 352.52(b)(1)(iii) through (b)(1)(vi) in this final rule and considers these and similar statements to be nonmonograph.

For the same reasons, the agency also considers extended wear claims concerning a specific number of hours of "protection" (or similar terminology) or an absolute claim such as "all-day protection" to be nonmonograph. Instead, the agency is including an accurate, simpler, and less confusing indication statement in this final rule using two bulleted statements under the "Uses" heading, as follows: "[bullet] helps prevent sunburn" and "[bullet] higher SPF gives more sunburn protection".¹

38. Several comments contended that terms such as "skin aging," "wrinkling," "premature skin aging," or "photoaging" should be permitted as indications for sunscreens, especially if protection is provided in the UVA II (320 to 340 nm) radiation region. One comment suggested that a label claim such as "Helps reduce the chance of skin aging caused by incidental (or casual) exposure to the sun" may help to further position the product as a cosmetic for consumers. The comment also suggested an indication statement: "Excessive, chronic sun exposure can lead to premature photoaging of the skin, characterized by drying, wrinkling and thinning of the skin. Regular use of a sunscreen can help protect against this condition."

The agency discussed the use of terms such as "skin aging," "wrinkling," "premature skin aging," or "photoaging" on sunscreen products in the tentative final monograph (58 FR 28194 at 28236 and 28287). As discussed in the response to comments 36 and 37, the agency has determined that the labeling should describe the product's use in preventing sunburn. A more expansive set of indications is currently unsupported. The agency notes, however, that the final "Sun alert" statement (discussed in section II.L, comment 51 of this document) does provide the consumer with information about the role of sunscreens in reducing skin aging, in a context that ensures that the information will not be misleading. The agency, however, is continuing to consider whether certain sunscreens may provide protection against photoaging (58 FR at 28287) and has discussed this in tentative final monograph amendments for certain sunscreens containing avobenzone or zinc oxide based upon specific data submitted to the agency (see section II.E, comment 22 of this document). The agency will evaluate this issue further when it completes the UVA portion of the sunscreen monograph, in a future issue of the Federal Register.

¹ See § 201.66(b)(4)

39. Several comments contended that the extensive labeling proposed in the tentative final monograph was excessive. For environmental concerns, the comments objected to the use of extra packaging materials as a method of including added labeling. One comment disagreed with the need for a specific statement of product indications on individual units of non-beach products properly labeled with an SPF value, and cited limitations on labeling space. The comment suggested that manufacturers be given the option to provide off-package information at the point-of-sale rather than be required to place the statement(s) on each individual unit of the product.

To balance the environmental and regulatory concerns, the agency has streamlined labeling in this final monograph by significantly reducing the amount of required labeling and making optional other labeling that was proposed as required in the tentative final monograph. The agency is also including § 352.52(f) in this final monograph to provide for additional labeling accommodations for sunscreen products that meet the small package specifications in § 201.66(d)(10) and are labeled for use on specific small areas of the face (e.g., lips, nose, ears, and/or around eyes) (see section IV, comment 6 of this document).

J. Comments on Warnings for Sunscreen Drug Products

40. One comment asked the agency to permit reduced warning statements for lip balm products containing sunscreens based on their safe market history. The comment argued that lip balms are not applied to the eye area, and thus extensive eye warnings are not required. Two comments cited the long history of safe use of lipstick products containing sunscreens and suggested the reduced warning, "Discontinue use if signs of irritation appear."

The agency discussed its rationale for proposing an eye warning for sunscreen-containing lip balms in comment 52 of the tentative final monograph (58 FR 28194 at 28229 to 28232), noting that some lip balms could be used on other areas of the face. However, the agency has received neither data concerning adverse reactions due to the use of sunscreen-containing lip balms near the eyes, nor information that such products are normally used in the eye area. These products also are consistent with the factors described in the final OTC standardized content and format labeling rule (64 FR 13254 at 13270) for considering additional labeling modifications. Accordingly, this final monograph allows sunscreen-containing

lipsticks to omit the eye warning in proposed § 352.52(c)(1)(i). As discussed in Section II.J, comment 42 of this document, the wording of this warning is modified in this final monograph. For lip balms, the agency expects to adopt the same modification when it issues the final monograph on OTC skin protectant drug products.

The proposed warning in § 352.52(c)(1)(iii) is now stated as a bullet under the "Stop use and ask a doctor if" subheading as follows: "[bullet] rash or irritation develops and lasts." This warning appears in § 352.52(c)(1)(ii) in this document. Finally, lipsticks (and lip balms, which will be addressed in the final monograph on OTC skin protectant drug products) will not be required to bear the "For external use only" warning. Accordingly, in this final monograph, § 352.52(c)(2) allows lipsticks to omit the warning in § 201.66(c)(5)(i).

41. One comment requested that an eye irritancy warning need not be required for products that contain titanium dioxide as the sole active ingredient. The comment stated that titanium dioxide is an inert inorganic oxide (and thus is chemically distinct from all other Category I sunscreen active ingredients, which are organic compounds) and is an FDA approved color additive for the eye area in both drugs and cosmetics. The comment argued that determination of eye irritancy should be based on total product formulation. A second comment concurred that the labeling for inorganic sunscreens, which are not eye irritants, should be differentiated from organic sunscreens, which may be irritants in the eye.

The agency agrees that the eye warning (proposed in § 352.52(c)(1)(ii)) is based on total formulation, not simply presence of an ingredient. The agency's rationale was discussed in comments 52 and 62 of the tentative final monograph (58 FR 28194 at 28229 to 28232 and 28241). Accordingly, this final monograph requires all sunscreen-containing drug products to bear the eye warning in § 352.52(c)(1)(i). Only products formulated as a lipstick (and lip balms, which will be addressed in the final monograph on OTC skin protectant drug products) may omit this warning (see § 352.52(c)(3) of this document). The agency will consider omitting the eye warning requirement for a particular formulation if data submitted in an NDA deviation (§ 330.11 (21 CFR 330.11)) from the sunscreen monograph demonstrate it is not an eye irritant.

42. One comment suggested restating the proposed warnings in § 352.52(c)(1).

more concisely, as follows: "For external use only. Keep out of eyes. If contact occurs, rinse thoroughly with water. If irritation or rash occurs, discontinue use. Consult a doctor if problem persists."

Since the tentative final monograph was published, the agency has published a final rule revising the format and content requirements for OTC drug product labeling (64 FR 13254). Section 201.66(c)(5)(i) requires the warning "For external use only" for all topical drug products not intended for ingestion. Therefore, it is not necessary to state that warning in this document and the warning in proposed § 352.52(c)(1)(i) is not included in this final monograph. The agency is shortening the proposed warning in § 352.52(c)(1)(ii). This warning appears in § 352.52(c)(1)(i) in this document as a bullet under the "When using this product" subheading as follows:

"[bullet] keep out of eyes. Rinse with water to remove." The agency is stating the proposed warning in § 352.52(c)(1)(iii) as a bullet under the "Stop use and ask a doctor if" subheading as follows: "[bullet] rash or irritation develops and lasts." This warning appears in § 352.52(c)(1)(ii) in this document. Section 201.66(c)(5)(x) requires the "Keep out of reach of children" and accidental ingestion warning set forth in 21 CFR 330.1(g) for these products.

43. One comment contended that the proposed warning about swallowing in § 352.52(c)(1)(i) would not be needed for so-called secondary sunscreen products because adults using these products (which, according to the comment, have traditionally been marketed as cosmetics) would know not to ingest them.

As discussed in section II.J, comment 42 of this document, the warning proposed in § 352.52(c)(1)(i) has been superseded by the warning required by § 201.66(c)(5)(i). The new required warning no longer contains the statement about not swallowing the product.

K. Comments on Directions for Sunscreen Drug Products

44. Two comments stated that the proposed directions in § 352.53(d)(4) for lipsticks and make-up preparations are unnecessary because these products are marketed primarily for their cosmetic uses, which are self-evident. One comment contended that it is unlikely that consumers will modify their habits of lipstick application and usage simply because the product contains a sunscreen. The other comment argued that failure to follow directions for these

products is unlikely to have serious consequences.

The agency has determined that directions for use in the labeling of lipstick products containing sunscreens would provide minimal benefit to consumers and the omission of a directions statement is not likely to have serious consequences (see section II.J, comment 40 of this document). However, the agency believes that directions would be useful for make-up products containing sunscreens because of the wide variety of make-up products that are available. Therefore, the agency is revising proposed § 352.52(d)(4) to read: "For products formulated as a lipstick. The directions in paragraphs (d)(1) and (d)(2) of this section are not required." The agency expects to finalize the same modifications for lip balm products when it finalizes the monograph for OTC skin protectant drug products.

45. Several comments contended that the proposed direction, "Children under 2 years of age should use sunscreen products with a minimum SPF of 4," is misleading and has no scientific basis. Some comments stated that the direction implies that an SPF 4 may be adequate for children and noted that the Skin Cancer Foundation advises use of SPF 15 or higher for both children and adults. The American Academy of Dermatology questioned why children should not have the benefit of a more highly protective sunscreen. Other comments suggested that this direction should only be required for products with an SPF lower than 4 because it would be nonsensical and a waste of label space on products with higher SPF values.

The agency agrees with the comments that this direction could mislead parents into believing SPF 4 is adequate for children under 2 years of age. Therefore, the agency concludes it is not appropriate and is not including it in § 352.52(d) in this document.

46. One comment stated that the words, "adults and children 6 months of age and over" in proposed § 352.52(d)(1) are unnecessary because there is a separate statement, "Children under 6 months of age: consult a doctor." Another comment suggested that lengthy directions for use by children 6 months to 2 years of age are not appropriate for many product types (e.g., a daily facial moisturizer with a sunscreen) and should be revised to "For adult use only." Another comment added that when "For adult use only" is used, then warning and cautionary statements concerning use by children would not be needed.

The agency agrees with the comment that the statement, "Children under 6 months of age: consult a doctor," provides sufficient information regarding the age limit for use and is retaining it under § 352.52(d) as a bullet with a small modification as follows: "[bullet] children under 6 months of age: ask a doctor". Therefore, the agency is removing the phrase, "Adults and children 6 months of age and over." The proposed directions for children 6 months to 2 years of age referred to by the comments in § 352.52(d)(1), (d)(2), (d)(3), and (d)(5) stated: "Children under 2 years of age should use sunscreen products with a minimum SPF of 4." As discussed in section II.K, comment 45 of this document, the agency concluded that this direction was misleading and did not include it in § 352.52(d) in this document. The agency finds it unnecessary to include the direction "For adult use only" in this document because there are only two age groups in the directions: Children under 6 months of age and all other users of the product.

47. One comment argued that the direction "apply generously" may be responsible for some skin irritation complaints from consumers. However, the comment did not provide data to support its position. The comment contended that application of smaller amounts of sunscreen may provide adequate coverage, but that in the case of sun protection, it may be best to err on the generous side. Another comment maintained that applying too little sunscreen may significantly lower protection in a geometric rather than a linear fashion, e.g., an SPF 25 sunscreen applied half as thick as the amount applied for the SPF test may only have the effect of SPF 8.

The agency agrees with the comments that adequate sunscreen should be applied to achieve full labeled SPF protection. Therefore, the agency concludes that the directions in § 352.52(d)(1) of this final monograph to apply "liberally" or "generously" convey the appropriate message to ensure that consumers adequately apply the sunscreen.

48. One comment stated that the agency should permit firms to provide reapplication instructions based on substantiation information the firm possesses. The comment noted that some products may not need to be applied as frequently as some select time period.

The agency is including a general reapplication direction in § 352.52(d)(2). Manufacturers who have data to support reapplication instructions based on specific substantiation information may

submit that information for approval via an NDA deviation as provided in § 330.11.

L. Comments on Product Performance Statements for Sunscreen Drug Products

49. Several comments recommended revisions to proposed § 352.52(e), the statement on product performance. For example, some comments suggested that multiple superlative category designations (e.g., "high," "very high," and "ultra high") may foster consumer confusion about the level of protection each SPF provides. Other comments stated that the current SPF scale does not encourage consumers to use higher SPF products. Other comments disagreed with the indication "permits no tanning."

The agency has revised proposed § 352.52(e) in this document by condensing the five proposed product categories to three broader ones, and has generalized the category designations. The new categories are: minimal sunburn protection for products with SPF 2 to under 12; Moderate sunburn protection for products with SPF 12 to under 30; high sunburn protection for products with SPF 30 or above. These product category designations (PCD) should appear under the "Other information" heading and may also appear on the PDP. Further, products are now described as providing minimal, moderate, or high protection against tanning, thus deleting the reference to tanning prevention that was proposed in § 352.52(b)(2)(v)(B).

50. Many comments opposed the "recommended sunscreen product guide" in proposed § 352.52(e)(4). Some comments noted that the guide is incomplete because it only considers skin type and not duration of exposure, season, geographic location, and other factors that influence choice of product. Other comments stated that the guide is deceptive and may encourage inappropriate use of lower SPF's for protection. Several comments stated that labeling for many products is too small to accommodate the guide. Other comments suggested that information in the guide should be disseminated to consumers through point of sale, television, and weather programs, rather than being required in product labeling.

The agency recognizes that various factors influence the purchase of a sunscreen product, including skin type, geographic location, hours exposed to the sun, and sun reflections. While the product guide was intended as a general guidance for using these products, the agency acknowledges that the guide is incomplete and could be confusing and misleading to consumers. Accordingly,

the agency is not including the recommended sunscreen product guide in this document.

51. Many comments requested that the "Sun alert" in proposed § 352.52(e)(6) be voluntary instead of required labeling and suggested this information could better be disseminated at the point of purchase or through consumer education programs. Some comments stated that the "Sun alert" is too weak and suggested alternate language. One comment observed that the "Sun alert" fails to warn consumers that UV radiation may harm the immune system, impairing the body's ability to fight infectious disease. The comment did not provide data to support this claim.

The agency agrees that the "Sun alert" should be optional on product labeling. Further, the agency has reevaluated the "Sun alert" and concludes that its purpose should be to describe the role of sunscreens in a total program to reduce harmful effects from the sun. Marks (Ref. 39) has noted that sunscreens "are normally recommended for use as an adjunct to other protection," such as clothing, hats, and avoidance of the sun near midday. The agency agrees with this concept, as do many researchers (Ref. 40), the American Academy of Dermatology (Ref. 41), Centers for Disease Control (Ref. 41), and the Governments of Australia and New Zealand (Ref. 42). For this reason, the agency has revised the "Sun alert" to include other protective actions consumers can take, and has clarified possible results. The agency is including skin cancer in the "Sun alert" instead of the body's ability to fight infectious disease because, to date, skin cancer is the best documented adverse effect of UV radiation on the immune system (Ref. 43). Accordingly, § 352.52(e)(2) in this document provides the following optional "Sun alert," which should appear under the "Other information" heading and may also appear on the PDP: "Limiting sun exposure, wearing protective clothing, and using sunscreens may reduce the risks of skin aging, skin cancer, and other harmful effects of the sun." The agency encourages sunscreen manufacturers to voluntarily include this "Sun alert" in the labeling and to otherwise make it available at point of purchase and through consumer education programs.

52. Several comments suggested that the term "sunblock," proposed in the definition in § 352.3(d) and as a labeling statement for products containing titanium dioxide that provide an SPF of 12 to 30 in § 352.52(e)(5), not be included in the final monograph. Some

comments argued that the term is unclear and may mislead and confuse consumers into thinking that the product blocks all of the sun, when in fact it does not. One comment stated that no product available totally blocks sun damage. Numerous other comments contended that the term "sunblock" should be applied to all sunscreen ingredients that provide an SPF of 12 or higher, as such products block at least 90 percent of the sun's UV rays. One of the comments submitted a study (Ref. 44) to show that micronized titanium dioxide absorbs short wavelength UV radiation and reflects and scatters long wavelengths, thereby functioning similarly to chemical UVB radiation sunscreens. The comment contended that the method in which micronized titanium dioxide performs as a sunscreen active ingredient further justifies the use of the term "sunblock" for all sunscreen products with an SPF of 12 or higher.

The agency has decided not to include the term "sunblock" in the final monograph and now considers this term nonmonograph. The agency's intention in the tentative final monograph was to provide information to consumers on the method of product performance, not to imply greater protection from using a product labeled as a "sunblock." The agency is concerned that the term "sunblock" on the label of sunscreen drug products will be viewed as an absolute term which may mislead or confuse consumers into thinking that the product blocks all light from the sun. For example, consumers might view an SPF 15 product labeled as a sunblock as superior to a product labeled as an SPF 30 broad spectrum sunscreen. As nonmonograph labeling, the term "sunblock" cannot appear anywhere in product labeling.

In addition, the proposed definition of "sunscreen opaque sunblock" in § 352.3(d) applied only to titanium dioxide and is inconsistent with how micronized titanium dioxide functions as a sunscreen active ingredient (Ref. 44). Further, it is the radiation from the UV portion (290 to 400 nm) of the sun's spectrum that reaches the earth's surface and may produce skin erythema, melanogenesis, and cancer. The agency believes that claims of protection beyond 400 nm (i.e., protection from visible and infra red light) are nonmonograph and not within the scope of this document. Therefore, to provide clear and consistent labeling, the agency is not including proposed §§ 352.3(d) and 352.52(e)(5) in this document.

M. Comments on Testing Procedures for Sunscreen Drug Products

53. Several comments questioned the ability of current testing methods to accurately and reproducibly determine SPF values for high SPF products. Some comments contended that the spectra of currently used solar simulators (especially around 290 nm and above 350 nm) could cause overestimation of SPF for high SPF sunscreens and recommended use of a specifications table that provided percent of erythema contribution by wavelength regions. Other comments submitted data in support of a high-SPF sunscreen control following concerns expressed by the agency in the proposed rule (58 FR 28194 at 28253 and 28254) that data were not sufficient to demonstrate that the testing methods 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. Several comments submitted data and information that questioned the ability of current testing methods to accurately and reproducibly determine SPF values for high SPF products and requested significant changes to proposed subpart D of § 352.70. Other comments requested changes to the testing procedures proposed in subpart D of the sunscreen monograph that were unrelated to products with high SPF values.

The agency believes that the test method proposed in the tentative final monograph (TFM), for measuring SPF values up to 30, represents at this time a straightforward, well-understood, and sound method for measuring these values. The agency therefore is finalizing the method proposed in the TFM. The agency recognizes, however, that testing methods in this area are evolving and that a number of comments raised useful ideas for proposed improvements in the accuracy and reproducibility of the agency's methodology. As discussed in response to comment 29 of section II.G of this document, the agency is also inviting interested persons to continue working on improving SPF testing methods, toward the development of accurate methods for measuring high SPF values. In future issues of the Federal Register, if appropriate, the agency will consider proposed improvements to its testing methodology.

54. One comment contended that the calculation of erythema effective exposure (E) serves no practical purpose in the calculation of SPF because the E constant is common to both the numerator and denominator of the

equation. Another comment stated that the definition of E is incorrect because it is defined as "dose" (Joules/square meter (m²)) on the left side of the equation $E = \sum V_i(\lambda) * I(\lambda)$, whereas the right side of the equation is in terms of irradiance (Watts/m²). The comment also stated that the unit of time exposure (seconds) is missing on the right side of the equation.

The agency acknowledges that this calculation is not technically necessary if the solar simulator emission spectrum does not change between exposures to protected and unprotected skin. The same result can then be obtained by measuring the difference (i.e., ratio) in time required to produce erythema on protected versus unprotected skin. However, the agency finds that the calculation of E provides valuable information and is necessary to demonstrate how the MED was determined during SPF testing. The agency agrees with the comment concerning the missing variable of time (in seconds) in the calculation of E and, accordingly, has modified the equation in § 352.73 of this document to read as follows: " $E = \sum V_i(\lambda) * I(\lambda) * t_{exp}$ "

III. Recent Developments

In the Federal Register of October 22, 1998, the agency proposed to amend the tentative final monograph to include zinc oxide as a single ingredient and in combination with any proposed Category I sunscreen active ingredient except avobenzone. Two comments supported the proposal. One comment disagreed with the agency's exclusion of avobenzone from combinations with zinc oxide. Two of the comments urged the agency to expeditiously review and approve a citizen petition (Ref. 45) to recognize this combination.

The agency has informed the petitioner that it is unable to approve the combination without appropriate UVA radiation effectiveness data to demonstrate the UVA radiation protection potential of zinc oxide in combination with avobenzone (Ref. 46). The agency will reconsider this combination for monograph status upon receipt of the appropriate data.

This final rule includes monograph conditions for zinc oxide as a sunscreen active ingredient at concentrations up to 25 percent when used alone or in combination with any monograph sunscreen active ingredient except avobenzone.

IV. Additional Changes

1. The agency has determined that for an active ingredient to be included in an OTC drug final monograph it is necessary to have publicly available

chemical information that can be used by all manufacturers to determine that the ingredient is appropriate for use in their products. Compendial monographs include an ingredient's official name, chemical formula, and analytical chemical tests to confirm the quality and purity of the ingredient. These monographs establish public standards for the strength, quality, purity, and packaging of ingredients and drug products available in the United States.

In the Federal Register of June 8, 1994, FDA deleted digalloyl trioleate, ethyl 4-[bis(hydroxypropyl)]aminobenzoate, glyceryl aminobenzoate, lawsone with dihydroxyacetone, and red petrolatum from the tentative final monograph due to the lack of interest in establishing USP compendial monographs for these ingredients. Lawsone with dihydroxyacetone subsequently remained under agency consideration due to increased interest by manufacturers in establishing a compendial monograph. Of the 18 remaining sunscreen active ingredients under consideration in the tentative final monograph (58 FR 28194 at 28295, amended at 61 FR 48645 and 63 FR 56584), 16 (aminobenzoic acid, avobenzene, cinoxate, dioxybenzone, homosalate, menthyl anthranilate, octocrylene, octyl methoxycinnamate, octyl salicylate, oxybenzone, padimate O, phenylbenzimidazole sulfonic acid, sulisobenzene, titanium dioxide, trolamine salicylate, and zinc oxide) currently have compendial monographs. Two (diethanolamine methoxycinnamate and lawsone with dihydroxyacetone) do not have a current or proposed compendial monograph.

The agency is including in § 352.10 of this document the 16 sunscreen active ingredients that currently have a compendial monograph. The agency is reserving the appropriate paragraphs in proposed § 352.10 for the two active ingredients without compendial monographs in case a monograph is developed for either ingredient. Dihydroxyacetone has been proposed for a compendial monograph, but none has been proposed for lawsone. Because these two active ingredients are used in conjunction, lawsone must have a compendial monograph in order for lawsone with dihydroxyacetone to be included in the sunscreen final monograph.

2. The agency has revised proposed § 352.52(b) in response to comments requesting reduction, streamlining, and flexibility of sunscreen labeling and in accordance with new data reviewed by the agency (see section II.I of this document). The agency has revised proposed § 352.52(b)(1) by: (1) Deleting

references to any other indication except that pertaining to the prevention of sunburn (see section II.I, comment 37 of this document), (2) adding (in § 352.52(b)(2) of this final rule) guidance on SPF selection due to simplification of the PCD in proposed § 352.52(e)(1) and deletion of the Recommended Product Guide in proposed § 352.52(e)(4) (see section II.L, comments 49 and 50 of this document), and (3) deleting the quantitative claims (i.e., "up to (insert SPF of product up to 30) times") and terms such as "screens," "shields," etc., concerning sunburn protection throughout proposed § 352.52(b) (see section II.I, comment 37 of this document).

3. The tentative final monograph allowed reduced labeling directions on sunscreen products if formulated as a make-up preparation, lipstick, lip balm, or skin preparation and labeled with claims relating only to the prevention of "lip damage," "freckling," or "uneven coloration." Because there is no convincing evidence that SPF testing predicts protection from anything but sunburn (see section II.I, comment 36 of this document), the agency is not including proposed § 352.52(b)(1)(v), (b)(1)(vi), (d)(4), and (d)(5) in this document. The agency will consider including such claims in the monograph when specific supportive data are provided or a specific clinically relevant final formulation test is developed.

4. Numerous comments requested deletion of the dual SPF testing of water resistant products in proposed § 352.50(b)(2) and (c)(2). The agency agrees with the comments (see section II.H, comment 32 of this document) and has revised proposed §§ 352.50(b)(2) and (c)(2) and 352.76 to require only the SPF value after water resistant testing. Further, the agency has modified and made optional the reapplication directions in proposed §§ 352.52(d)(1) and (d)(2) (see section II.K, comment 48 of this document). These changes to proposed § 352.52(d) provide flexibility by allowing manufacturers to expand on reapplication information necessary for specific sunscreen formulations and by equalizing requirements between products with and without water resistance claims and between sunscreen drug and drug-cosmetic products. Thus, the water resistance labeling in § 352.52(b)(1)(ii) and (b)(1)(iii) of this document should also serve as a directive for reapplication of the product. In summary, for products making water and/or sweat resistance claims, the agency has modified and combined water resistance statements formerly in proposed § 352.52(e)(2), (e)(3), (d)(1), and (d)(2) into

§ 352.52(b)(1)(ii) and (b)(1)(iii) in this document.

5. The agency has modified references to "tanning" and "prolongs exposure time" in proposed § 352.52(b)(2) by combining the PCD claim in § 352.52(e)(1) of this document with either the phrase "protection against sunburn" or "protection against sunburn and tanning." Based upon current information, the agency believes that the terms proposed in the tentative final monograph could send the wrong message relative to the dangers of even suberythemal UV radiation exposure and give consumers a false sense of security concerning sun exposure and sunscreen use. The agency has reduced and simplified the other optional, additional indications in proposed § 352.52(b)(2) to reflect a modified, simpler, combined version of the PCD in proposed § 352.52(e)(1) (see section II.L, comment 49 of this document) and the "Recommended Product Guide" in proposed § 352.52(e)(4) (see section II.L, comment 50 of this document). Because the agency has deleted reference to use of the term "Sunblock" in proposed section § 352.52(e)(5) (see section II.L, comment 52 of this document), it has deleted reference to "Reflects the burning rays of the sun" in proposed § 352.52(b)(3) for the same reasons.

6. Several comments requested labeling exemptions or flexibility for packages that are too small to accommodate all required information. Some comments specifically requested flexible labeling for products based upon their intended use, such as lipsticks and lip balms.

As discussed in the final rule establishing standardized format and content requirements for the labeling of OTC drug products (64 FR 13254 at 13267 to 13268 and 13289), the agency has established specifications for small packages in § 201.66(d)(10). The agency also stated in the final labeling rule that it will consider additional approaches for accommodating certain small-package products in their respective OTC drug monograph proceedings.

The agency considers the required OTC drug labeling information essential for the safe and effective use of these products and important to consumers for selection of an appropriate product. Nevertheless, the agency agrees that excessive labeling requirements may discourage manufacturers from marketing certain products, such as lipsticks or lip balms containing sunscreens, which provide significant public health benefit.

In this OTC drug rulemaking, the agency has included several accommodations for products such as

lipsticks (and lip balms, which will be addressed in the final monograph on OTC skin protectant drug products), taking into consideration the intended uses of these products, the limited areas to which these products are applied, and the overall safety profile of these products, and other factors described in the final OTC labeling rule (64 FR 13254 at 13270). The agency is including § 352.52(f) in this document to provide for labeling modifications for sunscreen products that meet the small package specifications in § 201.66(d)(10) and are labeled for use on specific small areas of the face (e.g., lips, nose, ears, and/or around eyes).

7. The agency has revised §§ 700.35 and 740.19 (21 CFR 700.35 and 740.19) in response to comments requesting clarification on whether certain products will be subject to regulation as drugs (see section II.B, comments 8 through 11 of this document). Section 700.35 has been revised to make clear that, generally, products that make sun protection claims, whether express or implied, are subject to regulation as drugs. Only those products that contain a sunscreen ingredient solely for a nontherapeutic, nonphysiologic use (e.g., as a color additive, or to protect the color of the product such as in a nail polish or hair coloring product) (see 58 FR at 28205), and which include a labeling statement that accurately describes that use, may be marketed as cosmetic products. Section 740.19 has been revised to make clear that the term "suntanning preparations" does not include products intended to provide sun protection or otherwise to affect the structure or any function of the body. Suntanning preparations include gels, creams, liquids, and other topical products that are intended to provide cosmetic effects on the skin while tanning through exposure to UV radiation (e.g., moisturizing or conditioning), or that are intended to give the appearance of a tan by imparting color through the application of approved color additives (e.g., dihydroxyacetone) without the need for exposure to UV radiation (i.e., sunless tanning products).

V. Conclusion

The agency is issuing a final monograph establishing conditions under which OTC sunscreen drug products are generally recognized as safe and effective and not misbranded; 16 ingredients listed in § 352.10 are currently a monograph condition. Any drug product labeled, represented, or promoted for use as an OTC sunscreen drug that contains any of the nonmonograph ingredients listed in

§ 310.545(a)(29), or that is not in conformance with the monograph (21 CFR part 352), may be considered a new drug within the meaning of section 201(p) of the act and misbranded under section 502 of the act. Such a drug product cannot be marketed for OTC sunscreen use unless it is the subject of an approved application under section 505 of the act (21 U.S.C. 355) and 21 CFR part 314 of the regulations. An appropriate citizen petition to amend the monograph may also be submitted in accord with 21 CFR 10.30 and § 330.10(a)(12)(i). The agency will address sunscreen active ingredients that have foreign marketing experience and data at a future time. Any OTC sunscreen drug product initially introduced or initially delivered for introduction into interstate commerce after the effective date of the final rule for § 310.545(a)(29) or this document that is not in compliance with the regulations is subject to regulatory action.

VI. References

The following references are on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Comment No. CP1, Docket No. 78N-0038, Dockets Management Branch.
2. Comment No. CP2, Docket No. 78N-0038, Dockets Management Branch.
3. Comment No. CP3, Docket No. 78N-0038, Dockets Management Branch.
4. Comment No. CP7, Docket No. 78N-0038, Dockets Management Branch.
5. Comité de Liaison des Associations Européennes de L'Industrie de la Parfumerie, des Produits Cosmétiques et de Toilette (COLIPA), SPF Test Method (Draft). The Recommendations of the COLIPA Task Force "Sun Protection Measurement," December 1992 in Comment No. C00365, Docket No. 78N-0038, Dockets Management Branch.
6. Peak, M. J., and J. C. van der Leun, "Boundary Between UVA and UVB," in *Frontiers of Photobiology*, edited by A. Shimizu et al., Excerpta Medica, Amsterdam, pp. 425-427, 1993.
7. Comment No. LET 135, Docket 78N-0038, Dockets Management Branch.
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9. Comment No. C00364, Docket No. 78N-0038, Dockets Management Branch.
10. Comments No. C00397 and SUP21, Docket No. 78N-0038, Dockets Management Branch.
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12. Comment No. TR3, Docket No. 78N-0038, Dockets Management Branch.
13. *Pharmacopeial Forum*, United States Pharmacopeial Convention, Inc., Rockville, MD, 22(4):2635-2636, July through August 1996.
14. *Pharmacopeial Forum*, United States Pharmacopeial Convention, Inc., Rockville, MD, 24(4):6547-6548, July through August 1998.
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18. Lavker, R., and K. Kaidbey, "The Spectral Dependence for UVA-Induced Cumulative Damage in Human Skin," *The Journal of Investigative Dermatology*, 108:17-21, 1997.
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20. Lowe, N. J. et al., "Low Doses of Repetitive Ultraviolet A Induce Morphologic Changes in Human Skin," *Journal of the American Academy of Dermatology*, 105:739-743, 1995.
21. Comment No. C00282, Docket No. 78N-0038, Dockets Management Branch.
22. Comment No. C00365, Docket No. 78N-0038, Dockets Management Branch.
23. Comment No. C00531, Docket No. 78N-0038, Dockets Management Branch.
24. Comment No. C00128, Docket No. 78N-0038, Dockets Management Branch.
25. Comment No. SUP16, Docket No. 78N-0038, Dockets Management Branch.
26. Thompson, S. C., J. D. Jolley, and R. Marks, "Reduction of Solar Keratoses by Regular Sunscreen Use," *The New England Journal of Medicine*, 329:1147-1151, 1993.
27. Marks, R. et al., "Spontaneous Remission of Solar Keratoses: The Case for Conservative Management," *British Journal of Dermatology*, 115:649-654, 1986.
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30. Kraemer, K. H., "Sunlight and Skin Cancer: Another Link Revealed," *Proceedings of the National Academy of Sciences U. S. A.*, 94:11-14, 1997.
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32. Burren, R. et al., "Sunlight and Carcinogenesis: Expression of p53 and Pyrimidine Dimers in Human Skin Following UVA I, UVA I + II and Solar Simulating Radiation," *International Journal of Cancer*, 76:201-206, 1998.

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45. Comment No. CP8, Docket No. 78N-0038, Dockets Management Branch.

46. Comment No. LET166, Docket No. 78N-0038, Dockets Management Branch.

47. Food and Drug Administration, "Supplement to the Economic Impact Analysis of the Sunscreen Drug Products for Over-the-Counter Human Use; Final Monograph," in OTC Vol. 06FR, Docket No. 78N-0038, Dockets Management Branch.

48. Eastern Research Group, Inc., "Over-the-Counter Drug Reformulation Changes," in OTC Vol. 06FR, Docket No. 78N-0038, Dockets Management Branch.

VII. Analysis of Impacts

FDA has examined the impacts of this final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act (2 U.S.C. 1501 et seq.).

Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is consistent with the principles identified in Executive Order 12866. OMB has determined that the final rule is a significant regulatory action as defined by the Executive Order and so is subject to review. Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Title II of the Unfunded Mandates Reform Act requires that agencies prepare a written assessment of anticipated costs and benefits before proposing any rule that may result in an expenditure in any 1 year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation) (2 U.S.C. 1532).

Because the rule may have a significant economic impact on a substantial number of small entities, this section of the preamble constitutes the agency's Final Regulatory Flexibility Analysis. Because the rule does not impose any mandates on State, local, or tribal governments, or the private sector, that will result in an expenditure in any 1 year of \$100 million or more, FDA is not required to perform a cost-benefit analysis according to the Unfunded Mandates Reform Act.

An analysis of the costs and benefits of this regulation, conducted under Executive Order 12291, was discussed in the tentative final monograph for OTC sunscreen drug products (58 FR 28194 at 28294). The agency received only one response to the specific request for data and comment on the economic impact of this rulemaking. This comment discussed the costs that would result from proposed changes in sunscreen product labeling and testing methods. The agency's review of this comment is included as follows.

A. Background

The purpose of this document is to establish conditions under which OTC sunscreen drug products are generally recognized as safe, effective, and not misbranded. The document sets specific requirements for appropriate monograph ingredients, labeling format and content, and SPF value and water resistant testing. Although the agency

cannot quantify the overall expected benefits, each provision of the rule will support the ability of consumers to take desired protective actions. Monograph ingredients have been proven safe and effective assuring the quality of sunscreen products. This benefits consumers because it ensures that the product will provide ingredients that safely protect against sunburn. The new product labeling will better inform consumers about the sunburn protection provided by the products; and if manufacturers choose to include the optional "Sun alert" labeling statement, the product labeling can reference that the use of sunscreens may reduce the risk of skin aging, skin cancer, and other harmful effects of the sun. These labeling requirements, in conjunction with the format requirements of the OTC uniform labeling rule (64 FR 13254) will provide clearer and more concise information that will benefit consumers in at least four ways: (1) They will increase understanding regarding the selection of sunscreen drug products, (2) they will make product comparison easier, (3) they will enhance the ability to make informed decisions regarding product purchases and proper use, and (4) they will make it easier to distinguish between sunscreen drug products that contain sunscreens and suntanning products that do not. Finally, the new requirements for product testing will assure the accuracy of the SPF value on the product label. By improving the accuracy of these ratings, this requirement will provide further assurance that consumers receive adequate sunburn protection.

The rule will require all manufacturers and distributors (or their agents) to relabel their OTC sunscreen drug products to comply with the monograph language. The labeling of certain suntanning products that do not contain sunscreens will need to include the new required warning statement. In some cases, the labeling of cosmetics containing sunscreens for nontherapeutic, nonphysiologic uses (e.g., to protect hair from sun damage) will need to describe the cosmetic role of the sunscreen ingredient(s). The SPF of some OTC sunscreen drug products may need to be retested using the method described in the final monograph. In addition, only products containing the active ingredients included in this final rule will be generally recognized as safe, effective, and not misbranded. Of the 18 active ingredients under consideration in the proposed rule, 16 currently have the required USP/N.F. compendial

monographs. The USP has not received applications for the remaining two ingredients. If either of these active ingredients are not included in the USP and added to the monograph by May 21, 2001, products containing these ingredients would need to be reformulated to replace the nonmonograph ingredient with a monograph ingredient, or the product must be removed from the market.

B. Number of Products Affected

Based on data from FDA's Drug Listing System, the agency estimates that there are approximately 2,800 OTC sunscreen drug products (different formulations, not including products that differ only by color) and about 12,000 individual stockkeeping units (SKU's) (individual products, packages, and sizes). All of the SKU's will need to be relabeled, some will require new SPF testing, and those products lacking approved active ingredients will need to be reformulated to stay on the market.

In addition, certain suntanning products and certain cosmetic products containing sunscreens will have to be relabeled. As FDA's Drug Listing System does not include suntanning products, the agency used 1995 data from A. C. Nielsen, a recognized provider of market data, to estimate that approximately 550 suntanning SKU's will be affected by the labeling requirements of this rule. New labels will also be needed for cosmetic products that contain a sunscreen for a nontherapeutic use and that include the word "sunscreen" or similar terms in product labeling. The agency is unable to identify the number of these cosmetic products, but does not believe that there are a large number of SKU's in this category.

C. Cost to Relabel

The relabeling costs for this rule will be moderated to the extent that manufacturers coordinate labeling changes for the final sunscreen monograph with labeling changes required by the recent rule establishing uniform format and content for OTC drug product labeling (64 FR 13254). These costs are not discussed in this analysis, however, because they are

already accounted for in the agency's analysis of its OTC drug product labeling rule. That is, the agency's economic analysis of that rule excluded redesign costs for all OTC drug products not marketed under current NDA's or current final monographs, explaining that the agency would attribute all redesign costs associated with future final monographs to each final monograph rule as it published. All redesign costs for this final sunscreen monograph therefore are attributed to this rule alone.

Approximately 12,000 sunscreen drug SKU's will have to be relabeled within a 2-year implementation period to comply with the labeling requirements of this final rule. In addition, approximately 550 suntanning SKU's will have to be relabeled within a 12-month implementation period. (As noted previously, FDA could not estimate the number of cosmetic products that contain a sunscreen for a nontherapeutic use and that include the word "sunscreen" or similar terms in product labeling. The agency believes, however, the relabeling of this group of cosmetic products will impose a minimal economic burden because some of these products already include the required labeling, and most manufacturers revise these labels for marketing considerations more frequently than the allowed 2-year phase-in period. Therefore, the agency's estimates do not include a cost for relabeling those products that contain sunscreens for a nontherapeutic, nonphysiologic use.)

Frequent labeling redesigns are a recognized cost of doing business in the OTC drug industry, particularly for drug-cosmetic and seasonal products. Thus, SKU's with labels that would normally be redesigned within the implementation periods were assumed to incur no additional costs. The cost for the remaining SKU's was calculated as the lost value of the remaining life-years of the existing label design. FDA estimates that labeling for the majority (90 percent) of the SKU's affected by this final rule are redesigned at least every 2 years. Of the remaining SKU's,

the agency assumes that half would be redesigned every 3 years and half every 6 years. Because the required labeling for OTC sunscreen drug products now includes fewer words than the previous language and the final rule contains a number of labeling modifications for products used on small areas of the face (which are usually marketed in small size packages), this rule is not expected to require manufacturers to increase the package size or available labeling space. (Although costs of redesigning labels for future final monographs were excluded from FDA's analysis of its OTC drug product labeling rule, costs for increased package sizes were considered in the analysis of impacts for that regulation (64 FR 13254 at 13283)).

FDA estimated the cost of redesign by counting only the value of the label-years that would be lost, after adjusting for the length of the traditional labeling cycle. The regulatory cost was calculated as the product of the number of SKU's, the number of years of labeling life lost, and the value of each year of labeling life lost (see 64 FR 13254 at 13278 through 13284).²

Table 1 in section VIII.C of this document details FDA's estimates of the distribution of relabeling costs resulting from the final rule. A weighted average cost to redesign a label of \$5,210 per SKU was used to calculate the relabeling cost of sunscreen drug products, whereas a weighted average cost of \$6,620 per SKU was used to calculate the cost of relabeling suntanning products. A detailed description of the cost analysis is on file with the Docket Management Branch (Ref. 47). As shown, the total incremental cost to relabel the approximately 12,000 sunscreen drug SKU's is about \$1.5 million, while the cost to relabel the approximately 550 suntanning SKU's was about \$1.8 million. The greater per SKU cost for relabeling suntanning products reflects the shorter, 12-month, phase-in period. With a shorter phase-in period, manufacturers are less able to incorporate labeling changes into voluntary redesign cycles and, therefore, lose label inventory.

TABLE 1.—ONE-TIME COST TO RELABEL SUNSCREEN AND SUNTANNING SKU'S (\$)

Size of Company	Type of Product		
	Drug	Suntanning	Total Cost
Small ¹	649,283	1,128,700	1,777,983

² Mathematically the following formula was used to calculate the incremental relabeling costs:
 $Cost_{j,x} = \sum N_x A_x (1/x)$, where $j = 1$ to $(x-y)$
 Total $Cost_x = Cost_{j,x} + Cost_{j,x} + Cost_{j,x}$

where:
 $x =$ life of labeling in years (2, 3, or 6)
 $y =$ phase-in period in years

$N_x =$ number of SKU's with labeling life of x years, and
 $A_x =$ amortized annual value of labeling with a life of x years.

TABLE 1.—ONE-TIME COST TO RELABEL SUNSCREEN AND SUNTANNING SKU'S (\$)—Continued

Size of Company	Type of Product		
	Drug	Suntanning	Total Cost
Large	860,677	691,800	1,552,477
Total Cost	1,509,960	1,820,500	3,330,460

¹ See section VII.G of this document.

The one comment that raised economic issues in response to the tentative final monograph expressed concern about available labeling space on small packages of sunscreen drug products. The comment stated that all text needs to be concise. The agency considered this comment in developing the final rule, which contains specific labeling modifications for small packages and for sunscreen products used on small areas of the face (e.g., lips, nose, ears, and/or around the eyes).

D. Cost to Retest SPF

FDA is uncertain about the number of OTC sunscreen drug products that have

not been tested using the monograph SPF test method. However, the SPF test method in this document is essentially the same as the method described in the proposed rule. If manufacturers have added new products, made formulation changes, or otherwise needed to test or retest the SPF of their products since 1993, they would probably have used the most current (i.e., the proposed) test method. Therefore, the agency estimates that from 15 to 30 percent of the sunscreen drug products will require retesting as a result of this document. The cost of the SPF test varies, depending on the product claim (water

resistant or very water resistant) and SPF factor tested, and ranges from \$2,500 to \$6,500. On the assumption that 50 percent of the traditional sunscreen drug products, and none of the make-up type sunscreen products, make water resistant claims, and 50 percent of the products that make water resistant claims make very water resistant claims, the estimated weighted average cost of the SPF test is \$3,514. FDA estimates the total cost of this requirement, therefore, to range from \$3.1 million to \$6.1 millions (see the following Table 2).

TABLE 2.—ONE-TIME COST TO RETEST SPF ASSUMING 15 PERCENT OR 30 PERCENT COMPLIANCE RATES (\$)

Size of Company	15 Percent Non-compliance	30 Percent Non-compliance
Small	1,300,000	2,600,000
Large	1,800,000	3,500,000
Total Cost	3,100,000	6,100,000

E. Cost to Reformulate

Reformulation costs will depend on the number of products, if any, that will have no active ingredients with completed USP compendial monographs by the end of the implementation period. At the present time, only two of the active ingredients being considered do not have a USP monograph. According to the agency's drug listing system, two products, manufactured by one company contain one of these ingredients. The agency is not currently aware of other products in the marketplace that contain these two ingredients.

The cost to reformulate a product varies by the nature of the reformulation, the type of product, and the size and complexity of the company.

Because OTC sunscreen drug products are well characterized topical formulations, FDA estimates the cost to reformulate at about \$350,000 per product. Thus, on the assumption that the manufacturer reformulates rather than removes the products from the market, the one-time cost of reformulation for two products would be \$700,000.

F. Total Incremental Costs

The estimated total one-time incremental cost of this rule, using the midpoint of the cost range for retesting and reformulation is \$8.6 million (see Table 3 of this document). These estimates are based on 16 of the 18 active sunscreen ingredients under consideration having USP compendial monographs. If a USP monograph is

completed for the one ingredient in these two products or if the two products are removed from the market, the cost of reformulation would be eliminated.

G. Small Business Impact

Based on the analysis of FDA's drug listing system and other data described previously, there are about 180 domestic companies that manufacture OTC sunscreen and suntanning products. Distributors were not assigned costs because manufacturers of OTC drug products are usually responsible for product labeling, testing, and formulation. Approximately 78 percent of these firms meet the Small Business Administration's definition of a small entity for this industry (less than 750 employees).

TABLE 3.—TOTAL INCREMENTAL COST TO INDUSTRY (\$)

Size of Company	Relabel Products		Retest SPF ¹	Reformulation ²	Total
	Drug	Suntanning			
Small	670,000	1,100,000	2,000,000	n/a	n/a
Large	840,000	700,000	2,600,000	n/a	n/a

TABLE 3.—TOTAL INCREMENTAL COST TO INDUSTRY (\$)—Continued

Size of Company	Relabel Products		Retest SPF ¹	Reformulation ²	Total
	Drug	Suntanning			
Total Cost	1,510,000	1,800,000	4,600,000	700,000	8,610,000

¹ Assumes 22.5 percent noncompliance (midpoint of range)

² Assumes 2 products would require reformulation

The rule will require manufacturers of sunscreens to relabel their products. Some firms will need to retest the SPF of these products, and one firm may have to reformulate or remove two products from the market. Because of the 2-year implementation period, most firms will be able to relabel during a normal relabeling cycle, at no additional cost. FDA cannot estimate with certainty the number of small firms that will need to retest or reformulate their OTC sunscreen products, but projects that from 15 to 30 percent of all products may need to be retested and that 2 products may need to be reformulated. Costs will vary by firm, depending on the type and number of products requiring relabeling, retesting, and reformulation. The firm-specific impact may vary inversely with the volume of product sales, however, because per unit costs will be lower for products with high volume sales. Thus, the relative economic impact of product retesting or relabeling may be greater for small firms than for large firms.

Because of the 2-year phase-in period allowed for sunscreen drug and drug-cosmetic products, which allows manufacturers the flexibility to incorporate regulatory changes with voluntary/market-driven changes, the economic impact of the relabeling requirement is relatively low (approximately \$3.3 million). However, for those small companies that may have to relabel a substantial number of products, the out-of-pocket costs could be significant.

Also, the cost to a small company needing to reformulate a product, estimated at approximately \$350,000 would be significant. This impact may be moderated by other options available, which may be more cost effective than reformulation. For example, a manufacturer may be able to substitute other formulations, shift production to a contract manufacturer with an approved formulation, or temporarily remove the product from the market and await the completion of a USP compendial monograph for the ingredient. Because the OTC drug industry is highly regulated, all firms are expected to have access to the necessary professional skills on staff or to make contractual

arrangements to comply with the paperwork and other requirements of this rule.

H. Analysis of Alternatives

The agency altered several proposed regulatory provisions to reduce the economic burden of this rule on industry. For example, FDA decreased the amount of required labeling and provided small package accommodations for certain products. The labeling required by the proposed rule would have increased the needed label and/or package size for as many as 90 percent of the sunscreen products. Such size adjustments could have imposed estimated additional one-time relabeling costs of \$18 million and annually recurring costs of \$22 million (see Eastern Research Group, "Cost Impacts of the Over-the-Counter Pharmaceutical Labeling Rule" (Ref. 48)). Also, in response to the comment (see section II.H, comment 32 of this document), the agency has reconsidered its position on SPF testing of water resistant and very water resistant products and eliminated the static test requirement for these products. As the average cost of the static test is approximately \$2,800, the estimated savings to industry due to the elimination of this test is about \$750,000.

The agency also considered a number of implementation alternatives to this final rule. Generally, the agency allows only a 1-year implementation period for final monographs. However, because most sunscreen products are produced seasonally, the 2-year period will substantially enhance the ability of the industry to relabel and reformulate its products, if necessary, and sell its existing product inventories. The 2-year period will also allow sunscreen manufacturers to coordinate the required labeling changes with routine industry-initiated labeling changes and changes required by the new OTC drug product labeling final rule (64 FR 13254).

A 3-year implementation period for sunscreen drug products was considered, but the agency determined that a 2-year period provides sufficient time to allow the required relabeling

and product retesting to be completed. The agency found that the savings to industry of delayed implementation (estimated to be about \$845,000) were not great enough to justify delaying appropriate use and safety information to consumers of OTC sunscreen drug products.

Finally, the agency is providing a 12-month implementation period for certain suntanning preparations to add new warning information. For this category, consumers may believe that these products are providing sun protection when, in fact, they do not. They may forego using other products that have been demonstrated to be effective in providing sun protection, believing that their tanning product provides some measure of protection. Because the new warning for suntanning preparations presents an important safety issue that needs to be conveyed to consumers at the earliest possible date, the agency considered requiring a 6-month implementation period for these products. However, given the seasonal nature of these products, the agency was concerned that some manufacturers may not have sufficient time to incorporate the labeling change without disrupting their production schedules. By providing an additional 6 months to implement the change, compliance costs were reduced by \$1.8 million.

VIII. Paperwork Reduction Act of 1995

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

IX. Environmental Impact

The agency has determined that under 21 CFR 25.31(c) 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.

List of Subjects

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 352

Labeling, Over-the-counter drugs.

21 CFR Part 700

Cosmetics, Packaging and containers.

21 CFR Part 740

Cosmetics, Labeling.

Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 352 is added and 21 CFR parts 310, 700, and 740 are amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b–360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b–263n.

2. Section 310.545 is amended by adding paragraph (a)(29), by revising paragraph (d) introductory text, by adding and reserving paragraph (d)(30), and by adding paragraph (d)(31) to read as follows:

§310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.

(a) * * *

(29) Sunscreen drug products.

Diethanolamine methoxycinnamate
Digalloyl trioleate
Ethyl 4-(bis(hydroxypropyl)) aminobenzoate
Glyceryl aminobenzoate
Lawsone with dihydroxyacetone
Red petrolatum

* * * * *

(d) Any OTC drug product that is not in compliance with this section is subject to regulatory action if initially introduced or initially delivered for introduction into interstate commerce after the dates specified in paragraphs (d)(1) through (d)(31) of this section.

* * * * *

(30) [Reserved]

(31) May 21, 2001 for products subject to paragraph (a)(29) of this section.

3. Part 352 is added to read as follows:

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

Subpart A—General Provisions

Sec.
352.1 Scope.
352.3 Definitions.

Subpart B—Active Ingredients

352.10 Sunscreen active ingredients.
352.20 Permitted combinations of active ingredients.

Subpart C—Labeling

352.50 Principal display panel of all sunscreen drug products.
352.52 Labeling of sunscreen drug products.
352.60 Labeling of permitted combinations of active ingredients.

Subpart D—Testing Procedures

352.70 Standard sunscreen.
352.71 Light source (solar simulator).
352.72 General testing procedures.
352.73 Determination of SPF value.
352.76 Determination if a product is water resistant or very water resistant.
352.77 Test modifications.

Authority: 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 quantity of erythema-effective energy (expressed as Joules per square meter) required to produce the first perceptible, redness reaction with clearly defined borders.

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

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

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

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

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

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

Subpart B—Active Ingredients

§352.10 Sunscreen active ingredients.

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

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

(b) Avobenzene up to 3 percent.

(c) Cinoxate up to 3 percent.

(d) [Reserved].

(e) Dioxybenzone up to 3 percent.

(f) Homosalate up to 15 percent.

(g) [Reserved].

(h) Menthyl anthranilate up to 5 percent.

(i) Octocrylene up to 10 percent.

(j) Octyl methoxycinnamate up to 7.5 percent.

(k) Octyl salicylate up to 5 percent.

(l) Oxybenzone up to 6 percent.

(m) Padimate O up to 8 percent.

(n) Phenylbenzimidazole sulfonic acid up to 4 percent.

(o) Sulisobenzene up to 10 percent.

(p) Titanium dioxide up to 25 percent.

(q) Trolamine salicylate up to 12 percent.

(r) Zinc oxide up to 25 percent.

§352.20 Permitted combinations of active ingredients.

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

(a) *Combinations of sunscreen active ingredients.* (1) Two or more sunscreen active ingredients identified in § 352.10(a), (c), (e), (f), and (h) through (r) may be combined with each other in a single product when used in the concentrations established for each ingredient in § 352.10. The concentration of each active ingredient must be sufficient to contribute a minimum SPF of not less than 2 to the finished product. The finished product must have a minimum SPF of not less than the number of sunscreen active ingredients used in the combination multiplied by 2.

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

- (b) [Reserved].
(c) [Reserved].

Subpart C—Labeling

§ 352.50 Principal display panel of all sunscreen drug products.

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

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

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

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

(2) "SPF (insert SPF value of the product, as stated in paragraph (a)(1) or (a)(2) of this section, after it has been tested using the water resistant

sunscreen product testing procedures in § 352.76)."

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

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

§ 352.52 Labeling of sunscreen drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "sunscreen."

(b) *Indications.* The labeling of the product states, under the heading "Uses," all of the phrases listed in paragraph (b)(1) of this section that are applicable to the product and may contain any of the additional phrases listed in paragraph (b)(2) of this section, as appropriate. Other truthful and nonmisleading statements, describing only the uses that have been established and listed in this paragraph (b), may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

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

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

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

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

(i) *For products that provide an SPF of 2 to under 12.* Select one or both of the following: "[bullet]" (select one of the following: "provides minimal," "provides minimum," "minimal," or

"minimum") "protection against" (select one of the following: "sunburn" or "sunburn and tanning"), or "[bullet] for skin that sunburns minimally".

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

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

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

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

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

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

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

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

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

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

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

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

¹ See § 201.66(b)(4) of this chapter.

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

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

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

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

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

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

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

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

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

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

(iv) The subheadings in § 201.66(c)(5)(iii) through (c)(5)(vii) of this chapter may be omitted, provided the information after the heading

"Warnings" states: "Keep out of eyes." and "Stop use if skin rash occurs."

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

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

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

§ 352.60 Labeling of permitted combinations of active ingredients.

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

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

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

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

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

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

(d) *Directions.* The labeling of the product states, under the heading "Directions," directions that conform to the directions established for each ingredient in the directions sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph. When the time intervals or age limitations for administration of the individual ingredients differ, the directions for the combination product may not contain any dosage that exceeds those established for any individual ingredient in the applicable OTC drug monograph(s), and may not provide for use by any age group lower than the highest minimum age limit established for any individual ingredient. For permitted combinations containing a sunscreen and a skin protectant identified in § 352.20(b).

Subpart D—Testing Procedures

§ 352.70 Standard sunscreen.

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

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

COMPOSITION OF PREPARATION A AND PREPARATION B OF THE STANDARD SUNSCREEN

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

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

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

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

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

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

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

(5) *Calculation of the concentration of homosalate.* The concentration of homosalate is determined by the following formula which takes into consideration the absorbance of the sample of the test solution, the dilution of the 1-percent solution (1:50), the weight of the sample of the standard homosalate sunscreen preparation (1 gram), and the standard absorbance value (172) of homosalate as determined by averaging the absorbance of a large number of batches of raw homosalate:

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

§ 352.71 Light source (solar simulator).

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

§ 352.72 General testing procedures.

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

Skin Type and Sunburn and Tanning History (Based on first 30 to 45 minutes sun exposure after a winter season of no sun exposure.)

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

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

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

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

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

VI—Never burns; deeply pigmented (insensitive).

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

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

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

(d) *Test site delineation—(1) Test site area.* A test site area serves as an area for determining the subject's MED after application of either the sunscreen standard or the test sunscreen product, or for determining the subject's MED when the skin is unprotected (control site). The area to be tested shall be the back between the beltline and the shoulder blade (scapulae) and lateral to the midline. Each test site area for applying a product or the standard

sunscreen shall be a minimum of 50-square centimeters, e.g., 5 x 10 centimeters. The test site areas are outlined with ink. If the person is to be tested in an upright position, the lines shall be drawn on the skin with the subject upright. If the subject is to be tested while prone, the markings shall be made with the subject prone.

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

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

be exposed to the varying doses of UV radiation in a randomized manner.

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

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

(h) *Response criteria.* In order that the person who evaluates the MED responses does not know which sunscreen formulation was applied to which site or what doses of UV radiation were administered, he/she must not be the same person who applied the sunscreen drug product to the test site or administered the doses of UV radiation. After UV radiation exposure from the solar simulator is completed, all immediate responses shall be recorded. These include several types of typical responses such as the following: An immediate darkening or tanning, typically greyish or purplish in color, fading in 30 to 60 minutes, and attributed to photo-oxidation of existing melanin granules; immediate reddening, fading rapidly, and viewed as a normal response of capillaries and venules to heat, visible and infrared radiation; and an immediate generalized heat response, resembling prickly heat rash, fading in 30 to 60 minutes, and apparently caused by heat and moisture generally irritating to the skin's surface. After the immediate responses are noted, each subject shall shield the exposed area from further UV radiation for the remainder of the test day. The MED is determined 22 to 24 hours after exposure. The erythema responses of the test subject should be evaluated under the following conditions: The source of illumination should be either a tungsten light bulb or a warm white

fluorescent light bulb that provides a level of illumination at the test site within the range of 450 to 550 lux, and the test subject should be in the same position used when the test site was irradiated. Testing depends upon determining the smallest dose of energy that produces redness reaching the borders of the exposure site at 22 to 24 hours postexposure for each series of exposures. To determine the MED, somewhat more intense erythemas must also be produced. The goal is to have some exposures that produce absolutely no effect, and of those exposures that produce an effect, the maximal exposure should be no more than twice the total energy of the minimal exposure.

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

§ 352.73 Determination of SPF value.

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

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

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

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

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

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

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

V_i = Weighting Factor (Erythema Action Spectrum)

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

t_{exp} = exposure time (seconds)

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

(c) *Determination of individual SPF values.* A series of UV radiation exposures expressed as Joules per square meter (adjusted to the erythema action spectrum calculated according to § 352.73(a)) is administered to the

subsite areas on each subject with an accurately-calibrated solar simulator. A series of seven exposures shall be administered to the protected test sites to determine the MED of the protected skin (MED(PS)). The doses selected shall consist of a geometric series of five exposures, where the middle exposure is placed to yield the expected SPF plus two other exposures placed symmetrically around the middle exposure. The exact series of exposures to be given to the protected skin shall be determined by the previously established MED(US) and the expected SPF of the test sunscreen. For products with an expected SPF less than 8, the exposures shall be the MED(US) times 0.64X, 0.80X, 0.90X, 1.00X, 1.10X, 1.25X, and 1.56X, where X equals the expected SPF of the test product. For products with an expected SPF between 8 and 15, the exposures shall be the MED(US) times 0.69X, 0.83X, 0.91X, 1.00X, 1.09X, 1.20X, and 1.44X, where X equals the expected SPF of the test product. For products with an expected SPF greater than 15, the exposures shall be the MED(US) times 0.76X, 0.87X, 0.93X, 1.00X, 1.07X, 1.15X, and 1.32X, where X equals the expected SPF of the test product. The MED is the quantity of erythema-effective energy required to produce the first perceptible, unambiguous redness reaction with clearly defined borders at 22 to 24 hours postexposure. The SPF value of the test sunscreen is then calculated from the dose of UV radiation required to

produce the MED of the protected skin and from the dose of UV radiation required to produce the MED of the unprotected skin (control site) as follows:

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

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

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

The general testing procedures in § 352.72 shall be used as part of the following tests, except where modified in this section. An indoor fresh water

pool, whirlpool, and/or jacuzzi maintained at 23 to 32 °C shall be used in these testing procedures. Fresh water is clean drinking water that meets the standards in 40 CFR part 141. The pool and air temperature and the relative humidity shall be recorded.

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

(1) Apply sunscreen product (followed by the waiting period after application of the sunscreen product indicated on the product labeling).

(2) 20 minutes moderate activity in water.

(3) 20-minute rest period (do not towel test sites).

(4) 20 minutes moderate activity in water.

(5) Conclude water test (air dry test sites without toweling).

(6) Begin solar simulator exposure to test site areas as described in § 352.73.

(b) *Procedure for testing a very water resistant sunscreen product.* For sunscreen products making the claim of "very water resistant," the label SPF shall be the label SPF value determined after 80 minutes of water immersion using the following procedure for the very water resistant test:

(1) Apply sunscreen product (followed by the waiting period after application of the sunscreen product indicated on the product labeling).

(2) 20 minutes moderate activity in water.

(3) 20-minute rest period (do not towel test sites).

(4) 20 minutes moderate activity in water.

(5) 20-minute rest period (do not towel test sites).

(6) 20 minutes moderate activity in water.

(7) 20-minute rest period (do not towel test sites).

(8) 20 minutes moderate activity in water.

(9) Conclude water test (air dry test sites without toweling).

(10) Begin solar simulator exposure to test site areas as described in § 352.73.

§ 352.77 Test modifications.

The formulation or mode of administration of certain products may require modification of the testing procedures in this subpart. In addition, alternative methods (including automated or in vitro procedures) employing the same basic procedures as those described in this subpart may be

used. Any proposed modification or alternative procedure shall be submitted as a petition in accord with § 10.30 of this chapter. The petition should contain data to support the modification or data demonstrating that an alternative procedure provides results of equivalent accuracy. All information submitted will be subject to the disclosure rules in part 20 of this chapter.

PART 700—GENERAL

4. The authority citation for 21 CFR part 700 continues to read as follows:

Authority: 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 sunscreen ingredients.

(a) A product that includes 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 act. Sunscreen active ingredients affect the structure or function of the body by absorbing, 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 may reduce the chance of premature skin aging, skin cancer, and other harmful effects due to the sun when used in conjunction with limiting sun exposure and wearing protective clothing. When consumers see the term "sunscreen" or similar sun protection terminology in the labeling 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" or similar sun protection terminology in a product's labeling generally causes the product to be subject to regulation as a drug. However, sunscreen ingredients may also be used in some products for nontherapeutic, nonphysiologic uses (e.g., as a color additive or to protect the color of the product). To avoid consumer misunderstanding, if a cosmetic product contains a sunscreen ingredient and uses the term "sunscreen" or similar sun protection terminology anywhere in its labeling, the term must be qualified by describing the cosmetic benefit provided by the sunscreen ingredient.

(b) The qualifying information required under paragraph (a) of this section shall appear prominently and

conspicuously at least once in the labeling in conjunction with the term "sunscreen" or other similar sun protection terminology used in the labeling. For example: "Contains a sunscreen—to protect product color."

PART 740—COSMETIC PRODUCT WARNING STATEMENTS

6. The authority citation for 21 CFR part 740 continues to read as follows:

Authority: 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. Repeated exposure of unprotected skin while tanning may increase the risk of skin aging, skin cancer, and other harmful effects to the skin even if you do not burn." For purposes of this section, the term "suntanning preparations" includes gels, creams, liquids, and other topical products that are intended to provide cosmetic effects on the skin while tanning through exposure to UV radiation (e.g., moisturizing or conditioning products), or to give the appearance of a tan by imparting color to the skin through the application of approved color additives (e.g., dihydroxyacetone) without the need for exposure to UV radiation. The term "suntanning preparations" does not include products intended to provide sun protection or otherwise intended to affect the structure or any function of the body.

Dated: April 22, 1999.

William K. Hubbard,

Associate Commissioner for Policy
Coordination.

[FR Doc. 99-12853 Filed 5-20-99; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF DEFENSE

Office of the Secretary

32 CFR Part 311

OSD Privacy Program; Correction

AGENCY: Department of Defense.

ACTION: Final rule; correction.

SUMMARY: This rule makes administrative corrections to the OSD Privacy Program rule published on April 28, 1999.

drugs or devices under the Service Act, there is any person who is not specifically provided for in such regulation, the procedure under which a review of appropriate scientific data shall take place shall be the same as in the case of a regulation of the Food and Drug Act.

CTS. Application or submission of any other similar form to the Secretary of Health, Education and Welfare for the purpose of submitting the request for the product, or for the receipt of the product, shall determine whether the product is a drug, and the reasons therefor, and the reasons for such determination, or for public health purposes, does not provide for in subsection (b), and subsection (a) shall apply to the Secretary of Health, Education and Welfare of the Food and Drug Act, as applicable, and with the written regulations based on sci-

CHAPTER VI—COSMETICS

ADULTERATED COSMETICS

SEC. 601. [361] A cosmetic shall be deemed to be adulterated—

- (a) If it bears or contains any poisonous or deleterious substance which may render it injurious to users under the conditions of use prescribed in the labeling thereof, or, under such conditions of use as are customary or usual, except that this provision shall not apply to coal-tar hair dye, the label of which bears the following legend conspicuously displayed thereon: "Caution—This product contains ingredients which may cause skin irritation on certain individuals and a preliminary test according to accompanying directions should first be made. This product must not be used for dyeing the eyelashes or eyebrows; to do so may cause blindness.", and the labeling of which bears adequate directions for such preliminary testing. For the purposes of this paragraph and paragraph (e) the term "hair dye" shall not include eyelash dyes or eyebrow dyes.
- (b) If it consists in whole or in part of any filthy, putrid, or decomposed substance.
- (c) If it has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health.
- (d) If its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health.
- (e) If it is not a hair dye and it is, or it bears or contains, a color additive which is unsafe within the meaning of section 721(a).

MISBRANDED COSMETICS

SEC. 602. [362] A cosmetic shall be deemed to be misbranded—

- (a) If its labeling is false or misleading in any particular.
- (b) If in package form unless it bears a label containing (1) the name and place of business of the manufacturer, packer, or distributor; and (2) an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count: *Provided*, That under clause (2) of this paragraph reasonable variations shall be permitted, and exemptions as to small packages shall be established, by regulations prescribed by the Secretary.
- (c) If any word, statement, or other information required by or under authority of this Act to appear on the label or labeling is not prominently placed thereon with such conspicuousness (as compared with other words, statements, designs, or devices in the labeling) and in such terms as to render it likely to be read and un-

derstood by the ordinary individual under customary conditions of purchase and use.

(d) If its container is so made, formed, or filled as to be misleading.

(e) If it is a color additive, unless its packaging and labeling are in conformity with such packaging and labeling requirements applicable to such color additive, as may be contained in regulations issued under section 721. This paragraph shall not apply to packages of color additives which, with respect to their use for cosmetics, are marketed and intended for use only in or on hair dyes (as defined in the last sentence of section 601(a)).

(f) If its packaging or labeling is in violation of an applicable regulation issued pursuant to section 3 or 4 of the Poison Prevention Packaging Act of 1970.

REGULATIONS MAKING EXEMPTIONS

SEC. 603. [363] The Secretary shall promulgate regulations exempting from any labeling requirement of this Act cosmetics which are, in accordance with the practice of the trade, to be processed, labeled, or repacked in substantial quantities at establishments other than those where originally processed or packed, on condition that such cosmetics are not adulterated or misbranded under the provisions of this Act upon removal from such processing, labeling, or repacking establishment.

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quired.

(e) Any officer or employee of the Department designated by
the Secretary to conduct examinations, investigations, or inspec-
tions under this Act relating to counterfeit drugs may, when so au-
thorized by the Secretary—

- (1) carry firearms;
- (2) execute and serve search warrants and arrest war-
rants;
- (3) execute seizure by process issued pursuant to libel
under section 304;
- (4) make arrests without warrant for offenses under this
Act with respect to such drugs if the offense is committed in
his presence or, in the case of a felony, if he has probable cause
to believe that the person so arrested has committed, or is com-
mitting, such offense; and

(5) make, prior to the institution of libel proceedings under
section 304(a)(2), seizures of drugs or containers or of equip-
ment, punches, dies, plates, stones, labeling, or other things, if
they are, or he has reasonable grounds to believe that they are,
subject to seizure and condemnation under such section
304(a)(2). In the event of seizure pursuant to this paragraph
(5)¹, libel proceedings under section 304(a)(2) shall be insti-
tuted promptly and the property seized be placed under the ju-
risdiction of the court.

RECORDS OF INTERSTATE SHIPMENT

SEC. 703. [373] For the purpose of enforcing the provisions of
this Act, carriers engaged in interstate commerce, and persons re-
ceiving food, drugs, devices, or cosmetics in interstate commerce or
holding such articles so received, shall, upon the request of an offi-
cer or employee duly designated by the Secretary, permit such offi-
cer or employee, at reasonable times, to have access to and to copy
all records showing the movement in interstate commerce of any
food, drug, device, or cosmetic, or the holding thereof during or
after such movement, and the quantity, shipper, and consignee
thereof; and it shall be unlawful for any such carrier or person to
fail to permit such access to and copying of any such record so re-
quested when such request is accompanied by a statement in writ-
ing specifying the nature or kind of food, drug, device, or cosmetic
to which such request relates, except that evidence obtained under
this section, or any evidence which is directly or indirectly derived
from such evidence, shall not be used in a criminal prosecution of
the person from whom obtained, and except that carriers shall not
be subject to the other provisions of this Act by reason of their re-
ceipt, carriage, holding, or delivery of food, drugs, devices, or cos-
metics in the usual course of business as carriers.

FACTORY INSPECTION

SEC. 704. [374] (a)(1) For purposes of enforcement of this Act,
officers or employees duly designated by the Secretary, upon pre-

¹ Probably should be "this paragraph".

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CHAPTER V—DRUGS AND DEVICES

SUBCHAPTER A—DRUGS AND DEVICES

ADULTERATED DRUGS AND DEVICES

SEC. 501. [351] A drug or device shall be deemed to be adul-
 terated—

(a)(1) If it consists in whole or in part of any filthy, putrid, or
 decomposed substance; or (2)(A) if it has been prepared, packed, or
 held under insanitary conditions whereby it may have been con-
 taminated with filth, or whereby it may have been rendered injuri-
 ous to health; or (B) if it is a drug and the methods used in, or the
 facilities or controls used for, its manufacture, processing, packing,
 or holding do not conform to or are not operated or administered
 in conformity with current good manufacturing practice to assure
 that such drug meets the requirements of this Act as to safety and
 has the identity and strength, and meets the quality and purity
 characteristics, which it purports or is represented to possess; or
 (C) if it is a compounded positron emission tomography drug and
 the methods used in, or the facilities and controls used for, its
 compounding, processing, packing, or holding do not conform to or
 are not operated or administered in conformity with the positron
 emission tomography compounding standards and the official
 monographs of the United States Pharmacopoeia to assure that
 such drug meets the requirements of this Act as to safety and has
 the identity and strength, and meets the quality and purity charac-
 teristics, that it purports or is represented to possess; or (3) if its
 container is composed, in whole or in part, of any poisonous or del-
 eterious substance which may render the contents injurious to
 health; or (4) if (A) it bears or contains, for purposes of coloring
 only, a color additive which is unsafe within the meaning of section
 721(a), or (B) it is a color additive the intended use of which in or
 on drugs or devices is for purposes of coloring only and is unsafe
 within the meaning of section 721(a); or (5) if it is a new animal
 drug which is unsafe within the meaning of section 512; or (6) if
 it is an animal feed bearing or containing a new animal drug, and
 such animal feed is unsafe within the meaning of section 512.

(b) If it purports to be or is represented as a drug the name
 of which is recognized in an official compendium, and its strength
 differs from, or its quality or purity falls below, the standards set
 forth in such compendium. Such determination as to strength,
 quality, or purity shall be made in accordance with the tests or
 methods of assay set forth in such compendium, except that when-
 ever tests or methods of assay have not been prescribed in such
 compendium, or such tests or methods of assay as are prescribed
 are, in the judgment of the Secretary, insufficient for the making
 of such determination, the Secretary shall bring such fact to the at-

drug products for administration to humans or animals.

(b) The current good manufacturing practice regulations in this chapter, as they pertain to drug products, and in parts 600 through 680 of this chapter, as they pertain to biological products for human use, shall be considered to supplement, not supersede, the regulations in this part unless the regulations explicitly provide otherwise. In the event it is impossible to comply with applicable regulations both in this part and in other parts of this chapter or in parts 600 through 680 of this chapter, the regulation specifically applicable to the drug product in question shall supersede the regulation in this part.

(c) Pending consideration of a proposed exemption, published in the FEDERAL REGISTER of September 29, 1978, the requirements in this part shall not be enforced for OTC drug products if the products and all their ingredients are ordinarily marketed and consumed as human foods, and which products may also fall within the legal definition of drugs by virtue of their intended use. Therefore, until further notice, regulations under part 110 of this chapter, and where applicable, parts 113 to 129 of this chapter, shall be applied in determining whether these OTC drug products that are also foods are manufactured, processed, packed, or held under current good manufacturing practice.

[43 FR 45077, Sept. 29, 1978, as amended at 62 FR 66522, Dec. 19, 1997]

§211.3 Definitions.

The definitions set forth in §210.3 of this chapter apply in this part.

Subpart B—Organization and Personnel

§211.22 Responsibilities of quality control unit.

(a) There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have

occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.

(b) Adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products shall be available to the quality control unit.

(c) The quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product.

(d) The responsibilities and procedures applicable to the quality control unit shall be in writing; such written procedures shall be followed.

§211.25 Personnel qualifications.

(a) Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in current good manufacturing practice (including the current good manufacturing practice regulations in this chapter and written procedures required by these regulations) as they relate to the employee's functions. Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them.

(b) Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or any combination thereof, to perform assigned functions in such a manner as to provide assurance that the drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess.

(c) There shall be an adequate number of qualified personnel to perform

and supervise the manufacture, processing, packing, or holding of each drug product.

§211.28 Personnel responsibilities.

(a) Personnel engaged in the manufacture, processing, packing, or holding of a drug product shall wear clean clothing appropriate for the duties they perform. Protective apparel, such as head, face, hand, and arm coverings, shall be worn as necessary to protect drug products from contamination.

(b) Personnel shall practice good sanitation and health habits.

(c) Only personnel authorized by supervisory personnel shall enter those areas of the buildings and facilities designated as limited-access areas.

(d) Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions that may adversely affect the safety or quality of drug products shall be excluded from direct contact with components, drug product containers, closures, in-process materials, and drug products until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of drug products. All personnel shall be instructed to report to supervisory personnel any health conditions that may have an adverse effect on drug products.

§211.34 Consultants.

Consultants advising on the manufacture, processing, packing, or holding of drug products shall have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained. Records shall be maintained stating the name, address, and qualifications of any consultants and the type of service they provide.

Subpart C—Buildings and Facilities

§211.42 Design and construction features.

(a) Any building or buildings used in the manufacture, processing, packing, or holding of a drug product shall be of suitable size, construction and location to facilitate cleaning, maintenance, and proper operations

(b) Any such building shall have adequate space for the orderly placement of equipment and materials to prevent mixups between different components, drug product containers, closures, labeling, in-process materials, or drug products, and to prevent contamination. The flow of components, drug product containers, closures, labeling, in-process materials, and drug products through the building or buildings shall be designed to prevent contamination.

(c) Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mixups during the course of the following procedures:

(1) Receipt, identification, storage, and withholding from use of components, drug product containers, closures, and labeling, pending the appropriate sampling, testing, or examination by the quality control unit before release for manufacturing or packaging;

(2) Holding rejected components, drug product containers, closures, and labeling before disposition;

(3) Storage of released components, drug product containers, closures, and labeling;

(4) Storage of in-process materials;

(5) Manufacturing and processing operations;

(6) Packaging and labeling operations;

(7) Quarantine storage before release of drug products;

(8) Storage of drug products after release;

(9) Control and laboratory operations;

(10) Aseptic processing, which includes as appropriate:

(i) Floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable;

(ii) Temperature and humidity controls;

(iii) An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or nonlaminar;

(iv) A system for monitoring environ-

record of the program shall be maintained along with appropriate validation data. Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained.

[43 FR 45077, Sept. 29, 1978, as amended at 60 FR 4091, Jan. 20, 1995]

§211.72 Filters.

Filters for liquid filtration used in the manufacture, processing, or packing of injectable drug products intended for human use shall not release fibers into such products. Fiber-releasing filters may not be used in the manufacture, processing, or packing of these injectable drug products unless it is not possible to manufacture such drug products without the use of such filters. If use of a fiber-releasing filter is necessary, an additional non-fiber-releasing filter of 0.22 micron maximum mean porosity (0.45 micron if the manufacturing conditions so dictate) shall subsequently be used to reduce the content of particles in the injectable drug product. Use of an asbestos-containing filter, with or without subsequent use of a specific non-fiber-releasing filter, is permissible only upon submission of proof to the appropriate bureau of the Food and Drug Administration that use of a non-fiber-releasing filter will, or is likely to, compromise the safety or effectiveness of the injectable drug product.

Subpart E—Control of Components and Drug Product Containers and Closures

§211.80 General requirements.

(a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures; such written procedures shall be followed.

(b) Components and drug product containers and closures shall at all times be handled and stored in a manner to prevent contamination.

(c) Bagged or boxed components of drug product containers, or closures shall be stored off the floor and suitably spaced to permit cleaning and inspection.

(d) Each container or grouping of containers for components or drug product containers, or closures shall be identified with a distinctive code for each lot in each shipment received. This code shall be used in recording the disposition of each lot. Each lot shall be appropriately identified as to its status (i.e., quarantined, approved, or rejected).

§211.82 Receipt and storage of untested components, drug product containers, and closures.

(a) Upon receipt and before acceptance, each container or grouping of containers of components, drug product containers, and closures shall be examined visually for appropriate labeling as to contents, container damage or broken seals, and contamination.

(b) Components, drug product containers, and closures shall be stored under quarantine until they have been tested or examined, as appropriate, and released. Storage within the area shall conform to the requirements of §211.80.

§211.84 Testing and approval or rejection of components, drug product containers, and closures.

(a) Each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit.

(b) Representative samples of each shipment of each lot shall be collected for testing or examination. The number of containers to be sampled, and the amount of material to be taken from each container, shall be based upon appropriate criteria such as statistical criteria for component variability, confidence levels, and degree of precision desired, the past quality history of the supplier, and the quantity needed for analysis and reserve where required by §211.170.

(c) Samples shall be collected in accordance with the following procedures:

(1) The containers of components selected shall be cleaned where necessary, by appropriate means.

(2) The containers shall be opened, sampled, and resealed in a manner designed to prevent contamination of their contents and contamination of other components, drug product containers, or closures.

(3) Sterile equipment and aseptic sampling techniques shall be used when necessary.

(4) If it is necessary to sample a component from the top, middle, and bottom of its container, such sample subdivisions shall not be composited for testing.

(5) Sample containers shall be identified so that the following information can be determined: name of the material sampled, the lot number, the container from which the sample was taken, the date on which the sample was taken, and the name of the person who collected the sample.

(6) Containers, from which samples have been taken shall be marked to show that samples have been removed from them.

(d) Samples shall be examined and tested as follows:

(1) At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.

(2) Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

(3) Containers and closures shall be tested for conformance with all appropriate written procedures. In lieu of such testing by the manufacturer, a certificate of testing may be accepted from the supplier, provided that at least a visual identification is conducted on such containers/closures by

the manufacturer and provided that the manufacturer establishes the reliability of the supplier's test results through appropriate validation of the supplier's test results at appropriate intervals.

(4) When appropriate, components shall be microscopically examined.

(5) Each lot of a component, drug product container, or closure that is liable to contamination with filth, insect infestation, or other extraneous adulterant shall be examined against established specifications for such contamination.

(6) Each lot of a component, drug product container, or closure that is liable to microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use.

(e) Any lot of components, drug product containers, or closures that meets the appropriate written specifications of identity, strength, quality, and purity and related tests under paragraph (d) of this section may be approved and released for use. Any lot of such material that does not meet such specifications shall be rejected.

[43 FR 45077, Sept. 29, 1978, as amended at 63 FR 14356, Mar. 25, 1998]

§211.86 Use of approved components, drug product containers, and closures.

Components, drug product containers, and closures approved for use shall be rotated so that the oldest approved stock is used first. Deviation from this requirement is permitted if such deviation is temporary and appropriate.

§211.87 Retesting of approved components, drug product containers, and closures.

Components, drug product containers, and closures shall be retested or reexamined, as appropriate, for identity, strength, quality, and purity and approved or rejected by the quality control unit in accordance with §211.84 as necessary, e.g., after storage for long periods or after exposure to air, heat or other conditions that might adversely affect the component, drug product container, or closure.

§211.89 Rejected components, drug product containers, and closures.

Rejected components, drug product containers, and closures shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

§211.94 Drug product containers and closures.

(a) Drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements.

(b) Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.

(c) Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use.

(d) Standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures.

Subpart F—Production and Process Controls

§211.100 Written procedures; deviations.

(a) There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit.

(b) Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall

be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified.

§211.101 Charge-in of components.

Written production and control procedures shall include the following, which are designed to assure that the drug products produced have the identity, strength, quality, and purity they purport or are represented to possess:

(a) The batch shall be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient.

(b) Components for drug product manufacturing shall be weighed, measured, or subdivided as appropriate. If a component is removed from the original container to another, the new container shall be identified with the following information:

- (1) Component name or item code;
- (2) Receiving or control number;
- (3) Weight or measure in new container;
- (4) Batch for which component was dispensed, including its product name, strength, and lot number.

(c) Weighing, measuring, or subdividing operations for components shall be adequately supervised. Each container of component dispensed to manufacturing shall be examined by a second person to assure that:

- (1) The component was released by the quality control unit;
- (2) The weight or measure is correct as stated in the batch production records;
- (3) The containers are properly identified.

(d) Each component shall be added to the batch by one person and verified by a second person.

§211.103 Calculation of yield.

Actual yields and percentages of theoretical yield shall be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product. Such calculations shall be performed by one person and independently verified by a second person.

§211.105 Equipment identification.

(a) All compounding and storage containers, processing lines, and major equipment used during the production of a batch of a drug product shall be properly identified at all times to indicate their contents and, when necessary, the phase of processing of the batch.

(b) Major equipment shall be identified by a distinctive identification number or code that shall be recorded in the batch production record to show the specific equipment used in the manufacture of each batch of a drug product. In cases where only one of a particular type of equipment exists in a manufacturing facility, the name of the equipment may be used in lieu of a distinctive identification number or code.

§211.110 Sampling and testing of in-process materials and drug products.

(a) To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include, but are not limited to, the following, where appropriate:

- (1) Tablet or capsule weight variation;
- (2) Disintegration time;
- (3) Adequacy of mixing to assure uniformity and homogeneity;
- (4) Dissolution time and rate;
- (5) Clarity, completeness, or pH of solutions.

(b) Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate. Examination and testing

of samples shall assure that the drug product and in-process material conform to specifications.

(c) In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, e.g., at commencement or completion of significant phases or after storage for long periods.

(d) Rejected in-process materials shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

§211.111 Time limitations on production.

When appropriate, time limits for the completion of each phase of production shall be established to assure the quality of the drug product. Deviation from established time limits may be acceptable if such deviation does not compromise the quality of the drug product. Such deviation shall be justified and documented.

§211.113 Control of microbiological contamination.

(a) Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed.

(b) Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process.

§211.115 Reprocessing.

(a) Written procedures shall be established and followed prescribing a system for reprocessing batches that do not conform to standards or specifications and the steps to be taken to insure that the reprocessed batches will conform with all established standards, specifications, and characteristics.

(b) Reprocessing shall not be performed without the review and approval of the quality control unit.

Subpart G—Packaging and Labeling Control

§211.122 Materials examination and usage criteria.

(a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials; such written procedures shall be followed. Labeling and packaging materials shall be representatively sampled, and examined or tested upon receipt and before use in packaging or labeling of a drug product.

(b) Any labeling or packaging materials meeting appropriate written specifications may be approved and released for use. Any labeling or packaging materials that do not meet such specifications shall be rejected to prevent their use in operations for which they are unsuitable.

(c) Records shall be maintained for each shipment received of each different labeling and packaging material indicating receipt, examination or testing, and whether accepted or rejected.

(d) Labels and other labeling materials for each different drug product, strength, dosage form, or quantity of contents shall be stored separately with suitable identification. Access to the storage area shall be limited to authorized personnel.

(e) Obsolete and outdated labels, labeling, and other packaging materials shall be destroyed.

(f) Use of gang-printed labeling for different drug products, or different strengths or net contents of the same drug product, is prohibited unless the labeling from gang-printed sheets is adequately differentiated by size, shape, or color.

(g) If cut labeling is used, packaging and labeling operations shall include one of the following special control procedures:

(1) Dedication of labeling and packaging lines to each different strength of each different drug product;

(2) Use of appropriate electronic or electromechanical equipment to conduct a 100-percent examination for correct labeling during or after completion of finishing operations; or

(3) Use of visual inspection to conduct a 100-percent examination for correct labeling during or after completion of finishing operations for hand-applied labeling. Such examination shall be performed by one person and independently verified by a second person.

(h) Printing devices on, or associated with, manufacturing lines used to imprint labeling upon the drug product unit label or case shall be monitored to assure that all imprinting conforms to the print specified in the batch production record.

[43 FR 45077, Sept. 29, 1978, as amended at 58 FR 41353, Aug. 3, 1993]

§211.125 Labeling issuance.

(a) Strict control shall be exercised over labeling issued for use in drug product labeling operations.

(b) Labeling materials issued for a batch shall be carefully examined for identity and conformity to the labeling specified in the master or batch production records.

(c) Procedures shall be used to reconcile the quantities of labeling issued, used, and returned, and shall require evaluation of discrepancies found between the quantity of drug product finished and the quantity of labeling issued when such discrepancies are outside narrow preset limits based on historical operating data. Such discrepancies shall be investigated in accordance with §211.192. Labeling reconciliation is waived for cut or roll labeling if a 100-percent examination for correct labeling is performed in accordance with §211.122(g)(2).

(d) All excess labeling bearing lot or control numbers shall be destroyed.

(e) Returned labeling shall be maintained and stored in a manner to prevent mixups and provide proper identification.

(f) Procedures shall be written describing in sufficient detail the control procedures employed for the issuance of labeling; such written procedures shall be followed.

[43 FR 45077, Sept. 29, 1978, as amended at 58 FR 41354, Aug. 3, 1993]

§211.130 Packaging and labeling operations.

There shall be written procedures designed to assure that correct labels, labeling, and packaging materials are used for drug products; such written procedures shall be followed. These procedures shall incorporate the following features:

(a) Prevention of mixups and cross-contamination by physical or spatial separation from operations on other drug products.

(b) Identification and handling of filled drug product containers that are set aside and held in unlabeled condition for future labeling operations to preclude mislabeling of individual containers, lots, or portions of lots. Identification need not be applied to each individual container but shall be sufficient to determine name, strength, quantity of contents, and lot or control number of each container.

(c) Identification of the drug product with a lot or control number that permits determination of the history of the manufacture and control of the batch.

(d) Examination of packaging and labeling materials for suitability and correctness before packaging operations, and documentation of such examination in the batch production record.

(e) Inspection of the packaging and labeling facilities immediately before use to assure that all drug products have been removed from previous operations. Inspection shall also be made to assure that packaging and labeling materials not suitable for subsequent operations have been removed. Results of inspection shall be documented in the batch production records.

[43 FR 45077, Sept. 29, 1978, as amended at 58 FR 41354, Aug. 3, 1993]

§211.132 Tamper-evident packaging requirements for over-the-counter (OTC) human drug products.

(a) *General.* The Food and Drug Administration has the authority under the Federal Food, Drug, and Cosmetic Act (the act) to establish a uniform national requirement for tamper-evident packaging of OTC drug products that will improve the security of OTC drug packaging and help assure the

and effectiveness of OTC drug products. An OTC drug product (except a dermatological, dentifrice, insulin, or lozenge product) for retail sale that is not packaged in a tamper-resistant package or that is not properly labeled under this section is adulterated under section 501 of the act or misbranded under section 502 of the act, or both.

(b) *Requirements for tamper-evident package.* (1) Each manufacturer and packer who packages an OTC drug product (except a dermatological, dentifrice, insulin, or lozenge product) for retail sale shall package the product in a tamper-evident package, if this product is accessible to the public while held for sale. A tamper-evident package is one having one or more indicators or barriers to entry which, if breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred. To reduce the likelihood of successful tampering and to increase the likelihood that consumers will discover if a product has been tampered with, the package is required to be distinctive by design or by the use of one or more indicators or barriers to entry that employ an identifying characteristic (e.g., a pattern, name, registered trademark, logo, or picture). For purposes of this section, the term "distinctive by design" means the packaging cannot be duplicated with commonly available materials or through commonly available processes. A tamper-evident package may involve an immediate-container and closure system or secondary-container or carton system or any combination of systems intended to provide a visual indication of package integrity. The tamper-evident feature shall be designed to and shall remain intact when handled in a reasonable manner during manufacture, distribution, and retail display.

(2) In addition to the tamper-evident packaging feature described in paragraph (b)(1) of this section, any two-piece, hard gelatin capsule covered by this section must be sealed using an acceptable tamper-evident technology.

(c) *Labeling.* (1) In order to alert consumers to the specific tamper-evident feature(s) used, each retail package of

section (except ammonia inhalant in crushable glass ampules, containers of compressed medical oxygen, or aerosol products that depend upon the power of a liquefied or compressed gas to expel the contents from the container) is required to bear a statement that:

(i) Identifies all tamper-evident feature(s) and any capsule sealing technologies used to comply with paragraph (b) of this section;

(ii) Is prominently placed on the package; and

(iii) Is so placed that it will be unaffected if the tamper-evident feature of the package is breached or missing.

(2) If the tamper-evident feature chosen to meet the requirements in paragraph (b) of this section uses an identifying characteristic, that characteristic is required to be referred to in the labeling statement. For example, the labeling statement on a bottle with a shrink band could say "For your protection, this bottle has an imprinted seal around the neck."

(d) *Request for exemptions from packaging and labeling requirements.* A manufacturer or packer may request an exemption from the packaging and labeling requirements of this section. A request for an exemption is required to be submitted in the form of a citizen petition under §10.30 of this chapter and should be clearly identified on the envelope as a "Request for Exemption from the Tamper-Evident Packaging Rule." The petition is required to contain the following:

(1) The name of the drug product or, if the petition seeks an exemption for a drug class, the name of the drug class, and a list of products within that class.

(2) The reasons that the drug product's compliance with the tamper-evident packaging or labeling requirements of this section is unnecessary or cannot be achieved.

(3) A description of alternative steps that are available, or that the petitioner has already taken, to reduce the likelihood that the product or drug class will be the subject of malicious adulteration.

(4) Other information justifying an exemption.

(e) *OTC drug products subject to approved new drug applications.* Holders of approved new drug applications for

OTC drug products are required under §314.70 of this chapter to provide the agency with notification of changes in packaging and labeling to comply with the requirements of this section. Changes in packaging and labeling required by this regulation may be made before FDA approval, as provided under §314.70(c) of this chapter. Manufacturing changes by which capsules are to be sealed require prior FDA approval under §314.70(b) of this chapter.

(f) *Poison Prevention Packaging Act of 1970.* This section does not affect any requirements for "special packaging" as defined under §310.3(l) of this chapter and required under the Poison Prevention Packaging Act of 1970.

(Approved by the Office of Management and Budget under OMB control number 0910-0149)

[54 FR 5228, Feb. 2, 1989, as amended at 63 FR 59470, Nov. 4, 1998]

§211.134 Drug product inspection.

(a) Packaged and labeled products shall be examined during finishing operations to provide assurance that containers and packages in the lot have the correct label.

(b) A representative sample of units shall be collected at the completion of finishing operations and shall be visually examined for correct labeling.

(c) Results of these examinations shall be recorded in the batch production or control records.

§211.137 Expiration dating.

(a) To assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use, it shall bear an expiration date determined by appropriate stability testing described in §211.166.

(b) Expiration dates shall be related to any storage conditions stated on the labeling, as determined by stability studies described in §211.166.

(c) If the drug product is to be reconstituted at the time of dispensing, its labeling shall bear expiration information for both the reconstituted and unreconstituted drug products.

(d) Expiration dates shall appear on labeling in accordance with the requirements of §201.17 of this chapter.

(e) Homeopathic drug products shall be exempt from the requirements of this section.

(f) Allergenic extracts that are labeled "No U.S. Standard of Potency" are exempt from the requirements of this section.

(g) New drug products for investigational use are exempt from the requirements of this section, provided that they meet appropriate standards or specifications as demonstrated by stability studies during their use in clinical investigations. Where new drug products for investigational use are to be reconstituted at the time of dispensing, their labeling shall bear expiration information for the reconstituted drug product.

(h) Pending consideration of a proposed exemption, published in the FEDERAL REGISTER of September 29, 1978, the requirements in this section shall not be enforced for human OTC drug products if their labeling does not bear dosage limitations and they are stable for at least 3 years as supported by appropriate stability data.

[43 FR 45077, Sept. 29, 1978, as amended at 46 FR 56412, Nov. 17, 1981; 60 FR 4091, Jan. 20, 1995]

Subpart H—Holding and Distribution

§211.142 Warehousing procedures.

Written procedures describing the warehousing of drug products shall be established and followed. They shall include:

(a) Quarantine of drug products before release by the quality control unit.

(b) Storage of drug products under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity of the drug products are not affected.

§211.150 Distribution procedures.

Written procedures shall be established, and followed, describing the distribution of drug products. They shall include:

(a) A procedure whereby the oldest approved stock of a drug product is distributed first. Deviation from this re-

quirement is permitted if such deviation is temporary and appropriate.

(b) A system by which the distribution of each lot of drug product can be readily determined to facilitate its recall if necessary.

Subpart I—Laboratory Controls

§211.160 General requirements.

(a) The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. The requirements in this subpart shall be followed and shall be documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified.

(b) Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:

(1) Determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration.

(2) Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials.

shall be representative and properly identified.

(3) Determination of conformance to written descriptions of sampling procedures and appropriate specifications for drug products. Such samples shall be representative and properly identified.

(4) The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used.

§211.165 Testing and release for distribution.

(a) For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release. Where sterility and/or pyrogen testing are conducted on specific batches of short-lived radiopharmaceuticals, such batches may be released prior to completion of sterility and/or pyrogen testing, provided such testing is completed as soon as possible.

(b) There shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms.

(c) Any sampling and testing plans shall be described in written procedures that shall include the method of sampling and the number of units per batch to be tested; such written procedure shall be followed.

(d) Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release. The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels.

(e) The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance with §211.194(a)(2).

(f) Drug products falling to meet established standards or specifications and any other relevant quality control criteria shall be rejected. Reprocessing may be performed. Prior to acceptance and use, reprocessed material must meet appropriate standards, specifications, and any other relevant criteria.

§211.166 Stability testing.

(a) There shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used in determining appropriate storage conditions and expiration dates. The written program shall be followed and shall include:

(1) Sample size and test intervals based on statistical criteria for each attribute examined to assure valid estimates of stability;

(2) Storage conditions for samples retained for testing;

(3) Reliable, meaningful, and specific test methods;

(4) Testing of the drug product in the same container-closure system as that in which the drug product is marketed;

(5) Testing of drug products for reconstitution at the time of dispensing (as directed in the labeling) as well as after they are reconstituted.

(b) An adequate number of batches of each drug product shall be tested to determine an appropriate expiration date and a record of such data shall be maintained. Accelerated studies, combined with basic stability information on the components, drug products, and container-closure system, may be used to support tentative expiration dates provided full shelf life studies are not available and are being conducted. Where data from accelerated studies are used to project a tentative expiration date that is beyond a date supported by actual shelf life studies, there must be stability studies conducted, including drug product testing at appropriate intervals, until the tentative expiration date is verified or the

appropriate expiration date determined.

(c) For homeopathic drug products, the requirements of this section are as follows:

(1) There shall be a written assessment of stability based at least on testing or examination of the drug product for compatibility of the ingredients, and based on marketing experience with the drug product to indicate that there is no degradation of the product for the normal or expected period of use.

(2) Evaluation of stability shall be based on the same container-closure system in which the drug product is being marketed.

(d) Allergic extracts that are labeled "No U.S. Standard of Potency" are exempt from the requirements of this section.

[43 FR 45077, Sept. 29, 1978, as amended at 46 FR 56412, Nov. 17, 1981]

§211.167 Special testing requirements.

(a) For each batch of drug product purporting to be sterile and/or pyrogen-free, there shall be appropriate laboratory testing to determine conformance to such requirements. The test procedures shall be in writing and shall be followed.

(b) For each batch of ophthalmic ointment, there shall be appropriate testing to determine conformance to specifications regarding the presence of foreign particles and harsh or abrasive substances. The test procedures shall be in writing and shall be followed.

(c) For each batch of controlled-release dosage form, there shall be appropriate laboratory testing to determine conformance to the specifications for the rate of release of each active ingredient. The test procedures shall be in writing and shall be followed.

§211.170 Reserve samples.

(a) An appropriately identified reserve sample that is representative of each lot in each shipment of each active ingredient shall be retained. The reserve sample consists of at least twice the quantity necessary for all tests required to determine whether the active ingredient meets its established specifications, except for the

sterility and pyrogen testing. The retention time is as follows:

(1) For an active ingredient in a drug product other than those described in paragraphs (a) (2) and (3) of this section, the reserve sample shall be retained for 1 year after the expiration date of the last lot of the drug product containing the active ingredient.

(2) For an active ingredient in a radioactive drug product, except for non-radioactive reagent kits, the reserve sample shall be retained for:

(i) Three months after the expiration date of the last lot of the drug product containing the active ingredient if the expiration dating period of the drug product is 30 days or less; or

(ii) Six months after the expiration date of the last lot of the drug product containing the active ingredient if the expiration dating period of the drug product is more than 30 days.

(3) For an active ingredient in an OTC drug product that is exempt from bearing an expiration date under §211.137, the reserve sample shall be retained for 3 years after distribution of the last lot of the drug product containing the active ingredient.

(b) An appropriately identified reserve sample that is representative of each lot or batch of drug product shall be retained and stored under conditions consistent with product labeling. The reserve sample shall be stored in the same immediate container-closure system in which the drug product is marketed or in one that has essentially the same characteristics. The reserve sample consists of at least twice the quantity necessary to perform all the required tests, except those for sterility and pyrogens. Except for those for drug products described in paragraph (b)(2) of this section, reserve samples from representative sample lots or batches selected by acceptable statistical procedures shall be examined visually at least once a year for evidence of deterioration unless visual examination would affect the integrity of the reserve sample. Any evidence of reserve sample deterioration shall be investigated in accordance with §211.192. The results of the examination shall be recorded and maintained with other stability data on the drug product. Re-

gases need not be retained. The retention time is as follows:

(1) For a drug product other than those described in paragraphs (b) (2) and (3) of this section, the reserve sample shall be retained for 1 year after the expiration date of the drug product.

(2) For a radioactive drug product, except for nonradioactive reagent kits, the reserve sample shall be retained for:

(i) Three months after the expiration date of the drug product if the expiration dating period of the drug product is 30 days or less; or

(ii) Six months after the expiration date of the drug product if the expiration dating period of the drug product is more than 30 days.

(3) For an OTC drug product that is exempt for bearing an expiration date under §211.137, the reserve sample must be retained for 3 years after the lot or batch of drug product is distributed.

[48 FR 13025, Mar. 29, 1983, as amended at 60 FR 4091, Jan. 20, 1995]

§211.173 Laboratory animals.

Animals used in testing components, in-process materials, or drug products for compliance with established specifications shall be maintained and controlled in a manner that assures their suitability for their intended use. They shall be identified, and adequate records shall be maintained showing the history of their use.

§211.176 Penicillin contamination.

If a reasonable possibility exists that a non-penicillin drug product has been exposed to cross-contamination with penicillin, the non-penicillin drug product shall be tested for the presence of penicillin. Such drug product shall not be marketed if detectable levels are found when tested according to procedures specified in 'Procedures for Detecting and Measuring Penicillin Contamination in Drugs,' which is incorporated by reference. Copies are available from the Division of Research and Testing (HFD-470), Center for Drug Evaluation and Research, Food and Drug Administration, 200 C St. SW., Washington, DC 20204, or available for inspection at the Office of the Federal

Register, 800 North Capitol Street, NW., suite 700, Washington, DC 20408.

[43 FR 45077, Sept. 29, 1978, as amended at 47 FR 9396, Mar. 5, 1982; 50 FR 8996, Mar. 6, 1985; 55 FR 11577, Mar. 29, 1990]

Subpart J—Records and Reports

§211.180 General requirements.

(a) Any production, control, or distribution record that is required to be maintained in compliance with this part and is specifically associated with a batch of a drug product shall be retained for at least 1 year after the expiration date of the batch or, in the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under §211.137, 3 years after distribution of the batch.

(b) Records shall be maintained for all components, drug product containers, closures, and labeling for at least 1 year after the expiration date or, in the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under §211.137, 3 years after distribution of the last lot of drug product incorporating the component or using the container, closure, or labeling.

(c) All records required under this part, or copies of such records, shall be readily available for authorized inspection during the retention period at the establishment where the activities described in such records occurred. These records or copies thereof shall be subject to photocopying or other means of reproduction as part of such inspection. Records that can be immediately retrieved from another location by computer or other electronic means shall be considered as meeting the requirements of this paragraph.

(d) Records required under this part may be retained either as original records or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques, such as microfilming, are used, suitable reader and photocopying equipment shall be readily available.

(e) Written records required by this part shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of

each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. Written procedures shall be established and followed for such evaluations and shall include provisions for:

(1) A review of a representative number of batches, whether approved or rejected, and, where applicable, records associated with the batch.

(2) A review of complaints, recalls, returned or salvaged drug products, and investigations conducted under §211.192 for each drug product.

(f) Procedures shall be established to assure that the responsible officials of the firm, if they are not personally involved in or immediately aware of such actions, are notified in writing of any investigations conducted under §§211.198, 211.204, or 211.208 of these regulations, any recalls, reports of inspectional observations issued by the Food and Drug Administration, or any regulatory actions relating to good manufacturing practices brought by the Food and Drug Administration.

[43 FR 45077, Sept. 29, 1978, as amended at 60 FR 4091, Jan. 20, 1995]

§211.182 Equipment cleaning and use log.

A written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use shall be included in individual equipment logs that show the date, time, product, and lot number of each batch processed. If equipment is dedicated to manufacture of one product, then individual equipment logs are not required, provided that lots or batches of such product follow in numerical order and are manufactured in numerical sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use shall be part of the batch record. The persons performing and double-checking the cleaning and maintenance shall date and sign or initial the log indicating that the work was performed. Entries in the log shall be in chronological order.

§211.184 Component, drug product container, closure, and labeling records.

These records shall include the following:

(a) The identity and quantity of each shipment of each lot of components, drug product containers, closures, and labeling; the name of the supplier; the supplier's lot number(s) if known; the receiving code as specified in §211.80; and the date of receipt. The name and location of the prime manufacturer, if different from the supplier, shall be listed if known.

(b) The results of any test or examination performed (including those performed as required by §211.82(a), §211.84(d), or §211.122(a)) and the conclusions derived therefrom.

(c) An individual inventory record of each component, drug product container, and closure and, for each component, a reconciliation of the use of each lot of such component. The inventory record shall contain sufficient information to allow determination of any batch or lot of drug product associated with the use of each component, drug product container, and closure.

(d) Documentation of the examination and review of labels and labeling for conformity with established specifications in accord with §§211.122(c) and 211.130(c).

(e) The disposition of rejected components, drug product containers, closure, and labeling.

§211.186 Master production and control records.

(a) To assure uniformity from batch to batch, master production and control records for each drug product, including each batch size thereof, shall be prepared, dated, and signed (full signature, handwritten) by one person and independently checked, dated, and signed by a second person. The preparation of master production and control records shall be described in a written procedure and such written procedure shall be followed.

(b) Master production and control records shall include:

(1) The name and strength of the product and a description of the dosage form;

(2) The name and weight or measure of each active ingredient per dosage unit or per unit of weight or measure of the drug product, and a statement of the total weight or measure of any dosage unit;

(3) A complete list of components designated by names or codes sufficiently specific to indicate any special quality characteristic;

(4) An accurate statement of the weight or measure of each component, using the same weight system (metric, avoirdupois, or apothecary) for each component. Reasonable variations may be permitted, however, in the amount of components necessary for the preparation in the dosage form, provided they are justified in the master production and control records;

(5) A statement concerning any calculated excess of component;

(6) A statement of theoretical weight or measure at appropriate phases of processing;

(7) A statement of theoretical yield, including the maximum and minimum percentages of theoretical yield beyond which investigation according to §211.192 is required;

(8) A description of the drug product containers, closures, and packaging materials, including a specimen or copy of each label and all other labeling signed and dated by the person or persons responsible for approval of such labeling;

(9) Complete manufacturing and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed.

§211.188 Batch production and control records.

Batch production and control records shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch. These records shall include:

(a) An accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed;

(b) Documentation that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished, including:

(1) Dates;

(2) Identity of individual major equipment and lines used;

(3) Specific identification of each batch of component or in-process material used;

(4) Weights and measures of components used in the course of processing;

(5) In-process and laboratory control results;

(6) Inspection of the packaging and labeling area before and after use;

(7) A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing;

(8) Complete labeling control records, including specimens or copies of all labeling used;

(9) Description of drug product containers and closures;

(10) Any sampling performed;

(11) Identification of the persons performing and directly supervising or checking each significant step in the operation;

(12) Any investigation made according to §211.192.

(13) Results of examinations made in accordance with §211.194.

§211.192 Production record review.

All drug product production and control records, including those for packaging and labeling, shall be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed. Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed. The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusions and followup.

§211.194 Laboratory records.

(a) Laboratory records shall include complete data derived from all tests

necessary to assure compliance with established specifications and standards, including examinations and assays, as follows:

(1) A description of the sample received for testing with identification of source (that is, location from where sample was obtained), quantity, lot number or other distinctive code, date sample was taken, and date sample was received for testing.

(2) A statement of each method used in the testing of the sample. The statement shall indicate the location of data that establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested. (If the method employed is in the current revision of the United States Pharmacopoeia, National Formulary, Association of Official Analytical Chemists, Book of Methods,² or in other recognized standard references, or is detailed in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice). The suitability of all testing methods used shall be verified under actual conditions of use.

(3) A statement of the weight or measure of sample used for each test, where appropriate.

(4) A complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, drug product container, closure, in-process material, or drug product, and lot tested.

(5) A record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors.

(6) A statement of the results of tests and how the results compare with established standards of identity, strength, quality, and purity for the component, drug product container, closure, in-process material, or drug product tested.

²Copies may be obtained from: Association of Official Analytical Chemists, 2200 Wilson Blvd., Suite 400, Arlington, VA 22201-2000

(7) The initials or signature of the person who performs each test and the date(s) the tests were performed.

(8) The initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

(b) Complete records shall be maintained of any modification of an established method employed in testing. Such records shall include the reason for the modification and data to verify that the modification produced results that are at least as accurate and reliable for the material being tested as the established method.

(c) Complete records shall be maintained of any testing and standardization of laboratory reference standards, reagents, and standard solutions.

(d) Complete records shall be maintained of the periodic calibration of laboratory instruments, apparatus, gauges, and recording devices required by §211.160(b)(4).

(e) Complete records shall be maintained of all stability testing performed in accordance with §211.166.

[43 FR 45077, Sept. 29, 1978, as amended at 55 FR 11577, Mar. 29, 1990]

§211.196 Distribution records.

Distribution records shall contain the name and strength of the product and description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of the drug product. For compressed medical gas products, distribution records are not required to contain lot or control numbers.

(Approved by the Office of Management and Budget under control number 0910-0139)

[49 FR 9865, Mar. 16, 1984]

§211.198 Complaint files.

(a) Written procedures describing the handling of all written and oral complaints regarding a drug product shall be established and followed. Such procedures shall include provisions for review by the quality control unit, of any complaint involving the possible failure of a drug product to meet any of its specifications and, for such drug products, a determination as to the

§211.192. Such procedures shall include provisions for review to determine whether the complaint represents a serious and unexpected adverse drug experience which is required to be reported to the Food and Drug Administration in accordance with §310.305 of this chapter.

(b) A written record of each complaint shall be maintained in a file designated for drug product complaints. The file regarding such drug product complaints shall be maintained at the establishment where the drug product involved was manufactured, processed, or packed, or such file may be maintained at another facility if the written records in such files are readily available for inspection at that other facility. Written records involving a drug product shall be maintained until at least 1 year after the expiration date of the drug product, or 1 year after the date that the complaint was received, whichever is longer. In the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under §211.137, such written records shall be maintained for 3 years after distribution of the drug product.

(1) The written record shall include the following information, where known: the name and strength of the drug product, lot number, name of complainant, nature of complaint, and reply to complainant.

(2) Where an investigation under §211.192 is conducted, the written record shall include the findings of the investigation and followup. The record or copy of the record of the investigation shall be maintained at the establishment where the investigation occurred in accordance with §211.180(c).

(3) Where an investigation under §211.192 is not conducted, the written record shall include the reason that an investigation was found not to be necessary and the name of the responsible person making such a determination.

[43 FR 45077, Sept. 29, 1978, as amended at 51 FR 24479, July 3, 1986]

Subpart K—Returned and Salvaged Drug Products

§211.204 Returned drug products.

Returned drug products shall be identified as such and held. If the conditions under which returned drug products have been held, stored, or shipped before or during their return, or if the condition of the drug product, its container, carton, or labeling, as a result of storage or shipping, casts doubt on the safety, identity, strength, quality or purity of the drug product, the returned drug product shall be destroyed unless examination, testing, or other investigations prove the drug product meets appropriate standards of safety, identity, strength, quality, or purity. A drug product may be reprocessed provided the subsequent drug product meets appropriate standards, specifications, and characteristics. Records of returned drug products shall be maintained and shall include the name and label potency of the drug product dosage form, lot number (or control number or batch number), reason for the return, quantity returned, date of disposition, and ultimate disposition of the returned drug product. If the reason for a drug product being returned implicates associated batches, an appropriate investigation shall be conducted in accordance with the requirements of §211.192. Procedures for the holding, testing, and reprocessing of returned drug products shall be in writing and shall be followed.

§211.208 Drug product salvaging.

Drug products that have been subjected to improper storage conditions including extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation due to natural disasters, fires, accidents, or equipment failures shall not be salvaged and returned to the marketplace. Whenever there is a question whether drug products have been subjected to such conditions, salvaging operations may be conducted only if there is (a) evidence from laboratory tests and assays (including animal feeding studies where applicable)

that the drug products meet all applicable standards of identity, strength, quality, and purity and (b) evidence from inspection of the premises that the drug products and their associated packaging were not subjected to improper storage conditions as a result of the disaster or accident. Organoleptic examinations shall be acceptable only as supplemental evidence that the drug products meet appropriate standards of identity, strength, quality, and purity. Records including name, lot number, and disposition shall be maintained for drug products subject to this section.

PART 216—PHARMACY COMPOUNDING

Subpart A—General Provisions [Reserved]

Subpart B—Compounded Drug Products

- Sec.
- 216.23 [Reserved]
- 216.24 Drug products withdrawn or removed from the market for reasons of safety or effectiveness.

AUTHORITY: 21 U.S.C. 351, 352, 353a, 355, and 371.

SOURCE: 64 FR 10944, Mar. 8, 1999, unless otherwise noted.

Subpart A—General Provisions [Reserved]

Subpart B—Compounded Drug Products

- §216.23 [Reserved]
- §216.24 Drug products withdrawn or removed from the market for reasons of safety or effectiveness.

The following drug products were withdrawn or removed from the market because such drug products or components of such drug products were found to be unsafe or not effective. The following drug products may not be compounded under the exemptions provided by section 503A(a) of the Federal Food, Drug, and Cosmetic Act:

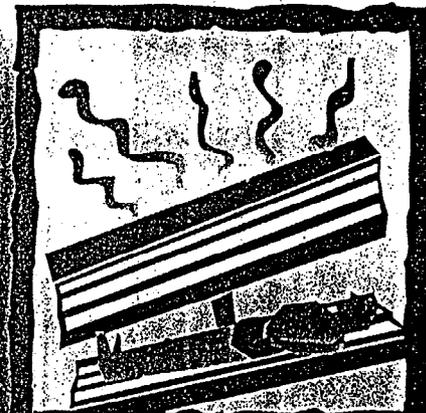
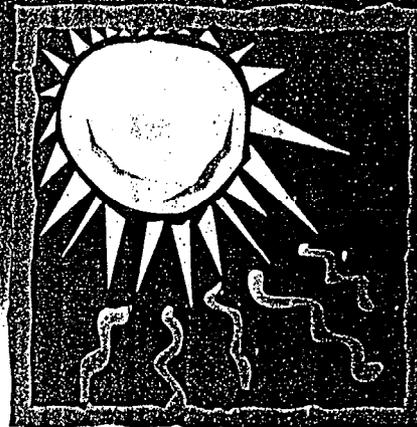
- Adenosine phosphate*: All drug products containing adenosine phosphate.
- Adrenal cortex*: All drug products containing adrenal cortex.
- Azaribine*: All drug products containing azaribine.

- Benoxaprofen*: All drug products containing benoxaprofen.
- Bithionol*: All drug products containing bithionol.
- Bromfenac sodium*: All drug products containing bromfenac sodium.
- Butamben*: All parenteral drug products containing butamben.
- Camphorated oil*: All drug products containing camphorated oil.
- Carbetapentane citrate*: All oral gel drug products containing carbetapentane citrate.
- Casein, iodinated*: All drug products containing iodinated casein.
- Chlorhexidine gluconate*: All tinctures of chlorhexidine gluconate formulated for use as a patient preoperative skin preparation.
- Chlormadinone acetate*: All drug products containing chlormadinone acetate.
- Chloroform*: All drug products containing chloroform.
- Cobalt*: All drug products containing cobalt salts (except radioactive forms of cobalt and its salts and cobalamin and its derivatives).
- Dexfenfluramine hydrochloride*: All drug products containing dexfenfluramine hydrochloride.
- Diamthazole dihydrochloride*: All drug products containing diamthazole dihydrochloride.
- Dibromsalan*: All drug products containing dibromsalan.
- Diethylstilbestrol*: All oral and parenteral drug products containing 25 milligrams or more of diethylstilbestrol per unit dose.
- Dihydrostreptomycin sulfate*: All drug products containing dihydrostreptomycin sulfate.
- Dipyron*: All drug products containing dipyron.
- Encainide hydrochloride*: All drug products containing encainide hydrochloride.
- Fenfluramine hydrochloride*: All drug products containing fenfluramine hydrochloride.
- Flosequinan*: All drug products containing flosequinan.
- Gelatin*: All intravenous drug products containing gelatin.
- Glycerol, iodinated*: All drug products containing iodinated glycerol.
- Gonadotropin, chorionic*: All drug products containing chorionic gonadotropins of animal origin.
- Mepazine*: All drug products containing mepazine hydrochloride or mepazine acetate.
- Metabromsalan*: All drug products containing metabromsalan.
- Methamphetamine hydrochloride*: All parenteral drug products containing methamphetamine hydrochloride.
- Methapyrilene*: All drug products containing methapyrilene.
- Methopholine*: All drug products containing methopholine.
- Mibefradil dihydrochloride*: All drug products containing mibefradil dihydrochloride.

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The Darker Side of Tanning



Public health and medical professionals continue to warn of the dangers of ultraviolet radiation from tanning beds, and sun lamp ultraviolet radiation (UVA) and (UVB). UVB has been recognized as being associated with sunburn. UVB has been recognized as penetrating radiations.

Although it's been some time that too much radiation can be harmful, information may not be as clear as warnings even more. Some scientists have recently found that there is an association between tanning and malignant melanoma, the most serious type of skin cancer.

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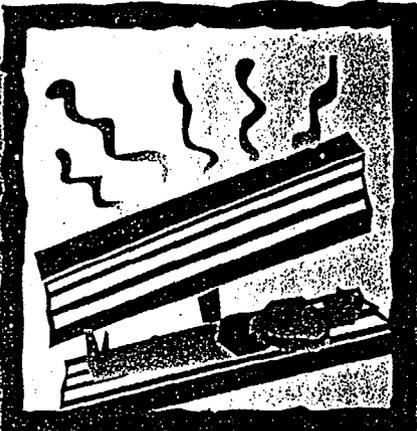


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American Academy of Dermatology

The Darker Side of Tanning



AAD
American Academy of Dermatology

Public health experts and medical professionals are continuing to warn people about the dangers of ultraviolet (UV) radiation from the sun, tanning beds, and sun lamps. Two types of ultraviolet radiation are Ultraviolet A (UVA) and Ultraviolet B (UVB). UVB has long been associated with sunburn while UVA has been recognized as a deeper penetrating radiation.

Although it's been known for some time that too much UV radiation can be harmful, new information may now make these warnings even more important. Some scientists have suggested recently that there may be an association between UVA radiation and malignant melanoma, the most serious type of skin cancer.

What are the dangers of tanning?

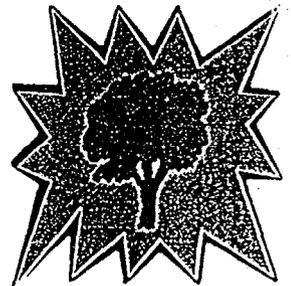
UV radiation from the sun, tanning beds, or from sun lamps may cause skin cancer. While skin cancer has been associated with sunburn, moderate tanning may also produce the same effect. UV radiation can also have a damaging effect on the immune system and cause premature aging of the skin, giving it a wrinkled, leathery appearance.

But isn't getting some sun good for your health?

People sometimes associate a suntan with good health and vitality. In fact, just a small amount of sunlight is needed for the body to manufacture vitamin D. It doesn't take much sunlight to make all the vitamin D you can use – certainly far less than it takes to get a suntan!

Are people actually being harmed by sunlight?

Yes. The number of skin cancer cases has been rising over the years, and experts say that this is due to increasing exposure to UV radiation from the sun, tanning beds, and sun lamps. More than 1 million new skin cancer cases are likely to be diagnosed in the U.S. this year.

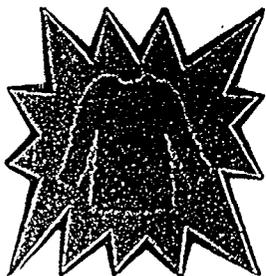


But aren't the types of skin cancer caused by the sun, tanning beds, and sun lamps easily curable?

Not necessarily. Malignant melanoma, now with a suspected link to UVA exposure, is often fatal, if not detected early. The number of cases of melanoma is rising in the U.S., with an estimated 38,300 cases and 7,300 deaths anticipated this year.

Why doesn't the skin of young people show these harmful effects?

Skin aging and cancer are delayed effects that don't usually show up for many years after the exposure. Unfortunately, since the damage is not immediately



visible, young people are often unaware of the dangers of tanning. Physicians and scientists are especially concerned that cases of skin cancer will continue to increase as people who are now in their teens and twenties reach middle age.

But why is it that some people can tan for many years and still not show damage?

People who choose to tan are greatly increasing their risk of developing skin cancer. This is especially true if tanning occurs over a period of years, because damage to the skin accumulates. Unlike skin cancer, premature aging of the skin will occur in everyone who is repeatedly exposed to the sun over a long time, although the damage may be less apparent and take longer to show up in people with darker skin.



Who is at greatest risk in the sun?

People with skin types I and II are at greatest risk.

Which skin type are you?

<i>Skin Type</i>	<i>Sunburn and Tanning History According to Skin Type</i>
I	Always burns; never tans; sensitive ("Celtic")
II	Burns easily; tans minimally
III	Burns moderately; tans gradually to light brown (Average Caucasian)
IV	Burns minimally; always tans well to moderately brown (Olive Skin)
V	Rarely burns; tans profusely to dark (Brown Skin)
VI	Never burns; deeply pigmented, not sensitive (Black Skin)

Since most sun lamps and tanning beds emit UVA radiation, doesn't that make them safer than natural sunlight?

No. It's true that most sun lamps emit mainly UVA radiation, and that these so-called "tanning rays" are less likely to cause a sunburn than UVB radiation from sunlight. But, contrary to the claims of some tanning parlors, that doesn't make them safe. UVA rays have a suspected link to malignant melanoma, and, like UVB rays, they also may be linked to immune system damage.

What's the government's position on using sun lamp products found in tanning parlors and in homes?

The Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) encourage people to avoid use of tanning beds and sun lamps.

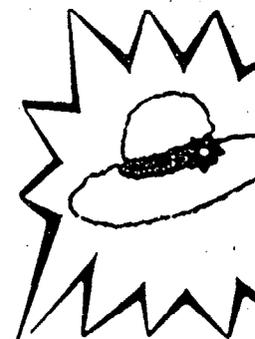
You can get a fact sheet on the hazards of indoor tanning from FDA's Facts on Demand system by calling 1-800-899-0381; the information will be faxed to you on the same day (select 2 and then Division of Device User Programs and Systems Analysis or DDUPSA). You can also go to the FDA Home Page on the World Wide Web at <http://www.fda.gov>. At this point, click on the Medical Devices and Radiological Health icon, click on Program Areas and choose Radiation Injuries.

Information on skin cancer is available on the American Academy of Dermatology (AAD) Home Page on the World Wide Web at <http://www.aad.org>.

What do medical professionals say about tanning?

The American Medical Association (AMA) and the AAD have warned people for many years about the dangers of tanning. In fact, AMA and AAD have urged action that would ban the sale and use of tanning equipment for non-medical purposes. Doctors and public health officials have recommended the following steps to minimize the sun's damage to the skin and eyes:

- Plan your outdoor activities to avoid the sun's strongest rays. As a general rule, avoid the sun between 10 a.m. and 4 p.m.
- Wear protective covering such as broad-brimmed hats, long pants and long-sleeved shirts to reduce exposure.
- Wear sunglasses that provide 100% UV ray protection.



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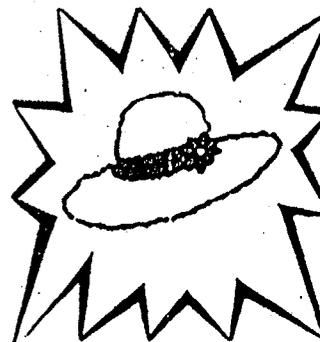
- **Always wear a broad-spectrum sunscreen** with Sun Protection Factor (SPF) 15 or more, which will block both UVA and UVB when outdoors and reapply it according to manufacturer's directions.

For more information on the levels of ultraviolet radiation reaching your area at noon, you can get the Ultraviolet Index (UVI) from local newspapers, radio or TV in many cities.

The UVI is a number from 0-10. The higher the number, the more intense the exposure. Call the EPA Hotline for more information on the UVI at 1-800-296-1996.

If you believe that some damage has already been done:

- **Seek immediate** medical attention if you receive skin or eye damage from the sun or if you experience an allergic reaction to the sun.
- **See your dermatologist or personal physician** if you develop an unusual mole, a scaly patch or a sore that doesn't heal.



PART BB
TANNING FACILITIES

Sec. BB.1 - Purpose and Scope.

- a. This Part provides for [the registration of tanning facilities using ultraviolet lamps, and] regulation of the maintenance and operation of tanning facilities.
- b. In addition to the requirements of this Part, all facilities are subject to the applicable provisions of other Parts of these regulations.
- c. Nothing in this Part shall be interpreted as limiting the intentional exposure of patients to ultraviolet radiation for the purpose of treatment or use commensurate with the licensed practitioner's use of a healing art.

Sec. BB.2 - Definitions. The following terms are defined for purposes of this Part.

"Act" means [cite State Radiation Control Act].

"Agency" means [cite appropriate State agency].

"Consumer" means any member of the public who is provided access to a tanning facility in exchange for a fee or other compensation, or any individual who, in exchange for a fee or other compensation, is afforded use of a tanning facility as a condition or benefit of membership or access.

"Healing arts" means [cite appropriate State definition].

"Individual" means any human being.

"Inspection" means an official examination or observation including but not limited to tests, surveys, and monitoring to determine compliance with rules, regulations, orders, requirements and conditions of the Agency.

"License" means a license issued by the Agency in accordance with regulations issued by the Agency.

"Licensee" means any person who is licensed by the agency in accordance with these regulations and the Act.

"Operator" means an individual designated by the registrant to control operation of the tanning facility and to instruct and assist the consumer in the proper operation of the tanning equipment.

"Person" means any individual, corporation, partnership, firm, association, trust, estate, public or private institution, group, agency, political subdivision of this State, any other State or political

subdivision or agency thereof, and any legal successor, representative, agent, or agency of the foregoing.

"Radiation" means ultraviolet radiation.

"Radiation machine" means any device capable of producing radiation.

"Registrant" means any person who obtains a registration, license, permit or other entitlement from the Agency, and who is obligated to obtain such registration, license, permit or other entitlement from the Agency pursuant to these regulations and the Act.

"Registration" means registration with the Agency in accordance with regulations adopted by the Agency.

"Tanning equipment" means ultraviolet lamps and equipment containing ultraviolet lamps intended to induce skin tanning through the irradiation of any part of the living human body.

"Tanning facility" means any location, place, area, structure or business which provides consumers access to tanning equipment.

"These regulations" means all parts of [cite appropriate rules or regulations].

"Ultraviolet radiation" means electromagnetic radiation with wavelengths in air between 200 nanometers and 400 nanometers.

Sec. BB.3 - Exemptions.

- a. General: The Agency may, upon application therefor or upon its own initiative, grant such exemptions or exceptions from the requirements of these regulations as it determines are authorized by law and will not result in undue hazard to public health and safety.
- b. Equipment intended for purposes other than the deliberate exposure of parts of the living human body to ultraviolet radiation, and which produce or emit ultraviolet radiation incidental to its proper operation are exempt from the provisions of this Part.
- c. Radiation machines while in transit or storage incidental thereto are exempt from provisions of this Part.

Sec. BB.4 - Application for Registration of Tanning Facilities.

- a. Each person having a tanning facility shall apply for registration of such facility with the Agency within [30] days following the effective date of these regulations or thereafter prior to the operation of a tanning facility. Application for registration shall be completed on forms satisfactory to the Agency and shall contain all the information required by the form and the accompanying instructions.

- b. The Agency shall require at least the following information on the Application for Registration of Tanning Facilities form:
 - i. Name, address and telephone number of the following:
 - (1) The tanning facility;
 - (2) The owner(s) of the tanning facility;
 - ii. The manufacturer, model number, and type of each ultraviolet lamp or tanning equipment located within the facility;
 - iii. The geographic areas within the State to be covered, if the facility is mobile;
 - iv. Name of the tanning equipment supplier, installer, and service agent;
 - v. A signed and dated certification that the applicant has read and understands the requirements of these regulations;
 - vi. A copy of operating and safety procedures unique to facility operation.
- c. Each applicant shall provide such additional information as the Agency may reasonably require.

Sec. BB.5 - Issuance of Certificate of Registration.

- a. Upon determination that an applicant meets the requirements of BB.4, the Agency shall issue a certificate of registration.
- b. The Agency may incorporate in the certificate of registration at the time of issuance or thereafter by appropriate rule, regulation or order, such additional requirements and conditions with respect to the registrant's receipt, possession, use and transfer of tanning facilities as it deems appropriate or necessary.
- c. No person shall operate a tanning facility until the agency has issued the certificate of registration [here insert reference to the relevant administrative procedures for response by the agency.]

Sec. BB.6 - Expiration of Certificate of Registration. Except as provided in BB.7b., each certificate of registration shall expire at the end of the specified day in the month and year stated therein.

Sec. BB.7 - Renewal of Certificate of Registration.

- a. Application for renewal of registration shall be filed in accordance with BB.4.
- b. In any case in which a registrant not less than 30 days prior to the expiration of his existing certificate of registration has filed an application in proper form for renewal, such existing

certificate of registration shall not expire until the application status has been finally determined by the Agency.

Sec. BB.8 - Report of Changes. The registrant shall notify the Agency in writing before making any change which would render the information reported pursuant to BB.4b.i., ii., iii. and vi., contained in the application for registration or the certificate of registration, no longer accurate. This requirement shall not apply for changes involving replacement of designated original equipment lamp types with lamps which have been certified with the Food and Drug Administration as "equivalent" lamps under the Food and Drug Administration regulations and policies applicable at the time of replacement of the lamps. The facility owner shall maintain manufacturer's literature demonstrating the equivalency of any replacement lamps.

Sec. BB.9 - Transfer of Certificate of Registration. No certificate of registration shall be transferable from one person to another or from one tanning facility to another.

Sec. BB.10 - Approval Not Implied. No person, in any advertisement, shall refer to the fact that he or his facility is registered with the Agency pursuant to the provisions of BB.4, and no person shall state or imply that any activity under such registration has been approved by the Agency.

Sec. BB.11 - Denial, Suspension, or Revocation of Certificate of Registration.

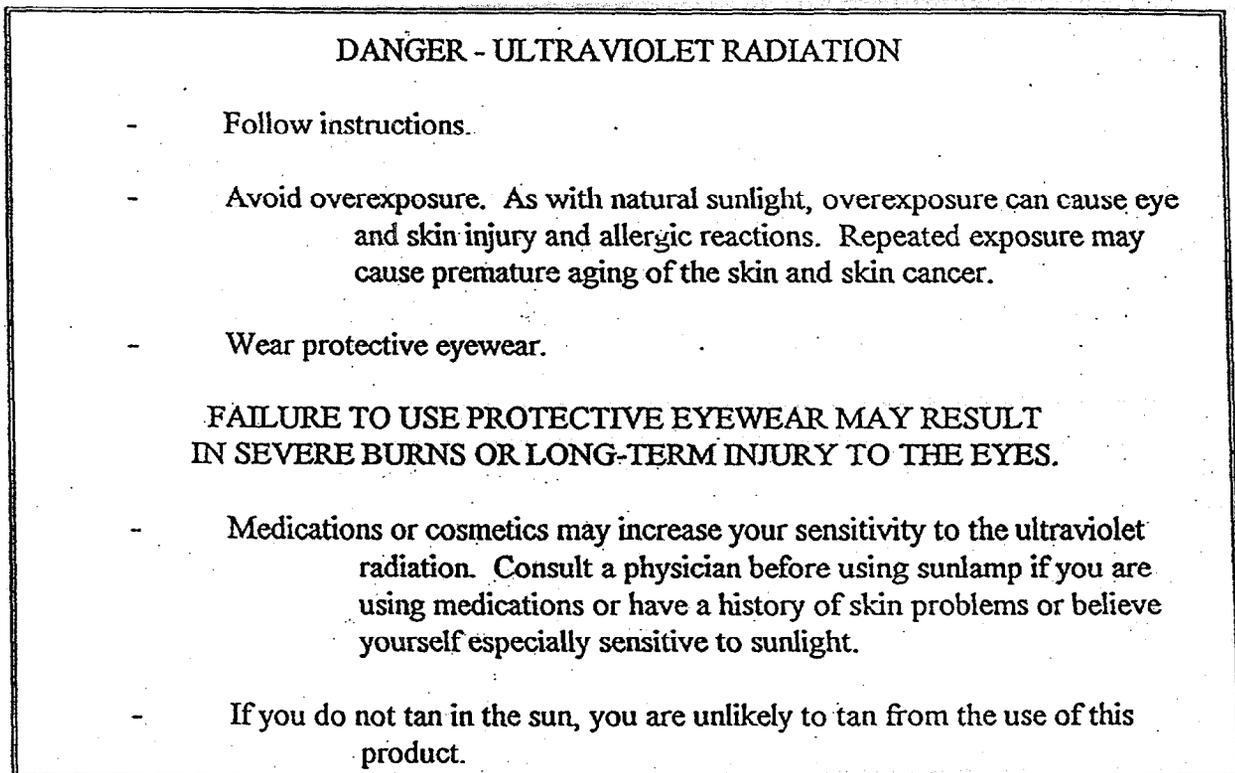
- a. The Agency may, for good cause shown, deny, suspend or revoke a certificate of registration sought or issued pursuant to these regulations for any of the following reasons:
- i. Failure of reports, plans or specifications to show that the tanning facility will be constructed, operated or maintained in accordance with the requirements of these regulations;
 - ii. Submission of incorrect, false or misleading information in the application, reports, plans, or specifications;
 - iii. Failure to construct, operate or maintain the tanning facility in accordance with the application, plans and specifications approved by the Agency except as such maintenance may involve the replacement of lamps by "equivalent" lamps which have been defined in BB.8 above;
 - iv. Operation of the tanning facility in a way that causes or creates a nuisance or hazard to the public health or safety;
 - v. Violation of any rules, regulations, standards, or requirements adopted by the Agency;
 - vi. Violation of any condition upon which the certificate of registration was issued;
 - vii. Failure to allow duly authorized agents of the Agency to conduct inspections at reasonable hours and in a reasonable manner;
 - [viii. Failure to pay any registration or inspection fees.]

- b. **Hearing:** If any certificate of registration is denied, suspended, or revoked, the applicant or registrant may request a hearing in accordance with [here insert reference to applicable administrative procedures act, hearing rules, etc.].

Sec. BB.12 - Construction and Operation of Tanning Facilities. Unless otherwise ordered or approved by the Agency, each tanning facility shall be constructed, operated, and maintained to meet the following minimum requirements:

a. **Physical Facilities.**

- i. The following warning sign shall be posted in the immediate proximity (within 1 meter) of each piece of tanning equipment; it shall be readily legible, clearly visible, and not obstructed by any barrier, equipment, or other item present so that the user can easily view the warning sign before energizing the ultraviolet light generating equipment:



The lettering on each warning sign shall be at least 10 millimeters high for all words shown in capital letters and at least 5 millimeters high for all lower case letters.

- ii. Only tanning equipment manufactured and certified to comply with 21 CFR Part 1040, Section 1040.20, "Sunlamp products and ultraviolet lamps intended for use in sunlamp products," shall be used in tanning facilities. Compliance shall be based on the standard in effect at the time of manufacture as shown on the device identification label required by 21 CFR Part 1010, Section 1010.3.

- iii. Each tanning equipment shall have a timer which complies with the requirements of 21 CFR Part 1040, Section 1040.20(c)(2). The maximum timer interval shall not exceed the manufacturer's maximum recommended exposure time. No timer interval shall have an error greater than 10% of the maximum timer interval for the product.
- iv. Tanning equipment shall meet the National Fire Protection Association's National Electrical Code.
- v. There shall be physical barriers to protect consumers from injury induced by touching or breaking the lamps.
- vi. Additional requirements for stand-up booths:
 - (1) There shall be physical barriers or other means such as handrails or floor markings to indicate the proper exposure distance between ultraviolet lamps and the consumer's skin;
 - (2) The construction of the booth shall be such that it will withstand the stress of use and the impact of a falling person;
 - (3) Access to the booth shall be of rigid construction; doors shall open outwardly. Handrails and non-slip floors shall be provided.
- [vii. Here insert references to other appropriate regulations dealing with health, hygiene, safety standards, including electrical standards such as Underwriters Laboratories, etc.]

b. Protective Goggles.

- i. Each consumer shall be provided with protective goggles and instructions for their use.
- ii. Protective goggles shall meet the requirements of 21 CFR Part 1040, Section 1040.20(c)(5).
- iii. Protective goggles shall be properly sanitized before each use. Exposure to the ultraviolet radiation produced by the tanning equipment itself is not considered a sanitizing agent.
- iv. Each consumer shall wear the protective goggles as instructed.

c. Operation.

- i. An operator must be present when tanning equipment is operated.
- ii. Prior to initial exposure each consumer shall be provided the opportunity to read a copy of the warning specified in BB.12a.i. The operator shall then request that the consumer sign a statement that the information has been read and understood. For illiterate or visually handicapped persons, the warning statement shall be read by the operator in the presence of a witness. Both the witness and the operator shall sign the statement.

- iii. A record shall be kept by the facility operator of each consumer's total number of tanning visits and tanning times.
- iv. A written report of any tanning injury shall be forwarded to the Agency within 5 working days of its occurrence or knowledge thereof. The report shall include:
 - (1) The name of the affected individual;
 - (2) The name and location of the tanning facility involved;
 - (3) The nature of the injury;
 - (4) Name and address of health care provider, if any;
 - (5) Any other information considered relevant to the situation.
- v. No minor shall be allowed to use the tanning facility unless the minor provides a consent form signed by the parent or legal guardian. The parent or guardian shall have been provided with the basic information required under BB.12a.i.
- vi. Defective or burned-out lamps or filters shall be replaced with a type intended for use in that device as specified on the product label on the tanning equipment, or, with lamps or filters that are "equivalent" under the Food and Drug Administration regulations and policies applicable at the time of lamp manufacture.
- vii. Each operator must be adequately trained. Proof of training must be maintained in the facility and available for inspection. Training shall include:
 - (1) The requirements of these regulations;
 - (2) Procedures for correct operation of the facility;
 - (3) Recognition of injury or overexposure;
 - (4) Manufacturer's procedures for operation and maintenance of tanning equipment;
 - (5) Emergency procedures in case of injury.
- viii. A list of operators trained in accordance with BB.12c.vii. shall be maintained and available at the facility.

Sec. BB.13 - Enforcement and Penalties. [here insert reference to relevant statutory authority to inspect, cite violations, and compel compliance and assess penalties.]

Sec. BB.14 - Severability. If any provision, clause, section, sentence or paragraph of these regulations or the application thereof to any person shall be held to be invalid, such invalidity shall not affect the

remaining provisions or applications of the regulations. The valid part of any provision, clause, section, sentence or paragraph shall be given independence from the invalid provisions or applications, and to this end these regulations are hereby declared to be severable.

Sec. BB.15 - Effective Date. [here insert relevant effective date.]

1996
RATIONALE

PART BB
REGULATIONS FOR TANNING FACILITIES

Introduction

The use of ultraviolet tanning equipment for cosmetic purposes has been a growing industry for a number of years, to the point where several million citizens, young and old, receive tanning sessions each year.

Concern over the health effects of ultraviolet exposure to these sources has caused the Food and Drug Administration to promulgate a performance standard for sunlamp products, which became effective May 7, 1980. This performance standard is chiefly a manufacturing standard.

While there is still an active home purchase market for ultraviolet tanning machines, a sizeable commercial tanning industry has also grown up. This market is not confined to commercial tanning salons alone. Rather, units can be found in, beauty parlors, health clubs, apartment complexes, nail shops, resorts, bars, etc.

Training of operators, instructions to clients, even time of exposure is left entirely to the whim of the unit owner or employee. This includes the crucial instructions on eye protection.

The Food and Drug Administration, the American Dermatology Association, and the U.S. Surgeon General's Office are but a few groups that recognize the hazard of ultraviolet tanning and support its control and regulations.

Part BB is concerned with the issuance of license/registration authorizing the exposure of the general population to artificial ultraviolet tanning sources, i.e., tanning beds, stand-up booths, and facial units.

This Part is needed to provide specific standards and performance objectives for facilities offering nonmedical or unintentional exposure to ultraviolet radiation to the public; in other words, facilities offering cosmetic exposure. These objectives include recordkeeping, equipment performance, safety posting, training of operators, and knowledgeable consent of the user.

Currently only Food and Drug Administration regulations are available and only cover manufacturing standards of commercial tanning equipment, and as such do not concern themselves with numerous safety aspects of the units once in the field, or how the licensee complies with those standards.