Contains Nonbinding Recommendations

Draft — Not for Implementation

Guidance for Industry

Enforcement Policy – OTC Sunscreen Drug Products Marketed Without an Approved Application

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact at Reynold Tan at (301) 796-2090.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

June 2011
Compliance

Contains Nonbinding Recommendations

Draft — Not for Implementation

Guidance for Industry

Enforcement Policy – OTC Sunscreen Drug Products Marketed Without an Approved Application

Additional copies are available from:
Office of Communications
Division of Drug Information, WO51, Room 2201
10903 New Hampshire Ave.
Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

June 2011
Compliance

TABLE OF CONTENTS

Guidance for Industry[1] Enforcement Policy – OTC Sunscreen Drug Products Marketed Without an Approved Application

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance is intended for manufacturers who market over-the-counter (OTC) sunscreen drug products without an approved application.[2] OTC sunscreens are not yet the subject of an effective final monograph, and we continue to evaluate information relevant to defining conditions under which such products are GRASE and not misbranded. However, OTC sunscreens marketed without approved applications and containing specified active ingredients (see section II of this guidance) are subject to a final rule issued in 2011 that establishes labeling and testing requirements. Several other ongoing and planned rulemaking proceedings also address these products. Because questions may arise about the agency's expectations in light of these various proceedings, this guidance document describes the Agency's intended enforcement approach with respect to OTC sunscreen products marketed without approved applications.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

We have previously published a number of *Federal Register* notices pertaining to rulemaking related to OTC sunscreen products. They can be found on our website: http://www.fda.gov/OTCRulemaking. Rather than discuss all of the proceedings, we summarize those that are most relevant to the enforcement policy described in this guidance.

[1] This guidance has been prepared by the Division of Nonprescription Regulation Development in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] See section 505 of the Federal Food, Drug and Cosmetic Act (FD&C Act) (21 U.S.C. 355). Approved applications under section 505 include both New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs). Some OTC sunscreen products are currently marketed under approved applications. This guidance document does not address those products.

In 1978, we published an advance notice of proposed rulemaking (ANPR) that included recommendations from an advisory review panel[3] on the safe and effective use of OTC sunscreen products (43 FR 38206). In the ANPR, we stated that the panel recommended 21 sunscreen active ingredients be determined as GRASE. The panel recommended all sunscreen products have SPF values of 2 or higher. The panel also recommended a maximum labeled SPF value of 15. The panel did not address broad spectrum protection,[4] nor did the panel address insect repellent-sunscreen combination products. The panel discussed OTC sunscreen products formulated as oils, lotions, creams, gels, butters, pastes, sticks, ointments, and sprays, but did not recommend classifying any specific dosage forms as GRASE.

In 1993, we published a proposed rule that included our proposed GRASE conditions for OTC sunscreen products (58 FR 28194). We proposed as GRASE the same active ingredients included in the ANPR except padimate A (i.e., 20 proposed GRASE ingredients). We proposed a minimum SPF value of 2 as stated in the ANPR and proposed a maximum labeled SPF value of 30. We did not propose broad spectrum protection requirements or address insect repellent-sunscreen combination products. In discussing proposed directions, we mentioned several dosage forms, but did not expressly discuss what dosage forms of sunscreens were considered to be GRASE and not misbranded. (See 58 FR 28243-44, 28297 (proposed 21 CFR 352.52(d) ("(e.g., cream, gel, lotion, oil, spray, etc.).")

We proposed two additional sunscreen active ingredients as GRASE after the 1993 proposed rule. In 1996, we proposed adding avobenzone as a GRASE active ingredient (61 FR 48645). In 1998, we proposed adding zinc oxide as a GRASE active ingredient (63 FR 56584).

In 1999, we published a final rule that resolved most of the issues in the 1993, 1996, and 1998 proposed rules (64 FR 27666). The final rule established a sunscreen monograph in part 352 (21 CFR part 352) that had an effective date of May 21, 2001. We included as GRASE conditions for sunscreens the following active ingredients with the following maximum concentrations (See § 352.10, now stayed; 64 FR 27666 at 27687):[5]

- Aminobenzoic acid (PABA), 15 percent
- Avobenzone, 3 percent
- Cinoxate, 3 percent

[3] The panel was a group of experts on sunscreens from outside FDA that we created to give us advice on developing an OTC sunscreen monograph.

[4] Broad spectrum protection means protection against ultraviolet B (wavelengths of 290 to 320 nanometers) and ultraviolet A radiation (wavelengths of 320 to 400 nanometers).

[5] The active ingredient names used in this list are the current established names for these active ingredients. Subsequent to the publication of the 1999 final rule, we issued another final rule in 2002 to amend the names used for four of those ingredients, to make them consistent with renaming of those ingredients in the corresponding USP monographs (67 FR 41823). Under section 502(e) of the FD&C Act, drug labels are required to bear the established name of the drug, and under section 508 of the FD&C Act, if the agency has not designated an official name, the compendial name is the established name. Consequently, to comply with section 502(e) of the Act, sunscreen drug products must bear the current compendial names for their active ingredients, and those are used in the text above. However, because the 2002 final rule that changed those names was published after the effective date of part 352 was stayed, those amendments have not yet been incorporated into the published monograph regulation.

- Dioxybenzone, 3 percent
- Ensulizole, 4 percent[6]
- Homosalate, 15 percent
- Meradimate, 5 percent[7]
- Octinoxate, 7.5 percent[8]
- Octisalate, 5 percent[9]
- Octocrylene, 10 percent
- Oxybenzone, 6 percent
- Padimate O, 8 percent
- Sulisobenzone, 10 percent
- Titanium dioxide, 25 percent
- Trolamine salicylate, 12 percent
- Zinc Oxide, 24 percent

We concluded that these ingredients at these concentrations could also be used in combination as long as each active ingredient contributes a minimum SPF of 2 to the finished product, except that avobenzone may not be combined with aminobenzoic acid (PABA), menthyl anthranilate, padimate O, titanium dioxide, and zinc oxide (See 21 CFR 352.20, now stayed; 64 FR 27666 at 27687-88). We identified the same dosage forms in the 1999 final rule as were included in the ANPR and 1993 proposed rule (21 CFR 352.52(d) and 352.72(e)). We raised the maximum labeled SPF value to 30. We did not propose broad spectrum protection requirements or address insect repellent-sunscreen combination products.

In 2000, we delayed the effective date for the 1999 final rule until December 31, 2002 (65 FR 36319). In 2001, we stayed the December 31, 2002 effective date of the 1999 final rule indefinitely (66 FR 67485). We delayed the effective date because we had not yet established UVA/broad spectrum testing and labeling requirements for OTC sunscreen products. We decided to include these requirements in the monograph before making it effective. Therefore, there has never been an OTC drug monograph in effect for sunscreen products.

In 2007, we published an ANPR requesting information and comment on specific topics including the effectiveness and safety of sunscreen products when combined with certain insect repellent ingredients (72 FR 7941). The 2007 ANPR discussed five insect repellents then registered by the Environmental Protection Agency (EPA), which regulates insect repellents under the Federal Insecticide, Fungicide, and Rodenticide Act: N,N-diethyl-meta-toluamide (DEET), oil of citronella, IR3535, p-menthane-3,8-diol, and picaridin. We stated that our historical enforcement policy has allowed the marketing of insect repellent-sunscreen drug products pending the establishment of an effective final sunscreen monograph, as long as the products contained sunscreen ingredients included in the FDA OTC sunscreen rulemaking and an insect repellent registered with EPA (72 FR 7941 at 7943). We stated that final regulations for insect repellent-sunscreen products would be based on information and comments submitted

[6] Referred to in the 1999 final rule as phenylbenzimidazole sulfonic acid. See footnote 6.
[7] Referred to in the 1999 final rule as menthyl anthranilate. See footnote 6.
[8] Referred to in the 1999 final rule as octyl methoxycinnamate. See footnote 6.
[9] Referred to in the 1999 final rule as octyl salicylate. See footnote 6.

in response to the 2007 ANPR. We have not published a proposed rule addressing insect repellent-sunscreen products at this time.

In 2011, we published a final rule (76 FR 35620), codified in § 201.327, that established labeling and testing requirements for OTC sunscreen products marketed without approved applications and containing only the ingredients specified in the stayed 1999 final rule (see above). For these "covered" products, the 2011 final rule:

- Established labeling for SPF and broad spectrum protection and specified test methods for establishing SPF values and broad spectrum protection
- Established labeling and testing for water resistance
- Addressed other elements of labeling, including directions for use and warnings

The final rule also identified specific claims that render a covered product misbranded or would not be allowed on any OTC sunscreen product marketed without an approved application. (21 CFR 201.327(c)(3) and (g) and 310.545(a)(29)(ii)). The final rule addressed labeling and testing comments raised in response to the 2007 sunscreen proposed rule, but did not address sunscreen active ingredients or combination products that include sunscreen active ingredients.

In 2011, we also published a proposed rule to limit the maximum labeled SPF value for OTC sunscreen products to "50+" (76 FR 35672). If the proposal were finalized, an OTC sunscreen product marketed without an approved application and labeled with a specific SPF value higher than 50 would be liable to regulatory action.

In 2011, we also published an ANPR requesting additional data on OTC sunscreen products in certain dosage forms (76 FR 35669). We listed those dosage forms of OTC sunscreen products that we currently considered potentially eligible for inclusion in the OTC sunscreen monograph (i.e., oils, lotions, creams, gels, butters, pastes, ointments, sticks, and sprays). For sprays, we requested additional data to address remaining questions about effectiveness and safety. We also invited comment on potential labeling and testing conditions for sunscreens in spray dosage forms, contingent on receiving additional data that would be needed to allow their classification as GRASE. We also identified certain dosage forms that we do not consider currently eligible for review for potential inclusion in the OTC sunscreen monograph (i.e., wipes, towelettes, powders, body washes, and shampoos).

III. ENFORCEMENT POLICY

Because there is no final OTC sunscreen monograph in effect, certain OTC sunscreen products have been marketed under our enforcement discretion since the OTC monograph process was established. We intend to continue to exercise enforcement discretion for certain OTC sunscreen products under the circumstances described in this guidance. Sections III.A through D describe the circumstances under which we intend to exercise enforcement discretion with respect to certain OTC sunscreen products marketed without approved applications until a final OTC sunscreen monograph becomes effective. Section III.E describes our approach to products formulated in certain dosage forms, particularly sprays. Section III.F describes our approach to products that contain both a sunscreen and an insect repellent, and section III.G describes

sunscreen products that must comply with the requirements of 21 CFR 330.14(h) in order to be marketed. Manufacturers should be certain to examine sections III.A through III.F to determine if the conditions in more than one of these sections apply to a single sunscreen product. In such a case, our enforcement policy is premised on adherence to all applicable recommendations.

A. General Enforcement Policy

Unless the failure to pursue regulatory action poses a potential health hazard to the consumer, we do not intend to object to the marketing without an approved application of OTC sunscreen products that have all of the following characteristics:

- Contain only the active ingredients or combinations of active ingredients listed in Section II of this guidance (previously included in 21 CFR 352.10 and 352.20, which are now stayed),
- Do not make claims addressed in 21 CFR 201.327(c)(3) and (g) and 310.545(a)(29)(ii),
- Comply with the requirements for OTC drugs under 21 CFR part 201 and 330.1, requirements for adverse event reporting for OTC drugs, and provisions of the FD&C Act addressing adulteration, and
- Follow labeling and testing requirements in § 201.327 (in accordance with the effective date and compliance dates established in the 2011 final rule) except as specific recommendations of this guidance address below.

It should be noted that cosmetic products labeled with sunscreen claims (e.g., including an SPF value) are regulated as drugs[10] and, therefore, covered by this enforcement policy.

B. Broad Spectrum Testing

The 2011 final rule includes an in vitro broad spectrum test procedure for assessing protection across both UVA and UVB regions of the UV spectrum (See 21 CFR 201.327(j)). Certain elements of labeling in the 2011 final rule apply only to products that are determined to be "Broad Spectrum" in accordance with this test procedure. FDA is aware that not all sunscreen active ingredients provide substantial protection against UVA wavelengths, and that OTC sunscreen products that do not contain certain ingredients are not likely to pass the broad spectrum test criteria. FDA does not expect a covered sunscreen to have been tested in accordance with 21 CFR 201.327(j) so long as it does not bear any labeling that the final rule specifies as applicable only for products that pass the broad spectrum test, or otherwise suggest that it provides broad spectrum protection or helps to decrease the risk of skin cancer or premature skin aging.

[10] See 21 CFR 700.35.

C. SPF Testing

Among other provisions, the 2011 final rule requires that labeling for covered OTC sunscreen products bear SPF values determined in accordance with the SPF testing requirements in § 201.327(i). We expect covered OTC sunscreen products initially marketed after June 17, 2011, to conduct SPF testing according to the method specified in § 201.327(i) and utilize this value in labeling by the compliance dates indicated in the rule.[11] In response to the 2007 proposed rule, we received submissions from sunscreen manufacturers requesting an implementation period of 3 years to comply with the 2011 final rule. The manufacturers expressed concern that testing laboratories would not have sufficient capacity to accommodate testing for all sunscreen products covered by the rule if we required a shorter implementation period. In light of this concern, we do not intend to initiate enforcement action before June 17, 2013, for OTC sunscreen products that:

- are subject to the 2011 final rule,
- were on the market prior to June 17, 2011, the date of publication of the final rule, and
- are labeled with an SPF value determined prior to June 17, 2011, using the SPF test method described in the 1999 final rule (64 FR 27666 at 27689-693) or the SPF test method described in the 2007 proposed rule (72 FR 49070 at 49114-119).

Such products should otherwise be labeled in compliance with the final rule and the recommendations of this guidance, as applicable. We believe that this additional time will be sufficient to permit testing of all formulations in compliance with the final rule without creating disruption in supply.

We do not intend to exercise enforcement discretion for OTC sunscreen products initially marketed prior to June 17, 2011, if they are labeled with an SPF that was generated by a method other than that included in the 2011 final rule, 1999 final rule, or 2007 proposed rule.

D. Products That Claim to Have Specific SPF Values Higher Than 50

This section describes how we intend to exercise our enforcement discretion with regard to sunscreen products that claim to have specific SPF values higher than 50. In the 2007 proposed rule, we proposed that OTC sunscreen products with SPF values higher than 50 be labeled as "SPF 50+" or "SPF 50 plus." In the 2011 proposed rule, we have retained this proposal. However, we intend to continue to exercise enforcement discretion for sunscreen products labeled with specific SPF values higher than 50 if those values are determined according to SPF testing as described in Section C of this guidance, until we issue a final rule based on the 2011 proposed rule. Therefore, sunscreen products that claim to have specific SPF values higher than 50 should be:

[11] Specifically, the compliance date for all products subject to the final rule with annual sales less than $25,000 is June 17, 2013, while the general compliance date for all other products subject to the rule is June 18, 2012,.

- Tested to determine the SPF value as described in Section C of this guidance, and
- Labeled in compliance with § 201.327 and § 310.545(a)(29)(ii), and the recommendations of this guidance, as applicable.

E. Dosage Forms

In the 2011 ANPR on dosage forms of OTC sunscreen products, we listed the following dosage forms as potentially eligible for inclusion in the OTC sunscreen monograph:

- oils
- lotions
- creams
- gels
- butters
- pastes
- ointments
- sticks
- sprays

During the pendency of rulemaking regarding these dosage forms, we do not intend to initiate enforcement action for OTC sunscreen products formulated in any of the listed dosage forms if they comply with the 2011 final rule or the recommendations of this guidance, as applicable. As stated in the 2011 ANPR, we tentatively conclude that the record is sufficient to support including these dosage forms, except for sprays, in the future OTC sunscreen final monograph under the conditions of labeling and testing included in new § 201.327. If we do not receive sufficient data for sprays in response to the ANPR, we intend to propose that sprays not be included in a final sunscreen monograph as a GRASE dosage form. Pending submission of the requested data that would allow establishment of monograph conditions for sunscreens formulated as sprays, we do not intend to object if manufacturers include the additional warning and directions discussed in the 2011 ANPR, including the variation from the direction in § 201.327(e)(1)(ii):

- Warnings:
  - **<u>When using this product</u>** keep away from face to avoid breathing it
- Directions:
  - spray liberally [*or* generously] and spread evenly by hand 15 minutes before sun exposure *(This direction can be provided in lieu of that described in § 201.327(e)(1)(ii.))*
  - hold container 4 to 6 inches from the skin to apply
  - do not spray directly into face. Spray on hands then apply to face
  - do not apply in windy conditions
  - use in a well-ventilated area

This labeling is intended to ensure that consumers use sunscreen sprays safely and effectively.

The 2011 ANPR on dosage forms also raises certain questions regarding both broad spectrum and SPF testing for sunscreen products in spray dosage forms. At the present time, however, all sunscreen products covered by the final rule are subject to the testing methods in § 201.327(i) and (j), regardless of dosage form. Therefore, while information is being collected on testing methods for sunscreens formulated as sprays, sunscreens formulated as sprays should be tested according to the rule and in light of the recommendations regarding testing described in Sections III.B and C of this guidance.

The 2011 ANPR also listed those dosage forms that we did not consider currently eligible for review for potential inclusion in the OTC sunscreen monograph:

- wipes
- towelettes
- powders
- body washes
- shampoos

OTC sunscreen products in these dosage forms are not currently eligible for review under the OTC sunscreen monograph, because we lack the evidence that such products existed in the OTC drug marketplace on or before May, 1972. OTC sunscreen products in these dosage forms also have not established eligibility for review under the Time and Extent Application (TEA) process (21 CFR 330.14(c)), because we have not received any TEAs for these products. (That regulation specifies the process and content for establishing eligibility for OTC drugs initially marketed in the United States after the OTC Drug Review began in 1972, or with no U.S. marketing experience.) OTC sunscreen products in these dosage forms that are marketed without an approved application therefore remain liable to regulatory action unless and until the requirements of § 330.14(h) are satisfied.

Manufacturers of OTC sunscreen products in dosage forms that are not currently considered eligible for the OTC Drug Review may submit the information needed to support the eligibility of these products. In the 2011 ANPR, we invite submitters to identify any additional sunscreen dosage forms that may be eligible for potential inclusion in the OTC sunscreen monograph based on marketing prior to the commencement of the OTC Drug Review in 1972. To establish such eligibility, a manufacturer should submit actual product labeling or a facsimile of labeling that documents the conditions of marketing prior to May 1972 (21 CFR 330.10(a)(2)). Conditions include active ingredient, dosage form, dosage strength, route of administration, and specific OTC use of the product (21 CFR 330.14(a)). Alternatively, a manufacturer of an OTC sunscreen product in a dosage form that was not marketed in the United States prior to the commencement of the OTC Drug Review in 1972 may submit a TEA to support the potential inclusion of the condition in the OTC sunscreen monograph. The requirements for establishing eligibility through a TEA are set forth in 21 CFR 330.14. If we determine that an OTC sunscreen product in any additional dosage form is eligible for inclusion in the OTC sunscreen monograph, we would then publish a notice of eligibility requesting the submission of data to address its safety and effectiveness. If these data support general recognition of sunscreens in this dosage form as GRASE, we would include the condition in the OTC sunscreen monograph.

F. Insect Repellent-Sunscreen Combination Products

Some sunscreen products subject to § 201.327 also contain an insect repellent registered by the EPA. Some of the labeling requirements in § 201.327 may conflict with EPA's labeling requirements for insect repellents, as discussed in the 2007 ANPR. We have not yet made a determination on these conflicts. We encourage manufacturers of these products to comply with the labeling in § 201.327 as closely as possible.

G. OTC Sunscreen Products Not Covered By the Intended Enforcement Discretion

Not all OTC sunscreen products lacking approved applications fall within the intended exercise of enforcement discretion described in this guidance. This includes products marketed without an approved application that have any of the following characteristics:

- Contain active ingredients or combinations of active ingredients not included in the list in Section II of this guidance (and previously included in 21 CFR 352.10 or 352.20, which are now stayed),
- Make claims that render a product misbranded or are not permitted on any OTC sunscreen marketed without an approved application, according to 21 CFR 210.327(c)(3) and (g) and 310.545(a)(29)(ii),
- Are formulated in dosage forms that were not marketed prior to the inception of the OTC Drug Review, or
- Contain an insect repellent ingredient that is not registered by EPA

In addition, OTC sunscreen products containing any active ingredients found eligible for possible inclusion in the OTC sunscreen monograph under a TEA cannot be legally marketed without an approved application unless and until we find the active ingredients GRASE and other procedural requirements are satisfied (21 CFR 330.14(h)). Consistent with this requirement, we do not intend to exercise enforcement discretion with respect to an OTC sunscreen product marketed without an approved application if it contains any of the following active ingredients found eligible for possible inclusion in the OTC sunscreen monograph under TEAs: amiloxate, bemotrizinol, bisoctrizole, enzacamene, diethylhexyl butamino triazone, octyl triazone, ecamsule, or drometrizole trisiloxane (68 FR 41386; 70 FR 2449; 71 FR 2405; 73 FR 53029, 75 FR 30838). However, any OTC sunscreen product that does not fall within our enforcement discretion (as defined in this guidance) or otherwise comply with the requirements of the regulations may be marketed under a new drug application approved under section 505 of the Act (21 U.S.C. 355).