

---

# **Nonprescription Sunscreen Drug Products — Safety and Effectiveness Data**

## **Guidance for Industry**

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

**November 2016  
OTC**

---

# Nonprescription Sunscreen Drug Products — Safety and Effectiveness Data

## Guidance for Industry

*Additional copies are available from:*

*Office of Communications, Division of Drug Information  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10001 New Hampshire Ave., Hillandale Bldg., 4<sup>th</sup> Floor  
Silver Spring, MD 20993-0002*

*Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353*

*Email: [druginfo@fda.hhs.gov](mailto: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)**

**November 2016  
OTC**

## TABLE OF CONTENTS

<b>I.</b>	<b>INTRODUCTION.....</b>	<b>1</b>
<b>II.</b>	<b>PHARMACEUTICAL QUALITY/MANUFACTURING INFORMATION .....</b>	<b>3</b>
<b>III.</b>	<b>SAFETY DATA NEEDED TO ESTABLISH THAT AN OTC SUNSCREEN ACTIVE INGREDIENT IS GRASE.....</b>	<b>4</b>
<b>A.</b>	<b>Clinical Safety Testing.....</b>	<b>5</b>
	<i>1. Human Dermal Safety Studies .....</i>	<i>5</i>
	a. Human irritation and sensitization studies .....	6
	b. Human photosafety studies .....	7
	<i>2. Human Absorption Studies/Maximal Usage Trial.....</i>	<i>7</i>
	<i>3. Pediatric Considerations .....</i>	<i>9</i>
<b>B.</b>	<b>Nonclinical Safety Testing.....</b>	<b>10</b>
	<i>1. Carcinogenicity Studies: Dermal and Systemic.....</i>	<i>10</i>
	<i>2. Developmental and Reproductive Toxicity Studies.....</i>	<i>11</i>
	<i>3. Toxicokinetics .....</i>	<i>11</i>
<b>C.</b>	<b>Postmarketing Safety Data.....</b>	<b>12</b>
<b>IV.</b>	<b>EFFECTIVENESS TESTING.....</b>	<b>13</b>
<b>V.</b>	<b>ANTICIPATED FINAL FORMULATION TESTING .....</b>	<b>14</b>

# **Nonprescription Sunscreen Drug Products — Safety and Effectiveness Data Guidance for Industry<sup>1</sup>**

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

## **I. INTRODUCTION**

This guidance addresses the current thinking of the Food and Drug Administration's (FDA or Agency) about the safety and effectiveness data needed to determine whether a nonprescription (also referred to as an over-the-counter (OTC)) sunscreen active ingredient,<sup>2</sup> or combination of active ingredients, evaluated under the Sunscreen Innovation Act (SIA) (21 U.S.C. Ch. 9, Sub. 5 Part I, enacted November 26, 2014) is generally recognized as safe and effective (GRASE) and not misbranded when used under specified conditions.

FDA is issuing this guidance in partial implementation of the SIA. Among other things, the SIA supplemented FDA's existing regulation for adding a new active ingredient or other condition to an OTC drug monograph<sup>3</sup> with new procedures and review time lines for determining whether or not a nonprescription sunscreen active ingredient is GRASE and not misbranded when used under the conditions specified in a final sunscreen order.<sup>4</sup> A critical step in that process is FDA's review of safety and effectiveness data submitted by the person requesting the GRASE

---

<sup>1</sup> This guidance has been prepared by the Division of Nonprescription Drug Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

<sup>2</sup> As defined in the SIA, the term *sunscreen active ingredient* refers to an active ingredient that is intended for application to the skin of humans for purposes of absorbing, reflecting, or scattering ultraviolet radiation (see section 586(10) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360fff(10)).

<sup>3</sup> FDA's existing regulation sets out the time and extent application procedure by which a new active ingredient or other condition (e.g., dosage form, dosage strength, or route of administration) can be considered for inclusion in the OTC drug monograph system (21 CFR 330.14).

<sup>4</sup> See section 586(4) of the FD&C Act (21 U.S.C. 360fff-1) (definition of "GRASE determination"); section 586A of the FD&C Act (21 U.S.C. 360fff-1) (submission of a new request for GRASE determination); section 586B of the FD&C Act (21 U.S.C. 360fff-2) (preliminary filing review, eligibility determination, and request for submission of safety and effectiveness data); and section 586C of the FD&C Act (21 U.S.C. 360fff-3) (GRASE determination and issuance of proposed and final sunscreen orders).

## *Contains Nonbinding Recommendations*

determination (sponsor).<sup>5</sup> If FDA determines that the active ingredient in question is GRASE and not misbranded for use in nonprescription sunscreens, it will issue a final sunscreen order setting out the conditions that sunscreen products containing the active ingredient must satisfy to be marketed without an approved new drug application (NDA).<sup>6</sup> Sunscreen products that satisfy those conditions and other requirements for nonprescription drugs may be marketed immediately upon issuance of the final sunscreen order, for as long as that order remains in effect. Any future rulemaking to amend the OTC sunscreen drug monograph must include the active ingredient found GRASE in the final order.<sup>7</sup>

The SIA also directed FDA to issue guidance on the data a nonprescription sunscreen active ingredient would need to meet the safety and efficacy standard for a GRASE determination.<sup>8</sup> The recommendations in this guidance will help sponsors identify and obtain the safety and effectiveness data needed to show that a sunscreen active ingredient is GRASE for use in nonprescription sunscreens, as a single active ingredient and/or as part of a combination of active ingredients. Unlike the review of sunscreen *products* under the new drug approval process,<sup>9</sup> for which premarketing testing focuses on individual product formulations, the GRASE review for *active ingredients* takes into account that the ingredient, if found GRASE, may be included in a variety of formulations that will be marketed without product-specific review and approval.

The recommendations in this guidance are designed to ensure that FDA's GRASE determinations for OTC sunscreen active ingredients under the SIA are consistent, up to date, and appropriately reflect current scientific knowledge and patterns of nonprescription sunscreen use by consumers. The recommendations reflect FDA's scientific expertise, existing technical guidance, experience from reviewing safety and efficacy data submitted for GRASE review of sunscreen active ingredients under current OTC drug regulations, and input from and concurrence by outside scientific experts. This guidance also addresses FDA's current thinking about an approach to safety-related final formulation testing that it anticipates adopting in the future.

---

<sup>5</sup> See section 586C of the FD&C Act. FDA will also consider other relevant public data submitted by other parties or otherwise available.

<sup>6</sup> See section 586C of the FD&C Act generally for detailed procedures.

<sup>7</sup> See section 586C(e)(1)(A) of the FD&C Act (effect of final sunscreen order for sunscreen active ingredient(s) found to be GRASE) and section 586C(e)(3) of the FD&C Act (any future amendments of the OTC sunscreen monograph must include any nonprescription sunscreen active ingredient(s) that is or are subject to an effective final sunscreen order that determined it or them to be GRASE and would set forth the conditions of use).

<sup>8</sup> See section 586D(a)(1)(B) of the FD&C Act (21 U.S.C. 360fff-4(a)(1)(B)); see also section 586D(a)(1)(A)(ii) of the FD&C Act. The SIA also requires FDA to issue three other guidances on procedural matters relating to nonprescription sunscreen active ingredients: (1) format and content of data submissions (section 586D(a)(1)(A)(i)); (2) process for withdrawing requests for a GRASE determination (section 586D(a)(1)(A)(iii)); and (3) process by which FDA will carry out section 586C(c) of the FD&C Act regarding advisory committee meetings (section 586D(a)(1)(A)(iv)).

<sup>9</sup> This process is described in 21 CFR part 314.

## *Contains Nonbinding Recommendations*

FDA's specific recommendations on the data and information needed to support a positive GRASE determination under the SIA are detailed in sections II (pharmaceutical quality/manufacturing information), III (safety data), and IV (effectiveness data). Section V presents FDA's current thinking on an approach to safety testing of final sunscreen formulations that it anticipates adopting in the future.

Although sunscreen products are typically formulated with two or more active ingredients, the recommendations in sections II through IV generally contemplate that testing will be performed using formulations including one active ingredient FDA anticipates that these data would also generally be sufficient to assess whether, and under what conditions, that active ingredient is GRASE for use as part of a combination of sunscreen active ingredients. In some situations, additional data and testing beyond what is recommended in this guidance may be needed to support a positive GRASE determination and to establish the associated conditions for a particular active ingredient. The following are examples in which additional data may be needed:

- Data suggest that there may be a safety or efficacy concern with a particular combination of active ingredients or active and inactive ingredients
- Information indicates that an active ingredient is unstable when exposed to sunlight and suggests that the active ingredient may need to be combined with a photostabilizer to be safe or effective

Other situations may occur in which additional data are needed (see, e.g., section III for some additional examples). Sponsors are encouraged to discuss with FDA any questions about whether additional data may be needed for a particular active ingredient.

In general, FDA's guidance documents 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. PHARMACEUTICAL QUALITY/MANUFACTURING INFORMATION**

FDA needs information that sufficiently characterizes the identity of each sunscreen active ingredient for FDA reviewers to determine how, if at all, the safety and efficacy studies submitted for review are relevant to the ingredient for which GRASE determination is sought.<sup>10</sup> This information would also be needed to appropriately characterize the active ingredient in the

---

<sup>10</sup> For example, if key studies were conducted using a related but different compound, or using a combination of active ingredients whose individual contributions to the observed results were not examined, those studies may have little relevance to a GRASE determination for the sunscreen active ingredient identified by the requested quality/manufacturing data.

## *Contains Nonbinding Recommendations*

final sunscreen order. Sponsors should provide the compendial status of the ingredient, including reference to a United States Pharmacopeia National Formulary monograph. Sponsors should also provide any known chemical and/or manufacturing characteristics of the active ingredient that may be relevant to FDA's GRASE evaluation and to the establishment of the conditions of any resulting final sunscreen order.<sup>11</sup> Such information should include known interactions with other sunscreen active ingredient(s) or commonly used sunscreen vehicle component(s) and particle size information for micronized or nanoscale active ingredients. In addition, sponsors should describe any aspects of formulation that are needed to ensure stability, or other characteristics of the active ingredient that are needed to establish conditions under which it is GRASE for use in sunscreens.

### **III. SAFETY DATA**

FDA's OTC drug regulations identify both the general types of safety information that sponsors should submit as evidence that an OTC drug is GRASE for use as labeled (§ 330.10(a)(2) (21 CFR 330.10(a)(2))) and the standard by which such safety information is to be judged (§ 330.10(a)(4)(i)). When applying these regulations to a given active ingredient, FDA uses its scientific expertise to determine what constitutes "adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use."<sup>12</sup>

FDA recognizes the contribution that broad spectrum sunscreens with a sun protection factor (SPF) value of 15 or higher can make to decrease the risk of skin cancer and early skin aging caused by the sun if used as directed with other sun protection measures. To protect the public health, it is also important for FDA to balance the potential benefits of these sunscreen products to consumers against their potential risks. Providing an adequate safety margin<sup>13</sup> for OTC sunscreen active ingredients and finished sunscreen products is a key element of FDA's risk assessment. When determining the specific testing and other data needed to adequately demonstrate that an OTC sunscreen active ingredient is safe, FDA considers both the circumstances under which OTC sunscreen products are intended to be used by consumers and current scientific knowledge and assessment technology.

---

<sup>11</sup> The determination of whether a sunscreen active ingredient is GRASE and not misbranded also requires the Agency to describe the conditions under which any future product incorporating that sunscreen active ingredient will be GRASE and not misbranded (see, e.g., section 586C(e) of the FD&C Act; see also section V of this document).

<sup>12</sup> § 330.10(a)(4)(i).

<sup>13</sup> For drugs with a known potential for adverse effects based on animal data, the anticipated level of risk for humans may be quantified using a safety margin calculation. A *safety margin calculation* takes the highest animal no observed adverse effect level and estimates a maximum safe level of exposure for humans. One caveat to the safety margin calculation is that animal studies do not always predict effects in humans, and the actual threshold for an effect in humans may be different (higher or lower) than in the species tested. The human sensitivity to a drug is often unknown. To account for this, the predicted safe exposure level in humans that is reflected in the safety margin is well below where toxicities were seen in animals.

## ***Contains Nonbinding Recommendations***

To ensure full discussion of the kinds of data needed to address sunscreen safety, FDA held a 2-day meeting of the Nonprescription Drugs Advisory Committee on September 4-5, 2014, at which FDA presented much of the same approach that is recommended in this guidance. There was consensus among the independent scientific experts on the committee that FDA's framework was a good starting point.<sup>14</sup> This guidance takes into consideration the recommendations FDA received from this committee meeting.

FDA's current approach for evaluating the clinical safety of potential nonprescription sunscreen active ingredients is based on our current scientific understanding regarding the safety evaluation of topical drug products for chronic use and thus is generally consistent with the safety data requirements that would apply to a new drug application (NDA) for a chronic-use cutaneous drug product (i.e., topical safety studies (irritation, sensitization, and photosafety), bioavailability (absorption), and evaluation of adverse events observed in clinical studies).<sup>15</sup> In addition, an evaluation of adverse events reported during the commercial marketing of sunscreen products containing the ingredient as well as other postmarketing safety information is also relevant to FDA's safety evaluation.

FDA's current approach to the nonclinical safety evaluation of these active ingredients takes into account that only active ingredients that have been marketed to a material extent and for a material time in OTC sunscreen products are eligible under the SIA for a GRASE determination.<sup>16</sup> In contrast to nonclinical data requirements for a chronic-use cutaneous drug product NDA, which include comprehensive nonclinical pharmacology and toxicology safety testing, the approach to nonclinical safety testing in this guidance is largely focused on potential long-term adverse effects or effects not otherwise readily detected from human use (i.e., carcinogenicity and reproductive toxicity). Please note, though, that testing beyond what is recommended in this guidance may be needed for active ingredients for which data suggest a concern about other long-term effects, such as hormonal disruption.

The following sections describe the specific safety data that FDA needs to determine whether an active ingredient is GRASE for use in sunscreens. However, FDA will consider alternative scientifically based approaches for addressing a particular data need. Sponsors are encouraged to discuss alternative proposals with FDA before initiating studies.

### **A. Clinical Safety Testing**

#### ***1. Human Dermal Safety Studies***

---

<sup>14</sup> See the minutes of the FDA September 4-5, 2014, meeting of the Nonprescription Drugs Advisory Committee (2014 NDAC Minutes) at <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/NonprescriptionDrugsAdvisoryCommittee/ucm380890.htm>.

<sup>15</sup> *Chronic use* is defined as continuous or intermittent use of a product for at least 6 months during a lifetime.

<sup>16</sup> See section 586B(a)(2) of the FD&C Act.

## ***Contains Nonbinding Recommendations***

Human dermal safety studies for topical products in which exposure to light after application is anticipated generally consist of two sets of studies—those conducted without specific exposure to light and those conducted to assess reactions after ultraviolet exposure (photosafety studies).<sup>17</sup> These study sets usually consist of dermal irritation patch testing, dermal sensitization patch testing, dermal phototoxicity testing, and dermal photoallergenicity testing.

Because marketed sunscreen products typically contain a combination of active ingredients and because brand name product formulations frequently change, it is difficult for FDA to determine causal links between individual active ingredients and reported irritation and hypersensitivity adverse events associated with a particular product. Therefore, FDA generally expects to use data from human irritation studies, human skin sensitization studies, and human photosafety studies, in conjunction with postmarketing adverse event data, to inform GRASE determinations and labeling. Nonetheless, in some cases, depending on the rigor of available postmarketing safety information, it may be reasonable for sponsors to omit human irritation studies, human skin sensitization studies, and/or human photosafety studies. For example, if FDA concludes that there is a positive risk-benefit for a sunscreen active ingredient but that it is known to be a sensitizer, it may be possible to develop safety labeling to address this risk without data generated in the human dermal safety studies described below. Sponsors who believe there is a scientific rationale that may preclude the need for some or all of the described studies are urged to contact FDA before initiating studies.

### **a. Human irritation and sensitization studies**

Studies of skin irritation and sensitization that use the repeat insult patch test or other relevant tests are recommended elements in FDA's safety evaluation of topical drug products that, like sunscreens, are applied to the skin repeatedly over long periods of time. These tests, which are designed to detect the potential of topical drug products for local dermatologic events with fewer subjects than might be observed in larger clinical trials, often involve applying product more frequently and/or for longer durations than the proposed clinical dosing of those drug products. In dermal irritation studies, a test substance is applied to a small pad (patch) and affixed to the test subject's skin, usually on the back, to determine whether the ingredient causes direct skin toxicity. Dermal sensitization studies are conducted similarly but are designed to detect immunologically mediated reactions, which require prior exposure to the allergen.

Nonprescription sunscreen active ingredients, when found to be GRASE, may be used in numerous, as yet unknown, product formulations. Therefore, FDA recommends that cumulative irritation studies evaluate (1) the proposed sunscreen active ingredient at the highest concentration for which a GRASE determination is sought, in an appropriate vehicle; (2) the vehicle alone; (3) a negative control; and (4) a positive control. The evaluation should include scoring of erythema, edema, and a papular response or skin erosion.

---

<sup>17</sup> See the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidance for industry *S10 Photosafety Evaluation of Pharmaceuticals*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

### *Contains Nonbinding Recommendations*

Skin sensitization studies, conducted to detect immunologically mediated reactions, should be conducted in the following three phases:

- (1) The induction phase (three weekly applications for 3 weeks)
- (2) The rest phase (no product application for 10 to 14 days)
- (3) The challenge phase (patch applications to new sites for 48 hours with a confirmatory rechallenge to exclude false positives)

Although FDA recommends separate dermal irritation and sensitization studies, irritation and sensitization studies can be combined in the same study as long as a sufficient number of subjects are included for sensitization evaluation.

#### b. Human photosafety studies

Topically applied dermatologic drug products should be tested for photosafety if they absorb light in the ultraviolet A, ultraviolet B, or visible spectra. FDA recommends that photosafety evaluations of sunscreen active ingredients that absorb light consist of skin photoallergenicity and skin phototoxicity testing. *Photoallergy* is an immunologically mediated reaction to a chemical, initiated by the formation of photoproducts (e.g., protein adducts) following a photochemical reaction. Similar to dermal sensitivity testing described above, photoallergy tests use an induction/rest/challenge/rechallenge multiphase design to assess erythema, edema, and vesiculation. *Phototoxicity* (or photoirritation) is an acute light-induced tissue response to a photoreactive chemical. Phototoxicity testing typically includes a test patch, a vehicle patch, and a sham patch application for 24 hours, followed by ultraviolet light exposure of the test area. A second set of patch application areas not irradiated with light serves as a control.

FDA recommends that photosafety studies of sunscreen active ingredients that absorb light be conducted using (1) the active ingredient at the highest concentration for which a GRASE determination is sought in an appropriate vehicle, (2) the vehicle alone, and (3) a negative control.

#### 2. *Human Absorption Studies/Maximal Usage Trial*

Because nonprescription sunscreens are topically applied, a critical safety consideration is whether dermal application results in skin penetration and systemic exposure to the active ingredient and, if so, to what extent. This information helps identify potential safety concerns and helps determine whether an adequate safety margin exists for an active sunscreen ingredient to be included in the OTC sunscreen monograph.

The principal barrier to cutaneous drug product penetration is the multilayered, lipid-rich stratum corneum. The passage of any drug product through this layer is influenced by many factors, including the drug product's physicochemical features, molecular weight, and vehicle/formulation properties. Vehicle/formulation properties are particularly important because the choice of vehicle can markedly affect the permeation potential of a drug product.

### *Contains Nonbinding Recommendations*

Effects can range from simple hydration of the stratum corneum by occlusive vehicles/formulations to direct permeation enhancement by solvent effects on the lipids in the stratum corneum. Products absorbed through the skin have the potential to cause systemic adverse effects, affecting the safety assessment. Because sunscreens are intended to work at the skin's surface, systemic absorption may also lower efficacy, affecting the efficacy assessment.

Since the mid-1990s, topical product NDAs have included a Maximal Usage Trial (MUsT) as part of the clinical pharmacology/bioavailability assessment. A MUsT is designed to capture the effect of *maximal use* on absorption into the blood with standard pharmacokinetic assessments (e.g.,  $C_{max}$ ,  $T_{max}$ , area under the curve, half-life, clearance, and volume of distribution). For a topical product NDA, the MUsT is usually conducted in subjects with the disease of interest, where disrupted skin is a feature. In situations where disrupted skin is not a feature of the disease or the topical drug product is intended for prevention of disease (e.g., sunscreens), the MUsT for a topical product NDA may be conducted in subjects with healthy, intact skin. The MUsT for a topical product NDA is conducted with the specific product formulation for which approval is sought, applied at the upper limit of surface area involvement that is studied in the phase 3 clinical trials and is proposed for labeling. That is to say, if the proposed labeling permits the product to be used on up to 30 percent of body surface area, then the coverage evaluated in the MUsT would be 30 percent of body surface area.<sup>18,19</sup>

FDA recommends that SIA sponsors of sunscreen active ingredients provide data from a MUsT to support an adequate assessment of safety.<sup>20</sup> Because a determination that an active sunscreen product is GRASE would permit its use in a variety of finished sunscreen products, FDA recommends that the MUsT to support the GRASE determination be conducted under maximal use conditions employing a minimum of four formulations containing the proposed sunscreen active ingredient as the only active ingredient. These formulations should be prepared using vehicle/formulation systems that are appropriate for sunscreen topical products (e.g., they are deployable or spreadable) and that are expected to produce the highest in vivo absorption. Justification for the formulations chosen, including results of in vitro testing using a human cadaver skin permeation system (e.g., static or flow-through cells),<sup>21</sup> should be included in the study protocol. The protocol should contain sufficient detail for others to reproduce the formulations and manufacturing processes.

---

<sup>18</sup> Bashaw, ED, DC Tran, CG Shukla, et al., January 2015, Maximal Usage Trial: An Overview of the Design of Systemic Bioavailability Trial for Topical Dermatological Products, *Ther Innov Regul Sci*, 49(1):108-115. available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4663190/>.

<sup>19</sup> See the FDA draft guidance for industry *Acne Vulgaris: Developing Drugs for Treatment*. When final, this guidance will represent the FDA's current thinking on this topic.

<sup>20</sup> See the response to Discussion Question 1 in the 2014 NDAC Minutes, *supra* note 15, at 6 (expressing the need for human maximal use studies in all cases).

<sup>21</sup> Bronaugh, RL and RF Stewart, January 1985, Methods for In Vitro Percutaneous Absorption Studies IV: The Flow-Through Diffusion Cell, *J Pharm Sci*, 74(1):64-67.

### *Contains Nonbinding Recommendations*

FDA anticipates that the use of multiple formulations will help identify the overall absorption potential of the sunscreen active ingredient of interest. The MUsT for a potential monograph sunscreen active ingredient should be conducted in subjects with healthy, intact skin<sup>22</sup> at the highest concentration of the ingredient for which a GRASE determination is sought and eligibility under the SIA has been established. Because sunscreens are recommended for use on all exposed skin, the exposed area should include at least 75 percent of the body surface area. Data from the formulation that produces the highest in vivo absorption would then be used to determine the safety margin.

The assay used in the MUsT should be properly validated according to current good laboratory practices (21 CFR part 58) and should be consistent with the FDA guidance for industry entitled *Bioanalytical Method Validation*. The assay's limit of quantitation-limit of detection should be sufficiently low to allow a signal-to-noise ratio that ensures confidence in detection of a derived concentration of 0.5 nanogram (ng)/milliliter (mL).

An important consideration for designing a MUsT is that it should include testing for a duration that allows for the attainment of steady state levels to ensure that maximum penetration of the ingredient has taken place and to optimize the chances of the ingredient being detected. Thus, for sunscreen ingredients, FDA expects that single application studies would be inadequate. Because the subjects in a MUsT represent an enriched dataset in the upper range of exposures, FDA currently recommends collection of safety-related data (such as vital signs or adverse skin events) from the study's regularly scheduled physical examinations. Sponsors are strongly encouraged to discuss their MUsT protocol with FDA before beginning the trial.

As discussed further in section V, if the sunscreen active ingredient is determined to be GRASE, the final order must set out the conditions under which any future product incorporating that sunscreen active ingredient will be GRASE and not misbranded. As such a condition, FDA is considering certain final formulation testing. FDA anticipates that the formulation that produces the highest in vivo absorption in the MUsT may be appropriate to designate as a standard control formulation for future in vitro human cadaver skin permeation system testing (e.g., static or flow-through cells) of each final sunscreen formulation that includes that active ingredient. In such a case, if in vitro permeation of the sunscreen active ingredient in the final product formulation were equal to or less than the value from in vitro testing of the standard control formulation (that was shown by the MUsT to have the highest degree of systemic absorption), FDA anticipates that the safety margin calculated would be considered adequate to support the safety of the finished formulation.

### *3. Pediatric Considerations*

Young children have a larger ratio of skin surface to body volume compared to adults, which can increase a child's systemic exposure to topically applied drug products. In addition, growing children have greater potential to experience deleterious developmental effects from drug exposure. If the calculated safety margin for a proposed monograph active ingredient (based on

---

<sup>22</sup> As discussed infra, the MUsT should be conducted in subjects with healthy, intact skin because sunscreens are intended for prevention rather than treatment.

## *Contains Nonbinding Recommendations*

nonclinical results and human MUsTs) supports a GRASE determination, but the safety margin is relatively small, FDA will exercise its scientific judgment to determine if either a sunscreen active ingredient MUsT in young children or other studies are warranted to ensure that the safety margin for marketed products containing the ingredient is within an acceptable range for this population.

### **B. Nonclinical Safety Testing**

#### *1. Carcinogenicity Studies: Dermal and Systemic*

FDA generally recommends that carcinogenicity studies be conducted for any pharmaceutical either with an expected continuous clinical use of at least 6 months or with an expected clinical use of a minimum of 6 months in an intermittent manner.<sup>23</sup> The animal carcinogenicity studies help characterize the potential tumor risks associated with a sunscreen active ingredient by identifying any observed tumors by type, the level of exposure at which tumors occur, and the highest level of exposure at which no adverse effects occur, referred to as the *no observed adverse effect level (NOAEL)*. The NOAEL would be used in determining the safety margin for human exposure to sunscreens containing the active ingredient. In addition to detecting carcinogenic potential, carcinogenicity studies in animals can help identify other systemic or organ toxicities that may be associated with the proposed ingredient.

To support the safety of OTC sunscreen active ingredients, FDA recommends that sponsors conduct a dermal carcinogenicity study that involves applying the product to the skin of mice or rats for 2 years. FDA also considers it important to study the effects of systemic exposure when human bioavailability data show that dermal application of a particular formulation could result in skin penetration and systemic exposure. After the active ingredient is marketed in nonprescription sunscreens, that active ingredient is likely to be used in a wide variety of product formulations that might alter its skin penetration. Therefore, FDA also generally recommends that sponsors conduct a second carcinogenicity study by a route that produces systemic exposure.<sup>24</sup> This study can be a 2-year study or a shorter (usually 6 months) alternative carcinogenicity model, but either study should be conducted in a species different from that used in the dermal carcinogenicity study. FDA notes that the absence of a carcinogenicity signal from

---

<sup>23</sup> See the ICH guidance for industry *The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals*.

<sup>24</sup> FDA expects that a systemic carcinogenicity study would not be needed to support a GRASE determination for a sunscreen active ingredient if both (1) an adequately conducted human pharmacokinetic MUsT results in a steady state blood level less than 0.5 ng/mL and (2) an adequately conducted toxicology program does not reveal any other safety signals for the ingredient or for any known structurally similar compound indicating the potential for adverse effects at lower levels. The threshold value of 0.5 ng/mL is based on the principle that that level would approximate the highest plasma level below which the carcinogenic risk of any unknown compound would be less than 1 in 100,000 after a single dose. This threshold value is consistent with the Threshold of Toxicological Concern concept, which was applied to impurities in the ICH guidance for industry *M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk*. FDA expects that the 0.5 ng/mL concentration will be sufficiently above the assay's limit of quantitation-limit of detection to allow a signal-to-noise ratio that assures confidence in either the derived concentrations (in the case of "exaggerated" values) or lack of concentrations.

## *Contains Nonbinding Recommendations*

an alternative transgenic carcinogenicity study (e.g., TgRasH2 mouse) would likely support the safety of a sunscreen active ingredient. However, if a carcinogenicity signal was observed in such a study, the study would not support the safety of a sunscreen active ingredient because there is no basis for calculating a safety margin with this study.<sup>25</sup> All carcinogenicity studies—regardless of route—should assess a full panel of tissues.<sup>26</sup>

### *2. Developmental and Reproductive Toxicity Studies*

FDA recommends that sponsors conduct developmental and reproductive toxicity (DART) studies to evaluate the potential effects that exposure to the sunscreen active ingredient may have on developing offspring throughout gestation and postnatally until sexual maturation, as well as on the reproductive competence of sexually mature male and female animals.<sup>27</sup> Gestational and neonatal stages of development may be particularly sensitive to active ingredients with hormonal activity (endocrine disruption). For this reason, FDA recommends that these studies include assessments of endpoints such as vaginal patency, preputial separation, anogenital distance, and nipple retention, which can be incorporated into traditional DART study designs to assess potential hormonal effects on the developing offspring. FDA also recommends that sponsors perform behavioral assessments (e.g., assessing mating behavior) of offspring, which may detect neuroendocrine effects.<sup>28</sup>

### *3. Toxicokinetics<sup>29</sup>*

FDA recommends that sponsors collect animal toxicokinetic data for sunscreen active ingredients because these data provide an important bridge between toxic levels seen in animal studies and any potential human adverse events associated with systemic exposure to the sunscreen's active ingredient (see section III.A.2). Toxicokinetic measurements are usually obtained during the course of ongoing nonclinical toxicity studies, such as in carcinogenicity or DART studies, rather than through separate studies.

---

<sup>25</sup> Jacobs, AC and PC Brown, July 2015, Regulatory Forum Opinion Piece: Transgenic/Alternative Carcinogenicity Assays: A Retrospective Review of Studies Submitted to CDER/FDA 1997-2014, *Toxicol Pathol*, 43(5):605-10.

<sup>26</sup> FDA recommends submitting the carcinogenicity study protocol(s) for review by CDER's Executive Carcinogenicity Assessment Committee prior to initiating the studies. For further guidance regarding carcinogenicity studies, see the FDA guidance for industry *Carcinogenicity Study Protocol Submissions*.

<sup>27</sup> See the ICH guidance for industry *S5A Detection of Toxicity to Reproduction for Medicinal Products*. FDA expects that studies to assess both fertility and prenatal or postnatal toxicity may not be needed if both (1) an adequately conducted human MUsT shows absorption that results in a steady state blood level less than 0.5 ng/mL and (2) there are no signals in an adequately conducted toxicology program indicating that the ingredient or any known structurally similar compound interacts with related pathways, such as endocrine function or signaling pathways related to growth and development. FDA would continue to recommend that effects on embryofetal development be assessed.

<sup>28</sup> See the FDA guidance for industry *Nonclinical Evaluation of Endocrine-Related Drug Toxicity*.

<sup>29</sup> See the ICH guidance for industry *S3A Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies*.

## *Contains Nonbinding Recommendations*

### **C. Postmarketing Safety Data**

In addition to the active ingredient safety data already described, FDA's GRASE evaluation also takes into consideration available information about serious adverse drug experiences and known or expected adverse effects associated with commercially marketed products that contain the active ingredient(s) under consideration. FDA specifically requests that sponsors provide the following information:

- A summary of all potentially associated serious adverse drug experiences.
- A summary of all available potentially associated nonserious adverse drug experiences.
- A summary of expected or frequently reported side effects, whether serious or nonserious.
- Copies of all available reports of potentially associated serious adverse drug experiences. Each report submitted should be in the form of an individual case safety report as described in 21 CFR 314.80 and refer only to an individual consumer or to a single attached publication.
- Any available safety information from studies of safety and effectiveness in humans.
- Relevant medical literature describing associated adverse events.

English translations should be provided for all foreign language materials.

For products marketed outside the United States, submissions should also state whether each country's system allows for adverse event reporting and, if so, how each country's system identifies and collects the adverse event information.<sup>30</sup> If adverse event information is not available from all countries where the active ingredient has been marketed in OTC sunscreen products, the sponsor should provide an explanation for the missing data. It is important to note, however, that even when countries have an adverse event reporting system that includes sunscreen products, underreporting is a significant limitation of any system that depends on spontaneous reports.

Many factors can influence whether an adverse event is reported, including whether a possible relationship between the event and an ingredient or product is recognized by consumers or health care providers. For example, adverse events that occur many years after a causal drug exposure may not be recognized as being related to that exposure, especially if the background rate of those adverse events is high (e.g., a common cancer or a developmental problem). Thus, an absence of reports does not necessarily equate to an absence of adverse events. Despite the limitations of adverse event reporting, FDA considers postmarketing data to be relevant both to

---

<sup>30</sup> See, e.g., 21 CFR 330.14(c)(2)(v).

## *Contains Nonbinding Recommendations*

the overall GRASE assessment of OTC sunscreen active ingredients and to labeling considerations because these data may reveal safety signals not otherwise observed in clinical or nonclinical testing.

### **IV. EFFECTIVENESS DATA**

FDA's OTC drug regulations generally identify both the types of effectiveness information that sponsors should submit as evidence that a drug product containing an active ingredient or other OTC drug condition could be GRASE for use as labeled (§ 330.10(a)(2)) and the standard by which effectiveness is to be judged, which requires controlled clinical investigations to support effectiveness (§ 330.10(a)(4)(ii)).

When applying these regulations to each potential sunscreen active ingredient, FDA requests that sponsors provide evidence from at least two adequate and well-controlled SPF studies showing that the active ingredient effectively prevents sunburn, because sunburn prevention is the minimum indication for an OTC sunscreen product. Two adequate and well-controlled SPF studies of the active ingredient at a lower concentration than the maximum requested should be conducted according to established standards.<sup>31</sup> These SPF studies should demonstrate that the selected concentration provides an SPF value of 2 or higher.

The current standard procedure for SPF testing is described in § 201.327(i) (21 CFR 201.327(i)).<sup>32</sup> Any new SPF tests for a particular ingredient should be performed as described in these regulations, using a test formulation containing the ingredient as the only active ingredient to identify its contribution to the overall SPF test results. These tests should also include a vehicle control arm to rule out any contribution the vehicle may have had on the SPF test results. Finally, as described in § 201.327(i), an SPF standard formulation comparator arm should be another component of the study design.

Current sunscreen testing and labeling regulations in § 201.327(j) also specify a broad spectrum testing procedure, which provides an *in vitro* measurement of a sunscreen product's ability to protect against both ultraviolet A and ultraviolet B radiation. Broad spectrum protection is often the result of the combined contribution of multiple active ingredients in a final sunscreen formulation; thus, FDA does not expect that a sunscreen active *ingredient* would undergo broad spectrum effectiveness testing to establish its effectiveness for a GRASE determination for use in OTC sunscreen products.

Under § 201.327, the determination of whether an individual sunscreen product subject to that regulation may be labeled as *broad spectrum* (and therefore bear the additional claims related to

---

<sup>31</sup> FDA expects that the upper bound of any concentration of the active ingredient ultimately established would be governed by the safety data, as well as by efficacy.

<sup>32</sup> Although this SPF testing procedure is used primarily for final formulation testing of finished products marketed without approved NDAs, it is equally applicable for determining whether or not a sunscreen active ingredient is generally recognized as effective as part of the overall GRASE determination.

## *Contains Nonbinding Recommendations*

that labeling) is made on a product-specific basis, applying the standard testing methods set forth in those regulations.<sup>33</sup> If a sunscreen active ingredient evaluated under the SIA is established to be GRASE for use in nonprescription sunscreens, the final sunscreen order can address broad spectrum testing and related labeling conditions for final sunscreen formulations containing that ingredient.

### **V. ANTICIPATED FINAL FORMULATION TESTING**

The preceding sections of this guidance have concentrated on recommendations for safety and effectiveness data needed to support FDA's determination that a sunscreen active ingredient is GRASE for use in sunscreens. FDA's determination that an active ingredient is GRASE will be made in the form of a final sunscreen order that will set out the conditions under which any future product incorporating that sunscreen active ingredient will be GRASE and not misbranded (see section I).<sup>34</sup> As noted in section III.A.2, variations among individual sunscreen products—and in particular, aspects of the lotion or other vehicle in which active ingredients are delivered—can affect their absorption and thus their safety and effectiveness.

To address the variability among sunscreen formulations, FDA currently requires final formulation testing of nonprescription sunscreen products to ensure their *effectiveness*—namely, testing for SPF value as well as broad spectrum protection and water resistance where those attributes are claimed in product labels.<sup>35</sup> FDA anticipates that final sunscreen orders issued for sunscreen active ingredients determined to be GRASE under the SIA will also include conditions requiring final formulation testing to ensure the *safety* of all sunscreen formulations permitted by the order.

The discussion that follows provides FDA's current thinking about such final formulation safety testing, to be conducted in the future. Note that FDA has not yet determined what particular final formulation testing, if any, will be specified in future final sunscreen orders for any given sunscreen active ingredient. Such requirements will be established on an ingredient-specific basis, taking into consideration the data recommended to be supplied under other parts of this guidance to support a GRASE determination (e.g., whether any safety signals are detected in well-conducted nonclinical carcinogenicity and DART studies). Interested parties can provide relevant information and comments regarding final formulation testing for an individual sunscreen active ingredient as part of the GRASE determination process for that ingredient.

---

<sup>33</sup> These standard testing methods are also described in the guidance for industry *Labeling and Effectiveness Testing: Sunscreen Drug Products for Over-The-Counter Human Use—Small Entity Compliance Guide*.

<sup>34</sup> See section 586D(e) of the FD&C Act.

<sup>35</sup> See § 201.327 for the current requirements for OTC sunscreens containing the active ingredients already evaluated under the monograph system. OTC sunscreens marketed under NDAs provide similar information in their product-specific applications to substantiate their labeling.

### *Contains Nonbinding Recommendations*

FDA's current thinking is that final formulation safety testing of nonprescription sunscreens would not generally call for an in vivo study. Instead, FDA expects that the conditions of marketing specified for sunscreen active ingredients in final sunscreen orders would require manufacturers to perform in vitro permeation testing before marketing each new formulation.<sup>36</sup> Consistent with the approach for final formulation efficacy testing required by § 201.327, FDA anticipates that it would not review the results of the in vitro final formulation safety testing before product marketing. Rather, FDA expects that final sunscreen orders would require manufacturers to maintain records of this testing; these records would be available to FDA.

First, as mentioned in section III.A.2, FDA anticipates establishing a standard control formulation for each sunscreen active ingredient, to be used in the final formulation testing of products containing that ingredient. The standard control formulation would be the formulation that produces the highest in vivo absorption in the MUSt. The results of in vitro human cadaver skin testing using this control formulation can then be used to bridge to a corresponding level of in vivo absorption from the MUSt used to establish the safety margin for the GRASE ingredient.

Then, FDA anticipates that final formulation testing would be conducted for each formulation intended to be marketed, using a specified human cadaver skin diffusion cell, either Franz (static) or Bronaugh (flow-through). The results of the in vitro permeation testing of the new formulation would be evaluated in light of the absorption found in the standard control formulation for the active ingredient it contains. If a final sunscreen formulation contains a combination of sunscreen active ingredients, FDA anticipates that the final formulation would be tested against the standard control formulations for each of the sunscreen active ingredients it contains. A standard control formulation might not be specified for a particular sunscreen active ingredient if FDA determines that the ingredient is unlikely to be absorbed through the skin.

If the in vitro permeation of each sunscreen active ingredient in the final formulated product is equal to or less than the value obtained from in vitro testing of the standard control formulation for that active ingredient, FDA anticipates that the product's safety margin would be considered to fall within the parameters judged to be GRASE and thus to support marketing of the new formulation. However, if the in vitro permeation of the active ingredient from the specific final formulation is greater than the value obtained from in vitro permeation testing of the standard control formulation for that active ingredient, FDA anticipates that the formulation would not be considered GRASE. In that situation, the sponsor would have the option to either (1) reformulate the product and conduct in vitro testing to establish that the reformulated product satisfies the final formulation testing condition set forth in the order; or (2) seek NDA approval for the new formulation.

---

<sup>36</sup> FDA recommends this approach as an alternative to final in vivo (MUSt) testing of final product formulations, which was recommended by the Nonprescription Drugs Advisory Committee (see the response to Discussion Question 2 in the 2014 NDAC Minutes, *supra* note 15, at 7).