EXHIBIT D

(Application Serial No. 87015660)

Questions and Answers: FDA announces new requirements for over-the-counter (OTC) sunscreen products marketed in the U.S.

[updated 6/23/2011]

On June 14, 2011 the U.S. Food and Drug Administration (FDA) announced new requirements for sunscreens currently sold over-the-counter (OTC) (i.e. non-prescription). These requirements support the Agency's ongoing efforts to ensure that sunscreens meet modern-day standards for safety and effectiveness. The new requirements, as well as several proposed changes for future rules, are outlined in four regulatory documents that include a Final Rule, a Proposed Rule, an Advance Notice of Proposed Rulemaking, and a Draft Guidance for Industry.

The following questions and answers provide a brief overview of the recent regulatory actions and highlight the most important information for consumers to know when buying and using sunscreen products.

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Q2. When will these changes take effect?

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Q10. Why is the Advance Notice of Proposed Rulemaking (ANPR) requesting additional data on sunscreen products in the form of sprays?

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Q14. Where can I find more information on sunscreen use?

Q1. Why is FDA making changes to how sunscreens are marketed in the United States?

A. FDA is making changes to how sunscreens are marketed in the United States as part of the Agency's ongoing efforts to ensure that sunscreens meet modern-day standards for safety and effectiveness and to help consumers have the information they need so they can choose the right sun protection for themselves and their families. Prior rules on sunscreens dealt almost exclusively with protection against sunburn, which is primarily caused by ultraviolet B (UVB) radiation from the sun, and did not address ultraviolet A (UVA) radiation, which contributes to skin cancer and early skin aging. After reviewing the latest science, FDA determined that sufficient data are available to establish a "broad spectrum" test for determining a sunscreen product's UVA protection. Passing the broad spectrum test shows that the product provides UVA protection that is proportional to its UVB protection.

Sunscreen products that pass the broad spectrum test are allowed to be labeled as "Broad Spectrum." These "Broad Spectrum" sunscreens protect against both UVA and UVB rays. Scientific data demonstrated that products that are "Broad Spectrum SPF 15 *[or higher]*" have been shown to reduce the risk of skin cancer and early skin aging when used with other sun protection measures, in addition to helping prevent sunburn. Other sun protection measures include limiting time in the sun and wearing protective clothing.

These testing and labeling requirements are necessary to provide consumers with the information they need to make informed choices when selecting sunscreens.

Q2. When will these changes take effect?

A. The Final Rule will take effect by the summer of 2012, but consumers may begin to see changes to sunscreen labels before the effective date.

Q3. What does the SPF value on sunscreen labels indicate?

A. The SPF value indicates the level of sunburn protection provided by the sunscreen product. All sunscreens must be tested according to an SPF test procedure. The test measures the amount of ultraviolet (UV) radiation exposure it takes to cause sunburn when a person is using a sunscreen in comparison to how much UV exposure it takes to cause a sunburn when they do not use a sunscreen.

The product is then labeled with the appropriate SPF value indicating the amount of sunburn protection provided by the product. Higher SPF values (up to 50) provide greater sunburn protection. Because SPF values are determined from a test that measures protection against sunburn caused by ultraviolet B (UVB) radiation, SPF values only indicate a sunscreen's UVB protection.

However, sunscreens that pass the new broad spectrum test will have demonstrated that they also provide ultraviolet A (UVA) protection that is proportional to their UVB protection. To pass the broad spectrum test, sunscreens with higher SPF values will provide higher levels of UVA protection as well. Therefore, under the new label requirements, a higher SPF value for sunscreens labeled "Broad Spectrum SPF [*value*]" will indicate a higher level of protection from both UVA and UVB radiation.

Q4. Does FDA believe sunscreens are still safe and effective? Do consumers need to throw away the sunscreens they are currently using?

A. The ingredients in FDA-approved sunscreens marketed today have been used for many years, and FDA has no reason to believe these products are not safe and effective when used as directed. Therefore, FDA is not advising consumers to throw away their current sunscreen products.

Sunscreens on the shelf today may have varying levels of ultraviolet A (UVA) radiation protection, but by next year, sunscreens that claim to provide UVA protection, otherwise known as broad spectrum protection, will be required to pass FDA's standardized test. This broad spectrum test will enable consumers to determine the level of UVA protection a sunscreen provides in addition to its ultraviolet B (UVB) radiation protection. This information will allow them to better manage their skin cancer and early skin aging risks. FDA does not want consumers to stop using currently marketed sunscreens in the meantime, as these products still offer sun protection.

It is also important to note that FDA is not questioning the safety of any ingredients used in marketed sunscreens. FDA believes the risk of not using sunscreen is much greater than any potential risk posed by sunscreen ingredients.

Q5. What do consumers most need to know when buying and using sunscreens?

A. Spending time in the sun increases a person's risk of skin cancer and early skin aging.To reduce these risks, consumers should regularly use a Broad Spectrum sunscreen with an SPF value of 15 or higher in combination with other protective measures such as:

- Limiting time in the sun, especially between the hours of 10 AM and 2 PM when the sun's rays are the strongest.
- Wearing clothing to cover skin exposed to the sun (long-sleeved shirts, pants, sunglasses, and broad-brimmed hats) when possible.
- Using a water resistant sunscreen if swimming or sweating.
- Reapplying sunscreen, even if it is labeled as water resistant, at least every 2

hours. (Water resistant sunscreens should be reapplied more often after swimming or sweating, according to the directions on the label.)

Consumers should also be aware that no sunscreens are "waterproof" because all sunscreens eventually wash off. Sunscreens can only be labeled as "water resistant" if they are tested according to the required SPF test procedure. Sunscreens labeled "water resistant" sunscreens will also be required to state whether the sunscreen remains effective for 40 minutes or 80 minutes when swimming or sweating, and all sunscreens will be required to provide directions on when to reapply.

Q6. What are the main points of the new Final Rule?

A. The new final rule includes the following requirements:

- **Broad Spectrum designation.** Sunscreens that pass FDA's broad spectrum test procedure, which measures a product's ultraviolet A (UVA) protection relative to its ultraviolet B (UVB) protection, may be labeled as "Broad Spectrum SPF [*value*]" on the front label. For Broad Spectrum sunscreens, SPF values also indicate the amount or magnitude of overall protection. Broad Spectrum SPF products with SPF values higher than 15 provide greater protection and may claim additional uses, as described in the next bullet.
- **Use claims.** Only Broad Spectrum sunscreens with an SPF value of 15 or higher can claim to reduce the risk of skin cancer and early skin aging if used as directed with other sun protection measures. Non-Broad Spectrum sunscreens and Broad Spectrum sunscreens with an SPF value between 2 and 14 can only claim to help prevent sunburn.
- **"Waterproof," "sweatproof" or "sunblock" claims.** Manufacturers cannot label sunscreens as "waterproof" or "sweatproof," or identify their products as "sunblocks," because these claims overstate their effectiveness. Sunscreens also cannot claim to provide sun protection for more than 2 hours without reapplication or to provide protection immediately after application (for example--"instant protection") without submitting data to support these claims and obtaining FDA approval.
- **Water resistance claims.** Water resistance claims on the front label must indicate whether the sunscreen remains effective for 40 minutes or 80 minutes while swimming or sweating, based on standard testing. Sunscreens that are not water resistant must include a direction instructing consumers to use a water resistant sunscreen if swimming or sweating.
- **Drug Facts**. All sunscreens must include standard "Drug Facts" information on the back and/or side of the container.

Q7. Does the Final Rule apply to cosmetics and moisturizers containing sunscreen?

A. Yes. All products that claim to provide Broad Spectrum SPF protection are regulated as sunscreen drug products. Therefore, the regulations FDA has developed for OTC sunscreen drug products apply to cosmetics and moisturizers labeled with SPF values.

Q8. What does the Proposed Rule address?

A. The proposed rule, if finalized, would limit the maximum SPF value on sunscreen labels to "50 +" because there is not sufficient data to show that products with SPF values higher than 50 provide greater protection for users than products with SPF values of 50.

The proposed regulation is available for public comment at **regulations.gov (http://www.regulations.gov/)** until September 15, 2011.

Q9. What is the purpose of the Advance Notice of Proposed Rulemaking (ANPR)?

A. The Advance Notice of Proposed Rulemaking (ANPR) allows the public a period of time to comment on regulations FDA may pursue as part of future rulemaking. In developing regulations for over-the-counter (OTC) sunscreens, FDA has not previously specified to which dosage forms the regulations would apply. Therefore, FDA is requesting additional data relating to sunscreen products in specific dosage forms to further our understanding of how dosage forms affect the safety and effectiveness of sunscreen products. For example, the ANPR invites public comment on possible directions for use of and warnings for sunscreen sprays, as well as supporting data or information for sprays and other sunscreen dosage forms including lotions, oils, sticks, gels, butters, ointments, creams, and pastes. The ANPR also explains how interested parties can supply information for FDA to consider other dosage forms, including powders, towelettes, body washes, and shampoos.

Q10. Why is the Advance Notice of Proposed Rulemaking (ANPR) requesting additional data on sunscreen products in the form of sprays?

A. Currently, the record (data and information) about sunscreens in spray dosage forms is not comparable to that for sunscreens in other dosage forms such as oils, creams, and lotions. The manner of application differs significantly between sprays and these other dosage forms. Therefore, we are requesting additional data to address questions of effectiveness and safety that arise from differences in the manner of application.

Q11. What is included in the Draft Guidance for Industry?

A. The Draft Guidance for Industry, entitled "**Enforcement Policy – OTC Sunscreen Drug Products Marketed Without an Approved Application (PDF - 83KB) (/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM259001.pdf)**," is an enforcement guidance that includes information to help sunscreen product manufacturers understand how to label and test their products in light of the new Final Rule, the Proposed Rule, and the Advance Notice of Proposed Rulemaking (ANPR).

Q12. Why isn't FDA finalizing all the proposed sunscreen changes under one rule?

A. FDA is finalizing those changes that are based on proposals it made in earlier

stages of rulemaking, including a 2007 proposed rule, on which it already received public comment. Those comments also helped to inform the Agency's thinking about additional aspects of sunscreen regulation, which in turn gave rise to the Proposed Rule and Advance Notice of Proposed Rulemaking (ANPR). The regulatory process requires FDA to give public notice and opportunity for comment before finalizing additional changes, which also gives the public and FDA an opportunity to further develop the record (data and information) on safety and effectiveness.

Q13. Where can I find more information on these various regulatory actions?

A. On June 17, 2011, FDA published the new sunscreen **Final Rule (PDF - 485KB) (http://www.gpo.gov/fdsys/pkg/FR-2011-06-17/pdf/2011-14766.pdf)**, the **Proposed Rule (PDF - 197KB) (http://www.gpo.gov/fdsys/pkg/FR-2011-06-17/pdf/2011-14769.pdf)**, the **Advance Notice of Proposed Rulemaking (ANPR) (PDF - 187KB) (http://www.gpo.gov/fdsys/pkg/FR-2011-06-17/pdf/2011-14768.pdf)** and the **notice of availability of the Draft Guidance for Industry (PDF - 217KB) (http://www.gpo.gov/fdsys/pkg/FR-2011-06-17/pdf/2011-14767.pdf)** in the *Federal Register*. The draft guidance entitled "**Enforcement Policy – OTC Sunscreen Drug Products Marketed Without an Approved Application" (PDF - 83KB) (/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM259001.pdf)**, is also available.

Q14. Where can I find more information on sunscreen use?

A. Additional information about FDA's changes to sunscreen regulations can be found at **www.fda.gov/sunscreen (/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/ucm239463.htm)**. At this link, consumers can see what new sunscreen labels will look like, what types of sun protection various sunscreens will provide, and how to use sunscreens safely and effectively.

In addition, FDA responded to common questions about the new sunscreen regulations submitted by the WebMD community via Twitter and Facebook. These questions and FDA's responses can be found at **WebMD Newsroom: FDA's New Sunscreen Rules - FAQ (http://blogs.webmd.com/breaking-news/2011/06/fdas-new-sunscreen-rules-faq.html)**.

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Related Information

- **Sunscreen Information (/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/ucm239463.htm)**

More in Understanding Over-the-Counter Medicines (/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/default.htm)

Medicines in My Home (MIMH) (/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/ucm092139.htm)

Choosing the right over-the-counter medicine (OTCs) (/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/Choosingtherightover-the-countermedicineOTCs/default.htm)

The Over-the-Counter Medicine Label (/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/TheOver-the-CounterMedicineLabel/default.htm)

Tips For Parents (/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/TipsForParents/default.htm)

Safe Use of Over-the-Counter Pain Relievers and Fever Reducers (/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/SafeUseofOver-the-CounterPainRelieversandFeverReducers/default.htm)

Safe Daily Use of Aspirin (/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/SafeDailyUseofAspirin/default.htm)

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:

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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
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Contains Nonbinding Recommendations

Nonprescription Sunscreen Drug Products — Safety and Effectiveness Data Guidance for Industry[1]

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,[2] 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[3] 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 .[4] A critical step in that process is FDA's review of safety and effectiveness data submitted by the person requesting the GRASE

[1] 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.

[2] 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)).

[3] 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).

[4] 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).

determination (sponsor).[5] 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).[6] 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.[7]

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.[8] 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,[9] 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.

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

[6] See section 586C of the FD&C Act generally for detailed procedures.

[7] 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).

[8] 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)).

[9] This process is described in 21 CFR part 314.

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.[10] This information would also be needed to appropriately characterize the active ingredient in the

[10] 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.

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.[11] 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."[12]

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[13] 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.

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[11] 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).

[12] § 330.10(a)(4)(i).

[13] 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.

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.[14] 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).[15] 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' 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.[16] 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

[14] 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.

[15] *Chronic use* is defined as continuous or intermittent use of a product for at least 6 months during a lifetime.

[16] See section 586B(a)(2) of the FD&C Act.

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).[17] 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.

[17] 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.

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.

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.[18,19]

FDA recommends that SIA sponsors of sunscreen active ingredients provide data from a MUsT to support an adequate assessment of safety.[20] 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),[21] should be included in the study protocol. The protocol should contain sufficient detail for others to reproduce the formulations and manufacturing processes.

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[18] 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/.

[19] 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.

[20] 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).

[21] 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.

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[22] 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

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

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.[23] 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.[24] 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

[23] See the ICH guidance for industry *The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals*.

[24] 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.

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.[25] All carcinogenicity studies—regardless of route—should assess a full panel of tissues.[26]

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.[27] 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.[28]

3. Toxicokinetics[29]

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.

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[25] 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.

[26] 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*.

[27] 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.

[28] See the FDA guidance for industry *Nonclinical Evaluation of Endocrine-Related Drug Toxicity*.

[29] See the ICH guidance for industry *S3A Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies*.

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.[30] 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

[30] See, e.g., 21 CFR 330.14(c)(2)(v).

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.[31] 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)).[32] 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

[31] 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.

[32] 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.

that labeling) is made on a product-specific basis, applying the standard testing methods set forth in those regulations.[33] 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).[34] 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.[35] 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.

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[33] 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*.

[34] See section 586D(e) of the FD&C Act.

[35] 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.

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.[36] 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.

[36] 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).

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.

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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
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Contains Nonbinding Recommendations

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Guidance for Industry

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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).

Nonprescription Sunscreen Drug Products — Format and Content of Data Submissions

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 — Format and Content of Data Submissions

Guidance for Industry

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U.S. Department of Health and Human Services
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Contains Nonbinding Recommendations

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Nonprescription Sunscreen Drug Products — Format and Content of Data Submissions
Guidance for Industry[1]

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 listed on the title page.

I. INTRODUCTION

This guidance addresses the current thinking of the Food and Drug Administration (FDA or Agency) on the format and content of information provided to support a request submitted under section 586A (586A request) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360fff-1), as amended by the Sunscreen Innovation Act (SIA) (21 U.S.C. Ch. 9 Sub. 5 Part I, enacted November 26, 2014), or in support of a *pending request*, as defined under section 586(6) of the FD&C Act (21 U.S.C. 360fff(6)).[2] The requests addressed in this guidance seek a determination from FDA of whether an over-the-counter (OTC or nonprescription) sunscreen active ingredient,[3] or a combination of nonprescription sunscreen active ingredients, is generally recognized as safe and effective (GRASE) for use under specified conditions and should be included in the OTC sunscreen drug monograph.[4] The GRASE determination is primarily based on FDA's review of safety and effectiveness data and other information submitted by the request's sponsor (GRASE data submission) but also on information and comments submitted to

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

[2] The SIA defines a *pending request* to mean a request for a nonprescription sunscreen active ingredient to be included in the over-the-counter monograph that was originally submitted as a Time and Extent Application under 21 CFR 330.14 and that was determined to be eligible for review and for which safety and effectiveness data were submitted prior to the enactment of the SIA (section 586(6) of the FD&C Act).

[3] As defined in the SIA, *sunscreen* means a drug containing one or more sunscreen active ingredients (section 586(9) of the FD&C Act), and the term *sunscreen active ingredient* means an active ingredient that is intended for application to the skin of humans for purposes of absorbing, reflecting, or scattering ultraviolet radiation (section 586(10) of the FD&C Act).

[4] See section 586(4) of the FD&C Act (21 U.S.C. 360fff-1) (definition of "GRASE determination"). Under the SIA, FDA must also make an initial determination of whether a nonprescription sunscreen ingredient or combination of sunscreen ingredients that is the subject of a 586A request has been marketed for a material time and to a material extent and thus whether that ingredient or combination of sunscreen ingredients is eligible for review under the SIA (section 586B(a) of the FD&C Act (21 U.S.C. 360fff-2(a))).

the public docket by other interested parties.[5] Before that review may begin, however, FDA must review the GRASE data submission for completeness and determine whether to file or refuse to file it for substantive review (filing determination). If the submission is not sufficiently complete to enable us to conduct a substantive GRASE review, including being formatted in a manner that will enable us to evaluate its completeness, we will refuse to file the submission.[6]

We are issuing this guidance as directed by the SIA, which calls for FDA to publish a draft and final guidance on the format and content of information submitted by a sponsor in support of a 586A request or a pending request. The recommendations in this guidance will help sponsors prepare GRASE data submissions for 586A requests that are sufficiently complete to be filed for substantive review,[7] as well as help guide FDA's filing determinations. Only data submissions provided by a sponsor are subject to a filing determination as described in this guidance, and we anticipate that information provided by other interested parties will supplement the sponsor's data submission rather than duplicate the full extent of a complete data submission as described in this guidance. However, we encourage other interested parties to follow the recommendations in this guidance to the extent that they are applicable to a given submission. We anticipate that the advice in this guidance will also be useful to persons who are preparing safety and effectiveness data submissions for review by FDA in other regulatory proceedings whose purpose is to determine whether particular nonprescription drug active ingredients or other OTC conditions are GRASE and therefore may be included in an applicable OTC monograph (such as in a future non-sunscreen Time and Extent Application (TEA) or in response to a request for additional data in an ongoing SIA proceeding).

Section II of this guidance provides background information on the sunscreen OTC monograph process and the new procedures governing GRASE determinations under the SIA (the SIA process). Section II also summarizes the filing determination process for GRASE data submissions and describes what sponsors can do if FDA refuses to file a GRASE data submission. Section III describes FDA's current thinking on the recommended format and content of a GRASE data submission that will be considered complete and therefore fileable for substantive review.

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.

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[5] Section 586B(b)(1) of the FD&C Act. An SIA *sponsor* is a person who has submitted a 586A request, a pending request, or any other application subject to the SIA (section 586(8) of the FD&C Act).

[6] Section 586B(b)(2) of the FD&C Act.

[7] The recommendations in this guidance are primarily pertinent to future 586A requests because initial GRASE data submissions for all pending requests were received before the SIA was enacted and did not require filing determinations when submitted. However, any pending request is now subject to proposed sunscreen orders that identify additional safety and effectiveness data needed to support a final GRASE determination. We recommend that any future data submissions regarding the eight pending requests follow the format and content recommendations outlined in this guidance to the extent practicable.

II. BACKGROUND

A. Regulation of Sunscreen Products[8]

All sunscreens are regulated as drugs in the United States under one of two processes:

- The new drug approval process described in part 314 (21 CFR part 314)
- The OTC drug monograph process (also known as the OTC Drug Review) described in part 330 (21 CFR part 330), as supplemented by the SIA

Products regulated under the new drug approval process may not be marketed without FDA's prior review and approval of either a new drug application (NDA) or abbreviated new drug application (ANDA) for each product. Products marketed under the OTC drug monograph process are not individually reviewed and approved prior to marketing. Instead, the OTC drug monograph process categorizes drugs by therapeutic categories, such as sunscreens. For each category, the monograph establishes conditions under which any drug that satisfies those conditions and FDA's general regulations for OTC drugs is considered to be GRASE and not misbranded when used under the conditions prescribed, recommended, or suggested in labeling.[9]

Initially, active ingredients that were not used in sunscreens in the United States prior to the inception of the OTC Drug Review were not eligible for the OTC Drug Review. FDA considered a drug that was ineligible for inclusion in the OTC monograph system to be subject to the new drug approval process.

In 2002, before the SIA was enacted, FDA published the TEA regulation in § 330.14(c). This TEA regulation established a process through which any person could request that an active ingredient or other OTC drug condition, including one not previously marketed in the United States before the inception of the OTC Drug Review, be added to an existing OTC drug monograph.

Now, for OTC sunscreens, the SIA process supplements the TEA regulation. The SIA amended the FD&C Act in part by providing new procedures for establishing that nonprescription sunscreen active ingredients or combinations of nonprescription sunscreen active ingredients are GRASE and not misbranded when used under the conditions specified in a final sunscreen order.[10] Active ingredients that are determined to be GRASE in a final sunscreen order may be

[8] We have previously published *Federal Register* notices about rulemaking actions for OTC sunscreen monograph products and about actions taken under the SIA. Information about these rulemaking actions can be found on our Status of OTC Rulemakings Web site (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/default.htm) and on our Sunscreens Web site (http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/ucm239463.htm).

[9] Part 330.

[10] Section 586C of the FD&C Act (21 U.S.C. 360fff-3).

used in U.S.-marketed sunscreens without first obtaining an approved NDA or ANDA. Because the monograph and SIA processes are public, anyone, not just the sponsor who originated the request, may submit data during public comment periods.

As with the TEA process, the SIA process calls for an initial eligibility determination,[11] followed by submissions of safety and effectiveness data, and a GRASE determination phase. However, the SIA process also requires FDA to make a filing determination as described in this guidance, and to make proposed and final GRASE determinations in the form of administrative orders rather than the rulemaking required by the TEA regulation. The SIA process also establishes strict timelines for the necessary administrative actions.

B. FDA's Filing Determinations and Refusal to File a Request

The SIA requires FDA to conduct an initial filing review to determine whether a sponsor's submission of safety and effectiveness data and other relevant information to support a 586A request for a sunscreen active ingredient is sufficiently complete to enable us to conduct a substantive GRASE review (including being organized so that we can determine its completeness).[12] The initial filing review will help conserve FDA resources and streamline the GRASE review for nonprescription sunscreen active ingredients by making the start of the GRASE review contingent on a determination that the submission is sufficiently complete to support a GRASE substantive review. As a result, it is the date of filing by FDA, and not the date when the submission was submitted to or received by FDA, that triggers FDA's statutory time frame for completing the GRASE determination and issuing a proposed sunscreen order (which in turn triggers various other action dates under the SIA).[13]

No later than 60 days after receiving a sponsor's GRASE data submission, FDA must take one of the following two sets of actions:

- If FDA determines that the submission is sufficiently complete, FDA will file the sponsor's 586A request, notify the sponsor in writing that the request has been filed, and make the notification publicly available.[14]

- If FDA determines that the submission is not sufficiently complete, FDA will refuse to file the sponsor's 586A request and GRASE data submission, notify the sponsor in writing of the determination to refuse to file the request, and make the notification

[11] Section 586B(a) of the FD&C Act.

[12] We note that section 586F(a)(1)(B) of the FD&C Act (21 U.S.C. 360fff-6) provides the possibility that sponsors of non-sunscreen TEAs submitted prior to enactment of the SIA may choose a review framework that would incorporate "an initial filing review under the processes and procedures described in section 586B(b)." FDA expects to conduct initial filing reviews for such applications in the same manner as 586A requests for sunscreen active ingredients.

[13] Section 586C(a)(1) of the FD&C Act.

[14] Section 586B(b)(2)(A) of the FD&C Act.

publicly available. The notification will explain the reasons for the refusal, including why the GRASE submission was not sufficiently complete.[15]

If FDA refuses to file the sponsor's request, the sponsor may, within 30 days of receipt of the notification, request in writing a meeting with FDA to discuss the refusal to file.[16] The sponsor may also submit additional data or other information to FDA. If the sponsor requests a meeting, FDA will convene that meeting within 30 days of the meeting request.[17] Following such a meeting, FDA may file the 586A request within 60 days after the meeting date, the sponsor may submit additional data or other information, or the sponsor may, within 120 days after the meeting, direct FDA to file the request over protest with or without amendments to correct any deficiencies in the request.[18] If the sponsor submits additional data or other information (before, after, or in the absence of a meeting), FDA must reconsider its initial refusal to file, along with this additional information, and make a new filing determination within 60 days of the data submission.[19] If, after a meeting, the sponsor elects to have FDA file the request, FDA will file the request over protest within 30 days of the sponsor's election, notify the sponsor in writing that the request has been filed, and make such notification public.[20]

C. Scope of This Guidance

This guidance describes our current thinking on the format and content of a complete and fileable request under the SIA. The recommendations in this guidance will provide advice to sponsors on how to prepare a successful GRASE submission, as well as guide FDA's filing determinations.

As noted in section II.B above, the "refusal to file" provision in the SIA applies only to GRASE data submissions made by sponsors to support 586A requests.[21] However, we anticipate that the advice in this guidance will also be useful to persons who are preparing safety and effectiveness data submissions for review by FDA in other regulatory proceedings whose purpose is to determine whether particular nonprescription drug active ingredients or other OTC conditions are GRASE and therefore may be included in an applicable OTC monograph (such as a future non-sunscreen TEA request or a request for additional data in an ongoing monograph or SIA proceeding).

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[15] Section 586B(b)(2)(B) of the FD&C Act.

[16] Section 586B(b)(3) of the FD&C Act.

[17] Section 586B(b)(3)(B) of the FD&C Act.

[18] Section 586B(b)(3).

[19] Section 586B(b)(3)(C) of the FD&C Act.

[20] Section 586B(b)(3)(B)(ii)((III) of the FD&C Act.

[21] As previously noted, non-sponsors also may submit partial or supplemental information and views to the applicable public docket (such as scientific articles, professional opinions, or statements from public advocacy groups). Although such submissions are not subject to filing review, we recommend that interested parties consult the recommendations in this draft guidance to the extent that they are applicable to a given submission.

This guidance does not detail the specific clinical and nonclinical studies and other data that should be submitted to support a GRASE determination for a nonprescription sunscreen active ingredient. Instead, this guidance broadly identifies the key structural elements, topics to be addressed, and recommended organization of a complete and fileable request, including a GRASE data submission. For the Agency's current thinking on the specific scientific testing and data recommended to support GRASE determinations for sunscreen active ingredients, see the FDA guidance for industry *Nonprescription Sunscreen Products--Safety and Effectiveness Data* (Safety and Effectiveness Data Guidance).[22] Sponsors are encouraged to read that guidance document and meet with FDA before preparing and submitting a GRASE data submission.

D. Related Guidance

In addition to this guidance, the SIA directs FDA to issue draft and final guidance documents on three other topics.[23] These topics include:

- The data required to meet the safety and effectiveness standard for determining whether a nonprescription sunscreen active ingredient is GRASE and not misbranded (Safety and Effectiveness Data Guidance)

- The process for withdrawing a 586A request or a pending request

- The process by which FDA will carry out section 586C(c) of the FD&C Act (21 U.S.C. 360fff-3), as amended by the SIA, including the process for requesting an advisory committee meeting, the circumstances that limit the number and frequency of advisory committee meetings that FDA is required to convene, and the number of requests to be considered per advisory committee meeting

FDA has issued guidances on these three topics. As they become available, guidances are posted on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

III. CHARACTERISTICS OF A COMPLETE GRASE DATA SUBMISSION

A. General Recommendations

FDA will refuse to file 586A requests for which the data and other information submitted are not sufficiently complete. GRASE data submissions that are materially incomplete or inadequately formatted do not permit FDA to conduct a substantive review. A complete submission by the sponsor should generally have the following characteristics:

[22] 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.

[23] Section 586D(a)(1)(A) & (B) of the FD&C Act (21 U.S.C. 360fff-4(a)(1)(A) & (B)).

1. A separate submission should be provided for each active ingredient that is the subject of a 586A request.

2. All data and information relevant to the requested GRASE determination should be provided in a single submission. A complete GRASE submission should include all of the data on which the sponsor intends to rely.[24]

3. If the sponsor wants FDA to consider data or information previously provided to FDA (such as data submitted to an NDA or ANDA, to the OTC sunscreen monograph proceeding, to another SIA docket, or in a citizen petition), the submission should identify the prior submission, submission date, and docket number (if applicable) and provide a complete copy of the previously submitted information.

4. If the submission refers to a literature search or searches, the submission should identify the databases included in each search, the date of the search, and the search terms used. The submission should include complete copies of scientific articles or other published materials that the sponsor wishes FDA to consider as part of its review. Each literature search should be placed (by subject) in the appropriate section of the submission, as described in section III.B of this guidance. Copies of scientific articles and other published materials should also be placed in the relevant sections by subject.

5. For electronic submissions, all items in reference lists and all in-text references citing scientific articles or other published materials should include a hyperlink to a full copy of the referenced article or other published material. If the submission is not electronic, each item in the reference list and all in-text references should provide specific location data for the full copy of the referenced material.

6. The submission should be in the English language. If any portion of a submission is in a foreign language, the sponsor should provide a complete and accurate English translation.

7. The SIA requires that any information included in a GRASE data submission that the sponsor considers to be confidential must be identified by the sponsor at the time of the submission.[25] However, the sponsor might consider not including in the submission any information that is clearly not relevant to the determination to be made, such as personal privacy information (e.g., the names of lower-level employees).

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[24] The recommendations in this guidance are primarily directed to sponsors who are preparing a complete safety and effectiveness data submission. After such a submission has been made, sponsors should limit any further (supplemental) submissions to important, newly acquired data (such as safety data or results of newly completed or newly published studies). A supplemental submission should both identify the original submission and the original submission date and include a label identifying the submission as a supplement.

Depending on the volume and complexity of a supplemental submission and when it is submitted, it may be difficult or impossible for FDA to conduct a thorough scientific review within the stringent timelines prescribed by the SIA. Nonetheless, FDA encourages the submission of important new adverse safety information at any time during the review process.

[25] Section 586B(b)(4) of the FD&C Act.

8. Safety and effectiveness data that are not available to the public cannot be relied on to support a conclusion that an active ingredient is *generally recognized* as safe and effective. Accordingly, **sponsors should not submit, and FDA generally does not intend to rely on, any evidence of safety and effectiveness that bears a confidential mark** unless the sponsor includes a statement that the information may be released to the public. Similarly, if the submission includes data or information marked as confidential by a third party (such as by a contract research organization or consultant), the sponsor should either include a statement that the sponsor is authorized to make the information publicly available or include an authorization from the third party permitting the information to be publicly disclosed. If a data submission includes studies or other information that were previously submitted to an NDA or ANDA submission without marking them as confidential, FDA intends to presume that the sponsor intends to make such data publicly available.

   To enable a timely filing review, Module 1[26] should include, under the heading "Confidential Information," a statement that all information considered by the sponsor to be confidential has been identified in the data submission, with a description of the method used to designate the information as confidential. All pages should be numbered.

9. FDA encourages electronic submissions.

B. Recommended Organization and Contents

FDA recommends that the GRASE data submission be organized using the general structure and table of contents (TOC) described in the Common Technical Document (CTD) in effect at the time of the submission.[27] The CTD is an internationally harmonized set of specifications for preparing applications relating to new drugs that is maintained by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and has been recommended by FDA in multiple guidance documents. This organized approach will streamline FDA's GRASE review because the CTD format is familiar to and routinely used by FDA's subject matter reviewers, and this approach is sufficiently flexible to accommodate a variety of types and sources of information.

A submission using the electronic CTD (eCTD) TOC should be organized into the following five modules:

1. Administrative Information
2. Summaries
3. Relevant Quality Information
4. Nonclinical Study Data

[26] For more information on Module 1, see section III.B.

[27] Current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidances and FDA guidances use the term *eCTD* (or electronic CTD) rather than *CTD* to reflect the transition to mandatory electronic submissions for regulatory submissions other than the GRASE data submissions addressed in this guidance.

5. Clinical Study Data

The TOC in a GRASE data submission should be detailed, including both major section headings and subheadings. However, **it is neither necessary nor recommended that GRASE data submissions meet the full technical specifications of an eCTD or include all of the information identified in the CTD TOC headings**. Because the eCTD TOC is designed to accommodate *multiple types* of regulatory applications, it contains many headings and subheadings that are not pertinent to the safety and effectiveness of sunscreen active ingredients. Only pertinent information identified in the CTD should be included in a GRASE data submission. However, we recommend that your TOC include all of the major headings from the CTD TOC (using the appropriate heading numbers) and indicate, when appropriate, that no information is being submitted for a given heading.

Whether the submission is electronic or paper, it should include navigation aids. If the submission is electronic, the TOC should include hyperlinks to each section. An electronic document that references another document in the submission should contain hyperlinks to the cross-referenced document or relevant part of the document. If a submission is not electronic, the submission should also be organized using the eCTD TOC. For paper submissions, cross-references to other documents should either point to a unique page number (or numbers) or clearly direct the reviewer to the cross-referenced document.

A complete GRASE data submission based on the eCTD TOC should generally have the following characteristics:

MODULE 1: ADMINISTRATIVE INFORMATION

- Should include any administrative and labeling information
- Should include statements about confidential information recommended in item 7 of section III.A
- Should include a cover letter that identifies the type of submission, the sponsor, the full contact information of the sponsor, the submission date, the active ingredient that is the subject of the submission, and the applicable docket number
- Should include any financial disclosure information, if applicable

MODULE 2: SUMMARIES

- Overall Summary: Should include a concise narrative summary of (1) the evidence supporting a conclusion that the active ingredient is GRASE for the intended nonprescription use and (2) the data that are not supportive of a determination that the active ingredient is GRASE. The summary should clearly identify and address each of the major topics addressed in the submission.

Should also include a summary table listing all studies included in the submission with their corresponding titles (as they appear in the study reports), study numbers, and location in the submission (with hyperlinks to each study if the submission is submitted electronically). There should be one clearly identified study number for each study submitted.

- Overall Quality Summary: Should include a summary of all chemistry and manufacturing data included in the submission.

- Nonclinical Summary: Should include a narrative summary of all nonclinical data included in the submission. This summary should address data that are both supportive and non-supportive of a determination that the ingredient is GRASE.

- Clinical Summary: Should include a narrative summary of all clinical data included in the submission. This summary should address data that are both supportive and non-supportive of a determination that the active ingredient is GRASE.

MODULE 3: QUALITY DATA

- Compendial Status: Should include the compendial status of the active ingredient(s), including the current status of the United States Pharmacopeia (USP) National Formulary (NF) monograph.

- Chemical and/or Manufacturing Characteristics: Should include any known chemical and/or manufacturing characteristics of the active ingredient that may be relevant to FDA's GRASE evaluation. Such characteristics should include both known interactions with other sunscreen active ingredients or commonly used sunscreen vehicle components and information on particle size for micronized or nanoscale active ingredients. Sponsors should also include any aspects of formulation needed to ensure stability or any other characteristics needed to establish conditions under which the active ingredient is GRASE for use in sunscreens.

MODULE 4: NONCLINICAL STUDY REPORTS

This module should include data and reports from the nonclinical studies discussed in the Safety and Effectiveness Data Guidance (for example, dermal and systemic carcinogenicity studies, developmental and reproductive toxicity studies, and animal toxicokinetic studies), as well as data and reports from any other types of nonclinical information (e.g., literature searches, scientific articles, or other published materials). Full copies of all published materials should be provided. The specific ingredient and formulation(s) used in each study should be described in detail.

Each individual study report in the submission should include its own TOC and summary. Complete data sets (not selected or summary data) should be included in the submission. We expect that data from studies provided only in summary form will generally not be considered sufficient evidence that an active ingredient is GRASE.

MODULE 5: CLINICAL STUDY REPORTS

Module 5 should include separate comprehensive integrated summaries of effectiveness and clinical safety. The summary of effectiveness should include the active ingredient's mechanism of action and the specific doses, concentrations, and formulations proposed for use. The summary of clinical safety should include exposure data, and, if available, address safety in specific populations, such as in children, the elderly, and pregnant or lactating women. The summary of clinical safety should also address specific safety issues expected with either the ingredient or its application. For sunscreens, examples of such safety issues could include dermal safety, hypersensitivity, accidental ocular exposure, or inhalational safety. All available effectiveness and safety data, including both supportive data and any data demonstrating potential safety signals, should be submitted.

This module should also include full reports of (1) all clinical effectiveness and safety studies and other clinical data and (2) all clinical pharmacology and human toxicokinetic data. In addition to actual study reports, all other types of clinical data (e.g., from literature searches, scientific articles, or other published materials) should be included in this module. Full copies of all published materials should be provided. Each study report should contain a description of the specific ingredient and formulation(s) used. For literature reports, this information may be included in the relevant summary document.

Human studies that should be included in Module 5 are discussed in the Safety and Effectiveness Data Guidance. These human studies include sun protection factor studies and other effectiveness studies (such as in vitro broad spectrum studies, if performed), human irritation and sensitization studies, human photosafety studies, human absorption studies, and human maximal usage trials.

Module 5 should also include reports of in vitro testing performed by the sponsor in connection with human maximal usage trials to support final formulation safety testing if the active ingredient is determined to be GRASE, as discussed in the Safety and Effectiveness Data Guidance.

Each individual study report in the submission should include its own TOC and summary. Complete data sets (not selected or summary data) should be included in the submission. Generally, we intend not to consider study data provided only in summary form to be sufficient evidence that an active ingredient is GRASE.

Further, postmarketing safety data as discussed in the Safety and Effectiveness Data Guidance should be included in Module 5. For adverse event reports, there should be a TOC with a separate link to each adverse event report. The section on adverse event reports should be organized according to the "System Organ Class" categories in the *Medical Dictionary for Regulatory Activities* MedDRA.[28]

[28] For more information on these categories, see the MedDRA Web site at www.MedDRA.org.

C. Characteristics of an Incomplete Request and GRASE Data Submission That Could Cause FDA to Refuse to File the Request

Some examples of incomplete information or an inadequate organization of GRASE data that may render the GRASE data submission insufficiently complete[29] for review are listed below.[30] These characteristics could cause FDA to refuse to file a GRASE data submission.

1. The submission is unreasonably disorganized—that is, its structure does not permit ready review for completeness because the submission, for example, lacks a recommended TOC that itemizes the submission's elements and data.

2. Electronic submissions cannot be opened or readily navigated (e.g., hyperlinks do not operate).

3. Data tabulations or graphic displays are not interpretable, are inadequately labeled, or do not indicate data sources.

4. Summaries or TOCs do not indicate or link to the location of specific discussions, studies, or other information referenced elsewhere in the submission.

5. The submission is materially incomplete on its face (e.g., it does not include sufficient information for FDA to make a GRASE determination because it fails to include some or all of the information identified in Section III.B of this guidance, unless the sponsor explains the reasons why the missing information is not included and why the active ingredient or other condition should be found to be GRASE in its absence).

6. All or essential portions of the submission are marked as confidential.

D. How and Where to Submit GRASE Data Submissions

GRASE data submissions can be sent (1) in hard copy to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852 or (2) electronically to http://www.regulations.gov using the previously established docket number. In addition, a copy of the cover letter should be sent to the Division of Nonprescription Drug Products, Food and Drug Administration, Bldg. 22, Mail Stop 5411, 10903 New Hampshire Ave., Silver Spring, MD 20993.

[29] See section 586B(b)(2) of the FD&C Act.

[30] Please note that this list is not exhaustive.

Food and Drug Administration

Cosmetic Labeling Guide

The Cosmetics Labeling Guide provides step-by-step help with cosmetic labeling, with examples and answers to questions manufacturers often ask about labeling requirements under U.S. laws and related regulations.

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Laws Regulating Cosmetic Labeling

Federal Food, Drug, and Cosmetic Act of 1938, as amended

To protect consumers from unsafe or deceptively labeled or packaged products by prohibiting the movement in interstate commerce of adulterated or misbranded food, drugs, devices, and cosmetics.

21 U.S.C. 321-392

The cosmetics marketed in the United States, whether they are manufactured here or are imported from abroad, must comply with the labeling requirements of the Federal Food, Drug, and Cosmetic (FD&C) Act, the Fair Packaging and Labeling (FP&L) Act, and the regulations published by the Food and Drug Administration under the Authority of these two laws.

The FD&C Act was enacted by Congress to protect consumers from unsafe or deceptively labeled or packaged products by prohibiting the movement in interstate commerce of adulterated or misbranded food, drug devices and cosmetics.

Fair Packaging and Labeling Act

To ensure that packages and their labels provide consumers with accurate information about the quantity of contents and facilitate value comparisons.

15 U.S.C. 1451-1460

The FP&L Act was passed by Congress to ensure that packages and their labels provide consumers with accurate information about the quantity of contents and facilitate value comparisons.

Federal Food, Drug, and Cosmetic Act

The FD&C Act prohibits the marketing of cosmetics that are adulterated or misbranded as well as their adulteration or misbranding while in interstate commerce.

Sec. 301, FD&C Act

The FD&C Act prohibits the marketing of cosmetics that are adulterated or misbranded as well as their adulteration or misbranding while in interstate commerce.

A cosmetic is considered misbranded if.....

- labeling is false or misleading
- label does not state

    - the name and address of the manufacturer, packer, or distributor
    - the net quantity of contents
- the required information is not stated prominently, with conspicuousness and in terms that it is read and understood by consumers under customary conditions of purchase and use
- the container or its fill is misleading

Sec. 602, FD&C Act

Sec. 602 of the FD&C Act defines the conditions which cause a cosmetic to be deemed misbranded.

Factors Determining Whether Labeling Is Misleading

1. **Representations made or suggested**
2. **Failure to reveal material facts:**
    a. **Material in light of such representations**
    b. **Material with respect to consequences resulting from the intended use**

Sec. 201(n), FD&C Act
21 CFR 1.21

Labeling may be considered misleading not only because a label statement is deceptive but also because a material fact is not revealed on a label.

A fact may be material in light of a statement made on a label or because certain consequences may result from the recommended use of a product.

Legal Definitions of Terms

What is a cosmetic?
A cosmetic is a product, except soap, intended to be applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance.
Sec. 201(i) FD&C Act

As defined in section 201(i) of the FD&C Act, a cosmetic is a product, except soap, intended to be applied to the human body for cleansing, beautifying, promoting attractiveness or altering the appearance.

In short, one may say that a cosmetic is a product intended to exert a physical, and not a physiological, effect on the human body.

The raw materials used as ingredients of cosmetic products are by law also cosmetics.

In section 701.20 of Title 21 of the Code of Federal Regulations [21 CFR 701.20], the Food and Drug Administration (FDA) defines the term "soap" as a product in which the non-volatile portion consists principally of an alkali salt of fatty acids, i.e., the traditional composition of soap; the product is labeled as soap; and the label statements refer only to cleansing. If cosmetic claims, e.g., moisturizing, deodorizing, skin softening etc., are made on a label, the product is a cosmetic. Synthetic detergent bars are also considered cosmetics, although they may be labeled as "soap."

"Intended use" within the meaning of the FD&C Act is determined from its label or labeling.

Senate Report No. 493
73d Cong. 2d Sess. (1934)
U.S. Courts of Appeals Decisions

According to Senate Report No. 493 and court decisions, the term "intended" in the legal definition of the term "cosmetic" or in other definitions means, with respect to the use of a product, its directed or prescribed use as determined from the statements made on a product's label or labeling.

The courts, in deciding whether a product is a "cosmestic", a "drug", or both a "drug" and a "cosmetic", have relied principally on the consumer's perception of the meaning of a label statement and less so on the interpretation of the meaning of a label statement by the labeler or a regulatory agency.

When is a cosmetic also a drug?
A cosmetic is also a drug when it is intended to cleanse, beautify or promote attractiveness as well as treat or prevent disease or otherwise affect the structure or any function of the human body.
Sec. 201(g) and (i), FD&C Act
Sec. 509, FD&C Act

A cosmetic is legally also a drug if it is intended to exert a physical as well as a physiological effect because the FD&C Act defines in section 201(g) the term "drug" to mean, among other things, "articles intended for use in the ... cure, mitigation, treatment, or prevention of disease ... and ... articles ... intended to affect the structure or any function of the body ..."

Section 509 of the FD&C Act provides that the categories of "drug" and "cosmetic" are not mutually exclusive.

What is a consumer commodity?
A product customarily distributed for retail sale for use by consumers or for the performance of services at home and usually consumed during such use.
Sec. 10(a), FP&L Act.

A cosmetic is legally also a drug if it is intended to exert a physical as well as a physiological effect because the FD&C Act defines in section 201(g) the term "drug" to mean, among other things, "articles intended for use in the ... cure, mitigation, treatment, or prevention of disease ... and ... articles ... intended to affect the structure or any function of the body ..."

Section 509 of the FD&C Act provides that the categories of "drug" and "cosmetic" are not mutually exclusive.

Package
A container or wrapping, other than a shipping container or wrapping, in which a consumer commodity is delivered or displayed to retail purchasers.
Sec. 10(b), FP&L Act
21 CFR 1.20

The term package is defined in the Fair Packaging and Labeling Act [sec. 10(b)] and the Code of Federal Regulations [21 CFR 1.20].

Essentially, the "package" is the outer container of a product as, for example, a box or folding carton. However, the "package" can also be the immediate container, e.g., bottle, jar or aerosol can that holds the product if the immediate container is not displayed in a box or folding carton.

Label
A written, printed or graphic display of information...

- **on the container of a cosmetic**

Sec. 201(k), FD&C Act.

- **affixed to or appearing on a package containing a consumer commodity**

Sec. 10(c), FP&L Act
21 CFR 1.3(b)

The term "label" is defined in the FD&C Act and the FP&L Act. The definitions differ in that under the FD&C Act definition a label is "a display of written, printed or graphic matter upon the immediate container," and under the FP&L Act definition "written, printed or graphic matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity."

One may say that the term "label" applies in the first instance to the information appearing directly on the immediate container and in the second instance to information attached to the immediate container and directly on or attached to the outer container if so packaged.

The FD&C Act, however, requires in sec 201(k) that any information required to appear on the label of the immediate container shall also appear on the outside container of the retail package or is legible through the outside container.

Labeling
All labels and other written, printed or graphic material on or accompanying a product in interstate commerce or held for sale
Sec. 201(m), FD&C Act
21 CFR 1.3(a)

The FD&C Act defines in sec. 201(m) "labeling" to mean "all labels and other written, printed or graphic matter on or accompanying such article."

This includes labels, inserts, risers, display packs, leaflets, promotional literature or any other written or printed information distributed with a product.

Principal Display Panel

The part of a label that the consumer sees or examines when displayed for retail sale
Sec. 10(t), FP&L Act
21 CFR 701.10

A label may consist of more than one panel. It may consist of a front panel, side panels and a back panel. Back and side panels are generally called information panels.

The FP&L Act also defines for consumer commodities, or packages containing a consumer commodity, the term "principal display panel," otherwise known for short as PDP.

The "principal display panel" is that part of a panel that is most likely to be shown or examined under customary conditions of display for retail sale. Usually, it is the front panel of the label of the outer package.

Placement and Size of Principal Display Panel

Location
Size
Multiple PDPs

Exceptions

Decorative containers
Compacts or pencils
Containers of 1/4 av. oz. or 1/8 fl. oz. capacity
Display cards

21 CFR 701.10 and 701.13(e)

As mentioned before, the PDP is that part of the label that is most likely to be shown or examined under customary conditions for retail sale.

Regulations [21 CFR 701.10] published by the FDA require that the PDP be large enough to accommodate all required label information with clarity and conspicuousness.

If a package bears more than one PDP, the information required to be placed on the PDP must be duplicated on all PDPs.

For the purpose of assuring uniform type size for declaring a product's net quantity of contents, the size of the surface area bearing the PDP, and not the size of the PDP itself, is the determining factor. The area of the PDP is for a:

Rectangular package: One entire side.

Cylindrical package: 40% of height x circumference.

Any other shape of container: 40% of total container surface, excluding top, bottom, neck, shoulder, flanges.

The PDP of a "boudoir-type" or decorative cosmetic container, e.g., cartridge, pill box, compact or special variety, and those containing 1/4 oz or less may be a tear-away tag or tape affixed to the container [21 CFR 701.13(e)(1)]. It may also be the display panel of a card to which the immediate container is affixed [21 CFR 701.13(e)(2)].

Placement of Information on Labels

Outer Container (Or Label of Single Container Product)

Principal Display Panel	**Information Panels**
Name of product	**Directions for safe use**
Identity	**Warnings**
§ 740.10 warning	**Name and place of business**
Net quantity of contents	**Ingredient declaration**
	Any other required information

The information above must appear on the label of the outer container which usually is a box, folding carton, wrapper etc. holding the inner (immediate) container. The immediate container holding the cosmetic product also is the outer container if it is not displayed in a box, folding carton etc.

Please note that only the label of an outer container has a PDP.

Statement of the brand name of the product is not a regulatory requirement under the FD&C or FP&L Act.

Inner Container (If Packaged in an Outer Container)

Front Panel	Information Panels
	Directions for safe use
	Warnings
Name of Product	Name and Place of Business
	Net Quantity of Contents
	Any Other Required Information

The information above must appear on the label of the inner (immediate) container holding the cosmetic product. The inner container is packaged and displayed in a non-transparent box, folding carton etc. If the outer container is removed and the product displayed for sale without it, the label of the immediate container becomes a label of an outer container.

Form of Stating Required Information

Section 602(c) of the FD&C deems a cosmetic misbranded if any word, statement, or other label or labeling information required by law or regulation is not placed on the label or labeling with such prominence and conspicuousness that it is likely to be read, or if it is not stated in such terms that it is likely to be understood by ordinary individuals.

Prominence and Conspicuousness

Regulations [21 CFR 701.2] published by the FDA offer detailed information on how to comply with the requirement for prominent and conspicuous placement of information on cosmetic labels or labeling.

Panel display: The required information must be on a panel which is presented or displayed under customary conditions of purchase. This eliminates placement of required information on a bottom panel of a cosmetic unless it is very small and customarily picked up by hand where inspected for possible purchase.

Panel Size: The label must be large enough to provide sufficient space for prominent display of the required information.

Style and Size of Letters: The type must be of such size, and at least of the required minimum size, and of such style that the required label statements are easily readable.

Background Contrast: The contrast must be sufficient to make the required label statements conspicuous and easily readable.

Obscuring Designs, Vignettes: The required statements must not be obscured by vignettes or other designs or by crowding with other printed or graphic matter.

21 CFR 701.2

Language

English Language Statements: All label or labeling statements required by law or regulation must be in the English language. Products distributed solely in Puerto Rico or a Territory where the predominant language is one other than English, may state the required label information in the predominant language in place of English.

Foreign Language Statements: If the label contains any foreign language representation, all statements required by regulation must also appear on the label in the foreign language. If labeling bears foreign language representations, the required statements must appear on the label or other labeling as required in English.

21 CFR 701.2(b)

Type Size

Ingredients: 1/16", 1/32" (Labeling surface, less than 12 sq. in.)

Net Contents:

- **1/16" (PDP less than 5 sq. in.)**
- **1/8" (PDP 5-25 sq. in.)**
- **3/16" (PDP 25-100 sq. in.)**

Warning: 1/16"

All Others: Reasonably related to panel size

21 CFR 701.2(a) (b), 701.3(b),
701.11(c), 701.13(i), 740.2(b)

Ingredient Declaration: Generally, in letters not less than 1/16" in height [21 CFR 701.3(b)]. If surface area available to bear label (excludes surfaces with decorative relief, sculptured surfaces) is less than 12 square inches, letter height may be not less than 1/32" [21 CFR 701.3(p)].

Net Contents Declaration on PDP: Minimum letter height determined by the **area** of the PDP. In the case of "boudoir-type" containers, including decorative cosmetic containers of the cartridge, pill box, compact or pencil type, and cosmetics of 1/4 oz. or less capacity, the type size is determined by the total dimensions of the container. If the container is mounted on a display card, the display panel determines the letter height [21 CFR 701.13(e) and (i)].

Warning Statements: Type size no less than 1/16" unless smaller size established by regulation [21 CFR 740.2].

Letter Height: The lower case letter "o" or equivalent when upper and lower case letters are used [21 CFR 701.13(h)].

Identity Labeling

Common or usual name
Descriptive name
Fanciful name
Illustration
Prominence
Placement

Sec. 10(t), FP&L Act
21 CFR 701.11

Sec. 4 of the FP&L Act [21 U.S.C. 14554] requires that a consumer commodity bear a statement of identity. Regulations [21 CFR 701.11] published by the FDA require that the identity statement appear on the PDP.

The identity of the commodity may be expressed in terms of the common or usual name of the cosmetic, a descriptive name, or when the nature of the cosmetic is obvious, a fanciful name. It may also be expressed in form of an illustration.

The identity statement must be in bold type and in a size reasonably related to the most prominent printed matter, which is usually the name of the cosmetic. It must be in lines generally parallel to the base on which the product rests when displayed at retail.

Name and Place of Business

Corporate name
Manufactured for...
Distributed by...
Address
Principal place of business

21 CFR 701.12

The name and business address appearing on the label may be those of the manufacturer, packer or distributor.

If the name and address is not that of the manufacturer, the name must be preceded by phrases such as "Manufactured for ...", "Distributed by ...", or other appropriate wording.

The name of the firm must be the corporate name, and the address may be that of the principal place of business. Stating also the name of a corporation's particular division is optional.

The business address must include the street address, name of the city and state, and the ZIP code. The street address may be omitted if the firm is listed in a current city or telephone directory.

The Tariff Act of 1930 requires that imported products state on the label the English Name of the country of origin.

Net Quantity of Contents Declaration

- **Location on Package**
  On PDP
  On information panel
  § 701.13 (e) and (f)(2)

- **Prominence**
  Placement
  Spacing
  § 701.13 (f) and (f)(1)

- **Conspicuousness**
  Contract
  Letter height
  Aspect ration
  Type size
  § 701.13 (h) and (i)

Location: If the cosmetic is sold at retail in an outer container, the net contents statement must appear (1) within the bottom 30% of the PDP of the outer container, generally parallel in line to the base on which the package rests, and (2) on an information panel of the inner container. The bottom location requirement is waived for PDPs of 5 square inches or less.

The PDP may be a tear-away tag or tape affixed to a decorative container or to a container of less than 1/4 oz., or it may be the panel of a display card to which the container is affixed.

Prominence: The declaration must be a distinct item, separated from other printed matter by a space equal to at least the height of the lettering used in the declaration and twice the width of the letter "N".

Conspicuousness: The print must be easily legible bold face type in distinct contract to background and other matter on the package. The letter height must be at least that of the lower case letter "o", and the aspect ratio of height to width must not exceed 3:1.

The type size, as determined by the **area** of the PDP must be at least 1/16 in. if PDP area $\leq$ 5 sq. in., 1/8 in. if PDP area > 5 to $\leq$ 25 sq. In., 3/16 in. if PDP area > 25 to $\leq$ 100 sq. in., and 1/4 in. if PDP area > 100 sq. in.

Exemptions from Net Contents Declaration

Cosmetics of less than 1/4 av. oz. or 1/8 fl. oz.

- **On display card**
- **In outer container**

21 CFR 1.24

Cosmetics in packages containing less than 1/4 av. oz. or 1/8 fl. oz. are exempt from the net quantity of contents declaration if affixed to a properly labeled display card or sold at retail in a properly labeled outer container [21 CFR 1.24].

When a cosmetic is required to bear net quantity of contents declarations on the inner and outer container, the declaration on the outer container must appear on the PDP; on the inner container, it may appear on an information panel other than the panel bearing the name of the product, i.e., the front panel.

Quantity of Contents

- Accuracy§ 701.13 (g) and (s)
- Declaration by Product Consistency§ 701.13 (a)
- Systems of Measures and Weights§ 701.13(b) and (r)
- Unit Terms and Abbreviations§ 701.13 (j) (2) & (n)
- Dual Form of Declaration701.13 (j) (1)
- Declaration of Fraction§ 701.13 (d)

Examples of Net Quantity Statements

"Net Wt. 6 Oz." or "6 oz. Net Wt."
"Net Contents 6 fl. Oz." or "Net 6 Fl. Oz." or "6 Fl. Oz."
"Net Wt. 1/4 Oz." or "Net Wt. 0.25 Oz."

"Net 1/8 Fl. Oz." or "0.12 FL. Oz."
"Net Wt. 24 Oz. (1-1/2 Lbet" or "Net Wt. 24 Oz. (1.5 Lb.)
"Net 56 Fl. Oz. (1 Qt. 1 Pt. 8 Fl. Oz.)" or "... (1 Qt. 1-1/2 Pt.)" or "... (1 Qt. 1.5 Pt.)"

Accuracy: The net quantity of contents (net contents) declaration must accurately reveal the quantity of cosmetic in the container in terms of weight, volume, measure, numerical count, or combinations of count and weight, volume or measure. Reasonable variations due to loss or gain of moisture, or deviations in good manufacturing practice, are acceptable. In case of an aerosol product, the net contents statement must express the net quantity of contents expelled.

Product Consistency: Unless there is a firmly established, general consumer usage or trade custom to the contrary, the statement must be in terms of fluid measure if the cosmetic is liquid and in terms of weight if the cosmetic is solid, semi-solid, viscous, or a mixture of solid and liquid. Fluid measures must express the volume at 68°F (20°C). The customary net contents declaration for aerosol products is in terms of weight.

Systems: Weight is expressed in terms of avoirdupois pound and ounce. Fluid measures are expressed in terms of the U.S. gallon, quart, pint and fluid ounce. Net contents may additionally be stated also in the metric system.

Unit Terms: The term "net weight" or "net wt." must be used in conjunction with a weight statement, and the term "net contents," "net" or nothing must be used in connection with a liquid statement.

Additional abbreviations are for: weight - wt., fluid - fl., gallon - gal., quart - qt., pint - pt., ounce - oz., pound - lb.

In case of a weight ounce statement, the term "oz." is sufficient. A fluid ounce is expressed as "fl. oz."

Examples:

- Net wt. 4 av. oz.
- Net contents 4 fl. oz.
- 4 av. oz. net wt.
- 4 oz. net wt.
- Net 4 fl. oz.
- 4 fl. oz.

Dual Declaration: If the net weight exceeds one pound but is less than 4 pounds, the net contents statement must reveal the total number of ounces followed, in parenthesis, by the number of pounds and ounces or by the number of pounds and fraction thereof. Fluid measures exceeding one pint, but being less than one gallon, must be expressed in terms of the total number of fluid ounces followed, in parenthesis, by the number of quarts, pints and ounces or by the fractions of the quart or pint.

Examples:

- Net Wt. 24 oz. (1 lb. 8 oz.)
- Net Wt. 24 oz. (1 - 1/2 lb.)
- Net Wt. 24 oz. (1.5 lb.)
- 56 fl. oz. (1 qt. 1 pt. 8 fl. oz.)
- 56 fl. oz. (1 qt. 1-1/2 pt.)
- 56 fl. oz. (1 qt. 1.5 pt.)
- 56 fl. oz. (1-3/4 qt.)

Declaration of fractions: Fractions may be expressed in terms of common fractions ranging from 1/2 to 1/32 or as decimal fractions of no more than two significant numbers.

Quantity of Contents on Principal Display Panel

"Economy Size" or "Budget Size"
"Giant Pint" or "Full Quart"
"Net 6 Fl. Oz." and "Six Applications"
"Net 6 Fl. Oz." and "6 Bottles of 1 Fl. Oz. Each"

Quantity of Contents on Information Panel

Any non-deceptive supplemental statement

21 CFR 1.31 and 701.13 (g)

Economy Size: Representations of this type are permitted if the firm offers at least one other packaged size of the same brand, only one is labeled "economy size," and the unit price of the package so labeled is substantially (at least 5%) reduced compared to that of the other package.

Giant Pint, Full Quart: Supplemental statements describing the net quantity of contents are permitted on panels other than the PDP. However, these statements must not be deceptive or exaggerate the amount present in the package.

Six Applications: Declarations by numerical count or linear or area measure may be augmented by statements of weight or size of individual units or total weight or measure to give accurate information. These are not regarded as separate statements and must appear on the PDP.

Cosmetic Kit: If a package contains the integral components making up a kit and delivers the components in the manner of an application as, for example, a home permanent wave kit, the net contents declaration may be stated in terms of the number of applications as per given instructions [21 CFR 701.13 (g) (2)].

Cosmetic Warning Statements

General Requirement:
Prominence

- Placement
- Spacing

Conspicuousness

- Contrast
- Type size

21 CFR 740 (1) and (2)

Regulations require that "[the label of a cosmetic product shall bear a warning statement whenever necessary or appropriate to prevent a health hazard that may be associated with the product" [21 CFR 740(1)]. A cosmetic not bearing a necessary warning statement may be considered misbranded under sec. 602(a) of the FD&C Act because it fails to reveal a fact "material ... with respect to consequences which may result from the use of the article" [sec 201(n), FD&C Act].

Prominence: A warning statement must appear on the label prominently and conspicuously as compared to other words, statements or designs so that it is likely to be read by ordinary consumers at the time of purchase and use.

Conspicuousness: The lettering must be in bold type on contrasting background and may in no case be less than 1/16 inch in height.

Cosmetics with Unsubstantiated Safety

***Warning*--The safety of this product has not been determined.**

21 CFR 740.10

A cosmetic is considered misbranded if its safety has not adequately been substantiated, and it does not bear the following conspicuous statement on the PDP:

Warning - The safety of this product has not been determined.

The safety of a cosmetic may be considered adequately substantiated if experts qualified by scientific training and experience can reasonably conclude from the available toxicological and other test data, chemical composition, and other pertinent information that the product is not

injurious to consumers under conditions of customary use and reasonably foreseeable conditions of misuse.

The safety of a cosmetic can adequately be substantiated by:

a. Reliance on available toxicological test data on its ingredients and on similar products, and
b. Performance of additional toxicological and other testing appropriate in the light of the existing data.

Even if the safety of each ingredient has been substantiated, there usually still is at least some toxicological testing needed with the formulated product to assure adequate safety substantiation.

Cosmetic Aerosols

***Warning*--Avoid spraying in eyes. Contents under pressure. Do not puncture or incinerate. Do not store at temperature above 120°F. Keep out of reach of children.**

21 CFR 740.11 (a)

The label of a cosmetic packaged in a self-pressurized container and intended to be expelled from the package under pressure must bear the warning stated below.

The words "Avoid spraying in eyes" may be omitted if the product is not expelled as a spray. Example: Aerosol shave cream.

The word "puncture" may be replaced by the word "break" if the product is packaged in a glass container.

If the product is intended for use by children, the phrase "except under adult supervision" may be added at the end of the last sentence of the warning.

***Warning*--Use only as directed. Intentional misues by deliberately concentrating and inhaling the contents can be harmful or fatal.**

21 CFR 740.11 (b)

If the propellant of a cosmetic packaged in a self-pressurized container consists in whole or in part of a halocarbon or hydrocarbon, the label must bear a second warning as stated below.

This second warning is not required for the following products:

1.Aerosol foam or cream products containing less than 10% propellant.
2.Products which do not expel the propellant at the time of use. Examples: products with built-in piston barrier or propellant bag.

3.Metered spray products of less than 2 oz. net contents.
4.Aerosol products of less than 1/2 oz. net contents.

Feminine Deodorant Sprays

***Caution*--For external use only. Spray at least 8 inches from skin. Do not apply to broken, irritated, or itching skin. Persistent, unusual odor or discharge may indicate conditions for which a physician should be consulted. Discontinue use immediately if rash, irritation, or discomfort develops.**

21 CFR 740.12

A feminine deodorant spray which, for the purpose of this regulation, is defined as "any spray deodorant product whose labeling represents or suggests that the product is for use in the female genital area or for use all over the body" must bear the caution stated below.

If the expelled product does not contain a liquefied halocarbon or hydrocarbon propellant, the sentence "Spray at least 8 inches from skin" may be omitted.

The regulation further states that the use of the word "hygiene" or "hygienic" or similar words renders any such product misbranded.

Foaming Detergent Bath Products

***Caution*--Use only as directed. Excessive use of prolonged exposure may cause irritation to skin and urinary tract. Discontinue use if rash, redness or itching occurs. Consult your physician if irritation persists. Keep out of reach of children.**

21 CFR 740.17

A foaming detergent bath product--also known as bubble bath product--is, for the purpose of this regulation, defined as "any product intended to be added to a bath for the purpose of producing foam that contains a surface-active agent serving as a detergent or foaming ingredient."

The caution stated above is required on the label of any foaming detergent bath product which is not clearly labeled as intended for use exclusively by adults. The following are two examples of label statements identifying a product as intended for use exclusively by adults: "Keep out of reach of children" and "For adult use only."

If the bubble bath product is intended for use by children, the phrase "Keep out of reach of children" may be expanded to further read "except under adult supervision."

The regulation further requires that the label "Shall bear adequate directions for safe use" of the product.

Cosmetic Ingredient Labeling

Declaration of ingredients except flavor, fragrance, and trade secret ingredients in descending order of predominance

21 CFR 701.3

Cosmetic ingredient labeling became an issue in the early 1970s. Guidelines for ingredient labeling were published in mid-1972. Regulations were proposed in early 1973. After publication of two final regulations, stays of final regulations, terminations of stays, and lengthy court proceedings challenging the legality of the published regulations, the requirement for cosmetic ingredient labeling became fully effective in early 1977.

The regulations requiring the declaration of cosmetic ingredients were published under the authority of the FP&L Act [secs. 5(c) and 6(a); 15 U.S.C. 1454 and 1455] and FD&C Act [sec. 701(e); 21 U.S.C. 371(e)].

Since the FP&L Act applies only to consumer commodities and their packages as defined in the Act, cosmetic ingredient declarations are required only on the label of the outer container of cosmetics customarily sold at retail or used in the performance of services conducted within the households. It does not apply, for example, to products used at professional establishments or samples distributed free of charge, unless such products are customarily also sold at retail, even if they were labeled "For professional use only."

The ingredients must be declared in descending order of predominance. Exceptions to this requirement are discussed later.

Prominence of Ingredient Declaration

Prominent and conspicuous to render it easy to be read and understood by ordinary individuals under normal conditions of purchase

Letter Height	**1/16 inch**
Exception: If total available labeling surface area is less than 12 sq. in.	**1/32 inch**
Information panel	
Firmly affixed tag, tape, or card	

21 CFR 701.3(b) and (p)

The ingredient declaration may appear on any information panel of the package which is the outer container in form of a folding carton, box, wrapper etc. if the immediate container is so packaged, or which is the jar, bottle, box etc. if the immediate container is **not** packaged in an

outer container. It may also appear on a tag, tape or card firmly affixed to a decorative or small size container.

Prominence: The declaration must appear with prominence and conspicuousness so that it is likely to be read and understood (read with ease) by ordinary individuals under normal conditions of purchase. The letters must not be obscured by design, vignettes, background or crowding.

Type Size: Not less than 1/16 inch in height. It may be not less than 1/32 inch in height if the total surface area available to bear labeling (which excludes bottom, shoulder, neck, flange, decorative or sculptured surfaces) is less than 12 square inches.

The type size consisting of upper and lower case letters is determined by the height of the lower case letter "o".

The ingredient declaration may appear on any information panel of the package which is the outer container in form of a folding carton, box, wrapper etc. if the immediate container is so packaged, or which is the jar, bottle, box etc. if the immediate container is **not** packaged in an outer container. It may also appear on a tag, tape or card firmly affixed to a decorative or small size container.

Prominence: The declaration must appear with prominence and conspicuousness so that it is likely to be read and understood (read with ease) by ordinary individuals under normal conditions of purchase. The letters must not be obscured by design, vignettes, background or crowding.

Type Size: Not less than 1/16 inch in height. It may be not less than 1/32 inch in height if the total surface area available to bear labeling (which excludes bottom, shoulder, neck, flange, decorative or sculptured surfaces) is less than 12 square inches.

The type size consisting of upper and lower case letters is determined by the height of the lower case letter "o".

Identification of Ingredients by Name

1. **The name established by the commissioner as specified in § 701.30.**
2. **The name adopted for the ingredient as listed in:**
   (a) CTFA Cosmetic Ingredient Dictionary
   (b) United States Pharmacopeia
   (c) National Formulary
   (d) Food Chemical Codex
   (e) USAN and the USP Dictionary of Drug Names
3. **The name generally recognized by consumers**
4. **The chemical or technical name or description**

21 CFR 701.3(c)

Section 701.3(c) requires that an ingredient be identified by the name established by the Commissioner for the purpose of cosmetic ingredient labeling or, in the absence of a name established by the Commissioner, the name adopted for that ingredient in the editions and supplements of the compendia listed below.

The Commissioner may establish a name as petitioned or propose such a name on his own initiative. See section 701.3(e). The names specified by the Commissioner are listed in section 701.30.

The currently recognized edition of the CTFA (Cosmetic, Toiletry and Fragrance Association, Inc.) Cosmetic Ingredient Dictionary is the second edition published in 1977. This edition is recognized only in part, i.e., not all names listed in the second edition have been adopted.

The third edition of the CTFA Cosmetic Ingredient Dictionary published in 1982 and the Supplement published in 1985 have not yet been recognized. However, FDA has informed the CTFA that the agency will not take regulatory action against products labeled in accordance with these editions while their review is in progress.

The compendia are listed in the descending order by which they must be utilized for identification of an ingredient name. If none lists a name for an ingredient, the name generally recognized by consumers, or the chemical or technical name or description, must be used.

Order of Ingredient Declaration

Descending Order of Predominance

Exceptions...
Active drug ingredients
Ingredients with less than 1% concentration
Color additives
"And other ingredients"

21 CFR 701.3(a), (d), (f) (2), (f) (3)

The ingredients must be listed in descending order of predominance. However, there are a few exceptions to this requirement.

> 1. If the cosmetic is also a drug, section 502(c) of the FD&C Act requires that the active drug ingredient(s) be declared before declaration of the cosmetic ingredients. A declaration, thus, would read as follows: "Active Ingredient: ... (Name of drug ingredient). Other (or Cosmetic) Ingredients: ... (Names of cosmetic ingredients in descending order)." [§ 701.3(d)]

2. Ingredients present at a concentration not exceeding 1% may be listed in any order after the listing of the ingredients present at more than 1% in descending order of predominance. [§ 701.3(f)(2)]

3. Color additives of any concentration may be listed in any order after the listing of the ingredients which are not color additives [§ 701.3(f)(3)].

4. The name of an ingredient accepted by FDA in accordance with the procedure established in § 720.8 as a trade secret need not be disclosed on the label. In lieu of declaring the name of that ingredient, the phrase "and other ingredients" may be used at the end of the ingredient declaration [§ 701.3(a)].

Order of Predominance

Lipstick

Incorrect Label Copy:	**Correct Label Copy:**
Caster Oil (58)	**Castor Oil**
Beeswax (6.5)	**Lanolin**
Candelilla Wax (6.5)	**Beeswax**
Carnauba Wax (3)	**Candelilla Wax**
Lanolin (8)	**Carnauba Wax**
Ozokerite (2)	**Ozokerite**
Propylene Glycol (and) BHA	**Propylene Glycol**
(And) Propyl Gallate	**BHA**
(And) Citric Acid (1.3)	**Propyl Gallate**
Titanium Dioxide (2)	**Citric Acid**
D&C Red No. 21 (2)	**Fragrance**
D&C Red No. 6 Barium Lake (4)	**Titanium Dioxide**
D&C Yellow No. 5 Aluminum Lake (5)	**D&C Red No. 21**
Fragrance (0.5)	**D&C Red No. 6 Barium Lake**
	D&C Yellow No. 5 Aluminum Lake

In this example, the correct ingredient declaration lists castor oil (58), lanolin (8), candelilla wax (6.5), carnauba wax (3), and ozokerite (2) in descending order of predominance. The concentrations (which need not be declared by regulation) are provided in parentheses.

The compounds of the proprietary antioxidant mixture dissolved in propylene glycol must be integrated into the product formulation and declared individually in order of decreasing predominance without the term "(and)."

The color additives titanium dioxide (2) etc. may be declared in any order after the other ingredients.

Declaration of Color Additives and Ingredients Present at One Percent or Less

Pressed Powder

Label Declaration:	Alternate Declaration:
Talc (75)	Talc
Kaolin (7.5)	Kaolin
Zinc Stearate (5)	Zinc Stearate
Titanium Dioxide (5)	Mineral Oil
Mineral Oil (3)	Lanolin
Iron Oxides (2.5)	Isopropyl Myristate
Isopropyl Myristate (0.9)	Fragrance
Lanolin Oil (0.5)	Lanolin Oil
Lanolin (0.2)	Titanium Dioxide
Fragrance (0.1)	Ultramarine Blue
Ultramarine Blue (0.05)	Iron Oxides

The hypothetical pressed powder formulation portrayed in this example illustrates the two options for the listing of ingredients.

On the left side, the ingredients are listed in descending order of predominance according to § 701.3(2).

On the right side, the ingredients are listed according to § 701.3(f)(1), (2), and (3), i.e., ingredients other than colors present at a concentration exceeding 1% in descending order or

predominance, followed by ingredients other than colors present at 1% or less in any order, followed by colors present at any concentration listed in any order.

Declaration of Fragrance and Flavor Ingredients

- **Fragrance**
- **Flavor**
- **Fragrance and flavor**

21 CFR 701.3(a)

Fragrance and flavor compounds may be declared in descending order of predominance as "fragrance" and "flavor." If a fragrance compound also serves as a flavor, it must be declared as "flavor and fragrance."

The components (ingredient) of a fragrance or flavor may also be declared individually by their appropriate label names.

The ingredient or mixture of ingredients acting as a masking agent, i.e., covering the undesirable off-odor of a product without adding a discernable odor to it, may be declared by their individual name(s) or as "fragrance" (in lieu of a better designation). A masking agent present in a product at an insignificant level may be considered an incidental ingredient under § 701.3(1)(2)(iii) in which case it need not be declared on the label.

Trade Secret Ingredients

Declaration of Trade Secret Ingredients

By the Phrase "And Other Ingredients"

If accepted by FDA as exempt from public disclosure pursuant to the procedure of § 720.8.

21 CFR 701.3(a)

The FP&L Act states in section 5(c)(3)(B) [15 U.S.C. 1454(c)(3)(B)] that "nothing ... shall be deemed to require that any trade secret be divulged." Accordingly, the cosmetic ingredient labeling regulation does not require the declaration of the identity of an ingredient FDA has accepted as exempt from public disclosure. In lieu of the declaration of the name of a confidential ingredient, the phrase " and other ingredients" may be used at the end of the ingredient declaration.

The policy the agency is following for processing requests for confidentiality of cosmetic ingredient identities has been codified under § 720.8.

What is a trade secret?

A trade secret may consist of any formula, pattern, device or compilation of information which is used in one's business and which gives one an opportunity to obtain an advantage over competitors who do not know or use it.

21 CFR 20.61

The question "what is a trade secret" may be answered by restating the definition of the term "trade secret" as provided in § 20.61(a) of regulations published in 1974 for enforcement of the law commonly known as the "Freedom of Information Act" (the public information section of the Administrative Procedures Act; 5 U.S.C. 552).

Procedure for Requesting Exemption of an Ingredient Identity From Public Disclosure

1. Submission of information

2. Review of data for adequacy

3. Tentative determination of trade secrecy

4. Final determination of trade secrecy

5. Judicial review under 5 U.S.C. Chapter 7

1. Submission of information

- **Cosmetic formulation or raw material composition statement (Form 2512 OR 2513)**
- **Statement of factual and legal grounds justifying trade secrecy**
- **Statement of prior non-disclosure (§ 20.81)**

21 CFR 720.8

The first step in processing a request for trade secrecy, i.e., a request for exemption from label declaration, of the identity of a cosmetic ingredient is the submission to FDA of the following information:

(a) A semi-quantitative cosmetic formulation statement of the product in question on forms FD-2512 and 2512a.

(b) A full statement of the factual and legal grounds for the request, including all data and other information on which the petitioner relies (as well as any information known to the petitioner that is unfavorable to petitioner's position).

The statement of factual grounds should include scientific or technical data, reports, tests, and other relevant information that address the factors FDA considers in determining whether the identity of an ingredient qualifies as a trade secret. (The factors FDA considers are stated elsewhere.)

(c) A statement that the identity of the ingredient in question has not previously been disclosed to anyone without appropriate safeguards for secrecy as further explained in § 20.81.

2. Review of data for adequacy

21 CFR 720.8

FDA reviews the submitted information to determine whether the data are sufficient to permit a review of the merits of the request.

A request that contains insufficient data to conduct a confidentiality review on the merits is returned and petitioner is advised about the additional information that is necessary to enable the agency to proceed with the review of the request.

3. Tentative determination of trade secrecy

21 CFR 720.8

When the submitted information is sufficient to permit a review of the merits of a request, FDA proceeds with the review.

When the agency concurs with petitioner and decides that the ingredient identity is a trade secret, the request for exemption from label disclosure is granted. If FDA does not concur with petitioner, the agency tentatively denies the request. The person requesting trade secrecy is informed in writing of the agency's determination. In case of a tentative denial, FDA informs petitioner of the grounds on which it relied in making this tentative determination.

Factors Considered in Determining Trade Secret Status

1. Is the information publicly known?

(a) Prior public disclosure by petitioner
(b) Public disclosure in the literature
(c) Measures taken to guard secrecy

When FDA reviews the merits of a confidentiality request and determines whether the identity of an ingredient qualifies as a trade secret, it considers the following three principal factors by seeking answers to the following three questions:

1. Is the ingredient's identity and intended use publicly known?
2. Does the intended use of the respective ingredient have value?
3. Can the identity of the ingredient readily be acquired by legal means and its intended use duplicated?

These questions are based on the factors considered in Comment B to section 757 of the Restatement of Torts in determining whether given information is a trade secret.

Since the same factors are also being considered by FDA in determining whether the identity of an ingredient qualifies as a trade secret, a person requesting trade secrecy must address them factually and convincingly in the statement of grounds.

Absence of public knowledge of an ingredient's identity under conditions of intended use may be demonstrated by documenting the extent to which the information is known by employees or others in petitioner's business, the extent the information is publicly disclosed in pertinent literature, and the extent of measures taken by petitioner to guard the secrecy of the information.

2. Does the information have value?

(a) Importance to the product
(b) Product profitability
(c) Future market performance of product
(d) Effort and financial resources invested

The value of knowing the identity and intended use of the ingredient in question may be determined in terms of the importance of the ingredient to the product formulation. It must be assumed that, to be of value, the ingredient significantly contributes to the claimed performance or other pertinent characteristics of the cosmetic and that a cosmetic not containing the claimed trade secret ingredient, or containing conventional substitutes in place of the respective ingredient, could not be expected to perform equally well or otherwise meet certain requirements. Appropriate comparative testing of a cosmetic containing the trade secret ingredient, or one containing conventional substitutes, as well as testing of petitioner's cosmetic against competitor's cosmetic of the same use category may provide factual documentation to this effect and thus demonstrate the value of the information to petitioner. The value of the ingredient information may also be determined in terms of future market performance of a cosmetic or its profitability. However, this kind of value assessment is usually a difficult and inexact task and often provides little factual data to support a value assessment.

Documentation of the effort expended and financial resources invested in the development of the product formulation containing the ingredient in question and providing the claimed characteristics may further support a request for trade secrecy.

3. Can the information readily be acquired or duplicated

The factor concerning the ease or difficulty with which the identity of the ingredient in question could properly be acquired or duplicated by others may be addressed by documenting an ingredient's rare or unexpected use for the intended purpose in cosmetics of a particular product category or by demonstrating the complexity of the analytical methodology necessary to identify it.

4. Final determination of Trade Secrecy

- **Cosmetic formulation or raw material composition statement (Form 2512 OR 2513)**
- **Statement of factual and legal grounds justifying trade secrecy**
- **Statement of prior non-disclosure (§ 20.81)**

21 CFR 720.8

When FDA tentatively decides to deny a request, the petitioner may withdraw the records for which FDA has tentatively denied a request for confidentiality. Petitioner may also submit, within 60 days from the date of receipt of the written notice of the tentative denial, additional relevant information and arguments and request that the agency reconsider its decision in light of both the additional material and the originally submitted information.

If the petitioner submits new data, the agency considers that material together with the initially submitted information and makes its final determination. This constitutes final agency action. The petitioner is informed of the agency's final determination in writing.

5. Judicial review under 5 U.S.C. Chapter 7

21 CFR 720.8

The agency's final decision may be challenged in the courts under 5 U.S.C., Chapter 7. If suit is brought within 30 days after such determination, FDA will not disclose the records involved until the matter is finally determined in the courts. If suit is not brought within 30 days and the petitioner does not withdraw the records for which a request for confidentiality has been denied, the records involved will be made part of FDA's files and will then be available to the public upon request.

It should be noted that until the agency has completed its determination that the identity of a cosmetic ingredient is a trade secret, the cosmetic product in question may not bear the label statement "and other ingredients" in lieu of a declaration of the identity of the ingredient for

which confidentiality has been requested. The phrase "and other ingredients" may be used on the label only after an ingredient is accepted by FDA as exempt from public disclosure or, when confidentiality has been denied, if suit is brought within 30 days after a final determination that the ingredient in question is not a trade secret.

Cosmetics That Are Also Drugs

Declaration

1. **The established name of any active drug ingredient and the quantity, kind, and proportion of any alcohol, in compliance with Sec. 502(e) of the FD&C Act, as "Active Ingredients"**
2. **The remaining ingredients, in compliance with § 701.3, as "Cosmetic Ingredients"**

21 CFR 701.3(d)

A product intended to be applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance is a cosmetic. If this product claims to accomplish these deeds through physiological activity or by changing the structure of the skin, it is also a drug. The product categories "drug" and "cosmetic" are not mutually exclusive. This is recognized in sec. 509 of the FD&C Act.

If a cosmetic is also a drug, the label must list first the established name of the drug ingredient(s) and the quantity, kind and proportion of any alcohol, in compliance with sec. 502(e) of the FD&C Act, as "Active Ingredients" and then the remaining ingredients, in compliance with § 701.3(a) or (f), as "Cosmetic Ingredients."

Aerosol Antiperspirant

Incorrect Label Copy:	**Correct Label Copy:**
Isobutane	Active Ingredient:
Silicone Oil	Aluminum Chlorohydrate
Butane	Cosmetic Ingredients:
Aluminum Chlorohydrate	Isobutane
Isopropyl Myristate	Cyclomethicone
Denatured Alcohol	Butane
Propane	Isopropyl Myristate
Bentone 38	SD Alcohol 40
	Propane
	Quaternium 18 Hectorite

This hypothetical aerosol antiperspirant formulation illustrates on the right side the correct label declaration of the ingredients of a cosmetic which is also a drug.

The active drug ingredient aluminum chlorohydrate is identified as "Active Ingredient" in accordance with sec. 502(e) of the FD&C Act. The remaining ingredients may be identified as "Cosmetic Ingredients" as shown or as "Other Ingredients."

Color Additives Added Sometimes for Color Matching

Listed after the declaration of other color additives and after the pharase"May contain"

21 CFR 701.3(g) (1)

A color additive(s) that is added to a cosmetic during manufacture for the purpose of color matching may be declared on the label of each batch or lot even if not present in each.

The color additive sometimes added for color matching is listed after the declaration of other color additives, or at the end of the declaration, and after the phrase "May Contain."

Toilet Water

Incorrect Label Copy:	Correct Label Copy:
SD Alcohol 39C	SD Alcohol 39C
Water	Water
Fragrance	Fragrance
Propylene Glycol	Propylene Glycol
Cetyl Lactate	Cetyl Lactate
FD&C Red No. 40	FD&C Red No. 40
FD&C Blue No. 1	FD&C Blue No. 1
	May contain:
	D&C Yellow No. 10

D&C Yellow No. 10 used for Color Adjustment

This hypothetical toilet water formulation in which D&C Yellow No. 10 is added to some batches for the purpose of color adjustment shows on the right side the correct label declaration of the color additive D&C Yellow No. 10.

Incidental Ingredients

Definition:
Any processing aid added and removed or converted to a declared ingredient
or
Any ingredient of another ingredient or processing aid present at an insignificant level and having no technical or functional effect

Need not be declared

Incidental ingredients need not be declared on the label.

An incidental ingredient is defined in § 701.3(1) as:

> 1. A substance added during manufacture and removed from the cosmetic in accordance with good manufacturing practices before the cosmetic is packaged in finished form. Example: Filter aid.

2. A substance that is added during manufacture of a cosmetic, is converted to an ingredient declared on the label, and does not significantly increase the concentration of the declared ingredient. Example: Sodium hydroxide added to a sodium stearate and stearic acid-containing cosmetic.

3. A substance added to a cosmetic during manufacture for its technical effect in processing but present in the finished cosmetic at an insignificant level and not having any technical or functional effect in that cosmetic. Example: Defoaming agent.

4. A substance added to a cosmetic as a component of a cosmetic ingredient and having no technical or functional effect in the finished cosmetic. Example: Preservative of a raw material added to a cosmetic as an ingredient at a concentration which reduces the preservative to a level at which it is no longer effective.

Multiunit or Multicomponent Packages

Examples:
Gift set of makeup assortment
Hair coloring kit or home permanent
Declaration:
On outside retail package only if components are not customarily sold individually.

21 CFR 701.3 (q)

The ingredients of the units of cosmetics marketed as multiunit or multicomponent packages must be declared on the label of the outside container. They must also be declared on the labels of the inside containers of the units if the inside containers are customarily separated from the outer container for individual retail sale.

A MULTIUNIT package is a package which contains an assortment of similar or dissimilar products. Examples: A shade assortment of eye shadows in an eye make-up kit or a gift set consisting of a lotion, powder and toilet water in a gift box.

A MULTICOMPONENT package is "a package which contains the integral components making up a complete kit, and which is designed to deliver the components in the manner of an application." See 21 CFR 701.13(g)(2). Examples: A hair coloring kit consisting of dye solution and hydrogen peroxide or a permanent wave set consisting of thioglycolate solution and sodium bromate solution.

Multiunit Packages (Assortments in Same Package)

Dissimilar products

Similar products intended same use

Labeling surface area
Less than 12 square inches
Over 12 square inches
Branded shade lines
Single units and assortments

For the purpose of cosmetic ingredient labeling and to take advantage of provisions for consolidated ingredient listing in place of sometimes repetitive listing of ingredients unit by unit, a distinction must be made between packages containing:

1. Dissimilar products. Example: Gift set containing a shave cream and an after shave lotion.

2. Products of similar composition and intended for the same use in a package with a total surface area available for labeling of **12 square inches or more**. Example: Two toilet waters of different fragrance or color in gift set.

3. Products of similar composition and intended for the same use in a package with a total surface area available for labeling of **less than 12 square inches**. Example: Eye shadows of different color in a compact case.

4. Products that are single units or assortments of a branded shade line. A branded shade line is a series of products of similar composition, intended for the same use, and sharing a common label with the same brand name. Example: A shade line of lipsticks.

Assortments of Dissimilar Products

Alternate Declaration
Single composite list of color additives with statement that list pertains to all products

21 CFR 701.3(h)

The package of an assortment of dissimilar products, i.e., a multiunit package, as, for example, a toilet water and a dusting powder in a gift box, may bear:

A **conventional** ingredient declaration in which each ingredient of each product is identified under an appropriate product heading, or

An **alternate** ingredient declaration in which the color additives of all products of the assortment are integrated into a single composite list that indicates that the list pertains to all products.

Please note that if the units of an assortment are customarily separated from the outer package for retail sale, the ingredients must also be declared on the label of each inside unit.

Toilet Water and Dusting Powder

Label Copy:	**Alternate Label:**
Toilet Water:	**Toilet Water:**
SD Alcohol 40	SD Alcohol 40
Water	Water
Fragrance	Fragrance
FD&C Red No. 40	**Dusting Powder:**
FD&C Blue No. 1	Talc
Dusting Powder:	Kaolin
Talc	Fragrance
Kaolin	Color Additives Pertaining to Both Products:
Fragrance	FD&C Red No. 40
D&C Red No 21 Aluminum Lake	FD&C Blue No. 1
	D&C Red No. 21 Aluminum Lake

This example of a hypothetical assortment of dissimilar products consisting of a toilet water and a dusting powder illustrates on the right side the alternate ingredient labeling option in which all color additives are declared in a single composite list. The declaration advises that the color additives pertain to both products.

If, for example, Red 40 or Blue 1 were present in both products, they would have to be listed only once in the declaration.

Assortments of Similar Products Intended for Same Use

Available Labeling Surface Area Less Than 12 Square Inches

Alternate Declaration

1. **Ingredients common to all products listed in cumulative descending order of predominance (or according to paragraph (f)), and**
2. **Ingredients not common to all products identified by product in which used, and**
3. **Single composite list of all color additives without product identification**

21 CFR 701.3 (O) (1)

An assortment of products of similar composition and intended for the same use in a package with a total surface area available for labeling of **12 square inches or more** as, for example, two toilet waters of different fragrance or color in a gift set, may bear either:

A **conventional** ingredient declaration in which the ingredients of each product are identified under appropriate product headings, listing either all the ingredients in descending order of predominance according to § 701.3(a) or listing the ingredients according to § 701.3(f), declaring first in descending order the ingredients other than colors present at concentrations exceeding 1%, followed in any order by the ingredients other than color present at concentrations of 1% or less, followed in any order by the color additives present at any concentration, or

An **alternate** ingredient declaration, listing:

1. The ingredients other than colors **common** to all products in cumulative descending order of predominance according to § 701.3(a), or according to § 701.3(f) [permitting listing of ingredients present at 1% or less in any order], followed by
2. The ingredients other than color **not common** to all products, identified by the products in which they are present, followed by
3. The color additives of all products without identification of products in which they are present.

Assortments of Similar Products Intended for Same Use

Available Labeling Surface Area Less Than 12 Square Inches

Alternate Declaration

Single list of all ingredients in cumulative descending order of predominance

or

Single list of all ingredients according to paragraph (f)

An assortment of products of similar composition and intended for the same use in a package with a total surface area available for labeling of **less than 12 square inches** as, for example, several eye shadows in a compact, may bear either:

A **conventional** ingredient declaration in which the ingredients of each product are identified under appropriate product headings, listing either all the ingredients in descending order or according to § 701.3(a) or listing the ingredients according to § 701.3(f), declaring first in descending order the ingredients other than colors present at concentrations exceeding 1%,

followed in any order by the ingredients other than color present at concentrations of 1% or less, followed in any order by the color additives present at any concentration,

or

An **alternate** ingredient declaration listing the ingredients of all products in a single integrated list in cumulative descending order of predominance according to § 701.3(a), or cumulatively according to § 701.3(f).

Assortments of Similar Products

Eye Shadow--Two Shades - Alternate Labels

Label Copy	Labeling Area 12 Sq. In. or More	Labeling Area Less Than 12 Sq. In.
Blue, Pearly Shade:	**Talc**	**Talc**
Talc	**Zinc Stearate**	**Zinc Stearate**
Zinc Stearate	**Kaolin**	**Kaolin**
Kaolin	**Mineral Oil**	**Bentonite**
Bentonite	**Bentonite in Blue Shade**	**Mineral Oil**
Mineral Oil	**Lanolin in Green Shade**	**Lanolin**
Bismuth Oxychloride	**Bismuth Oxychloride**	**Bismuth Oxychloride**
Titanium Dioxide	**Titanium Dioxide**	**Titanium Dioxide**
Ultramarine Blue	**Ultramarine Blue**	**Ultramarine Blue**
Ultramarine Violet	**Ultramarine Violet**	**Ultramarine Violet**
Green Shade:	**Ultramarine Green**	**Ultramarine Green**
Talc	**Chromium Hydroxide Green**	**Chromium Hydroxide Green**
Zinc Stearate		
Kaolin		
Mineral Oil		
Lanolin		
Titanium Dioxide		
Ultramarine Green		
Chromium Hydroxide Green		

21 CFR 701.3 (o) (2)

This example of an assortment consisting of two similar hypothetical eye shadow formulations demonstrates the optional ingredient declarations for packages with a total surface area available for labeling of **12 square inches or more** (center) and for packages with a total surface area available for labeling of **less than 12 square inches** (right side).

On the **left side** are shown two conventional ingredient declarations, each representing one shade.

In the **center** is shown the integrated ingredient declaration for the two shades in the package with **12 square inches or more** of available labeling area. Note that the ingredients other than color not common to all products are listed after the ingredients that are common and are identified by the products in which they are used. (Bentonite in Blue Shade, Lanolin in Green Shade.)

On the **right side** is shown the integrated ingredient declaration for the two shades in the package with **less than 12 square inches** of available labeling area. Note that the ingredients not common to all formulations need not be identified by the products in which they are used.

Branded Shade Lines and Branded Shade Line Assortments

Definition:
Individually packaged, or assortments of eye or facial makeup cosmetics or nail enamels bearing the same name

21 CFR 701.3 (g) (2) and (o) (3)
(g) (2) and (o) (4)

According to §§ 701.3(g)(2) and (o)(3), a branded shade line may be defined as a line of individually packaged eye or facial make-up cosmetics or nail enamels bearing a label that is shared with other products, i.e., bearing the same product name. Example: A line of lipsticks with the same brand name.

According to §§ 701.3(g)(2) and (o)4), a branded shade line assortment may be defined as several assortments of eye or facial make-up cosmetics or nail enamels in packages bearing the same label. Example: Several compacts with the same name and label, each containing several eye shadows.

According to 701.3(g)(2) and (o)(4), a branded shade line assortment may be defined as several assortments of eye or facial make-up cosmetics or nail enamels in packages bearing the same label. Example: Several compacts with the same name and label, each containing several eye shadows.

Branded Shade Lines and Branded Shade Line Assortments Alternate Declaration

Single ingredient declaration for all branded shades listing ...

1. **Ingredients common to all products, in cumulative descending order of predominance**
2. **Ingredients not common, identified by product in which used**
3. **Color additives common to all products, in any order**
4. **Color additives not common, preceded by "May contain"**

21 CFR 701.3 (g) (2) and (o) (3)
(g) (2) and (o) (4)

Branded shade lines and branded shade line assortments may bear either:

A **conventional ingredient** declaration for each product in which the ingredients of each product are identified in descending order of predominance according to § 701.3(a) or, alternately, according to § 701.3(f) [in the case of an assortment the ingredients may be declared cumulatively in a single list for each assortment according to §§ 701.3(a) or (f)]

or

An **alternate** ingredient declaration listing all ingredients for all branded shades in the cumulative order shown below. In this case, each shade of a branded shade line or each package of a branded shade line assortment bears the same ingredient declaration.

Branded Shade Lines and Branded Shade Line Assortments

Lipstick - Cherry Red

Incorrect Label Copy:	Correct Label Copy:
Castor Oil	Castor Oil
Isopropyl Myristate	Isopropyl Myristate
Beeswax	Beeswax
Candelilla Wax	Candelilla Wax
Oleyl Alcohol	Oleyl Alcohol
Ozokerite	Ozokerite
Sorbitan Trioleate	Sorbitan Trioleate in Pearl Peach and Pearl Cherry Shades
May contain:	Titanium Dioxide
Mica (and) Titanium Dioxide (and) Iron Oxides	D&C Red No. 21
D&C Red No. 21	D&C Orange No. 5
D&C Orange No. 5	May contain:
D&C Red No. 6 Barium Lake	Mica
D&C Red No. 7 Calcium Lake	Iron Oxides
D&C Red No. 27 Aluminum Lake	D&C Red No. 6 Barium Lake
D&C Orange No. 5 Aluminum Lake	D&C Red No. 7 Calcium Lake
D&C Yellow No. 10 Aluminum Lake	D&C Red No. 27 Aluminum Lake
	D&C Orange No. 5 Aluminum Lake
	D&C Yellow No. 10 Aluminum Lake

This example of a hypothetical shade of a line of lipsticks bearing the same brand name illustrates three common errors found in cosmetic ingredient declarations, namely:

1. Proprietary mixtures of ingredients identified in the ingredient dictionary by a parenthetical "(and)" are often declared on the label as shown in the dictionary section listing chemical/trade names and their respective label names. The compounds of such

mixtures must be separated, the "(and)" omitted, and the components treated as individual ingredients for labeling purposes. See "Mica (and) Titanium dioxide (and) Iron oxides."

2. Many labels list all color additives of a shade line after the phrase "May contain." The color additives common to all shades must be listed before "May contain", and only those **not** found in all shade formulations may be listed after "May contain."

3. The ingredients other than colors which are not included in all shade formulations must be identified as to the shades in which they are present.

Direct Mail Cosmetics

Definition

Cosmetics ordered by and delivered to consumers through the mail without involvement of an intermediary sales agent

21 CFR 701.3 (r)

Direct mail cosmetics may utilize off-package ingredient labeling as an alternative to the declaration of ingredients on an information panel.

For the purpose of cosmetic ingredient labeling, direct mail cosmetics are defined as cosmetics ordered by mail and delivered to consumers through the mail without the involvement of an intermediary sales agent.

Cosmetics sold to consumers through "door-to-door" salespersons are not considered direct mail cosmetics even though they may be delivered to consumers directly by mail.

Declaration on

labeling accompanying the mailed cosmetic

or

labeling furnished to each consumer ordering cosmetics by mail

21 CFR 701.3 (r)

As an alternative to the declaration of ingredients on an information panel, the declaration may appear in letters not less than 1/16 of an inch in height in:

Labeling that accompanies and specifically relates to the cosmetic(s) mailed, e.g., a brochure, insert or written directions for safe use, or

Labeling furnished to each consumer for personal use and from which cosmetics are ordered through the mail, e.g., a direct mail sales catalog or brochure.

Direct Mail Cosmetics Requirements

Notice in 3/16-inch lettering located or affixed to top, inside, or outside of package, stating:

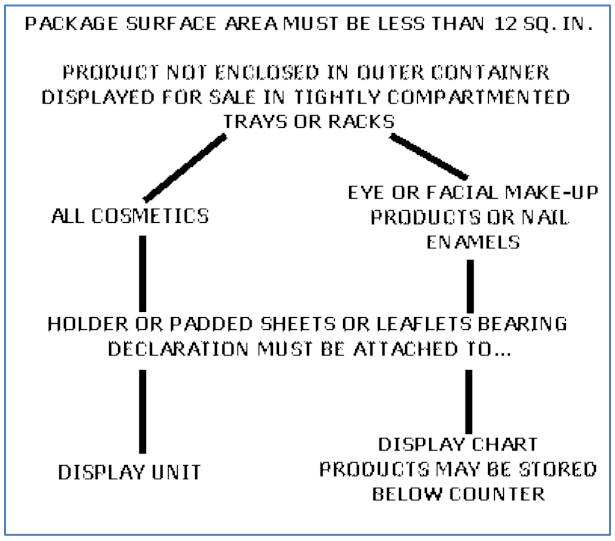
1. **Location of ingredient declaration**
2. **Availability on request through mail**
3. **Name and address of distributor**

21 CFR 701.3(r)

If the ingredients of cosmetics distributed to consumers by direct mail are made available through off-package labeling, the following requirement must be met:

> 1. The package mailed to consumers must be accompanied by a notice in 3/16 of an inch lettering informing the consumer of the location of the ingredient declaration(s), of the name and address of the mail order distributor, and that a copy of the ingredient declaration(s) will be mailed to any person requesting it.
>
> 2. The mail order distributor must promptly mail a copy of an ingredient declaration to any person requesting it.
>
> 3. The notice in 3/16 of an inch lettering must be located on, or affixed to, the top of the package; or it must be inside the package on top of the contents or on the face of the platform surrounding and holding the product(s) and must be readily visible to the consumer on opening.
>
> 4. The ingredient declarations must be conspicuous and presented in a way that the consumer can readily associate each ingredient declaration with each cosmetic.

Off-package Ingredient Labeling Qualifying Conditions



21 CFR 701.3(i)

The declaration of ingredients in labeling accompanying a cosmetic, i.e., off-package ingredient labeling, requires that:

(1)The product is not enclosed in an outer container,
(2)The total package surface area is less than 12 square inches, and
(3)The products are held for sale in tightly compartmented trays or racks.

The ingredient declaration must be in letters not less than 1/16 of an inch in height and may appear on padded sheets, leaflets or similar labeling accompanying the product.

Products which are **not** eye or facial make-up cosmetics or nail enamels must be displayed for sale in tightly compartmented trays or racks of a display unit. The holder of the padded sheets or leaflets bearing the ingredient declaration(s) must be attached to the display unit.

Products which **are** eye or facial make-up cosmetics or nail enamels may be held for sale in tightly compartmented trays or racks located below the sales counter. The holder of the ingredient labeling must be attached to a display chart which bears samples of the product shades and is displayed to purchasers.

Holder of Labeling

1. Must bear the following statement visible after last list has been taken:
"Federal law requires ingredient list to be displayed here."

21.CFR 701.3(j)

Among the various conditions described in §§ 701.3(j) and (k) that must be met if off-package ingredient labeling is utilized as an alternative to the declaration of ingredients on an information panel, the following deserve particular attention:

The display unit or chart must bear the statement "Federal law requires ingredient lists to be displayed here" in letters not less than 3/16 of an inch in height. This statement becomes conspicuous when the last ingredient list has been taken or may also be shown at all times adjacent to the holder of labeling bearing the ingredient declaration(s).

2. Padded sheets or leaflets must be attached to the display unit and be fully visible on the front

or

partially visible on the front and bear a notice in 3/16-inch lettering describing their location

or

located on the side only and bear the location notice.

21 CFR 701.3 (j)

The holder of off-package cosmetic ingredient labeling, e.g., padded sheets or leaflets, must be attached to the display unit or chart so that the labeling is in front of the display unit or chart and can be read in full by a purchaser facing the display under customary conditions of retail sale.

As an alternative to full display of off-package ingredient labeling, the labeling may also be on the side of the display unit or chart, but not at the top, back or bottom, in which case it must be accompanied by a conspicuous notice in 3/16 of an inch lettering on the front of the display unit, describing the location of the off-package labeling and stating "Federal law requires ingredient lists to be displayed here."

Additional Requirements

1. Leaflets must bear declarations of all products sold with display unit or chart.

2. Leaflets must be identical.

The following additional conditions must be met to comply with the requirements for off-package ingredient labeling of cosmetics:

1. The padded sheets or leaflets attached to the display unit or chart must declare the ingredients of all products sold with the display.

2. The padded sheets or leaflets must be identical.

3. Leaflets and displays must be shipped together.
The number of copies of padded sheets or leaflets provided with each shipment of a cosmetic must be sufficient so that each purchaser may obtain a copy of an ingredient declaration. Further, the display units and replacement labeling must be accompanied by appropriate instructions to the retailer to assure that retailers display the padded sheets or leaflets.

4. Leaflets must be sufficient in number and replaced with refills with replacement instructions to retailer.
Shipments of refill items also must be accompanied by sufficient copies of ingredient declarations, and the container holding the refill items and the respective copies of ingredient declarations must not contain other cosmetic products.

5. Label firm must send copy of ingredient declaration to requesting person.
The firm engaged in off-package cosmetic ingredient labeling must promptly mail a copy of the ingredient declaration to any person requesting it.

6. In case of formulation change, leaflet must declare both formulations.
In case of a formulation change, the new padded sheet or leaflet must be dated if not shipped together with the display unit or chart. If a padded sheet or leaflet is to be used in conjunction with the old and the new formulations, it must bear both ingredient declarations, and the declarations must be identified in a way that the purchaser can determine which declaration pertains to which product. As an alternative, the padded sheet or leaflet bearing the two ingredient declarations may advise the purchaser that the formulation has been changed and that either declaration may be applicable.

21 CFR 701.3 (k)