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# 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**

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## **Nonprescription Sunscreen Drug Products — Format and Content of Data Submissions Guidance for Industry<sup>1</sup>**

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance 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)).<sup>2</sup> The requests addressed in this guidance seek a determination from FDA of whether an over-the-counter (OTC or nonprescription) sunscreen active ingredient,<sup>3</sup> 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.<sup>4</sup> 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

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<sup>1</sup> 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.

<sup>2</sup> 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).

<sup>3</sup> 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).

<sup>4</sup> 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))).

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the public docket by other interested parties.<sup>5</sup> 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.<sup>6</sup>

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,<sup>7</sup> 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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<sup>5</sup> 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).

<sup>6</sup> Section 586B(b)(2) of the FD&C Act.

<sup>7</sup> 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.

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### **II. BACKGROUND**

#### **A. Regulation of Sunscreen Products<sup>8</sup>**

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.<sup>9</sup>

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.<sup>10</sup> Active ingredients that are determined to be GRASE in a final sunscreen order may be

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<sup>8</sup> 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>).

<sup>9</sup> Part 330.

<sup>10</sup> Section 586C of the FD&C Act (21 U.S.C. 360fff-3).

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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,<sup>11</sup> 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).<sup>12</sup> 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).<sup>13</sup>

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.<sup>14</sup>
- 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

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<sup>11</sup> Section 586B(a) of the FD&C Act.

<sup>12</sup> 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.

<sup>13</sup> Section 586C(a)(1) of the FD&C Act.

<sup>14</sup> Section 586B(b)(2)(A) of the FD&C Act.

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publicly available. The notification will explain the reasons for the refusal, including why the GRASE submission was not sufficiently complete.<sup>15</sup>

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.<sup>16</sup> 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.<sup>17</sup> 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.<sup>18</sup> 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.<sup>19</sup> 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.<sup>20</sup>

### **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.<sup>21</sup> 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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<sup>15</sup> Section 586B(b)(2)(B) of the FD&C Act.

<sup>16</sup> Section 586B(b)(3) of the FD&C Act.

<sup>17</sup> Section 586B(b)(3)(B) of the FD&C Act.

<sup>18</sup> Section 586B(b)(3).

<sup>19</sup> Section 586B(b)(3)(C) of the FD&C Act.

<sup>20</sup> Section 586B(b)(3)(B)(ii)(III) of the FD&C Act.

<sup>21</sup> 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.



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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).<sup>22</sup> 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.<sup>23</sup> 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:

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<sup>22</sup> 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>.

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

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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.<sup>24</sup>
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.<sup>25</sup> 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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<sup>24</sup> 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.

<sup>25</sup> Section 586B(b)(4) of the FD&C Act.

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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<sup>26</sup> 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.<sup>27</sup> 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

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<sup>26</sup> For more information on Module 1, see section III.B.

<sup>27</sup> 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.

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### 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.

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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.

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### 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.<sup>28</sup>

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<sup>28</sup> For more information on these categories, see the MedDRA Web site at [www.MedDRA.org](http://www.MedDRA.org).

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### **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<sup>29</sup> for review are listed below.<sup>30</sup> 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.

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<sup>29</sup> See section 586B(b)(2) of the FD&C Act.

<sup>30</sup> Please note that this list is not exhaustive.