

September 17, 2019

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
Attention: Dr. Theresa Michele
(via <http://www.regulations.gov>)

Re: Sunscreen Drug Products for Over-the-Counter Human Use; **Docket No. FDA-1978-N-0018**, Regulatory Information No. (RIN) 0910-AF43; Industry Workplan

Dear Dr. Michele:

The Personal Care Products Council (PCPC) is pleased to provide this draft Work Plan for the generation and compilation of sunscreen safety data on behalf of a member coalition of sunscreen manufacturers and ingredient suppliers (the "Work Group"). As we noted in our request letter of June 26, 2019, our members are committed to partnering with the Agency to support the generally recognized as safe and effective ("GRASE") status of sunscreen ultraviolet (UV) filters, which are recognized to help protect against the harmful effects of UV rays. Given the significant public health benefit of sunscreens, we understand and appreciate our shared responsibility of ensuring consumers have access to safe, effective, and aesthetically appealing sun protection options and look forward to collaborating with the FDA on the work ahead.

PCPC thanks you for conditionally granting a one-year deferral of inclusion in final rulemaking (based on the February 2019 FDA proposed rule for sunscreen drug products for over-the-counter (OTC) human use ("Proposed Rule")) for the eight (8) sunscreen ingredients specified in Section 4 of this document (the "Deferred Ingredients"). As it is our understanding that any future deferrals will also be granted on an annual basis, we submit this draft work plan which sets forth our proposal to further study the Deferred Ingredients (the "Work Plan"). Though we provide an overview of our anticipated activities, this Work Plan concentrates on those activities that will occur between the grant of any deferral and December 31, 2020. Additionally, accompanying this Work Plan, we have also included a request for a meeting in the letter transmitting this Work Plan.

I. Executive Summary

FDA's Proposed Rule set forth a proposed framework to support the GRASE status of UV filters. In this Work Plan, we describe a study plan based on this framework, which addresses human absorption, human dermal toxicity, and nonclinical endpoints, using a staged approach for each of these elements to facilitate decision-making at defined time-points given the interdependency of these complex studies.

For each Deferred Ingredient, and as outlined in this Work Plan, we plan to submit the following information by September 30, 2020 ("Stage One"):

- Maximal usage trial (MUsT) Protocol Development Plan Components
 - Habits and uses survey
 - Clinical use/actual use study of sunscreen products assessment
 - Sunscreen product survey
 - Identification and evaluation of formulation variables
 - Development plan for *in vitro* penetration tests (IVPT) of marketed sunscreen products
 - Identification of proposed test formulation for first MUsT pilot
- Analytical and bioanalytical method development for the active ingredient selected for first MUsT pilot
- Survey and submission of existing human dermal safety data for eight (8) sponsored sunscreen active ingredients not currently in the public domain
- Survey and submission of existing nonclinical safety data for eight (8) sponsored sunscreen active ingredients not currently in the public domain

We understand this work requires extended research that will run for a number of years, and we commit to ensuring studies are completed in a timely manner. We anticipate continued interaction with the agency, including public meetings over the coming years and appreciate the agency's guidance and partnership as we address these challenging questions together.

Additionally, and in subsequent communications, we would like to explore related ideas with the FDA which could be featured in subsequent work plans for the Deferred Ingredients. These ideas, which have previously been raised in comments during the

rulemaking process, include: 1) the concept of a GRASE formulation approach whereby formulas designed to minimize sunscreen absorption could be marketed under the monograph, 2) the concept of targeted application (e.g., to the face with potentially fewer applications per day) with modified direction for use, and 3) the methodology/rationale used to establish the threshold in human pharmacokinetic studies. We consider such ideas as potential practical solutions to meet GRASE criteria and advance innovation in the area of photoprotection.

I. Introduction

The OTC drug review monograph system is an established and recognized mechanism for manufacturers to market OTC drugs that were on the market in 1972. The process relies on public rulemaking to establish final monographs that identify acceptable ingredients, doses, and labeling for OTC drugs. The OTC drug review is a crucial regulatory pathway for sunscreen ingredients that are used in a wide variety of products including topical creams, lotions, sprays, powders if permitted in the monograph, and cosmetic products used by consumers to help protect their skin from the harmful effects of the sun.

PCPC is providing a foundation of scientific and technical support for products containing sunscreen active ingredients regulated by FDA's OTC monograph, and intended for topical use by consumers. We intend to initiate independent activities to address the areas that FDA has identified regarding human pharmacokinetics, human dermal safety, and nonclinical safety endpoints for these eight (8) Deferred Ingredients. We also plan to use a staged or tiered approach to the execution of the Work Plan for data generation and compilation whereby there are opportunities to confer with the Agency at various time-points, assess the current status of the data, and evaluate appropriate next steps. For example, we intend to follow the agency's advice found within the Proposed Rule and will use the results of the MUsT to inform the need for additional nonclinical safety studies for each active ingredient (see Figure 1 below). While we intend to apply this approach to all of the Deferred Ingredients, the timeline outlined in Figure 1 related to the MUsT study focuses on the work to be performed on the first active ingredient selected. We anticipate that MUsT studies for the remainder of the Deferred Ingredients will require additional time beyond that which is outlined here.

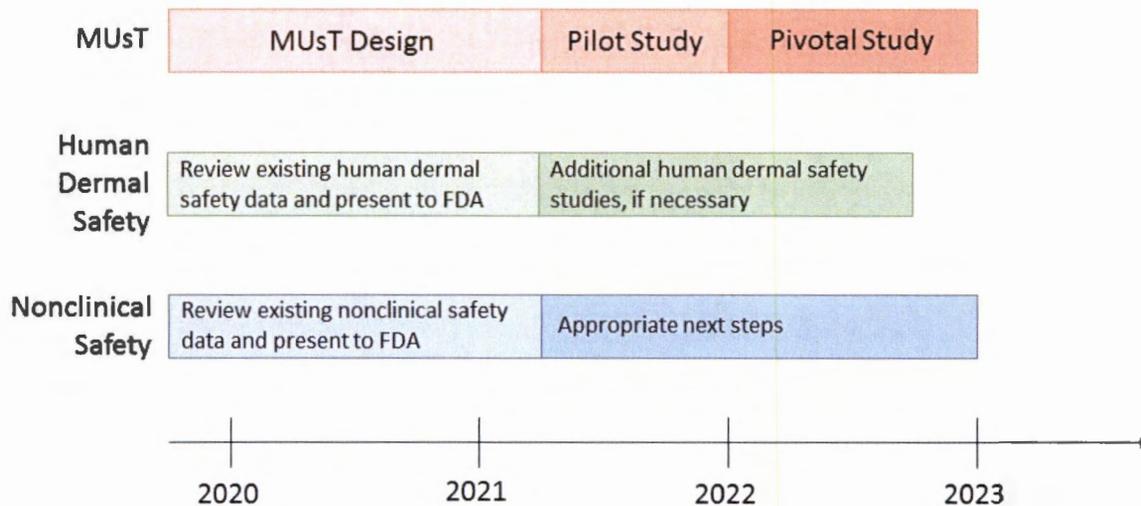


Figure 1. Draft Timeline to Compilation and Generation of Sunscreen Safety Information

In the beginning, the emphasis for the MUSt will be on establishing the correct study protocol and executing the protocol for one Deferred Ingredient and using the learnings from this study to thereafter address additional active ingredients in groups. These studies will be specified in subsequent work plans, as it would be highly speculative at this juncture to propose a plan for those other active ingredients.

While our initial MUSt will be for one Deferred Ingredient, we will collect existing clinical dermal safety data available to the Work Group for all eight Deferred Ingredients that are not currently available to FDA and submit it to the Agency. Following that activity, an assessment of the result will be made, and any remaining needs can be identified in partnership with the Agency and addressed after Stage One. Regarding nonclinical studies, our initial emphasis will also be on collecting existing data that is not currently in the public domain. We anticipate integrating modern toxicological models/methods as envisioned in National Research Council (NRC) 2007 report titled *Toxicity Testing in the 21st Century: A Vision and a Strategy (Tox21)* and more recently in FDA's *Predictive Toxicology Road map (2017)* and "*Using 21st Century Science to Improve Risk-Related Evaluations (2017)*," as well as read-across "or bridging" to structural analogs when appropriate.

Collectively, this approach is expected to address Agency questions regarding the 8 sunscreen active ingredients identified below.

II. Active Ingredients

We have identified eight sunscreen active ingredients that are of interest to our members and for which we intend to generate and compile additional information to support the rulemaking process and confirm the ingredients as GRASE:

- Avobenzone (CAS# 70356-09-1)
- Homosalate (CAS # 118-56-9)
- Octinoxate (CAS# 5466-77-3)
- Octisalate (CAS# 118-60-5)
- Octocrylene (CAS# 6197-30-4)
- Oxybenzone (CAS# 131-57-7)
- Ensulizole (CAS# 27503-81-7)
- Meradimate (CAS# 134-09-8)

III. Work Plan Activities: GRASE Ingredients Safety Studies

A. Clinical Safety: Human Pharmacokinetic Maximal Usage Trial (MUsT)

1. Introduction

In the Proposed Rule, FDA requested MUsT data for the active ingredients in order to assess the extent to which the ingredients were absorbed. In the recent FDA MUsT guidance,¹ the agency identified a number of study elements and considerations. An appropriate MUsT would attempt to simulate conditions that maximize the potential for drug absorption by incorporating the following design elements:

- Frequency of dosing
- Duration of dosing
- Formulation with appropriate potential for permeation
- Total body surface area to be treated at one time

¹ FDA. 2019. Maximal usage trials for topically applied active ingredients being considered for inclusion in an over-the-counter monograph: Study elements and consideration. Guidance for Industry. Available at: <https://www.fda.gov/media/125080/download>. U.S. Department of Health and Human Services, Food and Drug Administration.

- Amount applied per square centimeter
- Method of application/site preparation
- Sensitive and validated analytical method
- Multiple formulations aimed at addressing different product types (e.g. makeup products, facial skincare products, body skincare products and beach products).

We note that sunscreen products are intended to be used by consumers to prevent ultraviolet (UV) radiation penetration in order to lower the risk of acute and chronic skin damage. A number of the MUsT design elements for such products are determined by the usage habits and practices of the consumer, as conditions of use beyond directions related to frequency of reapplication are not specified on the product label at a level of detail typically found with prescription drugs.

Further, as proposed by the Agency, given the nature of the monograph process, and the multiplicity of formulations that are on the market, identifying a formulation that represents the highest potential for systemic exposure needs to be determined as well. It is our intent to use IVPT or human PK studies to identify the formulations with the highest potential for dermal penetration of active ingredients for use in each MUsT. The results of these initial IVPT studies may influence the direction of our planned studies for individual ingredients and will be discussed with FDA on a case-by case basis as the proposed workplans unfold.

We propose to conduct research to establish a number of the design elements for a MUsT and focus on a representative selection of active ingredients to gain experience in successfully executing a MUsT on sunscreen active ingredients. The initial focus will be on a single sunscreen active ingredient to gain experience with the MUsT and demonstrate the appropriateness of the approach. We will then study the remaining ingredients sequentially and work with FDA to establish timelines for completion of these studies. A description and timeline of the initial MUsT design is provided below in Figure 2 and the accompanying text.

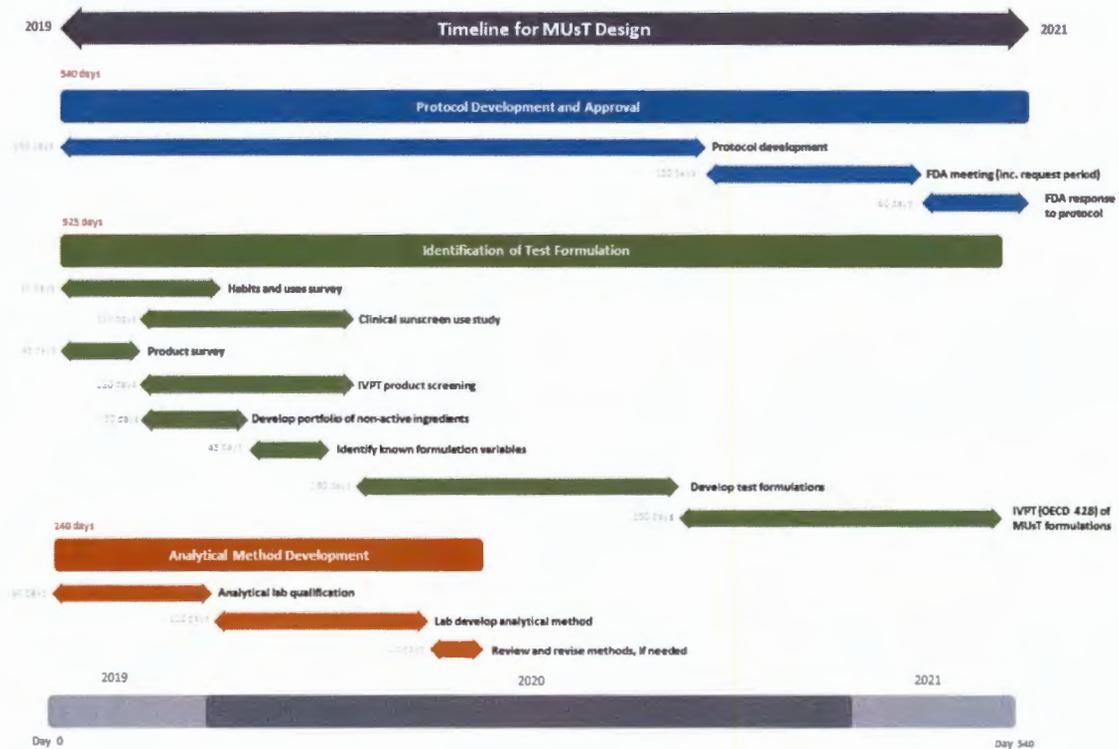


Figure 2. Timeline for MUSt Design

a. Determination of Dosing Frequency

FDA stated in the MUSt guidance that “[d]osing in a MUSt for sunscreens should use the same dosing interval as directed in OTC sunscreen labeling, every 2 hours” (21 CFR 201.327). Moreover, FDA indicated in a recent *Journal of the American Medical Association (JAMA)* study that it believes four sunscreen doses per day at 2-hour intervals represents maximal use conditions.² In order to better understand whether four sunscreen doses per day represents realistic maximal use, a consumer habits and uses survey will be conducted to better understand the real-world dosing frequency habits in the United States. We welcome an opportunity to discuss with FDA the appropriate dosing frequency based on the results of the consumer survey and recognize this may impact labeling directions in the future.

² Matta, M.K. et al. 2019. Effect of sunscreen application under maximal use conditions on plasma concentration of sunscreen active ingredients: A randomized clinical trial. *JAMA*. doi:10.1001/jama.2019.5586.

b. Formulation with Highest Potential for Permeation

As proposed by FDA, we plan to develop and execute a plan to identify commercially available sunscreen formulations with potentially high permeation of sunscreen active ingredients and create single UV filter formulations with the highest potential for permeation, similar to that described by FDA in a recent workshop on Topical Drug Development.³

i. Identification of Test Formulations and Creation of Test Formula

Given the numerous formulations on the market, a formulation that represents the highest systemic exposure needs to be identified. In order to do so, we propose to survey products that are currently in commerce in the United States to better understand ingredients and other formula variables⁴. This will also further our understanding of the range of products that are presently on the market. We propose to use either IVPT or human PK on marketed products to identify those products with the appropriate formula for the MUsT. The marketing data and IVPT/human PK data will be used to develop single filter test formulations for the MUsT, which are representative of real-world marketed formulations and represent potentially high systemic exposure products.

ii. IVPT and/or Human PK of Final Formulation

After acceptable test formulas have been created, IVPT and/or human PK studies will be conducted through a contracted laboratory on the test formulas for use in each MUsT to confirm their penetration potential and to be able to compare the IVPT/human PK results to the MUsT results. Per FDA's request, justification for the formulations chosen and results of the IVPT/human PK testing will be included in the MUsT protocol.

³ Yi, S. 2019. Integration of in vitro permeation test (IVPT) and maximal use trial (MUsT) into the safety assessment of topical OTC products. Workshop on Topical Drug Development—Evolution of Science and Regulatory Policy, Baltimore, MD. July 29–30; *see also* https://www.pharmacy.umaryland.edu/media/SOP/wwwpharmacyumarylandedu/centers/cersievents/topical/yi-presentation_073019.pdf.

⁴ *See* Sunscreen Tentative Final Monograph, "Sunscreen Drug Products for Over-the-Counter Human Use", 84 Fed. Reg. 38 (February 26, 2019), p. 6226.

c. Total Involved Body Surface Area for Treatment

The surface area treated is consistent with the monograph directions for use. The Proposed Rule recommended that the test formulation be applied to at least 75 percent of the body surface area, based on recommended sunscreen use on all exposed skin. We concur with FDA that this is a reasonable surface area to assess recreational sunscreens and plan to apply product to 75 percent of total body surface area for the duration of the MUsT. We would also like to potentially explore a pathway to account for sunscreens which are applied once daily and primarily used on the face and neck, and which could require their own MUsT protocol.

d. Analytical and/or Bioanalytical Method Development

We plan to work with a contracted analytical laboratory to develop and validate the analytical method for the active ingredient to be tested in each MUsT according to Bioanalytical Method Validation – Guidance to Industry (<https://www.fda.gov/media/70858/download>). Additionally, we will work with the laboratory and coordinate with the FDA to ensure we achieve the level of sensitivity required for the relevant blood concentration threshold for the Deferred Ingredients. The bioanalytical method will be validated before initiation of the pivotal MUsT study. In addition, analytical method development will be needed for the sunscreen actives in the final test formulations.

2. Pilot MUsT

We plan to conduct a Pilot MUsT for each sunscreen active prior to the Pivotal MUsT study. The purpose of the Pilot MUsT will be to identify the specific application procedure to run the Pivotal MUsT, address effect of formulation, and determine the duration of dosing by evaluating the time to steady state.

3. Pivotal MUsT

Upon the completion of the Pilot MUsT, PCPC will organize a meeting with FDA to present the Pilot MUsT data for the test materials, and to obtain agreement from FDA on the proposed Pivotal MUsT protocol.

B. Clinical Safety: Human Dermal Safety Data

As sunscreens are products intended to be applied directly to the skin and for which exposure to light after application is anticipated, FDA recommends specific human dermal safety studies: studies conducted without specific exposure to light and studies conducted to assess reactions after UV exposure (photosafety studies). Study sets are recommended to consist of dermal irritation patch testing, dermal sensitization patch testing, dermal phototoxicity testing, and dermal photoallergenicity testing.

In the Proposed Rule, FDA identified areas where additional information is sought. We will assemble, summarize and publicly file the existing dermal safety data that may be in the possession of the Work Group. To provide FDA with the information identified, we plan to work with these companies to discover potentially existing, nonpublicly available human dermal safety data on formulations or ingredients. We intend to make these data publicly available by submitting the data to FDA. We hope that the data will be sufficient, and we will partner with FDA to the extent the Agency believes additional data would be helpful.

C. Nonclinical Safety Data

In the Proposed Rule, FDA identified areas where additional information is sought in nonclinical safety endpoints among the sunscreen active ingredients and provided recommendations for filling those areas in order to make a GRASE determination. It is our understanding that the Work Group may have nonclinical safety data available that are not currently in the public domain. To provide to FDA the information identified, we plan to work with companies to discover potentially existing nonclinical safety data on formulations or ingredients that may not be in the public domain. We intend to make these data publicly available by submitting the data to FDA. After the data have been evaluated by FDA, we would welcome an opportunity to discuss any additional data that the Agency would find helpful. As FDA may be aware, PCPC and its member companies are committed to leveraging non-animal alternative methods and look forward to partnering with FDA to utilize these alternative methods.

IV. Study Timelines

We offer the following anticipated timeline for initial data development and submission to FDA in Table 1. We note that these timelines are estimates and could change depending on the feedback and timing of the approval of study design by FDA. However, given the

public health significance of this topic, we want to underscore our commitment to progress each of the outlined activities with a sense of urgency and sustained momentum.

Table 1. Draft Timeline for Initial Sunscreen Safety Activities

Activity	Initiation Date	Update to FDA
Clinical Safety: MUsT (conducted as part of Broader Dose-Ranging Exposure Studies)		
<i>Identification of Test Formulation</i>	10/1/2019	9/30/2020
Habits and uses survey	10/1/2019	9/30/2020
Clinical use study of Sunscreen products/actual use study	11/15/2019	9/30/2020
Sunscreen product survey	10/1/2019	9/30/2020
Identify portfolio of sunscreen ingredients	11/15/2019	9/30/2020
Identify known formulation variables	12/15/2019	9/30/2020
IVPT of marketed products	11/15/2019	9/30/2020
Develop formulations for first MUsT pilot	3/15/2020	9/30/2020
IVPT of formulations for first MUsT pilot	9/15/2020	3/15/2021
<i>Analytical Method Development</i>	10/1/2019	9/30/2020
Analytical laboratory qualification	10/1/2019	9/30/2020
Analytical method development and validation	10/1/2019	9/30/2020
<i>MUsT Protocol Development for First Active Formulation</i>	10/1/2019	9/30/2020
<i>Pilot MUsT for First Active Formulation</i>	3/1/2021	9/30/2021
Clinical Safety: Human Dermal Safety		
<i>Review of Existing Human Dermal Safety Data</i>	10/1/2019	9/30/2020
Nonclinical Safety		
<i>Review of Existing Nonclinical Safety Data</i>	10/1/2019	9/30/2020

V. Conclusion

We appreciate FDA engaging with industry on the Deferred Ingredients, which have played an instrumental role in protecting human health. This proposed Work Plan should serve as a roadmap for the process of evaluating these sunscreen active ingredients and producing data to support their GRASE determination. We look forward to collaborating with FDA closely on this Work Plan to facilitate determinations of the Deferred Ingredients.

We are available to respond to any questions or concerns you may have on this Work Plan.

Sincerely,

Alexandra Kowcz,
Chief Scientist, Executive Vice President- Science PCPC



Emily Manoso
Staff Counsel, Legal & Regulatory PCPC

