Docket No. FDA-1978-N-0018
Preliminary Comments for November 13, 2019 Meeting

MEETING PRELIMINARY COMMENTS

Personal Care Product Council
Attention: Alexandra Kowcz
Chief Scientist, Executive Vice President – Science PCPC
And
Emily H. Manoso
Staff Counsel, Legal & Regulatory PCPC
1620 L. Street, NW, Suite 1200
Washington, DC 20036

Dear Ms. Kowcz and Ms. Manoso:

We refer you to your correspondence dated September 17, 2019 providing a draft work plan for the eight sunscreen active ingredients for which you have requested deferral from final rulemaking and requesting a meeting to further discuss the details of your draft work plan.

We also refer to your meeting package dated and received October 18, 2019.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hard copy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance to 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The office record of this meeting will be the FDA-generated minutes.

If you have any questions, call CDR Trang Tran, Regulatory Project Manager at (240) 402-7945.

Sincerely,

Theresa M. Michele -S

Digitally signed by Theresa M. Michele -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300428996, cn=Theresa M. Michele -S
Date: 2019.11.08 18:26:19 -05'00'

Theresa Michele, MD
Director
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Date November 13, 2019
Time: 10:00 a.m. – 11:30 a.m.
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, MD 20903

FDA ATTENDEES (invited)

Office of New Drugs (OND), Office of Drug Evaluation IV, Division of Nonprescription Drug Products (DNDP)
Theresa Michele, MD, Director
Jenny Kelty, MD, Lead Medical Officer
Teresa A. Podruchny, MD, Medical Officer
Jane Sohn, PhD, Pharmacology-Toxicology Team Leader
D. Charles Thompson, RPh, PhD, Pharmacology-Toxicology Reviewer
Chibueze Ihunnah, PhD, Pharmacology-Toxicology Reviewer
Jennifer White, PhD, MPH, Pharmacology-Toxicology Reviewer
Steven Adah, PhD, Associate Director for Monograph
Sergio Coelho, PhD, Lead Interdisciplinary Scientist
Kristen Haslam, BSN, Regulatory Project Manager
Trang Tran, PharmD, MBA, Regulatory Project Manager

OND, Office of Drug Evaluation III, Division of Dermatology and Dental Products
David Kettl, MD, Clinical Team Leader

Office of Clinical Pharmacology
Edward (Dennis) Bashaw, PharmD, Senior Science Advisor

Office of Pharmaceutical Quality, Office of New Drug Products
Swapan De, PhD, Chemistry, Manufacturing and Controls Lead

Office of Regulatory Policy
Michael Bernstein, JD, Director, Division of Regulatory Policy II
Sharon Coleman, JD, Senior Regulatory Counsel

PERSONAL CARE PRODUCTS COUNCIL (PCPC) ATTENDEES

Alexandra Kowcz, Chief Scientist, Executive Vice President- Science PCPC
Tom Myers, General Counsel, Executive Vice President-Legal & Regulatory, PCPC
Linda Loretz, PhD, Director, Safety and Regulatory Toxicology, PCPC
Paul DeLeo, PhD, Principal, Integral Consulting
Gary Eichenbaum, PhD, Johnson & Johnson, VP Translational Science & Safety
Barbara Green, Johnson & Johnson, R&D
Jennifer Martin, Colgate-Palmolive, Director of Regulatory Affairs-North America
Espe Troyano, PhD, P&G, Director
J Nash, PhD, P&G, Research Fellow – Global Product Stewardship
Carl D'Ruiz, MPH, DSM Nutritional Products, Senior Manager North America Personal Care Regulatory Affairs
Dr. Peter Griem, Symrise AG Germany
Katherine Wszolkowski, Symrise Inc USA
Eduardo Ruvolo, Beiersdorf, Director Medical Affairs, Clinical Operations and Product Research
Kathleen Edgar, Edgewell Personal Care, Director, Global Product Safety and Regulatory
Steffi Bogart, Estee Lauder Companies, Senior Vice President and Deputy General Counsel
Jeremy Wong, PhD, Estee Lauder Companies, Executive Director, Product Safety and Toxicology
Gregory Berry, EMD Performance Materials, Manager of Regulatory-Performance Materials
Joseph P. Torella, PhD, DPhil, Ashland, Vice President of Skin Care & Business Intelligence
Tony Schatz, PhD, Ashland, Sr. Global Director of Product Stewardship & Regulatory Affairs
Ryan Hamilton, PhD, Ashland, Senior Manager of Product Safety & Global Chemicals Management

Introduction:

This material consists of our preliminary responses to your questions in preparation for the discussion at the meeting scheduled for November 13, 2019 from 10:00 a.m. – 11:30 a.m. between PCPC and FDA. We are sharing this material to promote a collaborative and successful discussion. The meeting minutes, which will be posted to the public docket, will reflect an overview of the discussion.

1.0 BACKGROUND

In response to the February 26, 2019 proposed rule *Sunscreen Drug Products for Over-the-Counter Human Use* (Proposed Rule) (Docket No. FDA-1978-N-0018), PCPC and CHPA submitted a joint correspondence dated June 26, 2019 requesting that FDA defer final rulemaking on the following eight sunscreen active ingredients:

- Avobenzone
- Homosalate
- Octinoxate
- Octisalate
- Octocrylene
- Oxybenzone
- Ensulizole
- Meradimate

It is our understanding that PCPC and CHPA requested that these ingredients be deferred from final rulemaking to allow time for completion of studies necessary to fill the data gaps identified in the Proposed Rule. As described in our previous correspondence to PCPC and CHPA, FDA anticipates that if it receives a satisfactory commitment to address the data gaps identified in the Proposed Rule for a specified active ingredient, we would defer further rulemaking for that ingredient for one year, subject to renewal. However, if studies have not been commenced, or if the studies in progress do not appear, in FDA's judgment, to be productive, the Agency expects to proceed with rulemaking for the ingredient after the initial deferral period.

The Proposed Rule sets forth the data gaps for each of the active ingredients for which you have requested deferral, and describes studies that would fill these gaps. As previously noted, FDA's agreement to defer further rulemaking for each ingredient depends on receiving satisfactory commitments to fill the data gaps in a timely fashion for that ingredient. On September 17, 2019, PCPC submitted a correspondence providing a draft work plan for the eight sunscreen active ingredients listed above and requested a meeting with FDA.

The objective for the meeting on November 13, 2019, as stated in the meeting request from PCPC, is to discuss and clarify several issues related to PCPC's proposed Phase 1 clinical safety testing program and planned longer-term (Phase 2) approach for supporting a positive GRASE determination for each deferred ingredient.

2.0 DISCUSSION

The Sponsor's questions are in **bold** font; FDA preliminary comments and responses are in *italics.*

2.1. Clinical Safety Testing

Maximal Usage Trial (MUsT)-Duration of Dosing

In the FDA guidance on the MUsT, FDA recommends that subjects be dosed until levels of the active ingredient have reached steady state. The FDA's 2018 Maximal Use Trial study of sunscreen active ingredients demonstrated that subjects achieve steady state within 1 to 2 days following a four-times-daily dosing with sunscreen over a 4-day period. In consultation with FDA, PCPC plans to make a determination of adequate dosing duration for each active sunscreen ingredient based on results from a pilot MUsT in order to ensure that maximum penetration of the ingredient has taken place and to confirm the attainment of steady state blood plasma levels. If supported by clinical pharmacokinetic data from the MUsT pilot and modeling, it is proposed that the duration of dosing for the pivotal MUsT be reduced from the pilot study. (PCPC Draft Work Plan Section III.A.2. Pilot MUsT (page 9)).

Question 1: Does FDA agree that it is reasonable to reduce the duration of dosing for a pivotal MUsT if supported by data from a pilot MUsT and appropriate modeling?

FDA Response to Question 1:

With regards to reduction in the duration of dosing, we refer PCPC to the response to Question 3.

As for the use of modeling approaches to support a reduction in dosing duration or for other purposes, at this time there is not a model specific to dermal delivery that has been developed or validated for topical products. Moreover, the sunscreen ingredients for which you seek deferral are somewhat heterogeneous when it comes to chemical properties and their absorption, and partitioning into the skin to different degrees would likely necessitate individualized models, rather than a general model. If and when such models are developed, FDA is open to considering their use as appropriate, but we do not believe such models are necessary to fill the data gaps we have identified. In addition, validation of such models will be important and there is a concern that developing, testing, re-evaluating, and validating the models for their predictive nature would require a significant amount of time and resources.

To aid in development, FDA is willing to work with the PCPC and their partners to develop a Master Protocol that would standardize the MUsT program across the ingredients and reduce the time and effort needed for PCPC to undertake the needed

MUsT studies. We are happy to leverage shared knowledge about the ingredients and the design and evaluation of such trials with PCPC and their partners. The early and complete evaluation of the dermal absorption profile of these ingredients can help to inform the complementary pharmacology/toxicology program.

FDA Clinical Trial Regarding the Assessment of the Human Systemic Absorption of Sunscreen Ingredients (ClinicalTrials.gov Identifier: NCT03582215; FDA MUsT Part 2)

Question 2: Can you provide additional learnings regarding the FDA MUsT Part 2 that you are currently conducting?

FDA Response to Question 2:

The study design for the second part of the study is available on clinicaltrials.gov, and we are pursuing publication of the second part of the study. We note that one of the key takeaways seen in part 1 of the study, and which has been demonstrated in other studies reported recently in the literature (see https://doi.org/10.1016/j.envint.2019.105068), is the uptake and formation of apparent depots in the skin that result in a prolonged elimination phase. This would have a marked effect on the duration of dosing and terminal phase sampling. The article referenced above also raised the issue of drug metabolism and the need to properly identify the "species of interest" for analysis. As part of the preliminary study design work, we recommend that PCPC or their designee survey the literature on these issues to ensure they are addressed in the study design.

Question 3: Have you evaluated reduced application products (face) or considered reduced dosing based on achieving steady state (e.g., 1 day vs. 4 days)?

FDA Response to Question 3:

With regards to the question about "reduced application products (face)": At this time, FDA is seeking data to support the use of sunscreens under the conditions proposed in the Proposed Rule. Those conditions include instructions that contemplate application over all skin exposed to the sun, with reapplication at a minimum of every two hours. The labeling currently required for sunscreens marketed without approved applications includes these instructions as well. See 21 CFR 201.327. Therefore, all products were tested consistent with these instructions, as described in the Journal of the American

Medication Association (JAMA) article of May 6, 2019.[1] See response to Question 6, for further information about the consideration of "reduced application products (face)".

With regards to the question of reduced duration of dosing, the duration of the trials in the pivotal MUsT program for each ingredient will be identified/developed from the observed data from the pilot studies that we believe will need to be conducted for each ingredient. We expect attainment of steady-state to be demonstrated in both the pilot study and the series of pivotal MUsT studies for each ingredient. Once the pilot studies have been conducted, we recommend that PCPC or their designee work with the FDA in designing the appropriate trial procedures, including the duration of treatment element for each individual sunscreen active ingredient being evaluated.

Question 4: Can the FDA MUsT Part 2 study protocol and analytical methods be shared with the Sunscreen Consortium?

FDA Response to Question 4:

As noted above, the study design for part 2 is available on clinicaltrials.gov. The study protocol and analytical methods for part 2 are in most cases identical to those described for part 1 of the study, which is available in the Journal of the American Medical Association article referenced above (published May 6, 2019). There are some differences, as discussed on clinicaltrials.gov. As noted in the response to Question 2, FDA intends to publish part 2, which will include a discussion of the protocol and the analytical methods.

Human Dermal Safety Data

The Sunscreen Consortium will assemble, summarize and submit to the Docket potentially existing, nonpublic available human dermal safety data on sunscreen formulations or ingredients that may be in the possession of the Sunscreen Consortium.

Question 5: Does FDA agree that submitting existing clinical data that has not yet been reviewed by the agency may be sufficient to satisfy the FDA requirement for human dermal safety data?

[1] Matta MK, Zusterzeel R, Pilli NR, et al. Effect of sunscreen application under maximal use conditions on plasma concentration of sunscreen active ingredients: a randomized clinical trial [published May 6, 2019]. JAMA. doi:10.1001/jama.2019.5586

FDA Response to Question 5:

While there may be various acceptable approaches to supporting local safety of topical drug products, the adequacy of your proposal cannot be determined until Agency review of the clinical data you submit. Submit full reports of investigations (rather than summaries of clinical trial data).

However, we note that the Proposed Rule requested that you submit any existing data you believe can address the safety data gaps during the comment period for the Proposed Rule (which ended on June 27, 2019 after an extension). If you are currently in possession of data that you believe can address a gap in safety information for any of the sunscreen ingredients for which you have sought a deferral—and thus limit the additional studies you propose to conduct -- and you have not yet submitted this information, we request that you do so as soon as possible.

Consumer Use Survey Data

The Consortium plans on utilizing a consumer habits and uses survey as described in the PCPC Draft Work Plan (Appendix II) to confirm the real-world use habits of sunscreen drug products in the United States. We are interested in exploring whether the results of the consumer survey, as well as the marketed use of various sunscreen products (e.g. makeup products for use solely on the face), can be used to set specific parameters for determining the formulations and application criteria for the MUsT studies.

Question 6: Does FDA agree that this data would be valuable for obtaining a more accurate read on consumer sunscreen use habits and practices and that such data would be useful for informing the MUsT studies?

FDA Response to Question 6:

No, we do not agree. Because the indications and directions for use for sunscreen products do not limit use or application of these products to the face, and in fact contemplate application over all exposed skin every two hours (as conditions necessary to assure the sunscreen product's effectiveness for its labeled "Uses"—see 21 CFR 201.327(c)), consumer survey data on sunscreen drug products "…for use solely on the face…" or otherwise under "real-world use habits" are not needed to set parameters for determining the formulations and application criteria for MUsT studies intended to support the inclusion of sunscreen active ingredients in the final monograph. Rather, FDA advises that for a MuST to support inclusion of a topical active ingredient in an

OTC monograph, (1) the amount of test article applied be consistent with existing or proposed directions, (2) the surface area treated be consistent with the intended monograph directions, and (3) the frequency of dosing be at the highest frequency sought for inclusion in labeling.[2] Accordingly, we see no scientific reason to delay the initiation of MUsT studies for the ingredients for which you seek deferral while such consumer surveys are conducted.

To the extent PCPC is interested in pursuing a separate indication for sunscreen products used to help prevent sunburn solely on the face (i.e., an indication based on the "…concept of targeted application (e.g., to the face with potentially fewer applications per day) with modified direction for use…" as described at page 23 of your meeting package), such an additional indication or indications would supplement, rather than replace, the existing indications (and directions for use) for sunscreens. While FDA is open to considering the potential addition of new indication(s) to the sunscreen monograph (including what testing/data would be needed to support a finding of general recognition of safety and effectiveness for such products), the potential addition of such new indication(s) would not obviate the need for studies (including the MUsT) supporting a finding of general recognition of safety and effectiveness of ingredients for use in sunscreen products subject to the existing indications and directions for use. Discussion of a separate indication for facial use is beyond the scope of deferrals for ingredient testing.

2.2. Nonclinical Safety Testing

There are relevant studies which have been run by the National Toxicology Program for which the associated final report has not been prepared or reviewed by the Consortium. Such data will be critical for informing the safety of key ingredients and may eliminate the need for conducting unnecessary animal testing.

<u>Question 7</u>: Can FDA take the necessary steps to ensure those studies are made publicly available, such as posting the results to the Sunscreen Docket?

<u>Question 8</u>: Alternatively, is there an approach to review and discuss study results with the Agency non-publicly as this could be helpful for existing data generated in response to other regulatory requirements and internal company clinical data?

[2] See Guidance for Industry, Maximal Usage Trials for Topically Applied Active Ingredients Being Considered for Inclusion in an Over-The -Counter Monograph: Study Elements and Considerations (https://www.fda.gov/media/125080/download).

FDA Response to Questions 7 and 8:

FDA has been in communication with NTP about its work in this area to help ensure that relevant studies and study reports are publicly released as soon as possible. Our understanding is that the data and statistical analyses for NTP's carcinogenicity study of oxybenzone are available in the Chemical Effects in Biological Systems (CEBS) database (which is publicly available at https://manticore.niehs.nih.gov/cebssearch) and that a draft of the NTP technical report for this study has been issued (84 FR 54908 (October 11, 2019)). We understand that manuscripts on NTP's developmental and reproductive toxicity (DART) studies on endocrine activity for oxybenzone, octinoxate, octisalate, and octocrylene are in preparation, and that the data will be available in CEBS when these papers are published. NTP has also indicated that the data from its multigenerational DART animal studies on oxybenzone and octinoxate are currently undergoing evaluation and analysis and that it hopes to have these data available in CEBS soon. (See PASS Coalition Letter to and Response from National Toxicology Program Regarding a Request for Pending Data Related to Toxicity and other Studies on Certain Sunscreen Ingredients, Appendix A to PASS Coalition Comment on Sunscreen Proposed Rule, available at https://www.regulations.gov/document?D=FDA-1978-N-0018-11596).

We remind you that draft reports are not sufficient to help establish final monograph conditions, including active ingredients. FDA will only consider final reports.

We anticipate that there are additional non-clinical toxicology studies that have been completed for many of our sponsored ingredients but are not in the public domain and are not our property since they are subject to other regulatory body consortium confidentiality agreements (e.g., REACH). However, the costs to acquire such studies is likely to be substantial and we are uncertain if the quality of the data is enough to meet FDA expectations. As such, it would be unproductive to make such studies publicly available only to have the studies not provide FDA with the information that it is seeking.

Question 9: To avoid the unnecessary and significant cost to acquire such studies, can FDA evaluate the quality of the data contained in such studies independently and on a confidential basis to advise whether the data are supportive of sunscreen safety? Alternatively, is there a non-public approach to sharing data?

Question 10: Given the confidential nature of certain studies that have been submitted to support sunscreen ingredients in different countries, can FDA provide a mechanism for submitting summaries of those studies publicly, while redacting portions of the study or maintaining those studies as confidential?

FDA Response to Questions 9 and 10:

It is unclear whether you are seeking to have FDA obtain independent access to unspecified additional non-clinical toxicology studies which may have been completed for certain of the ingredients you wish to have deferred (but which you believe are not in the public domain and are subject to confidentiality agreements). To the extent you are requesting that FDA determine if such studies exist and if so, obtain these studies independently, we note that FDA does not have independent knowledge of or access to such studies.

If there are studies or other materials you wish to submit to support a positive GRASE determination for a particular ingredient, under the current monograph system, information intended to support a finding of general recognition of safety and/or effectiveness needs to be made publicly available in order to enable such recognition. We note that FDA has supported the inclusion of a pathway in proposed OTC monograph reform legislation through which some studies/study-related information could be discussed confidentially with FDA in certain circumstances.

2.3. Regulatory/Administrative

Future Ongoing Interactions with FDA

a. Proposed Phase 1 Activities

i. Continued interaction with FDA is anticipated and described throughout Phase 1 of the PCPC draft Work Plan. These interactions would be to assess the current status of the data and evaluate appropriate next steps for Phase 2 when activities such as those listed below are completed. For example, as described in Table 1, Draft Timeline for Initial Sunscreen Safety Activities, numerous activities are scheduled to have updates provided to FDA by September 30, 2020.

1. **Collection and submission of existing dermal safety data**
2. **Collection and submission of existing nonclinical safety data**
3. **IVPT or human PK studies to identify formulations with the highest potential for dermal penetration of active ingredients for use in each MUsT**
4. **Completion of a consumer habits and uses survey**

5. **Development and validation of the analytical method for active ingredients to be tested in each MUsT**
6. **MUsT protocol development for first active formulation**

<u>Question 11</u>: When possible, could multiple activities be combined for discussion at one meeting?

<u>FDA Response to Question 11</u>:

Yes.

b. Proposed Phase 2 Approach

Currently, we envision that the longer-term (Phase 2) activities associated with comprehensively addressing endpoints that the agency has identified for each deferred ingredient (on a case-by-case basis) will be fully developed and submitted to the agency for review following the clinical results and data needs obtained from our Phase 1 activities. Furthermore, depending on the information obtained, the Sunscreen Consortium may decide to not pursue supporting specific ingredients based on a variety of factors. We expect to keep FDA appraised of key developments via routine communications throughout each Phase of our Work Plan.

<u>Question 12</u>: Our proposed Phase 2 will provide a more robust method for determining how best to address the preclinical data needs associated with each ingredient on a case-by-case basis. It will also prioritize ingredients on the basis of some ingredients having more available data than others as indicated by FDA in the TFM. We expect that a detailed plan substantiating our approach will follow submission of the Phase 1 activity results. Does FDA agree to review our approach for filling any non-clinical data gaps under such a framework?

*<u>FDA Response to Question 12</u>***:**

No, we do not agree with your proposed workplan or with your plan to test all deferred sunscreen ingredients sequentially.

If FDA agrees to defer final rulemaking for any of the active ingredients for which you seek deferral, we expect you to provide an update one year from the date that the deferral is granted on the information you are gathering to address all data gaps. We expect your update to include the following:

- *Proposed protocols for 2-year rodent dermal carcinogenicity studies and systemic carcinogenicity studies as appropriate for each ingredient for review by*

the Division, supported by adequate dose range-finding and toxicokinetic data. These studies are outlined in the Proposed Rule.

- *Study reports for developmental and reproductive toxicity (DART) studies. For example, submit study reports for embryofetal developmental toxicity studies (i.e., teratology or Segment II studies) in two species (one rodent, one non-rodent), employing a systemic route of exposure (e.g., oral) and supported by adequate dose range-finding and toxicokinetic data. The division does not routinely review protocols for DART studies. These studies are also outlined in the Proposed Rule.*

Note that the dermal carcinogenicity study and embryofetal development studies are expected to be needed for each of the sunscreen active ingredients for which you seek deferral, regardless of the outcome of systemic absorption findings from MUsT testing. The expected need for these data derives in general from the basic fact that sunscreens are 1) drug products and 2) are applied chronically by a topical dermal route of administration.

FDA anticipates that the need for any additional nonclinical data to support inclusion of a particular active ingredient in a final monograph, beyond the dermal carcinogenicity study and embryofetal development studies, will depend upon a full evaluation of the dermal carcinogenicity study and embryofetal development studies, other available information on the sunscreen active ingredient, any known structurally similar compound indicating the potential for adverse effects, and plasma drug exposure data derived from adequate and definitive MUsT studies. The expected need and rationale for these data is outlined in further detail in the Proposed Rule.

In addition, because the dermal carcinogenicity study and embryofetal development studies are expected to be needed for each of the sunscreen ingredients for which you are seeking deferral, we do not see a scientific rationale for delaying initiation of these nonclinical studies while waiting for the results of a MUsT study.

Note that FDA's current thinking about the safety and effectiveness data needed to support inclusion of an active ingredient in a final sunscreen monograph – including the studies mentioned above – is also reflected in the guidance for industry entitled "Nonprescription Sunscreen Drug Products – Safety and Effectiveness Data."

We also note your reference to FDA's Predictive Toxicology Roadmap to justify not conducting animal studies. While the Predictive Toxicology Roadmap you refer to identifies FDA's intended approach for evaluating new methodologies and technologies for their potential to expand FDA's toxicology predictive capabilities and to potentially reduce the use of animal testing, it also clearly indicates that Agency reliance on new toxicology methods to satisfy regulatory requirements in place of toxicology studies in animals or existing data in humans will depend on receipt of "convincing data as well as

continuous dialogue and feedback among all relevant stakeholders from development to implementation, including qualification". In this case, if you propose non-animal alternative assay(s) to address identified nonclinical data gaps, provide a full description of the validation or qualification program and results for each assay at the time of your submission for review. We note that no such information was provided in your meeting package.

Question 13: What are the regulatory ramifications for ingredients that may not be supported by the Consortium, and how would we notify FDA of such?

Question 14: What are the regulatory impacts for end use products if an ingredient is no longer supported?

Non-GRASE Sell Through Products

Question 15: Please advise on the permissible introduction into commerce (aka *sell through*) for products containing a sunscreen active ingredient which is found to be *not generally recognized as safe and effective* in a final monograph.

FDA Response to Questions 13, 14 and 15:

If at any time you choose not to continue to support an ongoing deferral for a particular active ingredient, submit a letter stating so to the docket (along with a courtesy copy by email to Trang Tran).

Until a final rule has been issued making a final GRASE determination for sunscreens containing a particular active ingredient, FDA intends to follow the enforcement approach described in the Proposed Rule with respect to the marketing of sunscreen products containing the active ingredient. As described in the Proposed Rule, FDA generally does not intend to object to the marketing of OTC sunscreen products that do not have an approved NDA or ANDA (unless the failure to pursue regulatory action poses a potential health hazard to the consumer) provided that these sunscreen products: (1) contain as sunscreen active ingredients only the active ingredients or combinations of active ingredients listed in 21 CFR 352.10 and 352.20 (both currently stayed); (2) do not make claims addressed in §§ 201.327(c)(3) and (g) and 310.545(a)(29)(ii); (3) comply with the requirements for OTC drugs set forth in part 201 and § 330.1 (21 CFR 330.1), the requirements for adverse event reporting for OTC drugs set forth in the FD&C Act (see section 760 (21 U.S.C. 379aa)), and the provisions of the FD&C Act addressing adulteration; and (4) follow applicable labeling and testing requirements for OTC sunscreens set forth in § 201.327.

Once a final rule has been issued making a final GRASE determination for sunscreens containing a particular active ingredient, FDA recognizes that industry will need time

after issuance of the rule to comply with its provisions. We have therefore proposed that we would not expect full compliance with such a final rule for units of sunscreen product initially introduced (or initially delivered for introduction) into interstate commerce until 1 year after the effective date of the final rule. We have proposed this extended compliance period both to allow for orderly implementation of the final rule and to help assure continued product availability to consumers. We have also proposed not to expect full compliance, even after this 1 year date, for units of product that were initially introduced (or initially delivered for introduction) into interstate commerce before the 1 year date -- such as those remaining in retail outlets. Our proposed implementation approach, which was described in the Proposed Rule and on which we solicited public comment, was informed, in part, by our understanding that there are no currently marketed sunscreen products containing the active ingredients FDA has proposed as Category II.

Question 16: Can FDA provide PCPC with further guidance on necessary next steps associated with exploring and discussing the potential alternative regulatory approaches proposed in Section 10b with the Agency?

FDA Response to Question 16:

In regards to your question as to whether alternative exposure thresholds might be applied to analysis of MUsT clinical study results in situations where there are data indicating a sunscreen active ingredient is not DNA reactive (mutagenic), we have the following comments: FDA does not expect to apply the 0.5 ng/mL threshold for sunscreen active ingredients in an identical manner as we would the threshold of toxicological concern in ICH guidance for industry M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk Guidance. For example, the 0.5 ng/mL threshold is not intended to determine if any and all nonclinical information is recommended for sunscreen active ingredients. As stated in the Proposed Rule, the systemic carcinogenicity study, and "studies to assess fertility and early embryonic development, and pre- or postnatal toxicity in rats will not be needed if an adequately conducted human MUsT shows a steady state blood level less than 0.5 ng/mL, and an adequately conducted toxicology program produces no signals indicating that the ingredient (including its clinically relevant metabolites) or any known structurally similar compound interacts with related pathways." We also refer you to the guidance for industry Nonprescription Sunscreen Drug Products – Safety and Effectiveness Data.

For example, if you have findings of concern in your dermal carcinogenicity study, which evaluates all tissues and organs, or in the embryo-fetal developmental toxicity studies in two species, the findings will be considered in determining whether a systemic carcinogenicity study, and the fertility and pre- and post-natal developmental toxicity studies, need to be conducted to support the safety of a given active ingredient.

As further background, the 0.5 ng/mL threshold that FDA believes to be appropriate for triggering a recommendation to conduct additional nonclinical systemic toxicity testing is based on the principles of ICH guidance for industry M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk Guidance. It is meant to reflect an estimated mean plasma concentration value that would result were a chemical, in an amount equivalent to the Threshold of Toxicological Concern (TTC) of 1.5 µg/day, instantaneously injected directly and distributed uniformly in the total plasma volume (~3000 mL) of an average adult human. FDA expects that our interpretation of the threshold from a risk assessment perspective will be driven by the adequacy of the MUsT study design(s) in terms of statistical power, blood sampling (ensuring attainment of steady state), bioanalytical methodology sensitivity, and inherent variability of the resulting data. Ultimately, determination of the need for additional nonclinical safety testing to support inclusion of an active ingredient in a final sunscreen monograph will be an FDA review issue based on a full evaluation of all available information at the time of your submission of the initial data from the dermal carcinogenicity and the embryofetal development studies.