

COMMENTS SUBMITTED BY



**Sunscreen Drug Products for Over-the-Counter Human Use, Tentative Final Monograph
Docket No. FDA-1978-N-0018**

June 26, 2019

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Introduction and Executive Summary

The Personal Care Products Council (Council)¹ and the Consumer Healthcare Products Association (CHPA)² collectively play a major role in advancing the science of sunscreen safety and efficacy. We are pleased to submit the following Comments in response to the Food and Drug Administration's ("FDA") Tentative Final Monograph for Sunscreen Drug Products for Over-the-Counter Human Use ("TFM"), published at 84 Fed. Reg. 6204 on February 26, 2019.

Sunscreens are among the most important OTC drug categories because they provide a vital public health benefit -- protecting consumers against the harmful effects of ultra-violet radiation and, most importantly, playing a critical role in the fight against skin cancer. The Centers for Disease Control and Prevention, the American Academy of Dermatology, the Skin Cancer Foundation, and health care professionals worldwide all emphasize the importance of sunscreen use as part of a safe sun regimen. The dangers of sun exposure are clear and universally recognized by public health professionals and dermatologists, hence the benefits of sunscreens are clear. Of particular concern, skin cancer is on the rise in the United States. In 2019, the American Cancer Society estimates there will be 96,480 new cases of malignant melanoma, the most serious form of skin cancer, and more than two million new cases of basal cell and squamous cell skin cancers in the United States.³

Because of their well-established role in protecting public health, the significant benefits provided by sunscreens need to be appropriately weighed against any potential risks.⁴ We support FDA's commitment to ensuring that sunscreens are safe and effective for their intended use. We are confident that currently marketed sunscreens are both safe and effective. This is

¹Based in Washington, D.C., the **Personal Care Products Council** is the leading national trade association representing the global cosmetic and personal care products industry. Founded in 1894, the Council's more than 600 member companies manufacture, distribute, and supply the vast majority of finished personal care products marketed in the United States. As the makers of a diverse range of products that millions of consumers rely on every day, from sunscreens, toothpaste, and shampoo to moisturizer, lipstick, and fragrance, member companies are global leaders committed to product safety, quality, and innovation. Visit www.personalcarecouncil.org

² The **Consumer Healthcare Products Association (CHPA)** is the 138-year-old national trade association representing the leading manufacturers and marketers of over-the-counter (OTC) medicines and dietary supplements. Every dollar spent by consumers on OTC medicines saves the U.S. healthcare system more than \$7, contributing a total of \$146 billion in savings each year. CHPA is committed to empowering self-care by preserving and expanding choice and availability of consumer healthcare products. www.chpa.org

³ See Key Statistics for Melanoma Skin Cancer, <https://www.cancer.org/cancer/melanoma-skin-cancer/about/key-statistics.html>, accessed June 21, 2019.

⁴ In the Tentative Final Monograph, FDA did not address the benefits of the active ingredients that the Agency proposed to re-classify as category III. Under FDA's regulations implementing the OTC Drug Review, FDA stated that the advisory review panels must consider the benefits of a drug in determining GRASE status. 21 C.F.R. § 330.10(a)(4)(iii); see also 37 Fed. Reg. at 9469 (May 11, 1972) ("In every instance the panel must evaluate whether, balancing the benefits against the risks, the target population will experience a beneficial rather than a detrimental effect."). The Agency also has a long history of considering benefits in the safety and effectiveness determination for various active ingredients. 65 Fed. Reg., at 24704 (Apr. 27, 2000). Given the important and well-established benefits that sunscreens provide, FDA should consider the substantial benefits of these active ingredients in the Agency's GRASE evaluation.

based on the long history of safe use of these products in the United States and around the world, the breadth of existing safety data, as discussed in more detail in this and prior submissions, and the established benefits that sunscreens provide. We strongly believe that sunscreens play a critical role in protecting the public health and their continued use must be encouraged, as FDA noted in its press release accompanying the February 23, 2019 Tentative Final Monograph (TFM).

In examining FDA's discussion of its proposals, however, we are concerned that the actions taken by the agency may be causing undue worry and confusing consumers about the exact purpose of FDA's actions. The TFM and associated messaging may result in unintended negative health effects by deterring consumers from using sunscreens. It also significantly departs from how the agency has handled other OTC rulemakings where it has requested additional information to establish GRASE status of certain active ingredients.

For these reasons, we are concerned by some of the key themes that run throughout the Tentative Final Monograph. Namely, the: proposed reclassification of twelve sunscreen active ingredients as Category III; failure to leverage existing safety data; lack of consideration of newer toxicological methods for certain endpoints; the underestimated test costs and economic impacts to industry; the potential for unintended consequences such as consumers not utilizing sunscreens during the critical "sun season" due to the perception that ingredients are unsafe; and that much of this TFM seems counter to the express aims of the Sunscreen Innovation Act.

First, as stated above, we are concerned that the proposed reclassification of twelve ingredients as Category III is creating consumer confusion about whether consumers should continue to use sunscreens and whether sunscreens are safe. While the agency explained in the TFM that "this proposed rule does not represent a conclusion by FDA that the sunscreen active ingredients included in the Stayed 1999 Final Monograph but proposed here as Category III are unsafe for use in sunscreens," the TFM itself entirely fails to expressly acknowledge the critical public health benefits of continued sunscreen use. We urge FDA in the final rulemaking to strongly reinforce its key message shared in its press release accompanying the February 26, 2019 Tentative Final Monograph ("TFM"): "Given the recognized public health benefits of sunscreen use, Americans should continue to use sunscreen with other sun protective measures as this important rulemaking effort moves forward."⁵ It is therefore imperative that FDA take more direct action to make clear to consumers that the agency still considers sunscreens to be safe, still recommends that the public uses sunscreen regularly, and is *not* proposing to remove sunscreens containing the active ingredients that FDA has proposed to re-classify as Category III from the market.

⁵ See "FDA advances new proposed regulation to make sure that sunscreens are safe and effective," Feb. 23, 2019, available at: <https://www.fda.gov/news-events/press-announcements/fda-advances-new-proposed-regulation-make-sure-sunscreens-are-safe-and-effective>.

To this point, immediately following the release of the TFM, the American Academy of Dermatology created a new webpage titled “Is Sunscreen Safe?” to address the “confusing regulatory language.”⁶ Headlines in the month following FDA’s publication of the TFM included the following:

- *FDA Admits Most Sunscreens Are Probably Unsafe*⁷
- *Parents Beware: FDA Report Claims Popular Sunscreens Might Not Be Safe or Effective*⁸
- *FDA crackdown: Most sunscreens “bamboozle” consumers*⁹
- *FDA Issues Updated Regulations on Sunscreen Products After Warning Many Contain Chemicals Not Proven Safe*¹⁰
- *Majority of sunscreens could flunk proposed FDA standards for safety and efficacy, report to say*¹¹

FDA has attempted to clarify this confusion in certain statements that the agency has subsequently made. This includes an online “Sunscreen Message for Consumers” in which the Director of the Center for Drug Evaluation and Research (“CDER”), Dr. Janet Woodcock, stated that the TFM

“does not mean that sunscreens are unsafe. It also does not mean that FDA is taking sunscreens off the market. . . We recognize the benefits of using sunscreens . . . I urge you and your family to use them.”¹²

However, we do not think these efforts are sufficient. As one example, the Environmental Working Group very recently issued a report stating that sunscreen should be a “last resort” in sun protection.¹³ We are very concerned about the levels of consumer confusion and fear that

⁶ “Is Sunscreen Safe?” The American Academy of Dermatology, February 21, 2019. <https://www.aad.org/public/spot-skin-cancer/learn-about-skin-cancer/prevent/is-sunscreen-safe>, accessed May 29, 2019.

⁷ <https://articles.mercola.com/sites/articles/archive/2019/03/13/sunscreen-safety-regulations.aspx>, accessed June 26, 2019.

⁸ <https://mom.me/news/273621-parents-beware-fda-report-claims-popular-sunscreens-might-not-be-safe-or-effective/>, accessed June 26, 2019.

⁹ https://article.wn.com/view/2019/02/21/fda_crackdown_most_sunscreens_8216bamboozle_8217_consumers/, accessed June 26, 2019.

¹⁰ <https://philadelphia.cbslocal.com/2019/02/22/fda-issues-updated-regulations-on-sunscreen-products-after-warning-many-contain-chemicals-not-proven-safe/>, accessed June 26, 2019.

¹¹ “Majority of Sunscreens Could Flunk FDA Proposed FDA standards for safety and efficacy, report to say.” CNN. May 21, 2019. <https://www.cnn.com/2019/05/15/health/sunscreen-fda-safety-standards-study/index.html>, accessed May 29, 2019.

¹² See “A Sunscreen Message for Consumers,” May 6, 2019, *available at*: <https://www.youtube.com/watch?reload=9&v=MtV0519rVU8>, accessed June 25, 2019.

¹³ <https://www.ewg.org/sunscreen/>, accessed June 21, 2019.

remain regarding the safety of sunscreens, particularly as we are in the summer months. In addition to consumers, there is the strong potential for retailer confusion such that retailers may question or institute “commercial bans” of products containing Category III ingredients.

Given the additional information that we discuss below relating to plans for additional safety testing, existing real-world safety data and post-market surveillance data, we do not think that the agency’s proposal to re-classify the twelve active ingredients as Category III is the most appropriate approach under the existing legal framework. If the agency moves forward in issuing a final monograph in the short term, we urge the agency to include in the final monograph only the two filters for which the agency has not requested additional data: titanium dioxide and zinc oxide, and to grant Category I status for those ingredients for which new information is submitted during the comment period that supports a positive GRASE determination. Separately, we urge the agency to withdraw its proposal to classify the remaining filters as Category III and to, instead, reissue a TFM proposing to classify these remaining filters as Category I. The existing and anticipated data supports such a proposal. Further, a proposal to classify these twelve active ingredients as Category I would clarify FDA’s message regarding the use of sunscreens containing these ingredients – i.e., that consumers should continue to use sunscreens and that FDA does not anticipate removing such sunscreens from the market.

Regarding the determination of ingredient safety, we know that this is a vital aspect of FDA’s mission. We submit that in order to achieve FDA’s goals, the determination of safety should use a holistic approach taking into account all information currently available and various approaches for generating additional information. In previous Comments pertaining to the FDA Guidance ‘Nonprescription Sunscreen Drug Products - Safety and Effectiveness Data’¹⁴, we recommended FDA include alternative approaches as part of the toxicological risk assessment and determination of an acceptable margin of safety (MOS). We also recommend that FDA consider information submitted utilizing such MoS assessments in the determination of GRASE for those ingredients. We advocated for the FDA to consider the input from experts and utilize more modern toxicological approaches when assessing the risk of an ingredient, noting that *in silico* and *in vitro* techniques together with traditional *in vivo* testing can provide a robust and quantitative risk assessment for ingredients and products. It is in the interest of public health for industry to work with FDA to reasonably bridge any data gaps that will allow for determination of an acceptable MOS for sunscreen ingredients under product intended use conditions.

To that end, industry remains very willing to work together with FDA to develop a work-plan for providing data to support the safety of sunscreen active ingredients. As explained in more detail below, we do not think the safety testing requirements that the agency set forth in the

¹⁴ Comment from the Personal Care Products Council and the Consumer Healthcare Products Association on Over-the-Counter Sunscreens: Safety and Effectiveness Data; Draft Guidance for Industry, Docket No. FDA-2015-D-4021, submitted Feb. 23, 2016.

TFM are the only mechanisms by which the safety of these ingredients can be affirmed, nor are these requirements necessarily consistent with current science and the recent approach that FDA has taken in evaluating the safety of other categories of medical products. As CDER purports to encourage,¹⁵ FDA should consider other potential categories of valid scientific evidence, including real world evidence and post-market surveillance data. This would meaningfully reduce the time that it will take for the agency to issue a final rule on the sunscreen ingredients for which deferral is requested and provide more certainty to the public around safe sun practices.

Regarding the other important elements of the TFM, we are grateful for the opportunity to provide comments on the spray and powder dosage forms for sunscreens and are confident that the recommendations and data provided in each section meaningfully address the points raised by FDA. Likewise, the TFM proposes several changes with respect to the sun protection factor (“SPF”) and broad spectrum claims. Our comments reflect the diversity of the sunscreen industry and the shared goals in providing consumers access to sunscreens that will protect them from the harmful effects of the sun. Additionally, the TFM includes provisions to revise the requirements for information on the Principal Display Panel (PDP) and modifications to the drug facts label. Our labeling comments will encompass the daily-use, beach-use and combination products--sunscreens/skin protectants. More specifically, these comments will cover the FDA proposed modifications to the PDP labeling, and the Drug Facts Box, as well as the lack of small package considerations.

We are also cognizant of the economic implications of the Tentative Final Monograph. Indeed, the TFM contemplates significant changes to the current framework under which sunscreen products are manufactured. The Agency’s Economic Impact Analysis acknowledges that this rule has significant economic impact on industry. Changes to the SPF test method and enhanced clinical laboratory controls will require sponsors and contract research laboratories to make changes to internal procedures and contractual agreements, which cannot be initiated until the rule is finalized at the end of November 2019. Some sunscreens may need to be reformulated to achieve the broad spectrum requirements proposed by FDA, and then will need to be re-tested following the modified method. Products affected by the proposed new requirements would need to undergo labeling changes and be relabeled to meet any new applicable labeling requirements. Like the February 2019 TFM, the June 2011 Final Rule on Sunscreen Labeling and Effectiveness Testing required a 12-month compliance period. In May 2012, FDA extended the Final Rule by six (6) months, due to “information received ... that indicates that full implementation of the 2011 final rule’s requirements for all affected products will require an additional 6 months.” However, unlike the 2011 Final Rule, the 2019 proposal could require many products to be reformulated. The TFM estimates there are more than 4,000 sunscreen products currently


¹⁵See “Real-World Evidence”, available at <https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence>, last accessed June 25, 2019.

on the U.S. market, and a significant percentage of these will therefore also require re-testing, further stretching laboratory capacity.

In the TFM, the agency acknowledged that “industry will need time after publication of any final regulations to comply with their provisions,” and proposed a compliance period of one year after the effective date of any final rule. Given the scope of changes in the TFM, one year is not sufficient time for industry to make the changes mandated by FDA. We strongly urge FDA to allow for at least a two-year compliance period. Two years is the minimum time needed to conduct newly required finished product testing with validated methods, reformulate products, and print new labels.

This timeframe is also consistent with the period of time FDA typically allows for compliance with new requirements that include labeling changes across product categories and will ensure that there is no disruption in the supply chain, which is particularly critical for this category of products. In its recent webinar on how to use voluntary standards, FDA states they allow 2-3 years to come into compliance with new standards based on the following reasons.¹⁶

Figure 1

Transition Periods 

- Standards that have been withdrawn and replaced
- Specified amount of time
- Located in the **Supplemental Information Sheet (SIS)** below the extent of recognition
- Standards that impact Quality Systems Regulations or other horizontal processes will receive a 2-3 year transition
- Will consider ISO/IEC implementation/withdrawal dates

Why?

- Allows the submitter to continue to test and develop without additional retesting
- Allows time to revalidate processes under 21 CFR 820.75(b)
- Allows testing laboratories time to validate new test methods

In addition, while the 2-year implementation period is the minimum needed to ensure a steady flow of products into the market, it is also important that industry have express authorization to sell-through inventories that are already in the market as of the compliance date to ensure continuous supply to consumers and reasonable supply chain flexibility for industry. For example, artwork for the 2020 summer sun season will be completed and in production prior to the finalization of the sunscreen monograph. Those 2020 products should be allowed by FDA to be sold through until they reach the end of their shelf life.

Finally, we understand that the TFM was published under the auspices and timelines dictated by the Sunscreen Innovation Act (the “Act”). While finalizing the sunscreen monograph

¹⁶ CDRH webinar, “Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices.” October 25, 2018. <https://www.fda.gov/media/117223/download>, accessed June 4, 2019.

is an important aspect of the Act, perhaps as critical are the stated goals of the Act: expediting the approval of new sunscreen active ingredients in the U.S. and greater consumer access to sunscreens. This is supported by a recent letter that United States Senators Johnny Isakson, Lamar Alexander, and Richard Burr wrote to the Secretary of Health and Human Services and the Acting FDA Commissioner on May 30th, 2019.¹⁷ As noted in the letter, the Sunscreen Innovation Act was intended to provide the American consumer with “new and innovative sunscreen products that are already available in many other countries.”¹⁸ We share the concerns of the Senators that, while it was likely not the intent of the FDA, the practical result of the Tentative Final Monograph is that the American consumer will likely have less access to sunscreen products if the TFM is made final in its current form.

In summary, we appreciate the opportunity to provide the FDA with our viewpoints and comments on the Tentative Final Monograph. We share in the agency’s goal of ensuring public health and, as an industry, we are committed to providing safe and effective products for our consumers. These comments reflect the time, experience, and resources of a diverse range of companies who are equally keen to see the U.S. sunscreen market aid the American consumer in protecting their skin from the damaging effects of sun. We thank the FDA for their consideration and look forward to continued work in this area.

Section II. – Safety of the Sunscreen Active Ingredients

A. Assessment of Data and Deferral Requests

The Sunscreen Monograph has identified the permitted active ingredients for sunscreens since 1978. Importantly, these ingredients do not represent “new chemical entities”. Moreover, at present, these UV filters are not considered “unsafe” as there are no human health risks identified from existing toxicological data or medical literature that would require their removal from the market. This is clearly acknowledged by the FDA in the TFM:

“ . . .we emphasize that this proposed rule does not represent a conclusion by FDA that the sunscreen active ingredients included in the Stayed 1999 Final Monograph but proposed here as Category III are unsafe for use in sunscreens. Rather, we are requesting additional information on these ingredients. . .”¹⁹

¹⁷ https://www.isakson.senate.gov/public/_cache/files/5a2ee884-0f07-4b96-b00d-9906e36dc768/05-30-19%20FDA%20sunscreen%20letter%20May%202019.pdf.

¹⁸ *Id.*

¹⁹ Tentative Final Monograph for Sunscreen Drug Products for Over-the-Counter Human Use, 84 Fed. Reg. 38, 6204-05 (Feb. 26, 2019).

In order to support the continued availability of a variety of sunscreen ingredients, PCPC/CHPA plan to request deferrals for eight of the organic ultraviolet (UV) filters moved from Category I to Category III in the Tentative Final Monograph: avobenzone, oxybenzone, homosalate, meradimate, octocrylene, octinoxate, octisalate, and ensulizole (the “Deferred Ingredients”). Industry is committed to work with FDA and to leverage formulation expertise to further demonstrate the safety of UV filters and develop a well-designed testing program. Due to the long history of use and the abundance of information and analysis generated regarding these ingredients as a result, we urge consideration of a work plan for these ingredients that acknowledges their current status.

Specifically, we propose that FDA and industry work together to enlist experts in toxicological risk assessment practices to advise and assist in the design of a testing program that uses a combination of traditional and modern approaches in the field of toxicology to address the Agency’s targeted concerns, including purported toxicological “data gaps”, and further support the continued use of these UV filters.

We look forward to creating workplans to address requests for generating additional data for each UV filter in coordination with guidance from the FDA’s Division of Nonprescription Drugs.

B. Use of All Available Data

Because the UV filters in Category III are not “new chemical entities” and have existing data supporting their safe use, the industry expects significant and collaborative dialogue with the FDA to discuss the work plans and prioritization for each UV filter. To this end, a compilation of all data, published and unpublished, for each UV filter should be assembled and made public for review to identify any potential critical toxicological effects. Only after this information has been identified, collected, and assessed can industry and FDA create the appropriate testing programs which have the greatest human relevance, and which employ the correct combination of techniques, including alternative methodologies. We note that other regulatory bodies are either currently evaluating or have conducted safety evaluations of many of these same ingredients. To our knowledge, these groups have not identified a concern related to exposure to the active ingredients currently proposed to be Category III by FDA. For example, we are aware that REACH dossiers exist for many of the UV filters and that relevant data may be found therein. We strongly encourage FDA to explore these resources and consider the data available.

Further, health authorities around the world have been reviewing their regulation of sunscreen and evolving their regulatory frameworks over the past few years. Historically and by the nature of the data that the authorities receive as a result of post market surveillance activities,

they adjust their risk map to determine 1) appropriate regulatory approach, and 2) the best use of available resources. As in the U.S., other countries with robust pharmacovigilance systems for OTC Drugs, or medicines, such as Australia and Canada, have been using signal detection data to modify their regulation of these types of products. A recent example of this evolution / progression are the Self Care Framework Initiative in Canada that has lowered the regulatory burden for sunscreens as well as other OTC drug categories, based on the fact these are self-applied products with well characterized safety profiles:

Health Canada is proposing to put in place one sensible system that treats self-care products with low risks the same way and does not create new burdens for industry. The proposed approach would also give Health Canada the authority to recall any product that may pose a danger to Canadians – while continuing to treat them differently than prescription drugs, which can pose more serious safety concerns.²⁰

In Australia, the Therapeutic Goods Administration (TGA) initiated Low Risk Products Reform in 2017, which pursues the reduction of regulatory burden for sunscreens because they are considered a low risk topical listed drug product and not a prescription medicine.²¹ Regardless of regulatory status, sunscreens have identical function, purpose and dosage forms globally and are not different in the mind of consumers. Therefore, consumers around the world should share the same level of confidence that sunscreens are safe.

Another source of available data is the National Toxicology Program (NTP), which has recently conducted a study on the ingredient oxybenzone and the potential for carcinogenesis.²² While we know that the official study reports are still in preparation, we are also aware that the data tables are available on the NTP's website. In addition, NTP has conducted a battery of *in vitro* and *in vivo* assays assessing endocrine activity for the commonly used organic UV filters which should be included as part of FDA's safety assessment. Given the Surgeon General's Call to Action on Skin Cancer, it seems disconcerting that FDA has not utilized the information generated by the NTP studies. To that end, while we recognize that NTP and the FDA are separate entities, we would hope to see greater intra-departmental collaboration when goals are shared i.e., the safety of products and public health. It is our position that there are existing data resources available which should be leveraged by the FDA to expedite the safety review process and avoid duplication of work already completed causing unnecessary use of resources and

²⁰ <https://www.canada.ca/en/health-canada/services/publications/drugs-health-products/self-care-products-and-health-canada-what-you-need-know.html>, accessed June 26, 2019.

²¹ "The Government required the Therapeutic Goods Administration (TGA) to examine whether the regulatory oversight applied to a range of products that represent a very low safety risk to consumers was consistent with the principles of best practice regulation, and further whether there were any opportunities for streamlining or simplifying current regulatory requirements for these products." (<https://www.tga.gov.au/future-regulation-low-risk-products>).

²² National Toxicology Program, Toxicology and Carcinogenesis Studies of 2-Hydroxy-4-methoxybenzophenone (CASRN 131-57-7) in Harlan Sprague Dawley SD Rats and B6C3F1 (M3) Mice (Feed Studies). Report in Preparation (<https://ntp.niehs.nih.gov/testing/status/agents/ts-10260-s.html>).

increased costs for both industry and government. We strongly encourage FDA to be more proactive in accessing all existing data.

C. Alternative Toxicological Methods

Once the available studies, both published and unpublished, are compiled for each UV filter, the data can be assessed to identify critical toxicological effects. In addition to reviewing existing data, the toxicological pathways most likely responsible for such toxicity will be proposed. Such “critical effects” and adverse outcomes pathways (AOPs) should be used to guide the discussion and design of testing programs that have the greatest human relevance and employ alternative techniques and technologies that would otherwise default to traditional animal testing.

The use of alternative studies, currently part of the evaluation process by FDA as presented in their “Predictive Toxicology Roadmap” and “Drug Safety Priorities 2018,” should be part of a program to build supportive data for the Deferred Ingredients. Such an approach was advocated by PCPC/CHPA in 2016 comments in response to FDA’s draft guidance “Nonprescription Sunscreen Drug Products — Safety and Effectiveness Data,” and represents the future of toxicology. The use of real-world evidence from safety surveillance advanced by many experts must also be part of this effort.

D. MUsT Studies

A key part of the work plan will be the human pharmacokinetic evaluation of each UV filter. It is the case that topical application of UV filters can be absorbed into the skin and lead to detectable concentrations in the central compartment, i.e., blood and/or plasma. While it is equally true that such measurable concentrations may not translate into any toxicological consequences. Again, there is no evidence that decades of exposure have elicited case reports of systemic effects. Rather, the conduct of human pharmacokinetic studies represents an important piece of information that may be used to calculate “safety margins” from representative endpoint studies.

The FDA proposed protocol for the human pharmacokinetic study, i.e., Maximal Usage Trial (MUsT), currently uses label instructions and quantities used to ensure reproducibility in efficacy testing (i.e., 2 mg/cm²). We would, however, like to work with FDA to design MUsT studies that incorporate consumer usage patterns based on data-driven real-world use of sunscreen products. Moreover, the use of MUsT study results needs to be defined in the context of suitable outcome: i.e., what is an acceptable margin of safety (MOS)? FDA’s initial MUsT study generated data in a small population of participants. We request FDA clarify that these

findings are preliminary in nature. We believe a robust program designed at full pharmacokinetic characterization of UV filters can be achieved in collaboration with FDA.

E. Data for skin sensitization, phototoxicity/photoallergy and cumulative irritation are available for most of the UV filters, alone and in combination. Dating back to the 1996 sunscreen Nonprescription Drugs Advisory Committee (NDAC) meeting with FDA, evidence from clinical testing i.e., human repeat insult patch test (HRIPT²³), phototoxicity/photoallergy and cumulative irritation tests has been presented showing the absence of skin sensitization and irritation. We recommend that for the CIT, no positive control be required. Pre-market clinical safety studies similarly demonstrate extremely low incidences of confirmed allergy.²⁴ These clinical safety studies are supported by post-market surveillance of sunscreen products, thus validating our pre-market clinical safety paradigm. We would like to discuss how this information can best be shared with FDA. We believe that the post-marketing surveillance data available from millions of consumers in conjunction with complementary evaluations from our pre-market clinical safety paradigm obviates the need to generate data regarding sensitization, phototoxicity/photoallergy and irritation, from new clinical studies on ingredients tested individually, as opposed to as part of finished products, and conducted on a limited number of subjects.

In conclusion, the industry looks forward to working with FDA in support of the continued safety of the UV filters currently included in the sunscreen monograph. This effort should be undertaken in consideration of existing data and decades of human exposure, with new data developed emphasizing human relevance and employing alternative techniques and technologies.

Section III. –Dosage Forms

A. Introduction to Powders

PCPC and its member companies support FDA's determination that the powder dosage form is eligible to be considered for inclusion in the OTC sunscreen monograph. As explained in detail below, we submit that powder sunscreen products should be generally recognized as safe and effective (GRASE) and provide important additional options for consumers who might prefer them to other sunscreen dosage forms or wish to augment other SPF products such as creams, lotions and sprays. In particular, powder sunscreen products are

²³ For the HRIPT, the standard Challenge patch is applied for approximately 24 hours, not 48 hours. We recommend that the FDA accept an approximately 24 hour Challenge patch. In addition, for most human patch tests, a positive control patch is not used for ethical reasons.

²⁴ Agin PP, Ruble K, Hermansky SJ, McCarthy TJ. (2008) Rates of allergic sensitization and irritation to oxybenzone-containing sunscreen products: a quantitative meta-analysis of 64 exaggerated use studies. *Photodermatol Photoimmunol Photomed.* 24(4):211-7.

effective because: (1) they are applied in similar amounts compared to other dosage forms, (2) they can easily be formulated to incorporate high concentrations of zinc oxide and titanium dioxide while maintaining favorable product aesthetics; (3) powder sunscreen products have the ability to maintain a high SPF level after water immersion; (4) because they are visible, powder sunscreens can easily be applied uniformly to the skin; (5) powder sunscreens are likely to be reapplied by consumers and enable application of sunscreen over make-up; (6) powder sunscreens provide another option for consumers, thereby increasing the likelihood of sun protection.

We understand that FDA has concerns regarding respiratory risk from potential unintended inhalation of powders. We include in these comments a risk assessment which addresses this concern and supports the safety of SPF powder products.

Below are our responses to the questions posed in the TFM. We would welcome the opportunity to work with the Agency to finalize a sunscreen monograph that includes the powder dosage form.

1. What amounts of powder sunscreens do consumers typically dispense?

There are two main categories of sunscreen powder products, most of which incorporate titanium dioxide and/or zinc oxide as their UV filters. Sunscreen is often incorporated in loose powder and pressed powder foundations and other powder make-up products as a secondary benefit to their cosmetic function. In addition, there are powder sunscreen products whose primary purpose is to provide sun protection. SPF powder products offer the particular benefit of being able to be applied over other skincare or makeup products.

For powder products whose primary purpose is to provide cosmetic coverage, we know that consumers apply amounts of such product sufficient to achieve the desired make-up benefit, which includes full visual coverage of the target area. Furthermore, this application often includes areas of the face that are particularly prone to burn, such as the upper cheeks, forehead and nose.

In the case of primary powder sunscreens, a large consumer study conducted a PCPC member company shows that consumers apply approximately 0.65mg/cm² per application.²⁵ This amount falls into the “real-world” range of reported dispensing levels for other dosage forms of sunscreens such as lotions ²⁶(see Table 1 below).

²⁵ Powder Sunscreen Use Study 1: A Consumer Application Study, Colorescience, Inc. May 1, 2019. Study Report included in Appendix D.

²⁶ Peterson B, and Wulf HC. (2014) “Application of Sunscreen, Theory and Reality” *Photodermatol Photoimmunol Photomed* 30: 96–101.

Table 1. Sunscreen Dosage

	Dosage (mg/cm²)
Average amount of powder used based on consumer use data ²⁷	0.65
Range of real-use amount of sunscreen applied ²⁸	0.39 – 1.0

2. What amounts of powder sunscreens are effectively transferred to the skin?

We believe that this is product- and application-dependent. We are unaware of any data that indicate less product is effectively transferred to the skin than may occur with other dosage forms. Manufacturers are sensitive to maximizing transfer and minimizing waste and messiness associated with product application. They are expert at tailoring the right application tool for their product and at incorporating coatings and polymeric binders and adhesives to ensure that products are efficiently transferred to the skin with negligible fallout.

3. How uniform is the sunscreen application across the sun-exposed area of the skin?

Powder sunscreens do not have any clear limitations regarding their ability to be applied uniformly across various sun-exposed areas of the skin. Iron oxides are frequently included in powder sunscreen formulations, making the product visible. Thus, a powder sunscreen user can see where the powder sunscreen has been applied.

4. How frequently do consumers reapply the product?

Powder sunscreens lend themselves to easy re-application. Based on survey data of 135 users of a primary powder sunscreen product, the average consumer applied the product

²⁷ Powder Sunscreen Use Study 1: A Consumer Application Study, Colorescience, Inc. May 1, 2019. Study Report included in Appendix D.

²⁸ Peterson B, at 96–101.

approximately 2.1 times per day²⁹. These findings are further corroborated by a user logbook of 19 health care professionals who were asked to keep track of the number of times they applied the product over the course of four consecutive days (Friday through Monday). The mean number of applications logged each day was 2.7 times³⁰.

Based on the data cited above, for powder sunscreens, the majority of reported doses are a result of reapplication vs. the initial dose. As shown in **Table 2**, between 52% and 62% of powder sunscreen applications are reported to be reapplication doses. These values compare favorably to other dosage forms as can be seen in data submitted to FDA in 2011³¹ and are consistent with published data from Australia which noted that based on a study of 985 consumers only between 25% to 31% of consumers applied more than 1 daily application of sunscreen to their face, head and neck³².

Table 2. Application and Reapplication Rates

	Initial Dose (%)	Re-application Dose (%)	Ratio/Initial to Reapplication
Powder Survey (n=136) ³³	47.6	52.4	0.90: 1
Powder Log (n=19) ³⁴	37.5	62.5	0.60:1
Sprays (n=387) ³⁵	71.3	28.7	2.48:1
Lotions (n=387) ³⁶	84.0	16.0	5.25:1

Several studies have demonstrated that reapplication rates are one of the most important attributes of cumulative UV exposure reduction.³⁷ A study of over 100 volunteers found that

²⁹ Powder Sunscreen Use Study 2: Survey of Consumer Use Patterns, Colorescience, Inc. June 7, 2019. Study report included in Appendix D.

³⁰ Powder Sunscreen Use Study 3: A Consumer Log of Application over 4 day period, Colorescience, Inc. May 12, 2019. Study report included in Appendix D.

³¹ Energizer Corp, submitted to FDA on October 17, 2011 Re: Comments to Docket No. FDA 1978-N-0018, RIN 0910-ZA40; (Section 7).

³² Neale R, Williams G, Green A. 2002. Application patterns among participants randomized to daily sunscreen use in a skin cancer prevention trial. *Archives of Dermatology* Vol 138(10), 1319-25.

³³ Powder Sunscreen Use Study 2: Survey of Consumer Use Patterns, Colorescience, Inc. June 7, 2019. Study report included in Appendix D.

³⁴ Powder Sunscreen Use Study 3: A Consumer Log of Application over 4 day period, Colorescience, Inc. May 12, 2019. Study report included in Appendix A.

³⁵ Energizer Corp, submitted to FDA on October 17, 2011 Re: Comments to Docket No. FDA 1978-N-0018, RIN 0910-ZA40; (Section 7).

³⁶ *Id.*

³⁷ See Diffey BL "When should Sunscreen be reapplied?" *Journal of American Academy of Dermatology* 2001; 45: 882-885; Pruijm B, Green A. "Photobiological aspects of sunscreen reapplication" *Australasian J. Dermatology* 1999; 40 14-18; Teramura T, Mizuno M., Asano H, Naito N "Relationship between sun-protection factor and

compared to the first application of sunscreen, the second application afforded 3.1 times more protection against minimal UVR – induced erythema³⁸. In addition, data under laboratory conditions have demonstrated that no significant differences were observed in SPF values achieved with either single or double applications resulting in the same total quantity of sunscreen product, implying that double application of 1mg/cm² may be as effective as a single application of 2mg/cm²³⁹.

A unique aspect of primary powder sunscreens is that these powders may be applied by users over make-up and other skincare products and even other sunscreen dosage forms (including lotions and sprays). Accordingly, powder dosage forms offer consumers an option to apply protective sun filters in instances where they normally would not due to the sunscreen's aesthetic and physical incompatibility with the relevant consumer's skincare or makeup regimen.

5. Does rubbing a powder into the skin change sunscreen effectiveness?

We do not believe that this is the case. While we understand that this is a relevant question for sprays, most powders are applied using a brush or sponge. Once applied, it is not necessary to rub a powder in and users are unlikely to further disturb the application area, since applicators are designed specifically to achieve the desired coverage.

6. Are powder dosage forms water-resistant? If they are not water-resistant, is a direction to reapply every 2 hours sufficient to assure their safe and effective use?

Powder sunscreens with hydrophobic coating have achieved water resistance. The data shown below in Table 3 demonstrates 80-minute water resistance for a primary sunscreen powder of SPF50 (four immersions of 20 minutes per the 2011 rule) where the FDA monograph and application methods were followed. Based on the strength of this data the Skin Cancer Foundation has rewarded this particular powder with its Active Seal of Approval (which takes into account SPF water testing results).

application thickness in high-performance sunscreen double application of sunscreen is recommended" *Clinical Exp Dermatology* 2012; 37: 904-908.

³⁸ See *Pruim B.*, at 14-18.

³⁹ See *Teramura*, at 904-908.

Table 3. SPF50+ after 80 minute Water Test⁴⁰

Sample Description: SPF 50 Powder							
FSTI Sample No.: 17-569							
Subjects Tested: 10							
Subject ID Number	Sex	Age	Skin Type	Base MEDu Joules/M2	19021 FDA Std SPF Static	17-569 00N1476-1M SPF Static	17-569 00N14761-1M SPF 80 Min WR
2214	F	57	II	59.50/59.50	18.00	57.50	50.00
1018	F	44	I	49.58/49.58	15.00	50.00	43.40
2215	M	18	I	49.58/49.58	15.00	57.60	57.60
1769	F	70	I	49.58/49.58	18.00	66.20	66.20
2105	M	52	II	59.50/59.50	18.00	66.17	57.50
2103	F	49	II	59.50/59.50	18.00	66.17	57.50
2217	M	22	II	59.50/59.50	15.00	57.50	57.50
2104	M	23	II	59.50/59.50	15.00	66.17	66.17
2220	F	18	II	59.50/59.50	18.00	50.00	50.00
1897	F	32	I	49.58/49.58	15.00	57.60	57.60
AVERAGE:					16.50	59.49	56.35
STD DEVIATION:					1.58	6.45	7.06
$\Lambda = ts / \text{sq root } n$					0.92	3.74	4.09
X - A					15.58	55.75	52.25
LABEL SPF					15	55	52

In order to assess how much product typically remains on skin after submersion in the 80- min water test, a study was conducted in which fifteen test sites on three different subjects were evaluated after exposure to the same water test applied for the SPF test. The investigators (Florida Skincare Testing) found that after an initial application of 2 mg/cm², the amount of product adhering to the skin after subjecting a patient to the 80 minute water resistance test protocol was calculated to be approximately 0.54 mg/cm².⁴¹

While the amount remaining on the skin was reduced from the starting concentration of 2 mg/cm², the SPF value was well-maintained (52 versus the initial value of 55, a reduction of less than 10%). Notably, the 0.54 mg/cm² is comparable to the dosage used by consumers as demonstrated in real world application data (0.65 mg/cm², Table 1). The maintenance of SPF may reflect the high starting levels of UV filters incorporated in powder sunscreens. The powder dosage form allows for incorporation of high levels of zinc oxide and titanium dioxide because the opacity of these ingredients can be mitigated by the use of high levels of coated iron oxides. This allows for greater concentrations in formulations while maintaining favorable product aesthetics leading to more use, including re-application.

⁴⁰ Static and Water Resistant test results from PCPC member company; complete report provided in comments to the TFM submitted by Colorescience, Inc.

⁴¹ Analytical Determination of Retained Powder Sunscreen Formula Following 80 Minute Water Immersion, April, 2019. Study Report included in Appendix D.

Regardless of the favorable results of water resistance testing, as with all sunscreen dosage forms, we believe that consumers, should be instructed to apply the product according to labeling instructions.

7. Can the powder dosage form be used safely and effectively over all areas of skin exposed to the sun, or should this dosage form be limited to the face?

Most SPF powders are, in fact, cosmetic-type products intended for application around the face. However, primary sunscreen powders are useful for application to other areas of exposed skin, not limited to the face. We do not believe there is any reason related to either safety or efficacy to limit usage to the face.

8. What factors, if any, should FDA consider in connection with particle size limitations or test methods for sunscreen powders?

We believe that substantial changes are needed to the particle size restrictions proposed by the FDA. We propose these changes based on the same type of quantitative risk assessment approach that has been embraced by the FDA and has been the basis of established practice by the Agency⁴².

FDA has proposed particle size limitations for both powder and spray dosage formats, essentially based on defining a boundary between respirable and non-respirable particles and assigning differing risk profiles to the fractions. With respect to proposed particle size limitations, the Tentative Final Monograph states:

“We propose that 90 percent of the particles dispensed from the consumer container must be at least 10 μ m or greater in order to limit exposure beyond the larynx, and to prevent deposition in the deep lung, the minimum particle size dispensed from the consumer container must be no less than 5 μ m. This limit was chosen because it is the lowest whole number above the generally accepted threshold (4 μ m) at which particles enter the unciliated airway and because it allows for experimental error that may be inherent in particle size measurements.”

With the concept of GRASE, we believe that any proposed limitations of this concept in the form of particle size restrictions should be made within the framework of a toxicology-focused quantitative health risk approach designed to protect human health against potential adverse effects from over-the-counter sunscreen products.

⁴² Peter Barton Hutt, Richard Merrill, and Lewis Grossman, “Food and Drug Law University Casebook Series” 4th edition, Foundation Press (1387-1394).

In considering a quantitative health risk approach it is noted that powder sunscreens generally consist of GRASE UV active ingredients (titanium dioxide and zinc oxide) in the powder state, GRAS FDA-approved colorants (21 CFR parts 73 and 74), and additional minor fraction excipients including liquids and binders. The constituent associated with the highest level of concern from a risk-based standpoint is titanium dioxide, which is considered GRASE by the FDA.

To provide FDA with a quantitative risk assessment, an analysis has been conducted by RHP Risk Management Consulting Services. The analysis is principally focused on titanium dioxide but also addresses the powder dosage format as a whole. As quantified in the RHP report (included in Appendix D), the threshold suggested in the tentative proposed monograph far exceeds the parameters associated with protecting the general population from the risk associated with inhaling a powder sunscreen. RHP applies a human-health risk assessment approach based on published No Significant Risk Levels (NSRL) coupled with empirical data for mass-based exposure concentrations during application of powder-form OTC sunscreens. RHP conducted multiple analyses that consider typical consumer use of powder sunscreens together with well-established National Institute for Occupational Safety and Health (NIOSH) values for particle size fractions of “fine” titanium dioxide (median aerodynamic diameter of 2.1 μm) and “ultrafine” titanium dioxide (median aerodynamic diameter of 0.1 μm).

In the most basic assessment, the RHP report concludes that in the case of a powder sunscreen having 100% airborne fraction of titanium dioxide with a 50% cut-point of 2.1 μm , the maximal excess risk at a 4-times per day application rate is approximately 1:8,000,000. In fact, the report concludes that for a “4-times per day application pattern, every day, over a 70-year lifetime, more than 300 applications per day (every day) would be required to reach an excess cancer risk level of 1:100,000”. We believe this analysis clearly illustrates the need for a reconsideration of the particle size restrictions proposed in the Tentative Final Monograph.

A second assessment in the RHP report considers the published particle size distribution data by Liu et al.⁴³ on powder formats that have been deagglomerated beyond a level experienced during normal consumer use. In this analysis, the NSRL associated with “fine” titanium dioxide is assigned to the fraction of particle size distribution $>5\mu\text{m}$ while the NSRL associated with “ultrafine” titanium dioxide is assigned to the fraction of particle size distribution $<5\mu\text{m}$. This is a very conservative approach given the particle fraction median values defined earlier. In this analysis, the maximal excess risk at a 4-times per day application rate is approximately 1:5,000,000.

⁴³ Liu X et al (2019) Particle Size Distribution Analysis of OTC Aerosol or Powder Drug Products with Potential for Inadvertent Inhalation Exposure to Consumers. *Pharm Sci.* 108(4):1506-1511.

In a third approach, RHP determines a “particle size exceedance fraction” consistent with NIOSH’s approach of associating a cut-point at 0.1µm to a stringent risk value and calculating the particle distribution fraction that would be required to meet an excess risk criterion of 1:1,000,000 based on consumer use. RHP concludes this risk level is met when “no more than 98.4% of the particles dispensed from the consumer container may be 0.1µm or smaller”.

The RHP analysis further discusses that the data in the Liu et al. publication were generated using a method that resulted in measurement of particle size distributions with a “greater prevalence of small diameter” particles than would be representative of use by the consumer. Proposed modifications to this basic method in order to properly reflect consumer use conditions will be discussed subsequently. Nevertheless, the particle size distributions reported in the publication cited by the FDA can be used, as in the RHP report, to formulate additionally conservative risk assessments. Based on the RHP assessment, we support the following proposals as they relate to particle size restrictions:

Proposal 1: Calculated Risk Level ≤ 1:5,000,000

Powder dosage formats as considered GRASE with no particle size restriction.

This proposal considers the particle size distributions in the publication cited by the FDA and associates them with NSRL values for fine and ultrafine particles of titanium dioxide where the size boundary is set to that associated with respirable particles as discussed in the Tentative Final Monograph.

Proposal 2: Calculated Risk Level ≤ 1:8,000,000

Powder dosage formats as considered GRASE with a particle size restriction set such that no more than 50% of the particles dispensed from the consumer container may be 2.1µm or smaller.

This proposal considers the particle size distributions in the publication cited by the FDA and associates them with NSRL values for fine particles of titanium dioxide which most closely reflects the measured particle size distributions of sampled commercial powder formats.

We believe that when taken together, these approaches all suggest an extremely low level of risk to the consumer and recommend that the FDA adopt a position that the powder dosage format be classified as GRASE with no particle size restriction in the final monograph. The FDA has previously established that a risk level of 1:1,000,000 is “for all practical purposes zero”⁴⁴, “the

⁴⁴ 50 Fed. Reg. 51551, 51557 (December 18, 1985).

functional equivalent of no risk at all”⁴⁵, and “so low as to effectively be no risk”⁴⁶, and this standard remains in effect today (*see* 21CFR500, for example). We propose that this well-established criterion serve as the basis for a quantitative risk assessment based on FDA’s recognized position.

We would additionally like to note that under current good manufacturing practices, sunscreen products could meet a threshold of 90% of the particle size distribution greater than 10 µm on a volume weighted basis (as proposed by the FDA); and 95% of the particle size distribution greater than 5 µm on a volume weighted basis (a slight modification from the FDA proposal). However, as explained above, we do not believe that there is credible scientific data to support even that restrictive of a setting. We also believe that restriction at this level would disassociate policy making from scientifically-based risk management.

Methodology Considerations for Particle Size Distribution Measurement

While we believe that no particle size measurement is necessary to support GRASE status of the powder sunscreen dosage format, we believe it is necessary to define appropriate conditions for measurement in the event that the FDA requires a particle size restriction.

Similar to the recommendations related to spray sunscreens, the industry believes that particles should be assessed during the product development process and not as part of lot-by-lot release. Particle size characteristics of a powder dosage form should be appropriately established during product development, as this property is defined prior to its manufacture. Particle size of the formulation is then verified during the course of product validation, consistent with cGMPs (21 CFR part 211). As a critical attribute, particle size should be built into the product design early in development, consistent with Quality by Design principles.⁴⁷ Particle size is reassessed if the manufacturing process or formulation undergoes significant changes which could have an impact on particle size. Therefore, there is no need for batch testing of particle size distribution prior to product release as this property has been established and properly validated.

We believe that any particle size measurement technique demonstrating the capability of accurately measuring aerodynamic diameter and that can be calibrated using National Institute of Standards and Technology (NIST) traceable standards over the particle size region of interest and which reflects real world use conditions (as further explained below) is suitable for determination of powder particle size distribution. Static light scattering (including laser diffraction) has been identified as one suitable method. This method uses the angular distribution of the intensity of scattered light by particles to derive particle size distribution. Commercial

⁴⁵ 51 Fed. Reg. 28331, 28344 (August 7, 1986).

⁴⁶ 50 Fed. Reg. 45530, 45541 (October 31, 1985).

⁴⁷ *See* International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Q8(R2); August 2009.

instruments are available to manufacturers, along with calibration standards in the form of uniform polymer particles traceable to NIST and having discrete sizes typical of those comprising sunscreen powders.

In addition to measurement method, the effect of test measurement conditions pertaining to sample introduction to particle size analyzers must be considered. Taking guidance from the proposed monograph relating to the spray dosage format, which is also applied to powders, the FDA states:

“For purposes of these proposed particle size requirements, we are using the term particle size broadly to mean the discrete unit emitted from the [spray] container that is available for inhalation by a consumer when the product is applied” [underlined for emphasis]

We agree with FDA that it is the size of the particle to which the consumer is exposed that is relevant. In the case of the powder dosage format, the discrete unit consists of the agglomerated and aggregated particles dispensed by the container. The UV actives and colorants are generally surface treated to impart hydrophobicity for multiple purposes including imparting water resistance (as tested per 21 CFR Parts 347/352), to aid in adherence to the skin and to aid in consumer acceptance with respect to aesthetics (skin feel). Accordingly, the powders are held together by electrostatic forces to form bound agglomerates the size of which may be influenced by external conditions such as those experienced during application by the consumer.

Consistent with FDA guidance in the proposed monograph, we agree that experimental conditions during particle size measurement should reflect those typical of conditions during dose format application. This is important to note since most commercial particle size analyzers are equipped with on-board measures designed to deagglomerate powders by imparting shear force. Experimentation recently undertaken at two laboratories has determined that employing any de-agglomeration measure necessarily leads to misleading distributions reflecting significantly smaller particles than would be dispensed from a consumer container (data not shown). Measurements should be made in the absence of any such applied shear forces beyond those imparted during the course of normal application of the dosage form.

The recommendations of industry for performing measurements and analysis are as follows:

1. The dosage format should be examined as a whole and not evaluated on the basis of constituent ingredients.
2. The measurement medium should reflect the application environment of the dosage form to the consumer. Measurement in the dry state is strongly recommended as dispersion in the liquid state does not represent the discrete particle unit applicable to the dosage form.

3. Powder deagglomeration should be limited to no more than is experienced during the application of the product by the consumer. The powder dose format should be directly dosed into the particle size analyzer or introduced via a reasonable proxy.
4. A particle size analyzer should be chosen to have demonstrated sensitivity in the particle size region of interest which can be validated and verified using NIST traceable particle size standards of appropriate size.
5. The instrumental configuration used should maintain a relatively short distance between sample entry and measurement locations representative of the distance typical of application to the face. This will discourage any re-agglomeration that may take place over larger distances and lead to larger sizes than what would be experienced during consumer application.
6. Analysis of light scattering-based measurements should use appropriate optical constants (real and imaginary refractive indices) that are representative of the composition of the powder sunscreen in total.
7. Data analysis of light scattering-based measurements should be conducted using an appropriate formalism (full Mie theory or the equivalent) such that the small particle fraction is not undercounted and is accurately reflected. Distributions should also be reported on a volume weighted basis.

9. Are there important differences among powder types (e.g., loose, compact) or applicators that would affect particle size testing?

In all cases, particle size testing should be conducted using validated methodology and measuring particles which are an accurate reflection of consumer exposure. Industry believes that product formulation is equally impactful of particle size consideration as is applicator or dose type. We believe that all powder sunscreens should follow the same particle size testing regardless of applicator or type.

B. Sprays

PCPC/CHPA support FDA's definition of spray sunscreen and the inclusion of sunscreen spray as a dosage form in the final rule. Current FDA-required SPF and broad spectrum tests are appropriate for evaluating the efficacy of sunscreens in spray dosage form. We understand that there are two primary safety concerns specific to sprays, respiratory risk from inhalation and flammability. We agree that both can be appropriately mitigated by formulation limitations, labeling requirements and adequate testing. We have more specific comments on these mitigating factors.

1. Formulation Limitations

Industry currently mitigates risk from inhalation during product development, when ingredients are carefully evaluated for safety based on expected exposure and type of application before incorporation into the final formulation. Because multiple factors affect particle size, including the composition of the formula, the choice of packaging/valve design⁴⁸, the propellant used and the concentrate to propellant ratio, these factors are considered and optimized during product development. Particle size measurements are therefore conducted during formulation qualification, not during lot release testing. This is consistent with cGMPs (21 CFR part 211) and Quality by Design principles⁴⁹ ⁵⁰, which encourage building quality into the products early in the development cycle vs. inspecting a product once manufactured.

In the event of significant manufacturing, packaging component (container/closure) or formulation changes, the tests to qualify the formulation are conducted again. Therefore, we request that FDA change the required testing to be performed as products are dispensed from the consumer container as part of the product formulation qualification and validation, and not as part of the lot release testing. Lot release testing would be a significant deviation from standard practice, is not necessary to ensure consumer safety and would place a significant burden, both economic and laboratory resources, on the industry. We further request that FDA modify the referenced USP general testing methodology (General Chapter 601 part B) to allow for validated alternatives, which is permitted by USP and is common industry practice. Similar principles for testing are in place for qualification of packaging, including child resistant packaging testing and human safety testing, such as dermal irritation.

We request that FDA amend the specification for particle size to include a lower limit. As written, “must be no less than 5 μm ” could be interpreted to mean that even one particle less than 5 μm would be unacceptable, or not GRASE. A lower limit is required to make this specification actionable. The size threshold that distinguishes respirable and non-respirable particles is subject to expert discussion. For example, 4 μm (instead of 5 μm) has been cited as the appropriate lower particle size threshold that can reach the alveoli and bronchioles that constitute the deep lung⁵¹. Therefore, we request that the specification be amended to allow “no

⁴⁸ Durand, L., Habran, N., Denis, C., Meulders, L., Henschel, V. and Amighi, K. Influence of different parameters on droplet size and size distribution of sprayable sunscreen emulsions with high concentration of UV-filters. *International Journal of Cosmetic Science*, 29: 461-471. 2007.

⁴⁹ International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Q8(R2); August 2009. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf, accessed April 23, 2019.

⁵⁰ Yu, L., Amidon, G., Khan, M., Hoag, S., Polli, J., Raju, G. and Woodcock, J. Understanding pharmaceutical quality by design. *The AAPS Journal*, 16: 771-783. 2014.

⁵¹ Reist, P., Basic aerosol science. In *Patty's Industrial Hygiene* 6th edition. Edited by Vernon E. Rose and Barbara Cohnsen. John Wiley & Sons, Inc: New York. P 190-240. 2011.

more than 1% of particles may be below 5 μm ". The revised specification would read "90 percent of the particles dispensed from the consumer container must be at least 10 μm or greater and no more than 1 percent of the particles dispensed from the consumer container may be less than 5 μm ". A review of serious adverse events associated with sunscreen sprays from FDA's FAERS database (2009-2018) shows that serious adverse events with sunscreens in general and spray sunscreens in particular are very rare⁵². These data support the proposed specification and testing during product qualification.

2. Spray Sunscreen Labelling and Testing

Sunscreen aerosol application is not a direct inhalation dosage, but a secondary risk factor. By limiting the number of particles that can be deposited in the deep lung to an inconsequential amount that is not directionally sprayed in the respirable area, these particles would have an insignificant probability of reaching the deep lung. Current use instructions in labeling guide consumers in ways to further avoid any risk of unintended inhalation.

We support the proposed labeling in the "Directions" section of Drug Facts Labeling to minimize unintended inhalation, which is widely used on currently marketed spray sunscreens, consistent with the 2018 Enforcement Policy for OTC sunscreens. We agree with the warning language in Drug Facts: Flammable or Combustible: keep away from fire or flame. We agree that it is not necessary to include labeling instructions to rub the spray sunscreens into the skin.

For flammable spray sunscreens, we propose the labeling state, "Wait until spray is dry to the touch before approaching a heat source or before smoking". This simplifies and shortens the instructions rather than adding wait times of 5 or 10 minutes, per FDA's proposal. Products with extended drying times are unlikely to be consumer-acceptable, but there is no justification for declaring them not GRASE. We agree with FDA's proposal to limit the flammability of spray products and require flammability labeling of spray sunscreens, when appropriate. We further agree that the category "extremely flammable" would not be GRASE.

3. Flammability Testing

It is important to note that not all spray sunscreens will be tested or labeled for flammability. Use of certain technologies and formulations does not result in flammable potential. For example, bag-on-valve technology could contain zero percent ethanol or nearly

⁵² Reports of Serious Adverse Events Associated with Spray Sunscreens in the United States Food and Drug Administration Adverse Event Reporting System Database. January 1, 2009 to December 31, 2018. Results Summary. Prepared for Consumer Healthcare Products Association by PharmaLex US Corporation and submitted to Docket FDA-1978-N-0018.

80% ethanol. Hence, it is critical that FDA require testing and labeling “as appropriate” to prevent unnecessary testing.

Similar to our comments for particle size, flammability characteristics and the associated testing, including dry time, is also performed during product development, not during lot release testing. This is consistent with cGMPs (21 CFR part 211) and Quality by Design principles which encourage building quality into the products early in the development cycle vs. inspecting a product once manufactured. Similar principles for testing are in place for qualification of packaging, including child resistant packaging testing and human safety testing, such as dermal irritation. In the event of manufacturing, packaging (container/closure) component or formulation changes requiring re-validation, the tests are conducted again. We request that FDA amend the TFM to state that “all sunscreen spray products be tested for flammability in accordance with 16 CFR 1500.43a, 16 CFR 1500.45 or validated alternative method, as appropriate, as part of product formulation qualification and validation in accordance with cGMP requirements”.

4. Summary and Conclusion

In summary, we believe the above comments provide the necessary data for FDA to finalize the sunscreen monograph and address the potential safety concerns that could be associated with sunscreen products formulated in spray dosage forms. We also believe that the materials provided here can mitigate the formulation limitations put forth by the TFM for labeling requirements and adequate testing.

We request the following changes be made prior to publication of the final monograph:

- Particle Size specification: “90 percent of the particles dispensed from the consumer container must be at least 10 μm or greater and no more than 1 percent of the particles dispensed from the consumer container may be less than 5 μm ;”
- Particle size testing completed during formulation qualification, not as part of lot release testing;
- Flammability testing completed during formulation qualification, not as part of lot release testing; and
- Flammability testing limited to those types of formulas that may present a risk based on flammability potential

We also request an extended implementation timeline to meet the finalized particle size and flammability testing requirements, given limited testing lab capacity, resource considerations and necessary time required to conduct method validation.

Section IV. SPF

A. SPF CAP 60+ and Labeling Ranges

The SPF value of a sunscreen product is a critical component of any sunscreen. Consequently, the FDA's proposal to cap the SPF value at 60+ generated much conversation with a variety of viewpoints and interest from industry. Because each individual company has a unique portfolio of products and intended consumer audiences, we anticipate that individual companies will file their own submissions with FDA outlining their stance on the proposed cap.

We are amenable to the concept proposed by the Agency to create ranges for SPF label claims shown below. We understand that in connection with the SPF cap at 60+, individual companies may also present proposed revisions to the labeling table consistent with their stance on the proposed SPF cap.

Labeling Table

TABLE 1 TO PARAGRAPH (b)(2)(i)—
SPF LABELING RANGES

Range of determined SPF values	Associated labeled SPF value
60-80	60+
50-59	50.
40-49	40.
30-39	30.
25-29	25.
20-24	20.
15-19	15.
2-14	Determined SPF Value.

B. SPF Testing Methodology and Calculations

It is our understanding that the 2019 TFM procedure for determining the SPF that would appear on the label of a sunscreen product would be as follows:

1. The Determination of SPF [Proposed Rule, p. 6269, §201.327 (7)] would be followed to calculate the mean, standard deviation and standard error (SE) from the valid individual SPF values in an SPF test panel. Using the Student's t-distribution table as described in (7), "the SPF value determined from the test results is equal to the largest whole number less than the mean SPF - (t*SE)". (This calculation remains essentially unchanged from the SPF calculation in the 2011 Final Rule on Labeling and Effectiveness Testing, p.35664 (6) "Determination of SPF".)

2. The “determined SPF” derived using the calculation above is also described in the TFM section §201.327 (b)(2) “Effectiveness claim” (PR page 6264), which similarly states that the “determined SPF value” refers to the calculated SPF value that equals the “largest whole number less than the mean SPF – (t*SE)”.
3. The “determined SPF” is reviewed per Table 1 (PR §201.327 (b)(2)(i)), where this determined value is matched to a “Range of determined SPF values” to find the appropriate “Associated labeled SPF value”.
 - For example, a “determined” SPF value of 37 based on a panel of test results would qualify for a label claim of SPF 30 per Table 1.
 - Similarly, a “determined” SPF value of 70 would qualify for a label claim of SPF 60+ per Table 1.
 -

Industry requests confirmation from FDA that our understanding as noted is correct.

C. Initial (Preliminary) MEDu Timing

In the 2019 TFM, FDA established the requirement to conduct the preliminary MEDu no more than one day before the product test. Previously, that timing was recommended, but not required. Industry’s concern regarding this “one day before” testing requirement for the preliminary MEDu would set up a situation where laboratories conducting SPF testing would be unable to begin FDA monograph testing on Mondays (as the preliminary MEDu would have to be done on Sunday). That would significantly reduce the number of product tests per week that could be completed. Laboratories report that the preliminary MEDu rarely changes. In addition, if required to perform the preliminary MEDu the day before each product test, each test panelist may have to make an extra visit to the lab during the test week, which would both increase testing costs and further reduce daily laboratory testing capacity due to the need to conduct initial MEDu tests daily, in place of product tests.

Currently, there is a shortage of capacity in clinical SPF laboratories, with a 3-4 month waiting time for test evaluations not unusual. Further diminishing the capacity of the testing labs with this restriction will only worsen this situation, especially given there was no data presented by FDA to warrant this restriction.

The initial MEDu does not play a part in the actual determination of the SPF value of the test product. It is used solely to help identify the UV exposure to be used to set the midpoint and exposures for the MEDu on the actual test day and to set the doses for the test product. The actual SPF determination is based only on the final MEDu determined on the same day and under the same conditions used when the test product is exposed.

We ask that consideration be given to adoption of the preliminary MEDu process as described in the globally recognized ISO 24444(2010)⁴ method which specifies that the initial MEDu can be conducted up to one week before the product test.⁵³ If alignment with ISO 24444 can be achieved for the preliminary MEDu timing, that would also limit problems introduced into the laboratory by having to identify two different pools of test subjects, those qualified for ISO SPF studies and those *only* qualified for FDA SPF method tests.

D. There is No Need to Retest Products for SPF Already Tested by the 2011 Final Rule Method

The Preliminary Regulatory Impact Analysis (p.52, section 6) requests that information on “*potential unintended effects of the proposed rule*” be submitted. Industry is concerned that the final monograph might require retesting of the SPF of current products. Members feel that such testing would not be necessary and would create both a clinical burden and an economic burden. As there is no mechanistic change to the test that would be expected to change the prior results, there is no basis for requiring new testing. Such testing, if required, would tax the capacity of SPF testing labs when there already is a capacity shortage. With the large volume of formulas that might need to be reformulated and thus, retested, it is anticipated that there would be both a large backlog of testing and a lack of the facility resources needed to complete testing to meet timing within an allowed implementation period. Additionally, there would be an ethical burden created related to retesting existing products already tested for SPF according to the FDA’s 2011 final rule for the determination of SPF. Retesting the formulations would result in unnecessary UV exposure of hundreds of test subjects, an unintended consequence that may not have been considered.

We also recommend that sunscreen products whose SPF has already been determined by the 2011 Final Rule method not be required to be retested for SPF for Final Monograph compliance. Ideally, the final rule will be written to specifically allow for existing testing to stand for current formulas and that any new requirements introduced in a Final Monograph would apply prospectively to newly marketed formulas introduced after the rule is implemented. We also request that no product would be deemed not GRASE and therefore misbranded due to failure to comply with the requirements of the monograph if its labeling relies on the results of final formulation testing that was conducted in compliance with all the applicable provisions of current 201.327 (e.g., 76FR35619, 76 FR 35665, 76 FR 38975) in place prior to this proposed final monograph.

If compliance with a Final Monograph would require hundreds of existing products with SPFs to be retested, the costs and time of conducting retesting would be excessive as well as

⁵³ ISO 24444 (2010): 6.5.2 Provisional MEDu.

unnecessary. While existing products previously qualified may need to be *re-labeled*, the SPF's already determined by the 2011 Final Rule method should be acceptable to establish the new SPF specified on the label as set forth in the TFM; SPF testing should not need to be repeated to do this.

E. Products with SPF's < 15

Section IX.B.3.c of the Tentative Final Monograph discusses the relative value of sunscreen products with SPF's below 15. In the TFM, FDA has opened for comment the utility of SPF 2 to 14 products while simultaneously observing that some consumers may choose not to use any sunscreen at all rather than use SPF ≥ 15 . Industry agrees with FDA proposal that products with SPF 2 to 14 which bear suitable labeling, may remain on the market without approved NDAs.

As noted in the TFM and by the Surgeon General, there are consumers who seek intentional sun exposure specifically to develop a tan. This group of consumers typically utilizes the lower SPF product to avoid sunburn while tanning. Because their primary objective is to obtain a tan, they avoid usage of higher SPF's as they believe these would prevent the tanning process. Presented in Appendix A are a sampling of comments from consumers that were posted 2 years ago regarding the discontinuation of an SPF 4 product. These reviews are still visible on the web page that presents the SPF 8 and 15 versions of the same product. Within these reviews are consumer requests to regain access to the SPF 4 formula instead of switching to the SPF 8. These comments fit into 3 themes: the desired level of protection, acceptable aesthetics, and avoidance of irritation/breakouts. While illustrative in nature, this example supports the assertion that this group of consumers are not likely to seek a higher-level SPF alternative, but instead would discontinue use of sunscreen protection.

We note that despite a lack of data on skin cancer and early skin aging reduction for products with SPF's less than 15, the same action spectra for these UV effects applies, and consumers who choose these products may accrue some benefits from the use of these products beyond mere sunburn prevention. This benefit would be enhanced if these products were broad spectrum. We believe the benefits that such sunscreen products confer on the consumers who choose them outweighs the risks of sunscreen drug exposure or of using no product at all in the sun.

Mintel published a survey of sunscreen use in the US in August 2018. One of the questions asked respondents was "*Which of the following do you use? Please select all that apply.*" The response options included 3 types of sunscreen-only forms, 2 types of cosmetic sunscreens, other tanning and self-tanning options, and '*none of the above*'. Due to the formatting of the question and responses available, a summary of results for specific groups of products provides only:

- **a lower limit** - the percentage selecting an individual response within a grouping. For example, of the 3 sunscreen-only forms, the lotion/cream option was selected at a higher frequency than the spray or stick forms. The value for the lotion/cream then represents the lowest percentage of respondents using a sunscreen-only product.
- **an upper limit** – the lower of either the sum across the product grouping or the total respondents that use at least one of the suncare product options within the question.

There are two other groups of consumers that may choose a lower level SPF. The first is composed of consumers of color. As documented in Table 4, at a minimum there are approximately 30% of consumers of color that report using sunscreen-only products. Avoidance of repeated burning provides a strong incentive to utilize increasing degrees of protection. Consumers of color tend to have a lower probability and experience of burning with sun exposure. Therefore, it is hypothesized that these consumers are more likely to be drawn to lower SPF products in general.

Table 4. Suncare Product Usage by Race and Origin (Mintel August 2018)

Race and Origin	Sample Size	Use \geq 1 suncare product listed within the question	Range of usage based on limits discussed above	
			Use \geq 1 form of sunscreen-only product	Use \geq 1 type of cosmetic sunscreen product
White, Non-Hispanic	1189	78%	37 – 78%	48 – 78%
Black, Non-Hispanic	291	61%	26 – 55%	35 – 55%
Asian, Non-Hispanic	128	75%	32 – 75%	48 – 75%
Other race, Non-Hispanic	80	68%	33 – 68%	44 – 68%
Hispanic (of any race)	312	74%	32 – 74%	46 – 74%
Total across all groups	2000	74%	46 – 74%	34 – 56%
Male	964	74%	43 – 74%	20 – 24%
Female	1036	74%	49 – 74%	47 – 74%

The last group of those choosing a lower level SPF consists of consumers utilizing cosmetic sunscreen products (for example, a moisturizer with SPF). As seen in Table 4, a minimum of 34% of the 2,000 respondents across all races and origins report using at least one

cosmetic sunscreen product. When parsing the data by gender, that number climbs to 43%. Cosmetic sunscreen products are intended for daily use for protection against incidental sun exposure. For this purpose, high level SPF protection is not necessarily sought or needed. These cosmetic products have a lower SPF value in general.

Per Information Resources, Incorporated (IRI) sales data, the dollar share of sunscreen-only products SPF 2 to 14 has averaged approximately \$42M per year from 2016-2018. At a conservative estimate of \$10/item this equates to over 4 million packages annually. The IRI numbers do not include the categories of colorless cosmetic or color cosmetic sunscreen products. Per Table 8 in the FDA's Preliminary Impact Analysis (*Docket No. FDA-1978-N-0018*), these cosmetic sunscreen items make up 50% of the total number of sunscreen products on the market and are estimated at approximately 30% of the consumption of sunscreens in 2016. Addition of the cosmetic categories will accordingly increase the annual estimate of consumption of SPF < 15 products especially as these daily use products are more likely than sunscreen-only forms to have a lower SPF value.

Given the evidence of significant annual sales of sunscreen products SPF 2 to 14 and the three key groups of consumers that may rely on these, we recommend that these products continue to be available on the market to meet this need. A related question is whether, sunscreens SPF 2 to 14 would be optionally allowed to have a broad spectrum benefit and claim. The discussion in section IX.B.3.c regarding the evidence concerning skin cancer / skin aging benefits and the statement specifying that products with SPF < 15 would not be required to pass the broad spectrum test, requires further clarification.

Close examination of PART 201 2. appears to indicate that a label claim of broad spectrum would be allowed as long as the formula met the testing criteria as laid out within the rule. Specifically 2.(b)(2)(i) indicates the formatting of the broad spectrum statement to be "*Broad Spectrum SPF [insert the labeled SPF value associated with the range into which the determined SPF value falls, as set forth in the following table.]*". (The referenced table, Table 1, includes on the bottom row a range of 2-14 determined SPF value.) However, 2.(d)(2) is titled "*For sunscreen products that are broad spectrum with determined SPF values of at least 2 but less than 15 according to the SPF test in paragraph (i) of this section or that have not been shown to pass the broad spectrum test in paragraph (j) of this section,*" thus indicating that the Skin Cancer/Skin Aging Alert would appear in the first statement under "*Warnings*" for any sunscreen SPF 2 to 14 regardless of whether the formula has met the broad spectrum testing criteria. Requiring this Alert, however, would be inconsistent with a broad spectrum claim, and yet, there is no direct mention of a restriction or limitation on these products being labeled "broad spectrum".

We request clarification of our understanding that a broad spectrum label claim can be made on sunscreen products of SPF 2 to 14 that have met the broad spectrum test criteria as long as they are labeled appropriately. We also request confirmation that a product labeled broad spectrum does not need the cancer alert

Section V. Proposed Broad Spectrum Requirements

A. Broad Spectrum Requirements

We acknowledge FDA for addressing the concerns related to the effects of UVA exposure to skin. We also note the significant public health benefits that sunscreens with UVA protection provide and the importance of communicating that benefit to consumers. In this respect, we accept FDA's requirement that all sunscreens with an SPF value of 15 or greater must also meet the standards for broad-spectrum. As we have also outlined later in this section and in others, it is our understanding that the provisions of the Final Rule will be prospective, not retroactive such that products manufactured before the implementation date of TFM would not need relabeling. Likewise, products manufactured after the compliance date would be required to pass the new UVA test. Importantly, we request that the agency clarify if our understanding is correct as we wish to emphasize that any new requirements should only apply prospectively.

Additionally, industry agrees that there should be a method for ensuring an increase in UVA I protection correlated to increase in SPF values. As FDA is aware, there are several scientific methods by which broad spectrum coverage can be calculated and assessed. The sunscreen industry is diverse in terms of the specific sunscreen products manufactured, ingredients selected for use in formulations, dosage forms, and participation in global markets. Accordingly, we request that companies be allowed to comply by using methods that most align with their company's needs: the UVAI/UV of 0.7 as proposed by FDA or through use of the SPF:UVAPF metric calculated using the FDA SPF test and either the ISO 24443 or ISO 24442 UVA test. While the UVAI/UV ratio will be achievable for many products and will help to assure a minimum height of UVA protection in combination with the Critical Wavelength requirement, if the primary goal of the agency is to increase UVA protection and provide broad spectrum coverage to consumers, we submit that this same goal can be achieved through various established methods listed here. Since the average consumer is unlikely to understand the nuances and technical underpinnings of any of the broad spectrum methods, whether a company complies with the broad spectrum requirement by utilizing the UVAI/UV 0.7 ratio or the ISO methods is unlikely to make a meaningful difference to the consumer's understanding so long as the broad spectrum claim and coverage is present. At the same time, we acknowledge that it is important for internal validation and recordkeeping principles that the specific method utilized be clearly identified and it is our intention to maintain such records.

As proposed, the UVA I/UV ratio would supplement (and be calculated using data from) the existing broad spectrum test. The existing broad spectrum test uses polymethylmethacrylate (PMMA) plates and the FDA has specified an application rate of .75 mg/cm², but allowed a choice of PMMA plate roughness from 2 to 7 microns. The application rate specified by ISO and recommended by one of the manufacturers is 1.3 mg/cm². We urge FDA to consider refining the proposed method to be more consistent with ISO and industry standards.

Further, Ferrero et al⁵⁴ have demonstrated that the ratio UVA/UVB, also known as the Boots ratio, can vary from 0.54 to 0.62 depending on the roughness of the plates (for the same amount of the sunscreen product applied). The study was conducted applying 1 mg/cm² of the product and with the roughness varying from 1.88 to 6.76 cm. The Critical Wavelength only varies from 375 to 377 nm under the same conditions. These authors concluded that the lowest variation (4%) is obtained with the Critical Wavelength endpoint and higher variability (13%) is obtained when a ratio of absorbance is calculated.

Thus, we request that FDA allow companies to satisfy their obligations for suitable UVA I protection under the sunscreen monograph by either utilizing the UVAI/UV ratio of 0.7 as calculated by the FDA Critical Wavelength test or ISO 24443, or through the use of the SPF:UVAPF metric calculated using the FDA SPF test and ISO 24443 or ISO 24442.”

Finally, regarding the *in vitro* broad spectrum test as outlined in the proposed revisions to 21 CFR 201.327, section (j) (Proposed Rule p. 6270) describes the broad-spectrum testing and (iii) describes the light source used for the test as “light source must produce a continuous spectral distribution of UV radiation from 290 to 400nm”. This can easily be mis-read as to mean the description of the “light source” utilized for the pre-irradiation procedure of the sunscreen treated plates – instead of the light source being used for the spectrophotometric measurement of the sample as it was intended. Later in paragraph (3) in the next column, it is stated that the sunscreen treated plate is to be irradiated with a solar simulator fulfilling the requirements of the clinical solar simulator(i)(2).

During the validation of ISO24443, testing was conducted to determine the potential effect of using a clinical solar simulator (meeting requirements of (i)(2) of this section of the TFM), and a broad-spectrum UV source that does not exclude the visible and IR from the exposure beam. Testing was also done to evaluate differences in the fluence rate on the amount of degradation of the filters and the absorption metrics (Critical Wavelength and UVA-PF) over the range of 20 to 800 W/m². It was determined that there was no influence of intensity on the degradation of the samples over the range of 20 – 200 W/m². It was found that there was no

⁵⁴ Ferrero L., Pissavini M., Dehais A., Margueire S., Zastrow L. Importance of Substrate Roughness for *In Vitro* Sun Protection Assessment. IFSCC Magazine, 9:2 2 13, April/June 2006.

light source (spectral) effect (UV only, versus UV+Visible+IR). Samples irradiated with the broad-spectrum source (UV through IR) had the same spectral and absolute absorbance degradation as did the samples irradiated with a clinical solar simulator (UV only).

We recommend therefore to eliminate the requirement of only using a solar simulator as described in (i)(2) of this section and optionally allowing for the use of a solar simulator configured using the same specification as is described in ISO24443 for the light source to be used to pre-irradiate the sunscreen treated sample plates –

“The spectral irradiance at the exposure plane of the UV exposure source that is used for irradiation shall be as similar as possible to the irradiance at ground level under a standard zenith sun as described by COLIPA (1994 or in DIN 67501 (1999). The irradiance must be within the following acceptance limits (measured at sample distance):

Total Irradiance (290-400nm) between 40 and 200 W/m²
 With a ratio of UVA₃₂₀₋₄₀₀:UVB₂₉₀₋₃₂₀ between 8-22.

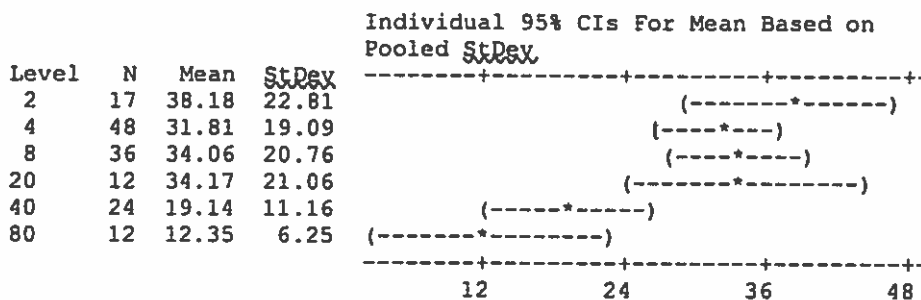
Samples should be maintained between 25° and 35°C during the exposure period.”

Figure 2

One-way ANOVA: % Degradation versus Irradiance

Source	DF	SS	MS	F	P
Irradiance	5	8644	1729	5.08	0.000
Error	143	48714	341		
Total	148	57358			

S = 18.46 R-Sq = 15.07% R-Sq(adj) = 12.10%



One-way analysis of variance of intensity versus degradation %. “Level” is the source intensity in terms of mW/cm². Mean is the mean % degradation of the samples.

Figure 3

One-way ANOVA: Final UVAPF versus Source

Source	DF	SS	MS	F	P
Source	1	3.2	3.2	0.12	0.724
Error	147	3763.1	25.6		
Total	148	3766.3			

S = 5.060 R-Sq = 0.08% R-Sq(adj) = 0.00%

Level	N	Mean	StDev	Individual 95% CIs For Mean Based on Pooled StDev
Suntest	56	8.091	6.074	(-----+-----+-----+-----+-----)
Xenon Arc	93	7.789	4.341	(-----+-----+-----+-----+-----)

One way analysis of variance of pre-irradiation light source type (Suntest – UV+Vis+IR: Xenon Arc – clinical UV (only) solar simulator. Mean is the mean UVA-PF determined for 5 sunscreen samples.

B. Broad Spectrum Recordkeeping Requirements

FDA is proposing a new metric for broad spectrum protection, a UVA1/UV ratio. While the broad spectrum products currently in the market that meet current requirements can use data theoretically generated using existing test methods to determine the newly proposed UVA1/UV ratio, this metric was not included in the final testing reports generated for SPF formulas up until now. This means industry will be forced to ask its testing providers to analyze the raw data from each study and calculate the ratio based on this information.

If the TFM is implemented as written, adding the results from broad spectrum testing proposed in 21 CFR 201.327(j)(1) is feasible. However, for broad spectrum testing completed between the publication date of the 2011 Final rule (June 17, 2011) and the TFM (February 26, 2019), this poses an undue burden.

While we understand the relevance of most of the records on FDA’s proposed list of information which should comprise a broad spectrum testing report, at least two of them are not relevant whatsoever. First, including a test product’s expected SPF value adds little value to a broad spectrum test result. The broad spectrum test is conducted by the testing laboratory in accordance with the method prescribed by FDA. The prescribed methodology is completely independent of SPF value and whether this information is provided to the testing laboratory, or not provided, will have no bearing on outcome as it relates to broad spectrum testing. We recommend FDA remove expected SPF from the list of records which would need to be included in a broad spectrum report.

Additionally, the proposed requirement for reporting sample weights, while providing additional detail, serves no purpose in a broad spectrum report. First, testing laboratories already assert their compliance with the prescribed testing methodology in each broad spectrum report (and thus asserting the prescribed sample weights were used⁵⁵). Second, sample weight has minimal effect on both critical wavelength and UVA1/UV ratio. While varying the sample weight up or down in a broad spectrum test will produce films of differing thicknesses and in turn affect the magnitudes of spectral transmittance values, work by Ferrero et al⁵⁶ studied effects of sample plate roughness and revealed that film thickness and film thickness variability have little effect on measurements of spectral transmittance ratios such as critical wavelength and UVA1/UV ratio.⁸ Work by Lutz et al⁵⁷ showed an average change in critical wavelength of just 0.5 nm when sample weight was increased from the FDA prescribed dosage of 0.75 mg/cm² up to 1.30 mg/cm². Hence, using thin film spectrophotometric techniques as is done in the broad spectrum test, ratios of spectral transmittance measurements, or ratios of spectral transmittance bands remain consistent and independent of sample weight, which makes inclusion of a sample weight record insignificant and unnecessary.

It is important to note that no guidance on broad spectrum report content was provided in 2011, or at any point since then, including up to the time of the publication of the TFM in February 2019. Therefore, attempting to recover all records on FDA's proposed list, from testing conducted up to nearly eight years in the past would be burdensome and perhaps unachievable, resulting in either a noncompliant report or forcing a product retest.

In summary, we respectfully request that FDA deem all prior broad spectrum reports to be compliant "as is", with no need to amend existing broad spectrum reports through inclusion of additional records that may no longer exist. Similarly, for products developed during the publication of the 2011 Rule and the compliance date of the Final Monograph we request that companies not be required to retest if records on the FDA's proposed list are not available.

Section VI. Labeling

A. Industry Overview of Labeling Comments

The TFM rule includes provisions to revise the requirements for information on the Principal Display Panel (PDP) and modifications to the drug facts label. Our comments will encompass the daily-use, beach-use and combination products - sunscreen/skin protectants. A

⁵⁵ See Appendix B.

⁵⁶ Ferrero, L., Pissavini, M., Dehais, A., Marguerie, S., Zastrow, L., Importance of substrate roughness for *in vitro* sun protection assessment, *IFSCC Magazine*, 9 (2006) 97-108.

⁵⁷ Lutz, D., Ongenaed, J., Guy, C., FDA rule for broad spectrum labeling: key substrate findings, *Cosmetics & Toiletries Magazine*, 126 (2011) 732-742.

crucial requirement for revising labeling requirements should be consumer comprehension of the label, followed by other important factors, including consistency with existing regulations and not burdening manufacturers of sunscreen product where there is no corresponding benefit to consumers. We believe that the addition of information to the principal display panel (“PDP”) and imposition of font size ratios will not have the intended effect of increasing consumer understanding of the sunscreen products and informing the purchase process and, in fact, create the risk of reducing comprehension and frustrating consumers, while also unduly impacting the marketability of sunscreen products. Consistent with our requests through these Comments, we also wish to emphasize that a one-year compliance period will be insufficient for the proposed labeling changes.

We have included graphical illustrations (in appendices) of PDP labeling proposed by the February 26, 2019 TFM and as modified by the requests herein. Specifically, Appendix C (daily products and beach products) includes sample PDP labeling “pairs” (FDA proposals and Industry proposals) for each of five product containers (tube, bottle, jar, stick and spray) as well as PDP labeling “pairs” for a combination skin protectant/sunscreen product with and without the “Skin Cancer/Skin Aging Alert” qualifier. The labels that are included in Appendix C are only shown to depict how the statements being proposed in the rulemaking would appear on some products. However, it should be noted that in this category, PDPs also contain additional information to highlight the product. This additional information may include design elements, product attributes, and other specific embellishments to differentiate the products from other competitive product offerings. It is common practice that companies include the SPF number as a larger callout (for ease of finding the SPF on shelf), product attributes (so a consumer can make an informed choice between products) and fanciful graphics associated with a brand’s trade dress (to distinguish on shelf).

Sunscreen UV filters are present in a range of health and beauty products such as over-the-counter (OTC) sunscreens and cosmetic daily-use moisturizers/ foundations. Beauty products containing sunscreen active ingredients are often regulated as drug/cosmetic combinations with labeling that fulfills the applicable requirements for both an OTC drug product and a cosmetic. The wide range of health and beauty product uses requires clear communication on the labeling to avoid consumer confusion, while also accommodating the small package sizes common to these types of products. Consequently, OTC monograph drug products have unique labeling requirements since products are directly purchased by consumers at retail, and there is limited space to communicate both safe use and product attributes. As such, the FD&C Act and 21 CFR have special provisions regarding the labeling of OTC drug and cosmetic products. The importance of clear, readable, legible, comprehensible, and consistent OTC drug labeling is key and is discussed in the rulemaking history by the FDA as an important factor when labeling OTC drug products.

This was discussed in the 1995 Over-the-Counter Drug Labeling; Public Hearing notice and request for comments as well as in the preamble to both the 1997 Over-The-Counter Human Drugs; Proposed Labeling Requirements proposed rule, and the 1999 Over-The-Counter Human Drugs; Labeling Requirements final rule.

In the notice of public hearing and request for comments, the Agency announced that “The purpose of the hearing is to solicit information and views concerning various aspects of OTC drug labeling design that would improve the communication of information to consumers. The Agency is particularly interested in hearing from individuals, industry, consumer groups, health professionals, and researchers with expertise in communicating information to consumers.” “FDA regulations require that the OTC drug product labeling present and display information in such a manner as to render it likely to be read and understood by the ordinary individual, including individuals of low comprehension, under customary conditions of purchase and use.” The Agency is “firmly committed to further improving OTC drug labels and labeling and making them easier to read and understand.”⁵⁸

In the proposed rule, the FDA noted that “The purpose of this proposed rule is to establish a standardized format for the labeling of all OTC drug products so that the labeling will be easier to read, have uniform presentation of information and consistent information in similar situations. The proposed rule is intended to help ensure the safe and effective use of OTC drug products.”⁵⁹ In the final rule, the Agency again emphasized that “The purpose of this final rule is to establish a standardization format for the labeling of all OTC drug products so that the labeling will be easier to read and understand, and will provide consistent information in like situations. Thus, the final rule will enhance the safe and effective use of OTC drug products by improving the ability of consumers to find, read, and understand important safety and use information.”⁶⁰

Consistency in labeling is important for the comparison of products, an important aspect of labeling as noted by the FDA: “The agency discussed at length its basis for proposing to improve labeling design (62 FR 9024 at 9027 through 9031). The Agency stated that a standardized labeling format would significantly improve readability by familiarizing consumers with the types of information in OTC drug product labeling and the location of that information. In addition, a standardized appearance and standardized content, including various ‘user-friendly’ visual cues, would help consumers locate and read important health and safety information, and allow quick and effective product comparisons, thereby helping consumers to select the most appropriate product. 51 Fed. Reg. 13254. “Consumers, however, are faced with a growing number of choices for purchase decisions and often find it difficult to determine the

⁵⁸ 60 Fed. Reg. at 42578.

⁵⁹ 62 Fed. Reg. at 9048.

⁶⁰ 64 Fed. Reg. at 13276.

product that is best for their particular condition. The absence of uniform and easily readable product information complicates product comparisons and can result in less than optimal health outcomes.”⁶¹

Although these statements refer to the Drug Facts Panel labeling, the PDP of OTC drugs is also part of labeling and would be expected to also abide by these requirements of clarity, readability, legibility, comprehensibility and consistency. The PDP is that part of a panel that is most likely to be shown or examined under customary conditions of display for retail sale and is typically the front panel of the label of the outer package.

By regulation, OTC drug products have specific information requirements (e.g., statement of identity) on the PDP for all therapeutic categories to insure consistency of information available at point of purchase (21 CFR 201.61). In the case of sunscreens, additional attribute statements are required such as the effectiveness statement (“Broad Spectrum SPF” or “SPF”) and the water resistance statement (“Water Resistant (40 minutes)” or “Water Resistant (80 minutes)”). The February 26, 2019 TFM has introduced new requirements for the Statement of Identity (SOI) as well as for the placement/prominence of certain information on the PDP. We feel some of these additional requirements are unnecessary for the reasons described below.

B. Request FDA Modify Certain Proposed Labeling Requirements

1. The SOI Should Not Be Required to Include a Listing of all the Sunscreen Actives

First and foremost, the requirement that the SOI consist of an alphabetical listing of the sunscreen active ingredients and the inclusion of the term “sunscreen” on the PDP creates crowding, which is inconsistent with 21 CFR 201.15(a)(6), which provides: a “word, statement, or other information required by or under authority of the act to appear on the label may lack that prominence and conspicuousness required by section 502(c) of the act by reason... of... crowding with other written, printed, or graphic matter”.

The Agency is proposing that the SOI consist of an alphabetical listing of the sunscreen active ingredients in the product, followed by “sunscreen,” further stating that this information would supplement other important elements of the PDP. To require the alphabetical listing of all OTC sunscreen active ingredients would be contrary to the requirements of 21 CFR 201.61 (shown below) and different from what is generally required for all other OTC drug products.

⁶¹ 51 Fed. Reg. 13277.

§201.61 Statement of identity.

(a) The principal display panel of an over-the-counter drug in package form shall bear as one of its principal features a statement of the identity of the commodity.

(b) Such statement of identity shall be in terms of *the established name of the drug, if any there be, followed by an accurate statement of the general pharmacological category(ies) of the drug or the principal intended action(s) of the drug.* In the case of an over-the-counter drug that is a mixture and that has no established name, this requirement shall be deemed to be satisfied by a prominent and conspicuous statement of the general pharmacological action(s) of the mixture or of its principal intended action(s) in terms that are meaningful to the layman. Such statements shall be placed in direct conjunction with the most prominent display of the proprietary name or designation and shall employ terms descriptive of general pharmacological category(ies) or principal intended action(s); for example, “antacid,” “analgesic,” “decongestant,” “antihistaminic,” etc. The indications for use shall be included in the directions for use of the drug, as required by section 502(f)(1) of the act and by the regulations in this part.

(c) The statement of identity shall be presented in bold face type on the principal display panel, shall be in a size reasonably related to the most prominent printed matter on such panel, and shall be in lines generally parallel to the base on which the package rests as it is designed to be displayed.

Emphasis added

According to this regulation, the active ingredient would only appear as part of the SOI if there is only one active ingredient in the OTC drug product. If the OTC drug product contains more than one active, only the drug category would appear as the statement of identity. “...the agency has interpreted the term ‘mixture’ as referring to a drug composed of a combination of active ingredients.” 51 Fed. Reg. at 13024. Only if there is an established name in an official compendium such as the USP, would the actives for mixtures be required on the PDP. Most Sunscreens are a mixture of UV filters; however, the combinations are not found in the USP and are therefore not considered to have established names. Frequently, when OTC drug products contain this mixture it is in the context of either a New Drug Application or as part of the CHPA Voluntary Cough/Cold Guidance, neither of which apply to sunscreens.

Consumers have become accustomed to and are familiar with the Drug Facts Box. They know where to find the active ingredients in an OTC drug product: in the very first section of the drug facts panel under the heading “*Active ingredients*” immediately after the title “*Drug Facts*”. Having the “*Active ingredients*” listed on the PDP and in the Drug Facts Box is redundant and crowds the PDP, reducing the readability and prominence of required labeling elements, such as the Statement of identity.

In addition, sunscreen ingredients fall under one pharmacological category, “**sunscreens**” and are already required to be listed within the Drug Facts. Sunscreen products are already required to include specific statements on the PDP related to Broad Spectrum and Water Resistance claims. Mandating additional information that is already available within the Drug Facts is redundant text, and that redundancy is further amplified if combining a sunscreen with a skin protectant. Placement of redundant information on the PDP could also dissuade a consumer from reading the Drug Facts which we encourage consumers to do. When consumers read the Drug Facts, they have access to active ingredients including their percentages within a formula, as well as other important information such as warnings and directions (including the “**Sun Protection Measures**”, etc.) that is contained in the Sunscreen Drug Facts Box.

We also wish to point out the labeling developments in Canada. Canada has been undergoing its own extensive review of Self-Care products, including the document “Consulting Consumers on Self-Care Product Labelling: A Report on What We Heard.” This covered Category IV Non-Prescription Drugs including Sunscreens. They issued monographs for both Non-Beach and Beach sunscreens, after their stakeholder meetings, including consumers, in preparation for the Canada Self-Care Products initiative. Session participants made it clear that self-care labels are important to them and are read when making purchasing decisions and in use of the products. While frequency of reading, thoroughness of reading and the reasons why they are read vary from individual to individual, from product to product, and from circumstance to circumstance, the information contained on labels is important to ensuring that the right decisions are being made when choosing self-care products.

In the Canadian study, a certain hierarchy was revealed in terms of importance of certain information, with Warnings, Ingredients and Dosage information in particular often cited as most important, there was a clear sense among participants that the information currently on labels is appropriate. Legibility, in terms of font size, font color and label layout, was determined to be important. The idea of streamlining the label layout and design into a table was also supported. Based on the information gathered,⁶² there is currently no requirement that active ingredients be included on the PDP in Canada.⁶³ Further, the primary placement of active ingredient information is within the body of the Drug Facts Table (DFT).

Thus, locating active ingredient information was much more readable, findable and preferred by Canadian consumers when in the Drug Facts Table. Test subjects felt a standard location was best for finding the information they desired. There is no reason to believe that these results would be different if studied in the United States. It is unlikely including sunscreen

⁶² <https://www.canada.ca/en/health-canada/topics/self-care-products/what-we-heard-product-labelling.html>

⁶³ *Food and Drug Regulations* (<https://laws-lois.justice.gc.ca/eng/regulations/C/>), including the December 7, 2018 issued monographs.

active ingredients in the statement of identity will add to consumer information and it is likely that the PDP will become less understandable if this change becomes part of the monograph based on the results of this study.

In summary, we are requesting the modification stated below to the TFM:

- Follow 21 CFR 201.61 that if an OTC drug product contains more than one active ingredient, only the drug category (“Sunscreen”) is required

2. *The SOI Should Not Be Required to Include Dosage Form if Included Elsewhere on the PDP*

The Agency also proposed including the product's dosage form (e.g., “lotion” or “spray”) following the principal intended action “sunscreen” in the SOI for the product. While in most cases it is obvious from the package what the dosage form would be (e.g., lotion, spray), we acknowledge that having this information on the PDP could be helpful to the consumer and support that the dosage form appears somewhere on the PDP, but not be required to be part of the SOI.

In summary, we are requesting the modification stated below to the TFM:

- Follow 21 CFR 201.61 in that the dosage form is not a required part of the statement of identity (SOI).

3. *There Should Not Be a Size Requirement for the SOI and Other Required Statements*

The Agency is also requiring that the Broad Spectrum/SPF effectiveness claim and water resistant statement be at least one-fourth the size of the most prominent printed matter on the PDP. We oppose the requirement of a mandated size requirement for the SOI, Broad Spectrum/SPF effectiveness and water resistant statements of “at least one-quarter the size of the most prominent printed matter on the PDP.” We agree to the bold face type as stated in 201.61 for the statement of identity.

The Agency's proposed changes in 21 CFR 201.327 for PDP prominence are not consistent with what is generally required for all other OTC drug products according to 21 CFR 201.15 and specifically, 201.16 for OTC drug products. While there are already special requirements for labeling sunscreen attributes on the PDP in section 201.327 from the June 2011 final rule, the proposed requirements are overly restrictive. Both 21 CFR 201.15 and current 201.327 are shown below with emphasis added by underlining the relevant parts.

§201.15 Drugs; prominence of required label statements.

(a) A word, statement, or other information required by or under authority of the act to appear on the label may lack that prominence and conspicuousness required by section 502(c) of the act by reason, among other reasons, of:

(1) The failure of such word, statement, or information to appear on the part or panel of the label which is presented or displayed under customary conditions of purchase;

(2) The failure of such word, statement, or information to appear on two or more parts or panels of the label, each of which has sufficient space therefor, and each of which is so designed as to render it likely to be, under customary conditions of purchase, the part or panel displayed;

(3) The failure of the label to extend over the area of the container or package available for such extension, so as to provide sufficient label space for the prominent placing of such word, statement, or information;

(4) Insufficiency of label space for the prominent placing of such word, statement, or information, resulting from the use of label space for any word, statement, design, or device which is not required by or under authority of the act to appear on the label;

(5) Insufficiency of label space for the prominent placing of such word, statement, or information, resulting from the use of label space to give materially greater conspicuousness to any other word, statement, or information, or to any design or device;
or

(6) Smallness or style of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter.

(b) No exemption depending on insufficiency of label space, as prescribed in regulations promulgated under section 502 (b) or (e) of the act, shall apply if such insufficiency is caused by:

(1) The use of label space for any word, statement, design, or device which is not required by or under authority of the act to appear on the label;

(2) The use of label space to give greater conspicuousness to any word, statement, or other information than is required by section 502(c) of the act; or

[41 FR 6908, Feb. 13, 1976]

June 2011 Rulemaking

201.327 (B)

(B) Prominence. The Broad Spectrum SPF statement shall appear as continuous text with no intervening text or graphic. The entire text shall appear in the same font style, size, and color with the same background color.

(ii) For sunscreen products that do not pass the broad spectrum test in paragraph (j) of this section. The labeling states “SPF [insert numerical SPF value resulting from testing under paragraph (i) of this section]”. The entire text shall appear in the same font style, size, and color with the same background color.

[76 FR 35620, 35660, June 17, 2011]

The “crowding” mentioned in the 21 CFR 201.15 (a)(6) makes a distinction between the mandated labeling from the company product branding information. However, by increasing the mandatory requirements (addition of actives, size requirements) on the PDP, the new requirements will create further needless crowding. Also, the additional mandatory requirements would be prohibitive for small packages which are common in the sunscreen category.

Accordingly, we request that the Agency retain the language within regulation 21 CFR 201.61(c) which states that the size be reasonably related to the most prominent printed matter on the PDP. This offers flexibility to ensure that the required elements of the PDP remain legible and prominent while still allowing companies to retain elements that establish their brand’s trade dress.

In summary, we are requesting the removal stated below to the TFM:

- Remove the statement “at least one-quarter as large as the size of the most prominent printed matter on the” PDP” in the proposed 201.327(b)(1)(ii), 201.327(b)(2)(iv) and 201.137(b)(3)(iii).

We agree to maintain the statement that appears in the June 2011 Rulemaking 201.327:

- (B) Prominence
- The entire text shall appear in the same font style, size, and color with the same background color

4. Consideration Should Be Given to Small Packages

Many OTC sunscreen drug products are also cosmetic products, and as such must comply with both the applicable drug and cosmetic regulations. Further “crowding” the PDPs of these products are the requirements for cosmetic products like the cosmetic statement of identity and other necessary information the consumer needs to select the correct product such as the correct

shade of a foundation makeup or a lipstick, the correct formula for oily, dry, or combination skin, etc. The PDPs of some of these products (e.g., foundation makeups) measure less than 1 ½ inches x ≈ 1 ½ inches. These obstacles to clarity, readability, legibility, comprehensibility and consistency are further magnified in small packages. In the June 2011 Labeling and Effectiveness Testing; Sunscreen Drug Products for Over-the-Counter Human Use final rule, the FDA rescinded the reduced labeling for small packages that had been previously included in the 2007 proposed rule, thereby making all (with the exception of some format requirements) labeling requirements applicable to small packages.

As noted, we believe that when comparing the proposed PDPs to the counter proposed PDPs shown in the Appendix, it is obvious that the latter are clearer, and easier to read and understand, thereby making it more likely that the consumer will read the information. In the 1999 Over-The-Counter Human Drugs; Labeling Requirements final rule (stayed), the FDA referenced two comprehension/readability labeling studies it had conducted (51 Fed. Reg. at 13254). It is unclear if the FDA conducted similar studies with regard to the proposed PDP labeling changes. If the FDA determines such a study would be beneficial should the FDA determine that the labeling comparisons between the proposed PDPs and the counter proposed PDPs are not sufficient to show how much more “consumer friendly” (i.e., compliant) the counter proposed labels are with regard to legibility, etc., Industry would be interested in working collaboratively with the FDA to conduct those studies.

Industry supports special sunscreen category labeling provisions that ensure the safety and effectiveness of product use. However, the changes described for the PDP are not based on any serious adverse event findings or other efficacy reasons. We believe current labeling requirements provide consumers with clear, readable, legible, comprehensible and consistent labeling. We share the FDA’s ultimate goal of communicating to consumers in the most effective manner possible using maximum labeling readability.

5. The Skin Cancer/Skin Aging Alert Statement on the PDP is Redundant

According to the proposed regulation, for products with an SPF less than 15 and/or not broad spectrum, the SPF number that appears on the PDP would be required to have an asterisk (*), directing the consumer to see the “Skin Cancer/Skin Aging Alert” in the Drug Facts Box. The statement “*Skin Cancer/Skin Aging Alert” would be required to appear in the bottom 30% of the PDP, in boldface type, at least one-fourth the size of the most prominent printed matter on the PDP, as text generally parallel to the base of the packaging, in the same font style, size and color with the same background color and as continuous text with no intervening text or graphic material. Note the graphic illustrations of the proposed labeling related to this and our counterproposal in Appendix C.

As shown in the illustration, this information already appears in the drug facts panel on the back of the label as the very first warning in the “*Warnings*” section in boldface type. The consumer has already learned to find it there and has many years of experience with the information contained and outlined in the Drug Facts Box. Requiring this qualifier on the PDP would further “crowd” the PDP. “Crowding” detracts from the clarity, readability, legibility, comprehensibility and consistency of information the consumer needs in order to select the correct OTC drug product. As previously noted, “crowding” is further magnified in small packages. In addition, the regulations for the declaration of net contents require that the net contents be placed in the bottom 30% of the label and be a distinct item not crowded or obscured by other label information.

Furthermore, the use of an asterisk (*) on OTC drug labeling has been reserved for inactive ingredients that may or may not be contained in the drug product. The asterisk is referenced at the bottom or end of the inactive ingredient section in the Drug Facts box (FDA Guidance, Labeling OTC Human Drug Products, Questions and Answers, December 2008). Since consumers are already familiar with the Skin Cancer/Skin Aging Alert in the Drug Facts Box, introducing multiple symbols may lead to consumer confusion.

We therefore request that the asterisk (*) and “*Skin Cancer/Skin Aging Alert” qualifier not be required to appear on the PDP.

6. Request FDA Modify Proposed Drug Facts Statements

Sunscreen products currently on the market are required to follow the June 2011 final rule in 21 CFR 201.327, which required broad changes to daily use and beach use sunscreens. The February 2019 TFM further changes the required language for the spray dosage form for both daily use and beach use sunscreens in the “*Directions*” and “*Warnings*” sections of the Drug Facts Box. Please refer to Section III. B. Sprays for our proposed language.

7. Request Alternate Directions for Use for Daily Use Products Containing Sunscreen

We request the FDA to remove the required direction; “for sunscreen use reapply at least every 2 hours” and replace with “reapply often or as needed.” The 2-hour reapplication direction is particularly inappropriate for daily use sunscreen products (e.g., foundations, concealers, facial and eye-area moisturizers and lotions, and lip products, such as lipsticks and lip glosses). For sunless tanners, this 2-hour reapplication direction is counter to the product benefits and leads to consumer dissatisfaction with the end results from the sunless tanner product use. The direction to “reapply at least every 2 hours” is inconsistent with consumers’ reapplication needs when using these types of daily use products and for certain products, consumers find the 2-hour reapplication directions to be confusing. They do not understand why when indoors, they need to

reapply their make-up. Manufacturers will therefore be discouraged from marketing these products with sunscreen, especially for long-wearing daily use cosmetic products. Thus, the 2-hour reapplication direction threatens the continued marketing and use of these products.

FDA has recognized that many consumers use facial cosmetics with sunscreen “as their primary and only source of sunscreen protection for that area of the body.” 72 Fed. Reg. at 49091; *see also* 72 Fed. Reg. at 49092 (“[M]akeup with sunscreen products may be the primary sunscreen for many consumers.”). FDA also recognizes that these products are important in addressing consumers’ need for sunscreen for frequent incidental sun exposure as contrasted with intentional exposure such as sunbathing.⁶⁴ If daily use sunscreen products are not on the market, consumers are unlikely to replace their use of these products, particularly lip products, for daily sun protection with “beach” products. The primary driver of selection of daily use products is their cosmetic benefit, specifically the color shade. As product aesthetics are important, consumers will continue to buy daily use products based on their color shade preference, even if these products no longer contain sunscreen. Furthermore, consumers are unlikely to use “beach” products on a daily basis with reapplications every two hours as directed, in place of daily use products. Rather, consumers would forgo daily sunscreen use altogether and use only cosmetics with no sunscreen if unable to purchase daily-use products.

In addition, the data FDA cited in support of the 2-hour reapplication direction does not support a requirement for 2-hour reapplication for daily use products. FDA did not fully evaluate, when implementing the 2-hour timeframe, the differences in the way consumers use daily use sunscreen products versus “beach” sunscreen products. The references supporting this time frame addressed intentional, direct and prolonged exposure to the sun, for protection from which consumers would typically choose a “beach” product. However, consumers typically use daily use sunscreens to protect against incidental daily sun exposure. Therefore, the 2-hour reapplication direction as applied to facial cosmetics is not supported by adequate science.

Section VII. Proposed Requirements Related to Final Formulation Testing and Recordkeeping.

A. General Approach to Final Formulation

Adequate and reliable recordkeeping are central to the success and operation of our member companies. These are obligations that our industry takes very seriously. In this respect, we acknowledge that FDA, industry, and consumers all have an interest in ensuring that sunscreen products are effective and accurately labeled. While we agree with the general ideas underpinning some of the changes that FDA has proposed in the Tentative Final Monograph, we are concerned about the unnecessary burdens that these changes would impose upon sunscreen

⁶⁴ 72 Fed. Reg. at 49092

manufacturers, distributors, and testing labs, thereby potentially resulting in increased cost to the consumer.

With respect to the key areas that FDA identified, we agree with FDA that it is critical for all clinical and nonclinical testing to be performed by properly trained and qualified personnel and that appropriate documentation of any training is maintained according to general recordkeeping requirements. We, however, believe that the requirements set forth in the Tentative Final Monograph are too restrictive, and accordingly we propose an alternative approach. As discussed more fully below, we do not dispute the role of IRB oversight for final formulation testing, but we do request further clarification.

Additionally, we are in alignment that an initial physical examination for potential nevi, moles, or other dermal lesions should be conducted by a qualified medical professional. It is not, however, necessary for a medical professional to review subjects for each subsequent test if the following conditions are present: If these subjects are part of a recurring panel, they can more reasonably be screened by a medical professional within the last 12 to 18 months. Then, at each individual sunscreen study, a non-medical professional who has undergone thorough and proper training could perform the subsequent skin check to confirm that there are no additional lesions since the subject's last examination. If a lesion is detected, a medical professional would then be contacted to perform an additional examination before the subject is enrolled in the clinical study. We believe that this approach is much more efficient and economical while also providing adequate assurance that subjects are appropriately screened for suitability to safely enroll for study participation.

We concur that training records of both medical and the non-medical investigative staff, should be maintained in accordance with good clinical practices and other general recordkeeping requirements. Furthermore, records would be updated as periodic training occurs. Consequently, by updating records contemporaneous with periodic training, laboratories will have the documentation necessary to assure FDA that qualified professionals are conducting the studies.

B. Specific Regulatory Proposals

1. Consequences of Failure to Observe Best Practices

We support FDA's efforts to bolster requirements in the regulations associated with final formulation testing and its commitment to "ensuring the reliability of all of the testing data that underlies sunscreen labeling" (84 FR 6240) by outlining consequences of failure to observe best practices. We agree with the agency's proposal "to incorporate the provisions of §201.327(a) through (l) into part 352 as conditions under which a sunscreen is GRASE and not misbranded"

and the agency's clear jurisdiction over mandatory regulated label claims that are based upon the results of final formulation testing.

We would appreciate further clarification around FDA's definition of "final formulation testing" – currently defined as "testing conducted on the sunscreen product formulation to be marketed". Specifically, we request that the agency confirm that the "final formulation testing" requirement does *not* require that testing be performed on each batch or lot of sunscreen or on each finished sunscreen product that is offered for retail sale, but instead only applies to each formulation of sunscreen product before it is marketed as part of final formulation testing. Further, we request that the agency confirm that the "final formulation testing" is the only testing required to support a declared SPF value, water resistance claim, or other mandatory regulated label claim.

Finally, we do not object to FDA's proposal to clarify in the introductory paragraph of 21 CFR 201.327 that a product is deemed not GRASE and therefore misbranded due to failure to comply with the requirements of the monograph if its labeling relies on the results of final formulation testing that is not conducted in compliance with all the applicable provisions of 201.327 provided that this is not a retrospective requirement. As discussed in other sections of these Comments, we are not supportive of requirements that apply retroactively and impact sunscreen products that were otherwise in compliance with applicable laws and regulations but for compliance with new requirements articulated in this TFM.

2. General Obligations of Responsible Persons

We are in alignment with the overall definition that FDA has proposed for the "responsible person." However, we note that some of the requirements placed upon the responsible person should be modified. For instance, in the TFM, FDA proposes several additional recordkeeping requirements as obligations of the "responsible person." We submit that this transfer of obligations can be fulfilled with a combination of 1) an agreement between the responsible person and the Investigator and 2) an Investigator signed document showing his/her acceptance of the investigational plan, i.e. the signed investigator statement.

Revised § 201.327(i)(1) would require that responsible parties inform all investigators testing a formulation if there are new observations about the drug, particularly with regard to adverse events or safe use. Industry supports this requirement and submits that this information can be communicated through a variety of formats.

To determine the likelihood of whether a product submitted for testing will cause a risk of adverse events, a screening-level safety assessment is performed by a qualified expert prior to study initiation. This is documented by a safety attestation letter. The safety attestation letter is sent to the investigator in connection with the study protocol. A safety assurance statement

attesting that the formulation does not represent a health hazard/risk for the volunteers participating in the SPF/WR test shall be sufficient, provided that the test conditions as defined in the protocol are accurately followed for this phase of the product development process. Further, final confirmatory clinical safety tests for sunscreens products are conducted prior to market launch of the end-use product. Additionally, results from similar formulations are leveraged as part of the evaluation such that minor changes should not require final confirmatory clinical safety testing of every product prior to market launch.

The safety assessment of final formulation involves a systematic and stepwise approach that starts from conservative assumptions and periodic refinement of the approach as needed. The safety assessments should utilize the most up to date scientific approaches available while considering current legal/regulatory requirements. Sunscreen products are formulations comprised of specific combinations of ingredient. In general, it is possible to assess their safety by considering and examining the relevant toxicological endpoints of their individual ingredients, and the likely local and systemic exposure to the product. To achieve this, the safety assessment follows a formal process that evaluates the safety and quality of all its ingredients as well as the finished product, which takes in account the following: Ingredient characterization through relevant physico-chemical data, purity and profile of impurities and chemical structure of constituent ingredients comprising a product.

3. Adequate Clinical Testing Procedures and Conditions

We note that clinical final formulation testing under 21 CFR § 201.327 requires Institutional Review Board (IRB) approval. We accept the explicit cross-reference of 21 CFR part 50 and part 56 in 21 CFR § 201.327 and do not have objections to this general principle. Notwithstanding this, we do have concerns that the proposed language of revised 21 CFR § 201.327 could be interpreted to require IRB review of every individual SPF test performed. If IRB review is required of each individual SPF test, it would cause undue delay and likely would not result in any meaningful assurances for FDA as clinical procedures and informed consent procedures do not change frequently. Instead, we propose an annual IRB review. Similarly, we propose that new IRB reviews would not be necessary if the only changes to the formulation qualify as minor changes as attested in a statement by a qualified safety expert.⁶⁵

4. Final Formulation

The Tentative Final Sunscreen Monograph revision uses the phrase “final formula” in reference to the testing required for product launch. The concept of “final formula” needs to be

⁶⁵See Guidance for Industry: Changes to an Approved NDA or ANDA, page 4 (“A minor change is a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.”)

clarified to indicate that it does *not* require that testing be performed on each batch or lot of sunscreen or on each finished sunscreen product. This in line with the current guidance for compositional changes set forth by the Scale-Up and Postapproval Changes (SUPAC)⁶⁶, which provide guidance on compositional changes as related to testing required as a result of such changes. SUPAC guidance from the U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines how to address changes to Products for Chemistry Manufacturing and Controls.

The SUPAC guidance defines the levels for compositional changes and testing requirements. Changes are characterized into Levels 1, 2, and 3 with testing requirements increasing with the Level. This allows for controlled changes which can be characterized, and the required testing executed. Under SUPAC guidelines Level 1 and 2, compositional changes do not require any *in-vivo* bioequivalence documentation. This implies the differences between two or more products are minimal and do not modify the results obtained in the efficacy tests.

Based on this premise, the extrapolation of efficacy results is possible when the product is originally developed, and the new product is proven to be similar in terms of qualitative and quantitative formula composition, as determined by the gates set forth in the SUPAC guidelines. Accordingly, SPF testing on certain final formulas is not necessary if this new formula can be sufficiently matched to an existing, already tested formula in accordance with the SUPAC guidelines.

The similarity evaluation can only be made on a case-by-case basis, following the SUPAC guidelines and certain common-sense principles. First, the alterations made in the product must be justified and *a priori*. Critically, industry would not be permitted to use extrapolation to test a new formula where such formula contains qualitatively and/or quantitatively different UV filters, and minimal excipients when compared to the reference (i.e. the original formula). Finally, any changes in the new formula when compared to the reference formula must be classified as minor and, those that are unlikely to have any detectable impact on formulation quality and performance. Some examples of acceptable changes include but are not limited to: modification, addition, deletion or partial deletion of an ingredient intended to affect (i) the fragrance or flavor of products (for example flavored sunscreen lip balms); or non-sunscreen related claims of a product where the SPF is a secondary claim (for example, in make-up).

Based on both the current SUPAC guidance on the testing required for compositional changes and the industry's ethical responsibilities to limit exposure and unnecessary testing on

⁶⁶See Nonsterile Semisolid Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation from 1997.

human subjects, the reference to “final formula” within the Sunscreen Monograph needs to reflect the current guidelines and allow for expert analysis of similarities of formulas and the resultant impact on the final efficacy testing.

Additionally, FDA raises the possibility of requiring ultraviolet (UV) filter *in vitro* dermal permeation data be generated in connection with new formulations at a future date. We believe that this requirement is not justified, as the information needed to assess exposure to UV filters from a new formulation can be obtained using other, equally valid, and more practical, methods. As an example, the use of pharmacokinetic (PK) modelling data can be used in place of dermal penetration testing. The use of PK modelling would offer increased flexibility and reliability while also avoiding the high variability inherent in *in vitro* dermal penetration testing. Rather than the proposed, dermal penetration testing, a reasonable alternative would be to require companies to have available the rationale and information that support the new formulation using alternative methods for review by FDA upon request.

Finally, we disagree with the underlying premise that an increase in UV filter dermal penetration relative to previously tested formulations would necessarily result in a conclusion that the product is not GRASE. The safety assessment for the UV filter in question would include calculation of a MoS. UV filter exposure from the new formulation would be assessed to determine whether the MoS continues to be adequate to support safety. The finding of greater dermal penetration does not necessarily raise any issues related to safety.

5. Research Monitoring—Risk Based Monitoring

We agree with FDA that proper communication and study monitoring are necessary for conducting appropriate clinical studies. Considering the characteristics of the SPF, UVA, and Water Resistance tests, the standard protocol dictating a short time to perform the test, and the several studies conducted in the same time, we submit that following the recommendation on the “Risk Based Monitoring FDA Guidance”⁶⁷ is sufficient.

6. Test Subject Selection

Proper inclusion and exclusion criteria for test subjects are critical components of clinical studies. We acknowledge the possibility for erythematous responses to remain for some time after an initial exposure to UV radiation. We note that on p. 6268 of the TFM, FDA has included the following statement regarding test subjects ((4)(B)(iii) (Physical examination)): “Conduct a physical examination to determine the presence of sunburn, suntan, scars, active dermal lesions,

⁶⁷ See Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring (August 2013). See <https://www.fda.gov/media/121479/download> for link to draft revised Risk Based Monitoring guidance

and uneven skin on the areas of the back to be tested. Adequate time must have passed following any previous UV exposure so that the test subject has no preexisting skin pigmentation at the time of enrollment.” We agree that the areas of skin to be tested must be free of all the conditions described in (4)(B)(iii) (Physical examination), including pre-existing pigmentation. No UV-induced responses can remain in skin sites to be tested, as this could interfere with the test results. The Woods lamp is indeed very helpful in the screening process.

FDA discusses the need for adequate inclusion and exclusion criteria. We would further recommend that the FDA change the wording of the section of (4)(B)(iii) “Physical examination” to “*Adequate time must have passed following any previous UV exposure (e.g. participation in a prior clinical study, tanning, etc.) so that the test subject has no preexisting skin pigmentation marks in the test sites to be used, at the time of enrollment.*” Further, while the proposed regulatory text found on page 6268 of the Tentative Final Monograph does not state a specific time or define “adequate time,” we acknowledge that on page 6242 FDA references a rest period of four weeks. It is unclear whether FDA intends to interpret the adequate time as proposed in the regulatory text to mean the four weeks referenced elsewhere. We recommend that testing entities be allowed to either rest subjects for four weeks following the initial exposure, or to rest test sites for four weeks following the initial exposure, provided that the testing entities maintain adequate records to demonstrate that no preexisting skin pigmentation remained at the time of subsequent testing. If FDA’s concern is the overall exposure of a subject, it is our position that each alternative would result in the same net amount of exposure. For instance, a subject could have his or her entire back tested at one visit and rest for four weeks or alternatively could come every week for four weeks and utilize a new test area on the back at each visit. At the end of four weeks, we anticipate that overall exposure would be the same for the subject.

7. Recordkeeping

With respect to recordkeeping requirements related to the SPF and broad spectrum tests, please see earlier Sections IV and V.

Section XIII. Sunscreen/Insect Repellent Combinations

Sunscreen-insect repellent products are useful and convenient for consumers requiring simultaneous protection from sun exposure which can lead to skin cancer and from insects associated with disease transmission. The frequency of adverse events reported to the leading manufacturer of this category is similar to that of their other consumer products, and reports of lack of efficacy of either component have been extremely rare.

Historically, FDA has used its enforcement discretion to allow the marketing of insect repellent-sunscreen drug products pending the issuance of the final sunscreen monograph so long as (1) the products contained sunscreen ingredients included in the FDA rulemaking; and (2) the insect repellents were registered with EPA. These types of products were first marketed before the OTC drug review began in 1972, and FDA has not explicitly addressed them at any time in the rulemaking for OTC sunscreen drug products. Because they have always contained a pesticide, the combination insect repellent-sunscreen products have also historically been registered with and regulated by EPA.

In the Federal Register of February 22, 2007 (72 Fed. Reg. 35, 7941), the U.S. Food and Drug Administration (FDA) issued a notice seeking information to support marketing of sunscreen-insect repellent combination products, specifically:

- Whether there are manufacturing conflicts with regard to manufacturing standards and conditions;
- Whether there are labeling conflicts regarding the USEPA requirements for labeling pesticide products (due to the presence of insect repellent) and FDA requirements for sunscreen components;
- Whether there are functional formulation conflicts between the various components;
- Whether there are safety and efficacy issues when both sunscreen and insect repellent components are present;
- Whether the various components of the combination products result in enhanced dermal absorption of some of the components.

Under the TFM recently issued in February, FDA tentatively determined that these products are not GRASE for nonprescription sunscreen use, and requested comments with respect to that determination. The Personal Care Products Council (PCPC) maintains that such a determination is premature given the ongoing review of sunscreen ingredients, and that FDA should continue its enforcement discretion at least until the review is complete. To support this position we present a review of the toxicology of IR3535[®], a common repellent active ingredient (a.i.) used in this class of products, and our conclusion that, based on a comprehensive exposure and risk assessment, the combination products pose no additional risks to the consumer over exposures to sunscreen active ingredients and IR3535[®] separately. In addition, these products

provide a clear public health benefit in circumstances where consumers need protection from sun exposure and insects simultaneously. Without the convenience of the combinations, consumers may forgo either sun or insect protection or apply separate products with potentially incompatible delivery systems, compromising the efficacy of either or both active *ingredients*.

A. Toxicology of IR3535®

The toxicology profile of IR3535® is extremely favorable for this type of product. IR3535® is associated with very low toxicity by all tested exposure routes. By the oral route of exposure, IR3535® is not acutely toxic, and there were no deaths or gross abnormalities reported at necropsy following the 14-day observation period at the limit dose of 5,000 mg/kg bw in rats⁶⁸. By the dermal route of exposure, there were no effects at 10,000 mg/kg bw in rats⁶⁹. By the inhalation route, there were no deaths or gross pathological findings at a test concentration of 5.1 mg/L (the highest concentration tested⁷⁰). Under USEPA interpretation, this places IR3535® in the lowest category of toxicity for these exposure routes (Category IV), in which no hazard “signal words” are required on the product label. Based on available testing, IR3535® causes only slight dermal irritation, which is reversible once exposure ceases. IR3535® is not a dermal sensitizer⁷¹. No adverse effects were observed in oral 1997⁷² or dermal⁷³ repeated-dose studies (28-day or 90-day studies) at the highest doses tested, ranging from 2,700 to 3,000 mg/kg/day, which constitutes the limit dose for these kinds of studies. There was no evidence of

⁶⁸ Heusener, A. (1997) Insect Repellent 3535—Acute Toxicity Study in Rats after Oral Administration: Lab Project Number: T14215. Unpublished study prepared by Institute of Toxicology, Merck KGaA. 25 p. USEPA MRID 44270820. Submitted to USEPA on 15 April 1997.

⁶⁹ EU. (2014). Regulation (EU) n°528/2012 concerning the making available on the market and use of biocidal products. Evaluation of active substances assessment report: Ethyl butylacetylaminopropionate. Product-type 19 (insect repellent), March 13, 2014 report. [https://circabc.europa.eu/sd/a/ec60f5be-2b75-465c-9533-d0a7e10d9353/IR3535%20-%20PT19%20\(assessment%20report%20as%20finalised%20on%2013.03.2014\).pdf](https://circabc.europa.eu/sd/a/ec60f5be-2b75-465c-9533-d0a7e10d9353/IR3535%20-%20PT19%20(assessment%20report%20as%20finalised%20on%2013.03.2014).pdf)

⁷⁰ Gamer, A.; Leibold, E.; Hoffman, H. (1996) Study on the Acute Inhalation Toxicity LC50 of (Insekt-Repellent 3535) as a Liquid Aerosol in Rats 4-Hour Exposure: Final Report: Revised: Lab Project Number: 13I0189/957012. Unpublished study prepared by BASF Aktiengesellschaft. 49 p. USEPA MRID 44270821. Submitted to USEPA on 15 April 1997.

⁷¹ Morris, T. (1997) Delayed Contact Hypersensitivity Study in Guinea Pigs (Buehler Technique): IR3535 Technical: Lab Project Number: 96-8304-21. Unpublished study prepared by Hill Top Research Ltd. 41 p. USEPA MRID 44297902. Submitted to USEPA on 15 April 1997.

⁷² Phillips, S., comp. (1997) Toxicology Summary and U.S. Army Hazard Evaluation: (Insect Repellent 3535). Unpublished report compiled by Technical Assessment Systems and E. Merck. 38 p. USEPA MRID 44270832. Submitted to USEPA on 15 April 1997.

⁷³ Pfister, T.; Luetkemeier, H.; Stegehuis, D.; et al. (1996) Insect Repellent 3535: 90-Day Subchronic Toxicity Study with Dermal Application to Rats: Final Report: Lab Project Number: 398834. Unpublished study prepared by RCC, Research and Consulting Co., Inc.; RCC Pharamalytics, Ltd.; and BRL, Biological Research Labs, Ltd. 501 p. USEPA MRID 44297903. Submitted to USEPA on 15 April 1997.

developmental or reproductive effects when IR3535[®] was administered to rabbits ⁷⁴ or rats ⁷⁵, respectively. Based on the available mutagenicity and genotoxicity data on IR3535[®], the weight-of-evidence supports the lack of concern for potential for these effects for IR3535[®].

B. Exposure and Risk Assessment

In the TFM, FDA's concerns appeared to focus on (1) potential conflicts between required application instructions for the two components that could lead to overexposures to one or both, and (2) the potential for co-administration of sunscreen and repellent ingredients to cause increased absorption of either component. To address these questions, a dermal exposure assessment was conducted. A full exposure and risk assessment covering all exposure routes, including dermal, inhalation, (aerosol and pump spray products) and the hand-to-mouth (HTM) exposure pathway for toddlers with mouthing behavior, was also conducted but since these routes were found to contribute only minimally to overall exposure only dermal exposure is considered here.

The dermal exposure model was based on arithmetic mean use rates for aerosol, pump spray, and lotion combination products, which are 1.1 mg product/cm², 0.62 mg product/cm², and 2.0 mg product/cm², respectively. Assuming the reapplication frequency of the combination product to be 2 hours to match the label directions for sunscreen protection and using the USEPA human-activity data for the length of time spent outdoors per day, approximately 4 applications of the lotion formulas and the label maximum of 3 applications of the aerosol or pump spray formulas would be applied. Using the available dermal absorption data converted to hourly penetration rates, the time-normalized absorbed doses for IR3535[®] in this model were determined to be on the order of only 1 to 2 percent per hour.

FDA's concern that co-administration of sunscreen and repellent ingredients would be associated with enhanced dermal absorption arose from *in vitro* studies of DEET and oxybenzone showing enhanced permeation of both ingredients across skin models and artificial membranes with simultaneous treatment. Results from *in vivo* studies of the two ingredients administered together have consistently shown up to a doubling in DEET concentrations in urine, skin and other organs when administered in sunscreen preparations together with oxybenzone⁷⁶

⁷⁴ Schardein, J. (1997) A Development Toxicity Study of IR 3535 in Rabbits: Final Report: Lab Project Number: WIL-149021. Unpublished study prepared by WIL Research Labs., Inc. 347 p. USEPA MRID 44323301. Submitted to USEPA on 15 April 1997.

⁷⁵ Gleitch, J. (1997) Insect Repellent 3535: 2-Generation Study with Oral Administration to Rats: Final Report: Lab Project Number: T 9381. Unpublished study prepared by Merck KGaA. 778 p. USEPA MRID 44297904. Submitted to USEPA on 15 April 1997.

⁷⁶ Kasichayanula S, House JD, Wang T, Gu X. (2007) Percutaneous characterization of the insect repellent DEET and the sunscreen oxybenzone from topical skin application. *Toxicol Appl Pharmacol.* 2007 Sep 1;223(2):187-94. Epub 2007 Jun 4.

⁷⁷ ⁷⁸. However, the results for oxybenzone absorption are mixed, with most studies showing no effect.

In a risk assessment, the measure of safety is expressed as the MOS, which is the No-Observed-Adverse-Effect-Level (NOAEL) for the chemical divided by the calculated absorbed dose. In the case of IR3535[®], all of the calculated MOSs far exceeds the target MOS of 100. The high MOSs for IR3535[®] indicate that, even if enhancement of dermal absorption occurred, and led to a doubling of absorption, no adverse impacts would be expected.

By design, sunscreen and insect-repellent active ingredients must be poorly absorbed through human skin in order to remain present on the outer layers of skin and maintain efficacy. Therefore, enhanced dermal absorption through the co-presence of sunscreen and insect-repellent active ingredients, as well as matrix effects, is anticipated to be minimal if the products are to be effective. The extremely low frequency of reports of reduced efficacy of either component from marketed products supports this conclusion.

C. Conclusions and Recommendations

Combination sunscreen-insect repellent products provide a significant public health benefit in terms of simultaneous protection from UV radiation associated with melanoma and other skin cancers and protection from insects that may carry disease (e.g. Zika, West Nile Virus). In the absence of combination products, consumers may either choose to forgo either sun or insect protection or apply separate products with untested and potentially incompatible delivery systems. The combination products offer a vehicle which insures better application control and proven efficacy for both benefits over application of individual products.

Concerns related to DEET may not be applicable to IR3535[®]. The very low toxicity of IR3535[®] and the high MOSs for IR3535[®] minimize the likelihood of adverse effects even in worst-case exposure scenarios. Data from in vivo studies of DEET and oxybenzone co-administration indicate marginal, if any, increased absorption of oxybenzone over independent administration. The very low toxicity of IR3535[®] and the high MOSs for IR3535[®] minimize the likelihood of adverse effects when combination products with IR3535[®] are used as directed, even in the worst-case scenario observed in the studies.

Conflicting application instructions for the sunscreen and insect repellent components on the combination products containing IR3535[®] do not pose any safety concerns. Dermal absorption

⁷⁷ Yiin LM, Tian JN, Hung CC. (2015) Assessment of dermal absorption of DEET-containing insect repellent and oxybenzone-containing sunscreen using human urinary metabolites. *Environ Sci Pollut Res Int*. 2015 May;22(9):7062-70.

⁷⁸ Fediuk DJ, Wang T, Raizman JE, Parkinson FE, Gu X. (2010) Tissue deposition of the insect repellent DEET and the sunscreen oxybenzone from repeated topical skin applications in rats. *Int J Toxicol*. 2010 Dec;29(6):594-603.

of IR3535[®] when applied at the recommended frequency for sunscreens is well within the margin of safety. Safety concerns related to application of sunscreen-repellent combination products containing IR3535[®] are not different from concerns FDA has expressed relative to sunscreens applied alone. Therefore, FDA should continue enforcement discretion to allow marketing of products in this category until its sunscreen review is complete.

Section IX. Economic/Regulatory Impact Analysis

The Tentative Final Monograph contemplates significant changes in how sunscreen products are manufactured. Many of these changes will result in tremendous economic consequences for sunscreen manufacturers, distributors, testing laboratories, and ultimately the consumer. Additionally, the regulatory impact analysis does not adequately address the negative benefits if the final rule results in reduced sunscreen use and increased consumer exposure to UV radiation, which would lead to a significant long-term financial impact on consumers in the form of increased healthcare. The same logic FDA applied in the “willingness to pay” analysis should apply to the discussion of these potential negative benefits. Finally, we note two additional, specific areas in our comments:

- The costs of changes and of safety studies are underestimated, particularly given the strain on testing lab capacity and under-estimates on the costs of a MUSt study. Seasonality and the compliance date of a final rule will have a material impact on label change costs and testing costs.
- Costs will be disproportionately borne by a limited number of firms marketing or manufacturing sunscreens or their active pharmaceutical ingredients.

A. Benefits will be overstated if there are markedly fewer SPF15+ or 30+ products available.

The analysis of benefits of avoided skin cancer in the regulatory impact analysis appropriately speaks to the gains of increased sunscreen usage or broad spectrum requirements. And while the analysis references what may be the most important element of benefits – *negative* benefits from possible *reduced* sunscreen use – the same analytical logic and modeling are not applied. A number of studies have looked at the cost-effectiveness of skin cancer prevention through promotion of daily sunscreen use. For instance, a study of white populations in Australia found a quality-adjusted life-year (QALY) gain from sunscreen intervention of AU\$40,890 versus a control group thanks to reduced skin cancers.⁷⁹ The intervention group was encouraged to apply broad-spectrum SPF 15+ daily versus control group participants who were

⁷⁹ Hirst, et al., “Lifetime cost-effectiveness of skin cancer prevention through promotion of daily sunscreen use,” 15 Value in Health 261 (2012).

instructed to use sunscreen at their own discretion.⁸⁰ The authors note their conservative modeling likely understates gains of sun protection in younger people because of their model's discounting of outcomes.⁸¹

The Australian study QALY finding is not dissimilar to the FDA analysis's own "willingness to pay" conclusions in Table 37. Further, the Australia cost-effectiveness study builds on other work documenting the costs of treating skin cancers contrasted with the risk reduction gains provided by sunscreen use. More specifically:

- The annual cost of treating skin cancers in the U.S. is estimated at \$8.1 billion – approximately \$4.8 billion for nonmelanoma skin cancers and \$3.3 billion for melanoma.⁸²
- About 90% of nonmelanoma skin cancers are associated with exposure to UV radiation from the sun.⁸³
- Regular daily use of an SPF 15 or higher sunscreen reduces the risk of developing squamous cell carcinoma by roughly 40%.⁸⁴
- The vast majority of melanomas are caused by the sun. One UK study found that 86% of melanomas can be attributed to exposure to UV radiation from the sun.⁸⁵
- Regular daily use of an SPF 15 or higher sunscreen reduces the risk of developing melanoma by 50%.⁸⁶

We cite these studies to underscore a critical point: Implications of the proposed rule that would lessen sunscreen use will have a meaningfully negative impact on public health. The implications include:

⁸⁰ *Id.*

⁸¹ *Id.*

⁸² Guy, et al., "Prevalence and costs of skin cancer treatment in the U.S., 2002-2006 and 2007-2011," 48 *Am J Prev Med* 183-187 (2011).

⁸³ Koh HK, et al., "Prevention and early detection strategies for melanoma and skin cancer: Current status," 132 *Arch Dermatol* 436-442 (1996).

⁸⁴ Green A, et al., "Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomized controlled trial," 354 *The Lancet* 723-729 (1999).

⁸⁵ Parkin DM, Mesher D, Sasieni P. Cancers attributable to solar (ultraviolet) radiation exposure in the UK in 2010. *Br J Cancer* 2011; 105:S66-S69.

⁸⁶ Green AC, Williams GM, Logan V, Strutton GM. Reduced melanoma after regular sunscreen use: randomized trial follow-up. *J Clin Oncol* 2011; 29(3):257-263.

- (a) More costly products: If fewer and higher cost active ingredients are needed to achieve the proposed testing results and/or if a significant number of the chemical active ingredients were removed from the market, we anticipate a costlier product mix. For instance, a member company internal analysis calculated prices per ounce of private label sunscreens where prices are orders of magnitude higher for physical active ingredients compared to products with chemical active ingredients:

SPF30: Chemical = \$0.89/per ounce v. physical = \$3.40/per ounce

SPF40-50: Chemical = \$0.74/per ounce v. physical - \$3.26/per ounce⁸⁷

- (b) Fewer products: As FDA already notes, the proposed rule projects discontinuation of products, in turn leading to less consumer use. In addition to the assumptions discussed in the analysis (discontinued insect repellent and sunscreen combinations, no sunscreens with SPF above 80, and discontinued cosmetic sunscreens), two factors would exacerbate this reduction in benefit: First, the removal of active ingredients from the market could accelerate product discontinuation. Second, even with existing active ingredients, the proposed UV ratio requirements will make it more challenging for higher SPF products to meet the UV ratio, thus risking a reduction in products.
- (c) Product shortages: If the rule is finalized as proposed, as discussed in section 2.a. below, we project a testing bottleneck given the limited number of firms that conduct SPF, broad spectrum, and water resistance testing. Companies report waiting times of 3-4 months for testing today, with timelines from submission for testing to product availability date *without* further reformulation at 60+ weeks. If initial test results require further reformulation, that adds approximately 6 months. As suggested elsewhere in these comments, any compliance date short of 2 years will only further strain testing lab capacity, with the risk of product shortages. If the recommendation discussed in Section IV on SPF is not adopted, and products that do not need to be re-formulated require new tests to fill gaps against methods proposed, the risk of shortages is compounded.

Finally, we note the analysis assumes a *benefit* of fewer generally recognized as safe and effective ingredients, yet the same analysis and the proposed rule itself concede “we do not know if these active ingredients pose health risks to consumers.” Based on this circular logic, a “benefit” of ingredient removal should be removed from the analysis.

⁸⁷ Internal CHPA and PCPC member company analysis using market research firm data. Proprietary sources on file. April 25, 2019.

B. The costs of changes and of safety studies are underestimated and could create shortages.

1. Re-formulating and testing.

Even where a product is not re-formulated, the proposed rule would necessitate re-testing continued products, as older tests using FDA's 2011 methodologies do not include all of the information FDA now proposes. As discussed in Section IV on SPF, we do not believe such testing is necessary and it would create both a clinical and economic burden. Such testing, if required, would tax the capacity of SPF testing labs when there already is a capacity shortage.

Using FDA's upper estimate of 10 testing facilities that conduct SPF, broad spectrum, and water resistance testing, and using a member company-provided estimate from 3 testing facilities, an upper range of completed studies yields a testing capacity of 1,920/year. If *all* formulations had to be re-tested, at current capacity it would take over 4 years for testing alone. This is in the context of manufacturers report waiting times of 3-4 months today.

Using FDA's estimated 1750 reformulated formulations, while this testing at full capacity and the upper range could be completed within a year, this does not account for the introduction of new products and it under-counts products and formulations in prestige channels. As the agency's analysis notes, publicly available information on formulations, products, and sales through prestige channels are not available (this information is highly proprietary). Even if testing alone could be conducted in a year, an additional year or more is needed before product availability, virtually assuring shortages without a 2 year compliance date. The timing of a final rule will also have an impact, as on-going business testing needs for new products are highest in the fall and early spring.

Further, information provided by member companies projects testing costs will increase by roughly 25 to 30% based on proposed changes in testing protocols that would (a) reduce the frequency with which a given test subject may be re-tested, and (b) reduce the number of sites on the body for a given test subject. These cost increases would come from the need to recruit more panelists and to spread out tests with overtime/weekend work.

2. Conduct of safety studies (to extent needed beyond MUSt).

Table 16 of the analysis provides estimates on a range of safety studies per active ingredient. Using FDA's primary estimate on total cost, an association member survey found a large disparity between FDA's estimates and our own for MuST and DART studies. Carcinogenicity studies are modestly higher under our estimates.⁸⁸

⁸⁸ CHPA/PCPC survey of sunscreen manufacturers, April-May 2019.

Total cost estimates (in \$ thousands)	MusT	Pediatric	Carcinogen-icity (dermal and systemic)	DART	Toxicokinetic	Total
FDA	\$201	\$201	\$4,087	\$1,006	\$107	\$5,602
Company survey	\$1,433	Not available	\$4,505	\$1,600	\$165	\$7,703

Further, while the analysis provides safety testing and direct associated administrative costs, estimates do not appear to take into account other significant administrative and economic costs for necessary activities, including:

- Development costs associated with identifying, evaluating and preparing appropriate formulations for each of the tests required;
- Preliminary dose-ranging studies and assessments for toxicological studies;
- Analytical method development and validation of methods required for each study;
- Company and CRO study monitoring and quality assurance costs;
- Recruiting costs associated with clinical studies;
- Meeting and travel costs associated with lab qualification and study design and protocol development, etc.; and
- Electronic data reporting and formatting costs which typically require the use of specialized companies to prepare and submit.

3. *Label change costs.*

FDA's analysis of label change costs is consistent with information gathered for these comments. We note two caveats that would lead to an understatement of FDA's primary estimate: First, products with deferred ingredients under study could require subsequent label changes, leading to a higher number of product lines and SKUs undergoing relabeling. Second, in instances where the new label requirements trigger changes in packaging configuration to accommodate additional information, that would add costs for stability studies and potential changes to a manufacturing line.

As with re-testing, label changes costs will be sensitive to the timing of the compliance date so as not to disrupt planning cycles in a highly seasonal business. Transition costs will increase if the compliance date falls close to the latter portion of a third quarter through a fourth quarter of a calendar year, given demands of completing changes when firms are building product inventory for shipments to meet heavier consumer use in late spring and summer seasons.

4. *Particle size and flammability testing.*

FDA's analysis of particle size and flammability testing is consistent with information gathered for these comments.

C. Costs will be disproportionately borne.

Many of the firms supplying active ingredients, providing contract manufacturing services, or providing products that are not a significant part of their business will have little incentive to participate in generating safety study data to support GRAS/E status for deferred ingredients. We therefore anticipate disproportionate or distributional effects: The costs of safety studies will be borne by a minority of businesses manufacturing or marketing sunscreen products without an impact on who may gain from the benefit of these studies.

As the analysis already notes, there will be a disproportional impact on spray and powder dosage forms, with additional test requirements (dryness testing; flammability testing; and particle size testing). Estimates gathered from member companies for these test requirements do not differ materially from those provided by FDA.

X. Conclusion

We appreciate the opportunity to provide the FDA with our comments on the Tentative Final Monograph. Should you have any questions, please contact Emily Manoso at manosoe@personalcarecouncil.org or Barbara Kochanowski at bkochanowski@chpa.org.



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APPENDICES

Appendix A to Comment: Products with SPF's < SPF 15

Sampling of review comments on Coppertone website: Coppertone Defend & Glow Sunscreen Lotion page (currently available in SPF 8 & 15)

Information captured April 11, 2019:

1. ★★★★★3 out of 5 stars.

Shoefly · 2 years ago

Bring Back SPF 4

I called and was informed Coppertone® Tanning Sunscreen Lotion SPF 4 is no longer produced as of November 2016. I'm extremely disappointed as this was our primary sunscreen. I'd like to request this product be reinstated and made available.

Living and boating in the North West, we used a lot of the SPF 4. It's the perfect level of protection and this is the best sunscreen we've found. SPF 8 is not an acceptable alternative for us in the North West. We do use the SPF 8 and SPF 15 lotions when traveling to Hawaii and the Caribbean.

Helpful?

Yes · 168 people found this review helpful. No · 8 people did not find this review helpful.

2. ★★★★★5 out of 5 stars.

Nita · 2 years ago

coppertone tanning lotion spf 4

I have used this product every day for 25 years for both a moisturizer and sun protection. It's been the only product I have used all that time. Loved that it never felt heavy or greasy and it smelled fresh. PLEASE bring it back, there is NOTHING out there that compares. Even tried the spf 8 in desperation, but does not absorb as well into skin and don't care for the fragrance. If you bring it back I will buy it for another 25 years, Promise!!

Helpful?

Yes · 116 people found this review helpful. No · 5 people did not find this review helpful.

3. ★★★★★5 out of 5 stars.

Alisa · 2 years ago

Coppertone SPF 4

Please bring back SPF 4. I've been using this product for 40 years and it works!! Living in ME you don't get too many beach days nor do we spend more than 2-3 hours at the beach. Other SPF 4 lotions burn my skin, give me hives and worse of have a scent that attracts all kinds of insects. My husband, who is bald, loves the SPF 4 too. It's the only lotion that doesn't break out his head. PLEASE BRING BACK SPF 4!!! Thank you

Helpful?

Yes · 60 people found this review helpful.

No · 3 people did not find this review helpful

4. ★★★★★★1 out of 5 stars.

Anonymous · 2 years ago

SPF 4 IS ALL I CAN USE!!!

I have been using Coppertone SPF 4 for many many years. It is the only sunscreen I have found that does not break me out. I am so unhappy to find out you are no longer making this!!! Please, please, please bring it back!!! Apparently, I am not the only person asking!!! I would give it a 5 star rating if you still had it. Otherwise, I am a very disappointed customer!!!

Helpful?

Yes · 48 people found this review helpful.

No · 1 person did not find this review helpful.

5. ★★★★★★5 out of 5 stars.

JJRogie · 2 years ago

Bring back Coppertone 4

I have been looking for Coppertone 4 everywhere I could not find it anymore that is why I have gone to this website hoping I could buy it for myself and a brother who uses it. Sad to see you are not offering it anymore? Why? Hope you will bring it back again. :0(

Helpful?

Yes · 132 people found this review helpful.

No · 3 people did not find this review helpful.

6. ★★★★★★5 out of 5 stars.

Vale · 2 years ago

Very disappointed

I have used Coppertone lotion all my life. It gets harder and harder to find but I have been loyal- buying and searching online. I love the SPF 4!!! Other brand cause my skin to burn and sting- don't know what I will do now. Please bring it back!!

Helpful?

Yes · 135 people found this review helpful.

No · 4 people did not find this review helpful.

7. ★★★★★★1 out of 5 stars.

Hogan55 · 2 years ago

Very disappointed!

I can't believe I can no longer buy your SPF 4 lotion or spray any longer! I've been using Coppertone for 50+ years but no longer can. Very sad I have to switch brands after all these years.

Helpful?

Yes · 147 people found this review helpful. No · 7 people did not find this review helpful.

Appendix B: Comments on Broad Spectrum

Assertion of compliance to FDA 2011 broad spectrum test methodology

Example 1

Objective:
To evaluate the critical wavelength of sunscreen test products after irradiation with a full spectrum UV dose of 4 MEDs (800 effective J/m²), according to the FDA Final Rule of June 17, 2011.

Example 2

FDA CRITICAL WAVELENGTH TESTING SUMMARY

Objective:
This test was conducted to measure the specified test product's critical wavelength.

Formula Tested: [REDACTED]
MFN: [REDACTED]
Batch #: [REDACTED]

Testing Laboratory Name: [REDACTED]
Testing Laboratory Study #: [REDACTED]
[REDACTED]

Methodology:
The test was conducted [REDACTED], FDA IN-VITRO BROAD SPECTRUM TEST method. This method is in full compliance with the procedure and analysis set forth in FDA 1978-N-0018 2011 Final Rule for Labeling and Effectiveness Testing: Sunscreen Drug Products for Over-the-Counter Human Use.

Results Summary:
Test Date: October 6, 2017

Test Plate #	Critical Wavelength Value (nm)
1	371.00
2	371.40
3	371.00
Mean:	371.13

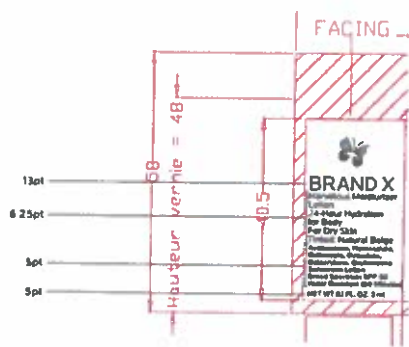
Based on the results from this study, the formula listed above passes does not pass the 370 nm criteria established by FDA and therefore can cannot make FDA broad spectrum claims.

[REDACTED] [REDACTED]

Appendix C: Proposed Labeling Changes

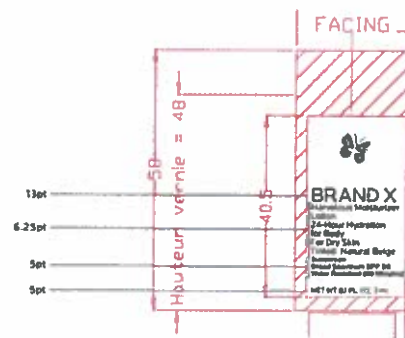
MOISTURIZER/BROAD SPECTRUM SUNSCREEN (TUBE)

FDA PROPOSAL:



(Actual Size)

INDUSTRY PROPOSAL:

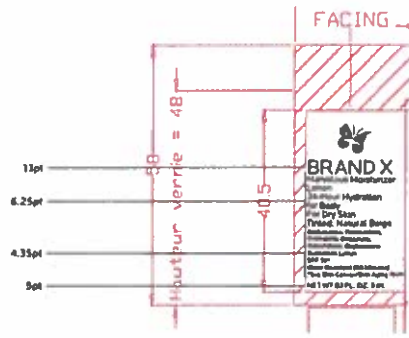


(Actual Size)

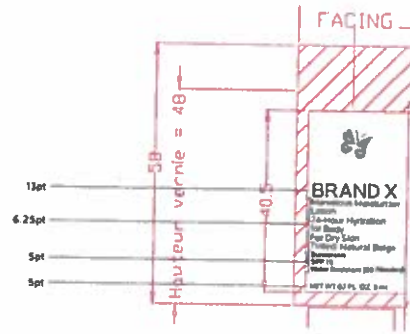
MOISTURIZER/NOT BROAD SPECTRUM SUNSCREEN (TUBE)

FDA PROPOSAL:

INDUSTRY PROPOSAL:



(Actual Size)



(Actual Size)

COMBINATION/BROAD SPECTRUM SUNSCREEN/SKIN PROTECTANT (STICK)

FDA PROPOSAL:



(Actual Size)

INDUSTRY PROPOSAL:

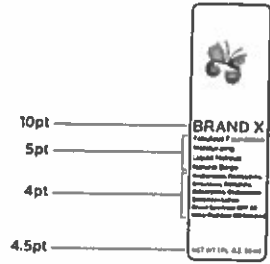


(Actual Size)

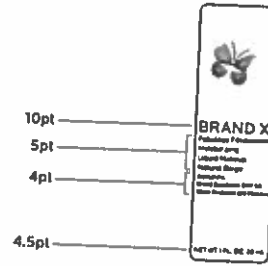
FOUNDATION/BROAD SPECTRUM SUNSCREEN (BOTTLE)

FDA PROPOSAL:

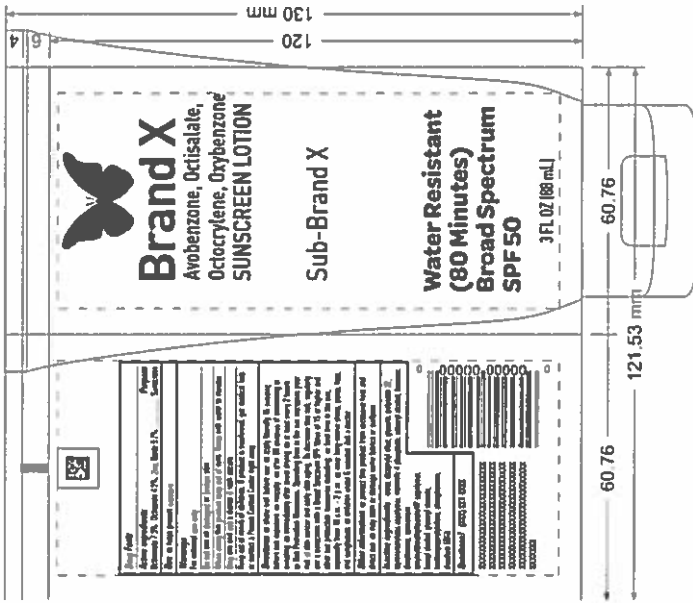
INDUSTRY PROPOSAL:



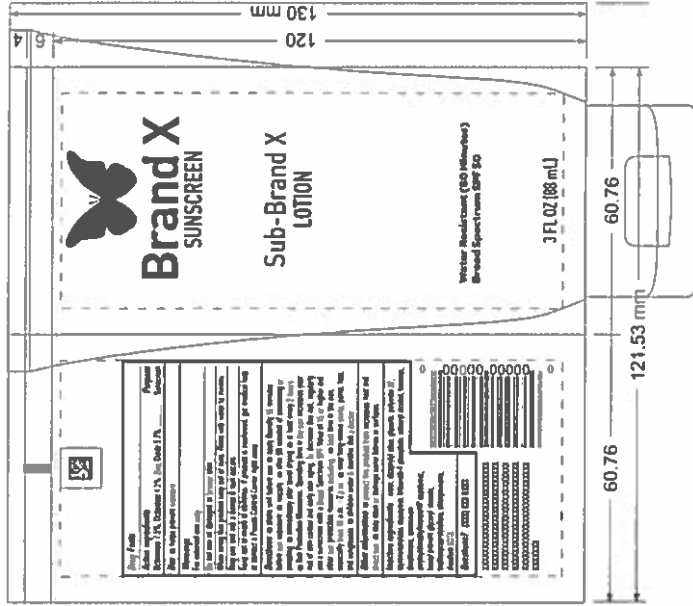
(Actual Size)



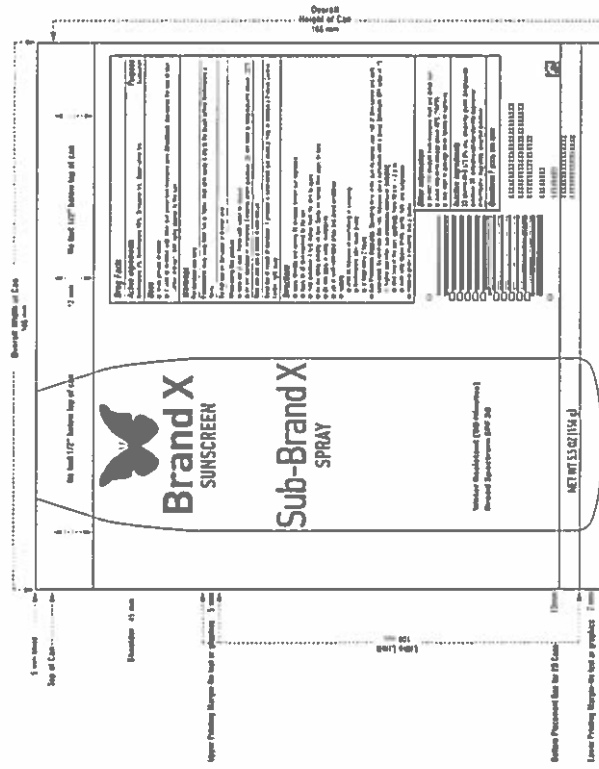
(Actual Size)



FDA OPTION

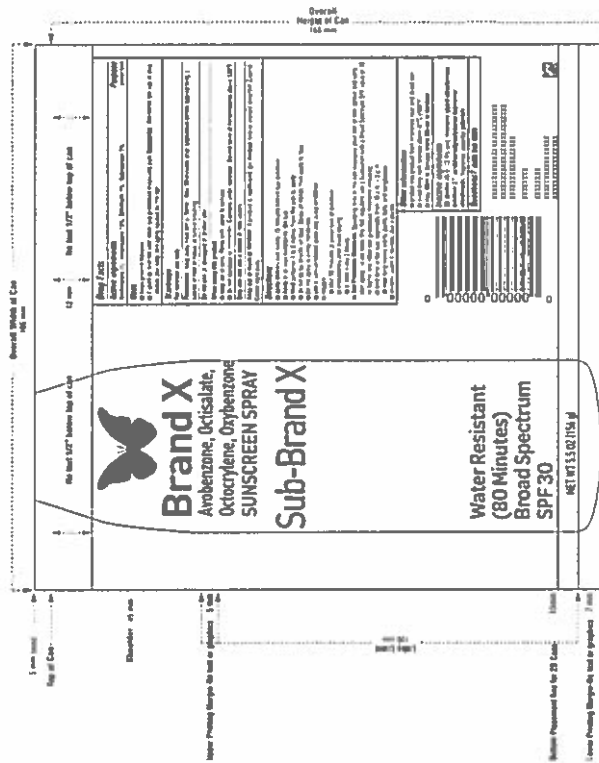


INDUSTRY OPTION



53 ± 1MS Nixed CG
7mm/line

INDUSTRY OPTION



53 ± 1MS Nixed CG
7mm/line

FDA OPTION

Appendix D: Powder Dosage Forms

1. Review and Commentary on Proposed FDA Monograph for OTC Sunscreens
2. Solesence FSTI Study Report
3. Powder Sunscreen Use Study #1: A Consumer Application Study
4. Powder Sunscreen Use Study #2: Survey of Consumer Use Patterns
5. Powder Sunscreen Use Study #3: A Consumer Log of Application Over 4 Day Period



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Review and Commentary on Proposed FDA Monograph for OTC Sunscreens

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Date:

June 20, 2019



Executive Summary

This report presents RHP's comments following a review of the Food and Drug Administration (FDA) proposed rule for "Sunscreen Drug Products for Over-the-Counter Human Use" and supporting information including a study by Liu (2019).^{1,2} RHP Risk Management Inc. (RHP) is an independent private consulting firm of health scientists which has been retained by The Personal Care Product Council (PCPC) to provide this critical review of the proposed FDA rule during the open comment period.

RHP's comments are focused on aspects of the proposed rule which address powder dosage forms only. Considering that FDA crafted the language in §4 "Powder Dosage Forms" with significant reference back to §3 "Safety and Effectiveness of Spray Sunscreens", RHP's comments reference elements of §3 to the extent they bear relevance to §4. Further, RHP's comments are focused on concepts presented in the proposed rule which relate to FDA's assessment of "potential harm from inhalation of sunscreen components".

The proposed rule contemplates whether powder dosage forms of OTC sunscreens should be considered GRASE and reviews information pertaining to efficacy and safety, including potential health risks from inhalation of sunscreen components. FDA proposes limits on the size of particles dispensed from consumer containers for spray-form and powder-form OTC sunscreens in order for such products to be considered GRASE and defines two criteria including: 1) 90% of the particles dispensed from the consumer container must be at least 10 μ m or greater; 2) the minimum particle size dispensed from the consumer container must be no less than 5 μ m. The technical basis for particle inhalation information considered by FDA is significantly based upon a single study conducted by Liu (2019).² Summarily, the Liu study was conducted in a manner suitable for material science research but presents significant shortcomings in application of the findings towards exposure science. In the proposed rule, FDA has applied the findings of the Liu study in a manner which generalizes risks in a non-specific manner based upon particle size only and does not consider the toxicological profile of the active ingredients. This results in proposed criteria which are technically unachievable as it is scientifically impossible to demonstrate compliance with a standard that requires "zero" particles less than 5 μ m. Accordingly, FDA should revise the monograph to include criteria that are scientifically defensible, rooted in generally accepted human-health risk assessment processes, and technically feasible to demonstrate compliance. We present an alternate set of risk-based criteria for consideration which are derived from data in the published scientific literature as compiled by the National Institute for Occupational Safety and Health (NIOSH) in development of Current Intelligence Bulletin (CIB) 63, as well as publicly presented data developed by ENVIRON International Corp. (ENVIRON) in 2014.^{3,4}

¹ Federal Register (February 26, 2019). Vol. 84, No. 38, pp.6204-6275.

² Liu, X., et al. (2019). *Particle Size Distribution Analysis of OTC Aerosol or Powder Drug Products with Potential for Inadvertent Inhalation Exposure to Consumers*. Pharm Sci. 108(4):1506-1511.

³ NIOSH (2011). Current Intelligence Bulletin 63. Occupational Exposure to Titanium Dioxide. <https://www.cdc.gov/niosh/docs/2011-160/pdfs/2011-160.pdf>

⁴ Persky, J. (2016). *Nanoscale titanium dioxide in cosmetics: Is everything beautiful?* British Occupational Health Society annual conference, Glasgow, Scotland. <https://www.oh2019.com/files/2015/08/3c-PERSKY-2016-BOHS-TiO2.pdf>



We believe that a regulatory criterion which is based upon a “particle size exceedance fraction” approach is unwarranted for powder-form OTC sunscreen products. A quantitative risk-assessment approach for TiO₂, arguably the active ingredient potentially of “greatest concern” used in powder-form OTC sunscreens, demonstrates that the excess cancer risks associated with an inhalation exposure route over a lifetime of typical product usage would be far less than 1:1,000,000, a standard the FDA has relied upon in the past for policy setting.⁵ The quantitative risks are influenced minimally by consideration of toxicity differences between particle size fractions (e.g. fine, ultrafine, respirable, inhalable), and are primarily driven by product use frequency and task duration. Considering reasonable bounds for the frequency and duration parameters of calculating dose yields the conclusion that the risks are “not unacceptable” and in our opinion consistent with the concept of GRASE ingredients. We present the following 8 key findings in support of this position.

Key Findings

In the proposed rule, FDA inquires “What factors, if any, should FDA consider in connection with particle size limitations or test methods for sunscreen powders?” In response, we present the following 8 key findings for consideration.

- 1. The Liu (2019) study provides an insufficient basis for promulgating criteria values which limit particle size dimensions in spray and powder OTC sunscreens due to study design limitations. Liu (2019) is a material science study, not an exposure assessment study.**

There are few peer-reviewed studies published in the scientific literature that compare the particle size distributions for spray and powder forms of sunscreen products. In relying significantly upon the results of a single study, Liu (2019), for purposes of preparing the draft rule, study design limitations appear to have been overlooked when applying the study findings to assess human inhalation exposure potential.

We understand the intended outcome of the FDA proposed rulemaking is to protect human health against potential adverse effects from over-the-counter sunscreen products. Assessing exposure potential, in the context of human health risk assessment, is most appropriately evaluated via an exposure assessment which considers human factors in addition to chemical and physical properties of the material. The primary goal of exposure assessment studies is to accurately reflect how a human interacts with, and may be affected by, a hazard with the aim of quantifying exposure to that hazard such that risk can be assessed. Rothe and Steiling explain that to prepare a proper safety assessment for aerosolized products, the best knowledge about intended use conditions should be applied.^{6,7} Liu (2019) is not an exposure assessment study;

⁵ Sadowitz, M., Graham, J. (1995). *A Survey of Residual Cancer Risks Permitted by Health, Safety and Environmental Policy*. RISK: Health, Safety & Environment. Vol.6(1). <https://scholars.unh.edu/cgi/viewcontent.cgi?article=1218&context=risk>

⁶ Steiling, W. et al. (2018). *Principles for the Safety Evaluation of Cosmetic Powders*. Toxicology Letters. (297) 8-18. <https://doi.org/10.1016/j.toxlet.2018.08.011>

⁷ Rothe, H. et al. (2011). *Special Aspects of Cosmetic Spray Safety Evaluations: Principles on Inhalation Risk Assessment*. Toxicology Letters. (205) 97-104. <https://doi.org/10.1016/j.toxlet.2011.05.1038>



rather it is best characterized as a material science study. Material science studies may address the potential relationship between study findings and public health concerns, but often rely on assumptions or generalizations about human interaction and product use scenarios to infer exposure potential and associated risk. Material science studies can produce useful information for exposure assessment needs, but their purpose is not to accurately characterize “real-world” exposure potential to product users.

The Liu (2019) particle distribution study applies aerosol generation mechanisms for powder-form and spray-form OTC sunscreen products which are unrelated to methods of human product application. Accordingly, the product behavior, including particle releasability and the particle size distributions generated, are not representative of potential human exposure conditions for anticipated product use methods. Liu (2019) uses two different mechanical aerosol generation techniques, one for spray products and another for powder products. These mechanized processes afford excellent reproducibility for study repetitions, a desirable attribute for material science research, but lacking in relevance to human exposure potential as used in the Liu study. For example, the powder aerosolization mechanism used by Liu exerts shear forces on the powder which likely exceeds forces generated by human application techniques and increases separation of agglomerates into small diameter secondary particles or primary particles. Further, no evidence is provided as to the comparability of these two different aerosol generation mechanisms or measurement devices. For spray-form products, a countertop laser diffraction (LD) instrument (Sympatec HELOS H1845) was placed in the centerline of a spray plume at a 15cm distance from the discharge nozzle of the container. This measurement approach bears no relevance to reasonable human product use. For powder-form products, a countertop LD instrument (Malvern Mastersizer 3000) was used with an automatic “dry dispersion unit” attachment that aerosolizes a powder sample within a test cell. Both instruments collected particle distribution measurements from aerosols generated at concentrations greater than reasonable human use conditions, which increases the likelihood of measuring particle sizes that may not be measurable, or even present at all, in the breathing zone during realistic product-use scenarios by a human.

Consequently, the study findings presented in Liu (2019), and relied upon for proposed rulemaking, are misleading. The amount of variance between particle size fractions for spray-form products vs. powder-form products is represented by Liu to be attributable solely to the different physical properties of ingredients and delivery mechanisms. Such is not proven by Liu because all spray-form products were tested using the Sympatec HELOS using one aerosol measurement technique, and all powder-form products were tested using the Malvern Mastersizer 3000 using a different aerosol measurement technique, and no demonstration of comparability between the measurement methods for these two instruments was provided. It is possible that much of the observed difference in particle size distributions for these two different categories of OTC sunscreen products could be related to the use of different measurement instruments or aerosol generation techniques.



2. **Mass-based data are essential for conducting an inhalation exposure assessment. Coupling the count-based data reported by Liu with published mass-based exposure data for active ingredients in powder-form sunscreen products yields quantitative risks which have been previously demonstrated as “safe” in comparison to rules established by other authoritative agencies. Criteria setting to define a “safe” exposure level using a “particle size exceedance fraction” approach is not necessary, as even the most conservative assumptions yield negligible quantitative risks. Quantitative excess cancer risks calculated for exposure to active ingredients over a lifetime of normal product use would be far less than 1:1,000,000 which is a risk-based threshold previously accepted by FDA.⁸ Using OTC powder-form sunscreens as intended over a lifetime does not represent an unacceptable level of risk; we find this to be consistent with the concept of GRASE.**

Liu presents a final conclusion that acknowledges *“The measurement of particle size distribution is an important determinant of the exposure to end users because knowing the mass of respirable particles is essential for an inhalation exposure assessment.”* (emphasis added) However, the methods in this study do not measure particle mass. The study methods used provide particle count information only and do not address whether the composition of counted particles relates to primary particles or secondary agglomerates/aggregates, nor provide information about particle density. Accordingly, it is not possible to derive mass-based information from the data provided. However, additional information exists within the published scientific literature which facilitates such calculations and conversion of the Liu data to mass-based equivalencies followed by evaluation to risk-based lifelong cumulative exposure (dose) thresholds.

A study conducted by ENVIRON International Corp. measured unbound airborne respirable titanium dioxide (UART) concentrations in the personal breathing zone during application of 5 powder-form consumer products including eye shadow, nail powder, foundation face powder, blush, and sunscreen powder.⁹ The study demonstrated that airborne concentrations of UART were undetectable on a mass-basis and no greater than 0.0284 mg/m³ during a task duration of 9 to 11 minutes during which three sequential applications of product were performed. This exposure data was then coupled with risk-based information published in NIOSH CIB 63, Table 4-7 (shown below), which presents a quantitative risk-based approach to exposure limit setting for occupational exposures considering both fine and ultrafine forms of TiO₂.

⁸ Sadowitz, M., Graham, J. (1995). *A Survey of Residual Cancer Risks Permitted by Health, Safety and Environmental Policy*. RISK: Health, Safety & Environment. Vol.6(1).
<https://scholars.unh.edu/cgi/viewcontent.cgi?article=1218&context=risk>

⁹ Persky, J. (2016). *Nanoscale titanium dioxide in cosmetics: Is everything beautiful?* British Occupational Health Society annual conference, Glasgow, Scotland. <https://www.oh2019.com/files/2015/08/3c-PERSKY-2016-BOHS-TiO2.pdf>



Table 4–7. Model average estimates[†] of mean airborne mass concentrations of fine and ultrafine TiO₂ in humans and related human lung burdens (TiO₂ * surface area dose) associated with various levels of excess risk of lung cancer after a 45-year working lifetime

Particle size and lifetime added risk estimated from rat dose-response data for lung tumors [†]	Critical dose in human lungs [†]				Mean airborne exposure [†]	
	Particle surface area (m ² /lung)		Particle mass (g/lung)		MPPD (ICRP) lung model (mg/m ³)	
	MLE	95% LCL	MLE	95% LCL	MLE	95% LCL
<i>Fine TiO₂ (2.1 μm, 2.2 GSD; 6.68 m²/g):</i>						
1 in 500	114.2	24.9	17.1	3.7	16.1	3.5
1 in 1000	93.5	17.0	14.0	2.5	13.2	2.4 ^{††}
1 in 2000	76.3	11.1	11.4	1.7	10.8	1.6
1 in 5000	57.5	6.2	8.6	0.9	8.1	0.9
1 in 10,000	46.4	3.8	6.9	0.6	6.5	0.5
1 in 100,000	21.4	0.5	3.2	0.1	3.0	0.1
<i>Ultrafine TiO₂ (0.8 μm, 1.8 GSD; 48 m²/g)^{**}:</i>						
1 in 500	114.2	24.9	2.38	0.52	1.97	0.43
1 in 1000	93.5	17.0	1.95	0.35	1.62	0.29 ^{††}
1 in 2000	76.3	11.1	1.59	0.23	1.32	0.19
1 in 5000	57.5	6.2	1.20	0.13	0.99	0.11
1 in 10,000	46.4	3.8	0.97	0.08	0.80	0.07
1 in 100,000	21.4	0.5	0.45	0.01	0.37	0.01

^{††} denote the NIOSH REL values adopted for fine and ultrafine fractions at the 1:1,000 risk level.

The quantitative risk-based approaches used by NIOSH in developing an occupational Recommended Exposure Limit (REL) may be adapted for quantitative risk-assessment of other non-occupational exposure profiles by time-adjustment and selection of a different target risk level. For example, instead of assuming steady-state exposure conditions for a 40-hr workweek every week for a 45-year working lifetime at a target risk level of 1:1,000, a more conservative risk level may be selected (e.g. 1:100,000 is commonly used for population-based human health risk assessment) and time-adjusted to fit the exposure profile of interest, such as OTC sunscreen application up to 4 times per day for a 70-year statistical lifetime as applied by Mata et al (2019) in a FDA MUsT study.¹⁰

Such a time-adjustment approach has been used to derive a No Significant Risk Level (NSRL) for TiO₂ at the 1:100,000 risk level for a 70-yr lifetime exposure pattern in compliance with California

¹⁰ Matta, et al (2019). *Effect of Sunscreen Application Under Maximal Use Conditions on Plasma Concentration of Sunscreen Active Ingredients*. JAMA. doi:10.1001/jama.2019.5586



“Proposition 65” requirements.¹¹ Toxservices LLC (2014) calculated an inhalation NSRL of 910 µg/day for fine TiO₂ and 97 µg/day for ultrafine TiO₂.^{12,13} Others have estimated the NSRL value to be as high as 7,000 µg/day.¹⁴

Coupling of the ENVIRON (2014) task-duration exposure data for TiO₂ in powder-form OTC sunscreens with derived NSRL values can be performed following three different approaches to gain insight.

Approach 1 – Application of the NSRL value for “fine” TiO₂ of 910 µg/day

Considering a 4-times per day application pattern, every day, over a 70-year lifetime, more than 300 applications per day (every day) would be required to reach an excess cancer risk level of 1:100,000. The maximal excess risk at a 4x/day application rate is calculated to be approximately 1:8,000,000. (See sample calculation 1 in Attachment 1). This approach assumes 100% of airborne TiO₂ pertains to the “fine” fraction which is defined as having a MMAD of 2.1µm. Such an assumption appears conservative in comparison to the particle size distribution data published by Liu which presents MMAD values in the range of 6.9µm to 10.2µm for 6 powder products.

Approach 2 – Incorporation of the particle size distribution data published by Liu to calculate a weighted NSRL value which combines differing risk levels for both “fine” and “ultrafine” TiO₂.

A cut point of 0.1µm was selected by NIOSH for purposes of differentiating risks related to exposure to fine and ultrafine forms of TiO₂. The selection of this cut point, which relates to the definition of nanoparticles, is based upon the reported shift in toxicological properties of particles as bioavailable surface area increases greatly in the nano-size range as compared to larger diameter particles constituting the same total mass.³ Separately, Liu selected a cut point of 5µm to “generally” define the boundary between respirable and non-respirable particles in his study for purposes of ascribing greater risk to respirable-sized particles and lesser risk to non-respirable sized particles.

If one takes the approach of mapping the “greater-risk” category from the Liu study (fraction of particle distribution ≤5µm) to the “greater-risk” NSRL value of 97µg/day for “ultrafine TiO₂”, and similarly map the “lower-risk” category from the Liu study (fraction of particle distribution >5µm) to the “lower-risk” NSRL value of 910µg/day for “fine TiO₂”, a weighted NSRL value can be calculated which quantifies risk in a highly conservative manner and considers the Liu data. The outputs of these calculations yield product-specific NSRL values in the range of 564µg/day for powder product 6, to 817 µg/day for powder product 1. If the most conservative of these values is selected (powder product

¹¹ Toxservices LLC (2014). *Establishing a No-Significant Risk Level (NSRL) Derivation for Titanium Dioxide (CAS #111-42-2)*. <https://www.ebookonlinesale.com/establishing-a-no-significant-risk-level-nsrl-derivation-for-titanium-dioxide-cas-111-42-2>

¹² Fine TiO₂ is defined as particles with a mass median aerodynamic diameter of 2.1µm.

¹³ Ultrafine TiO₂ is defined as particles with a mass median aerodynamic diameter of 0.8µm.

¹⁴ Shammas, M., et. al. (2015). *Suggested safe harbor limit for titanium dioxide: an exposure level which protects consumers from cancer incidence*. *Frontiers in Oncology*. doi: 10.3389/fonc.2015.00076



6, which generated an aerosol with 42.51% of particles $\leq 5\mu\text{m}$ per Liu), and considering a scenario involving application 4-times per day, every day, over a 70-year lifetime, the calculated excess risk is approximately 1:5,000,000. To reach an excess cancer risk level of 1:100,000 would require more than 200 applications daily, every day, for a lifetime. (See sample calculation 2 in Attachment 1).

Approach 3 – Adoption of a “Particle size exceedance fraction” approach which, consistent with NIOSH’s approach sets a cut-point at $0.1\mu\text{m}$ for transition to a more stringent risk value, would result in a 1:1,000,000 excess cancer risk level for TiO_2 defined by the criteria:

No more than 98.4% of the particles dispensed from the consumer container may be $0.1\mu\text{m}$ or smaller.

If a “particle size exceedance fraction” approach to criterion setting is desired, then the criterion values should be based upon a quantitative risk-based approach. Considering a target not-to-exceed risk level of 1:1,000,000 and an exposure profile considering application 4-times per day, every day, over a 70-year lifetime, it is permissible that a powder-form OTC sunscreen product could contain up to 98.4% of particles smaller than $0.1\mu\text{m}$ and still meet the risk-based criteria. (See sample calculation 3 in Attachment 1).

The main conclusion of these theoretical calculations is that the risk driver is not the portion of aerosol fraction which is respirable or within the nano-size range, but rather frequency of product use. Considering the extremely low levels of potential exposure, coupled with a realistic upper bound to the number of daily product applications, it is not feasible to achieve a risk level which would be considered unacceptable (e.g. greater than 1:100,000 or 1:1,000,000). Accordingly, criteria setting by FDA to define “safe” exposure levels as a function of a “not-to-exceed fraction of the aerosol for particle sizes $<5\mu\text{m}$ ” is not necessary. The risk-science supports that up to 100% of the aerosol may fit within the $<5\mu\text{m}$ portion of the particle size distribution and still not yield unacceptable risk given a realistic exposure profile and product use pattern consistent with the intended use. We believe this finding is consistent with the concept of GRASE.

3. Liu overly generalized a fundamental scientific concept relating to particle size fractions and potential for particle deposition by inhalation. The selection of $5\mu\text{m}$ as an “absolute” cut point by which to represent respirable particles is unsupported by scientific consensus that defines the term “respirable” by convention as a curve, in which $5\mu\text{m}$ is the median cut-point. Nonetheless, if a particle-size value were to be used in defining a cut point to ascribe greater risk to particles with smaller dimensions, we believe that the risk-science supports selection of $0.1\mu\text{m}$ as a more suitable value than $5\mu\text{m}$ for approximating the boundary where particle bioavailable surface area becomes a driving characteristic for human-health risk assessment purposes involving the deposition of poorly-soluble particles in the respiratory tract.

If a particle-size value were to be used in defining a cut point to ascribe greater risk to particles with smaller dimensions below the cut point, we believe that the risk-science, as supported within peer reviewed scientific literature and advocated by NIOSH CIB 63, supports that $0.1\mu\text{m}$ is a more suitable value than $5\mu\text{m}$ for approximating the boundary where particle bioavailable



surface area becomes a driving characteristic for human-health risk assessment purposes. It is our opinion that if FDA were to establish criteria based using a “particle size exceedance fraction” approach, 0.1 μ m would be a more appropriate selection. However, considering the frequency and duration of exposure for OTC powder-form products, we do not believe any criteria is necessary because quantitative risk-based approaches suggest that using OTC powder-form sunscreens as intended over a lifetime would not represent an unacceptable level of risk.

4. The verbiage of “harmful levels” used by FDA is vague and implies that there is a meaningful potential for harm to occur from exposure to sunscreen ingredients (like TiO₂ and ZnO) during normal product use conditions, which is unproven. The concept of requiring “zero exposure” to “reduce or eliminate harm” lacks scientific basis and is counter to key concepts of human health risk assessment. Exposure at some non-zero level is frequently demonstrated to be “not unacceptable” through human health risk assessment processes.

In regard to the toxicity of sunscreen ingredients, the FDA stated that they are “proposing that exposure to harmful levels of such ingredients can effectively be minimized by imposing particle size limitations on spray sunscreen products.” Without further explanation from FDA, the term “harmful levels” can be interpreted in many different ways. Based on the FDA website, harm usually means the damage to health caused by exposure to a product.¹⁵ The threshold for exposure to a “harmful level” of a substance is typically established based on the risk, or the likelihood and severity, that harm will occur. The Occupational Safety and Health Administration (OSHA) recognizes risk as the probability that an adverse effect will occur.¹⁶ The U.S. Environmental Protection Agency (EPA) considers a risk to be the chance of harmful effects to human health or to ecological systems.¹⁷

It is noted that the FDA has previously undertaken risk-based approaches for evaluating other dosage forms in previous rulemaking and the proposed approach to criteria setting for powder-forms using a “zero-risk” target appears to apply an inconsistent approach. It is also notable that NIOSH has already concluded that there is insufficient data to classify “fine” particles of TiO₂ as carcinogenic.^{3,18}

To control for potential risk or harmful effects of substances, regulatory agencies assign limitations or levels to meet or to not exceed. These are based on thorough quantitative risk assessments performed before criterion levels are proposed and ingredients are deemed potentially harmful. By example, California’s Proposition 65 standard involves a list of chemicals that are known to cause cancer, birth defects, or other reproductive harm.¹⁹ The standard clearly defines what a “harmful level” of a substance is, based on a quantitative risk assessment approach to derive a NSRL value considering a lifetime of exposure. Quantitative risk assessment

¹⁵ FDA. *ORA Risk Management in 7 Steps*. Accessed 6/14/19.

https://www.accessdata.fda.gov/ORAU/ORARiskManagement/terminology_and_principles_harm.html

¹⁶ OSHA. *Guidance for Hazard Determination*. Accessed 6/14/19. <https://www.osha.gov/dsg/hazcom/ghd053107.html>

¹⁷ EPA. *About Risk Assessment*. Accessed 6/14/19. <https://www.epa.gov/risk/about-risk-assessment>

¹⁸ NIOSH defines “fine TiO₂” as a particle size fraction with MMAD 2.1 μ m, 2.2 GSD, 6.68 m²/g.

¹⁹ OEHHA. *About Proposition 65*. Accessed 6/14/19. <https://oehha.ca.gov/proposition-65/about-proposition-65>



is one approach to tangibly defining what is meant by the verbiage “harmful levels” such that products can be developed, which under normal use conditions, effectively minimize the potential for harm. Additionally, a quantitative risk assessment will provide specific data that harmful effects can be mitigated or avoided at levels above “zero”.

5. The proposed criterion limit of “zero exposure to particles under 5 μ m” is technically unachievable.

Criterion limits set by regulatory agencies recommending exposure limits should possess two essential features: 1) The limit should be technically feasible; 2) The limit should be measurable such that compliance can be demonstrated.

“Zero” is not a technically feasible criterion as it is not a measurable value. All analytical methods have associated limits of detection and the absence of detection by a particular method does not demonstrate “zero”, but rather non-detect at a value that is the detection limit for the method. Accordingly, well defined exposure limits should specify a not-to-exceed limit for a value that is both measurable and technically feasible via an existing analytical technique. What is not measurable in the present may become measurable in the future as analytical instrument capabilities advance and analytical sensitivities continue to improve.

The FDA’s proposed monograph sets a lower criterion limit of “zero” particles less than 5 μ m that can be dispensed from a consumer container. This proposed criterion is problematic because it is technically unachievable as it is impossible to demonstrate “zero”; it is only possible to demonstrate non-detect at a specific detection-limit for a method.

6. The proposed criteria of having “zero” particles <5 μ m is unrealistic and would unduly burden manufacturers of powder-form sunscreen products.

Table 1 in Liu (2019) presents particle size distribution data for 32 products and 1 reference active ingredient. The column titled “D10 (μ m)” represents the value, in microns, for which 10% of the overall particle distribution is of equal or smaller size. Accordingly, 90% of the overall particle distribution is *greater* than the value in this same column. Any value in this column that is greater than 10 μ m would therefore meet the first of two proposed criteria by FDA. Considering that 18 of the values in the D10 column of Table 1 are *below* 10 μ m, they would fail to meet this criterion.

Table 2 in Liu (2019) presents the percentage of the particle population for 32 products and 1 reference active ingredient that are less than or equal to 5 μ m. The second of two criteria proposed by FDA require that “zero” particles be less than 5 μ m. Only one product (aerosol product 3) *potentially* meets this requirement of reportedly generating 0.00% particles \leq 5 μ m. The other 31 products and 1 reference active ingredient were found to have particles sized \leq 5 μ m representing a range of 0.01% to 42.65% of the overall particle population. For aerosol product 3, it should be noted that despite a reported value of “0.00%” particles \leq 5 μ m, in actuality considering the Sympatec HELOS Laser Diffraction System used to collect the measurement is only capable of providing an analytical sensitivity down to 0.1 μ m, a more accurate statement



would be that no particles were detected in the range of 0.1-5 μ m. Such does not preclude a bi-modal particle distribution pattern for this product and it is possible that respirable particles <0.1 μ m may have been present, and therefore it is possible that aerosol product 3 may not even meet the second of two criteria proposed by FDA which requires “zero” particles less than 5 μ m. This example illustrates quite well the inability to demonstrate compliance with a standard that requires “zero” particles less than 5 μ m.

While citing to Liu (2019) as the basis, FDA states:

“FDA has conducted particle distribution testing on five powder sunscreens. The powder sunscreens tested had a larger proportion of relatively small particles compared to the sprays. Only one of the five powder sunscreens would have complied with the requirement we are considering that no more than 10 percent of the particles could be smaller than 10 μ m in diameter, and that product was also the only one that would have met the prospective limitation of no particles smaller than 5 μ m in diameter.”

None of the data published in Liu supports the above statement. Of the 5 powder products tested, the one that comes closest to this result is “Powder product 1” which had 38.03% of the particle distribution below 10 μ m and therefore approximately 62% of the particle distribution was above 10 μ m. Powder product 1 also had 11.48% of the particle population \leq 5 μ m which means that there were “more than zero” particles smaller than 5 μ m in diameter when substantial shear forces were applied during measurement.

- 7. Mechanical agitation to generate an aerosol, as performed by Liu (2019), would unnaturally disaggregate particles from shear forces atypical of a realistic user scenario and lead to measurement of particle size distributions with greater prevalence of small diameter secondary particles or primary particles.**

The FDA proposed rule states “[f]or purposes of these proposed particle size requirements, we are using the term particle size broadly to mean the discrete unit emitted from the spray container that is available for inhalation by a consumer when the product is applied.”

Products like spray and powder sunscreens contain a wide array of particle sizes in dry or wet form, but not all particles behave the same in air or in the body. Primary particles represent the smallest, individual elements of a particulate system or original substance.²⁰ They are usually characterized by their surface area, shape, and size. How a particle travels through the air and potentially down the respiratory tract is largely dependent on its physical characteristics.

In many cases, the primary particles within a spray or powder product may “stick” together to form secondary agglomerates. Agglomerates are an assembly of primary particles (e.g. joined

²⁰ Lu, P.J., et al (2018). *Characterization of titanium dioxide and zinc oxide nanoparticles in sunscreen powder by comparing different measurement methods*. Journal of Food and Drug Analysis (26)1192-1200. <https://doi.org/10.1016/j.jfda.2018.01.010>



together at the corners or edges), whose total surface area does not differ appreciable from the sum of specific surface areas of primary particles.²¹ Aggregates are an assembly of primary particles that have grown together and are aligned side by side; the total specific surface area is less than the sum of the surface areas of the primary particles.²¹ Agglomerates usually form when the initial concentration of particles is very high, and the particles are in the ultrafine diameter size range.²¹ Electrostatic and diffusion forces allow these particles to remain stuck together until they are detached via other mechanical forces.

The powder aerosolization mechanisms used by Liu likely exerted shear forces on the powder which would exceed forces generated by human application techniques and therefore increase separation of agglomerates into smaller diameter secondary particles and possibly primary particles. These aggregates and agglomerates are inherently fundamental to the powder substance that is applied to a consumer, in the same manner that water molecules which hold the primary particles in a spray form are applied to a consumer.

- 8. FDA states that there is a lack of potential inhalation toxicity data related to ingredients in spray-form and powder-form OTC sunscreens. Aside from the active ingredients, principally TiO₂ and ZnO, the remaining ingredients are commonly found in cosmetics and are not regulated by “particle size exceedance fractions” in other products.**

The use of TiO₂ as an active ingredient in powder-form OTC sunscreens is not unacceptable from a quantitative risk assessment perspective (per finding #2), and the toxicological profile for ZnO indicates lower potency than TiO₂ pertaining to an inhalation exposure route.²²

Both FDA and CDC/NIOSH are agencies under the auspices of the Department of Health and Human Services (DHHS). In April of 2011, NIOSH issued CIB 63 on fine and ultrafine TiO₂ exposures in occupational settings. TiO₂ and ZnO are the most common, and only commercially identified, active ingredients in powder-form OTC sunscreens. Other components of powder sunscreens tend to include mineral ingredients such as iron oxide or mica and are consistent with other powder cosmetic products, which are not currently proposed to be impacted by a particle size restriction.

As already noted, the NIOSH investigators extensively reviewed the TiO₂-specific animal and human health effects data, used dose-response information and performed a quantitative risk assessment to recommend two occupational exposure limits based upon particle size. NIOSH CIB 63 ultimately concluded that there is insufficient data to classify “fine” particles of TiO₂ as carcinogenic.^{3,18} Specifically, CIB 63 states that epidemiologic and animal inhalation studies were inconclusive. Particle surface area in lieu of particle size was used as a dose metric throughout the quantitative risk assessment. It is important to note that NIOSH derived their conclusions for occupational exposures. Nevertheless, understanding their reasoning behind such decisions

²¹ Walter, D. (2013). *Primary Particles – Agglomerates – Aggregates*. https://application.wiley-vch.de/books/sample/3527335714_c01.pdf

²² ATSDR (2005). *Toxicological Profile for Zinc*. <https://www.atsdr.cdc.gov/toxprofiles/tp60.pdf>



regarding particle size and surface area, for an ingredient readily found in powder sunscreens, is relevant. It is especially important to recognize the chemical-specific approach to quantitative risk assessment taken by a fellow federal agency on a related topic.

The NIOSH research directly pointed to particle surface area as the “critical metric” for human health risk assessment pertaining to the inhalation exposure route.³ Mass-based potency was greater in ultrafine TiO₂ particles than fine particles due to the larger surface area of the ultrafine particles in rat studies. Hence, a dose-response relationship with fine and ultrafine TiO₂ particles was found for pulmonary inflammation and lung tumors in rats when the dosage was presented as particle surface area. Animal inhalation studies, in general, showed the same dose-response curve for ultra-fine and fine particles as total particle surface area in the lungs. When comparing between particle mass and surface area in pulmonary inflammation studies, low toxicity particles (like TiO₂) and high toxicity particles (like crystalline silica) all have very different dose response relationships by particle mass; but when expressed as surface area, the low toxicity particles have the same dose response curve and crystalline silica has a completely different dose-response curve. In a rat lung tumor study, a higher proportion of lung tumors were found as the surface area of low toxicity particles (of various sizes) increased. This supports the notion that active ingredients of similarly low toxicity, such as TiO₂ and ZnO, are likely to share similar dose-response curves when expressed as surface area.

Additionally, it is also suggested that the morphology of a particle may contribute to the toxicity of a substance. NIOSH CIB 63 presented data that the crystalline structure, along with particle size and surface area, of TiO₂ can affect the reactive species, cytotoxicity, and acute lung response. Nevertheless, even with this potential acute reaction, the overall dose-response for chronic exposure is not affected.

NIOSH CIB 63 also concluded that particle size and surface area are the primary determinants of TiO₂ acting through a secondary genotoxicity mechanism.³ This means that tumor response was more related to the physical form (surface area) of TiO₂ than the to the actual chemical compound. The secondary genotoxicity mechanism includes a series of events, including cellular proliferation and the overloading of cilia or other lung clearance mechanisms, which NIOSH deems are better characterized by particle surface area than by their mass dose. Nonlinear dose-response curves show that carcinogenic potency of TiO₂ decreases as surface area decreases. Thus, it was concluded that there is an increase in potency with an increase in particle surface area of poorly soluble and low toxicity particles like TiO₂.

The ATSDR toxicological profile for zinc addresses inhalation exposure route concerns primarily related to metal fume fever at exposure concentrations many orders of magnitude higher (77 to 600 mg Zn/m³) than would be expected in association with powder-form OTC sunscreen usage. ATSDR provides a summary of two epidemiological studies for occupational exposures and no association between cancer mortality and zinc exposure was identified. In comparison to TiO₂, the toxicological profile for ZnO may be generalized as the “safer of two safe active ingredients” in powder-form OTC sunscreens.



CLOSING

Risk assessment is said to be the bridge between science and policy.²³ Quantitative risk assessments provide the scientific basis for NIOSH recommended exposure limits (RELs), U.S. EPA's permissible levels, OSHA permissible exposure limits (PELs), and other agency regulatory levels. Many of these standards use particulate airborne exposure data or models and their corresponding inhalation curves to define not the lowest inhalation level possible, which would in theory always be zero, but the lowest feasible level or the maximum level to not exceed in order to prevent harm. In regard specifically to particle science, Rothe (2011) stated that the use of mass percentage and not particle number is common practice in existing inhalation studies and that particle number is not a practical tool in risk assessment that would allow for direct comparison between animal toxicological studies and human exposure data.⁷ By applying a human-health risk assessment approach prepared by NIOSH, coupled with empirical data for mass-based exposure concentrations during application of powder-form OTC sunscreens, the particle size distribution data from Liu (2019) can be shown to yield quantitative risks which are significantly less than 1:1,000,000 for reasonably anticipated consumer product use scenarios over a lifetime. We believe these findings are consistent with the concept of GRASE and contribute further to FDA's prior hazard identification work which determined both titanium dioxide and zinc oxide to be GRASE for other forms of use.

Respectfully Submitted,

A handwritten signature in black ink that reads 'Jacob Persky'.

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²³ Hertz-Picciotto (1995). *Epidemiology and quantitative risk assessment: a bridge from science to policy*. *Am J Public Health*. Apr;85(4):484-91. <https://doi.org/10.2105/ajph.85.4.484>



**RISK
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Attachment 1

Sample Calculations



Sample Calculations

Input variables:

ENVIRON data (2014) for three scenarios to measure airborne concentrations of unbound airborne respirable titanium dioxide during application of powder-form OTC sunscreen.

1. Powder Sunscreen A = non-detect at LOD of $<0.0181 \text{ mg/m}^3 \text{ TiO}_2$ in the personal breathing zone during triplicate repeat application for a total of 0.06g over an 11 minute duration.
2. Powder sunscreen B = non-detect at LOD of $<0.0221 \text{ mg/m}^3 \text{ TiO}_2$ in the personal breathing zone during triplicate repeat application for a total of 0.18g over a 9 minute duration.
3. Powder sunscreen C = non-detect at LOD of $<0.0221 \text{ mg/m}^3 \text{ TiO}_2$ in the personal breathing zone during triplicate repeat application for a total of 0.11g over a 9 minute duration.

Adult breathing rate = $20 \text{ m}^3/\text{day}$

Maximum # application times per day = 4 applications / MUSt day

No Significant Risk Level at 1:100,000 = $910 \text{ } \mu\text{g}/\text{day}$ for NIOSH-defined "fine" fraction TiO_2 .

No Significant Risk Level at 1:100,000 = $97 \text{ } \mu\text{g}/\text{day}$ for NIOSH-defined "ultrafine" fraction TiO_2 .



Sample equation 1

$$< 0.0221 \frac{\text{mg UART}}{\text{m}^3} \times \frac{9 \text{ min}}{\text{application}} \times \frac{20 \text{ m}^3}{\text{day}} \times \frac{1 \text{ day}}{1440 \text{ min}} = \frac{0.00276 \text{ mg UART}}{\text{application}}$$

$$\frac{0.00276 \text{ mg UART}}{\text{application}} \times \frac{4 \text{ applications}}{1 \text{ MUsT day}} \times \frac{1,000 \text{ ug}}{1 \text{ mg}} = \frac{11.1 \text{ ug UART}}{1 \text{ MUsT day}}$$

$$\frac{11.1 \text{ ug UART}}{1 \text{ MUsT day}} \times \frac{1 \text{ MUsT day}}{910 \text{ ug UART}} = 0.012 \rightarrow 1.2\% \text{ of NSRL for Fine UART at } 1:1E5 \text{ risk level}$$

$$\frac{1E5}{0.012} = 8.3E6 \rightarrow 1 \text{ in } 8.3 \text{ million calculated risk level}$$



Sample equation 2

Considering the 6 powder products in Table 2 of Liu (2019), select the powder with the greatest %D $\leq 5\mu\text{m}$ which is powder 6 (%D $\leq 5\mu\text{m}$ = 42.51%).

To calculate a product-specific NSRL value that is weighted using the highly conservative approach of mapping:

- mass fraction reported by Liu (2019) for %D $\leq 5\mu\text{m}$ \rightarrow NSRL ultrafine UART of 97 ug/day
- mass fraction reported by Liu (2019) for %D $> 5\mu\text{m}$ \rightarrow NSRL fine UART of 910 ug/day

$$42.51\% D_{\leq 5\mu\text{m}} \times \frac{97 \text{ ug UART}}{\text{day}} + (1 - 42.51\%) D_{> 5\mu\text{m}} \times \frac{910 \text{ ug UART}}{\text{day}} = \frac{564 \text{ ug UART}}{\text{day}}$$

$$< 0.0221 \frac{\text{mg UART}}{\text{m}^3} \times \frac{9 \text{ min}}{\text{application}} \times \frac{20 \text{ m}^3}{\text{day}} \times \frac{1 \text{ day}}{1440 \text{ min}} = \frac{0.00276 \text{ mg UART}}{\text{application}}$$

$$\frac{0.00276 \text{ mg UART}}{\text{application}} \times \frac{4 \text{ applications}}{1 \text{ MUsT day}} \times \frac{1,000 \text{ ug}}{1 \text{ mg}} = \frac{11.1 \text{ ug UART}}{1 \text{ MUsT day}}$$

$$\frac{11.1 \text{ ug UART}}{1 \text{ MUsT day}} \times \frac{1 \text{ MUsT day}}{564 \text{ ug UART}} = 0.020 \rightarrow 2.0\% \text{ of calculated NSRL at } 1:1\text{E}5 \text{ risk level}$$

$$\frac{1\text{E}5}{0.020} = 5.0\text{E}6 \rightarrow 1 \text{ in } 5 \text{ million calculated risk level}$$



Sample equation 3

Reverse engineering of sample equation 2 to calculate the maximum value for %D_{≤5μm} which yields a calculated risk equal to 1 in 1 million.

Step 1: calculate the weighted NSRL value that equates to a 1 in 1E6 risk level.
Note assumption: linear extrapolation from 1E-5 risk level → 10% of NSRL_{1E-5} = 100% NSRL_{1E-6}

$$\frac{11.1 \text{ ug UART}}{1 \text{ MUsT day}} \times \frac{1 \text{ MUsT day}}{110 \text{ ug UART}} = 0.1 \rightarrow 10\% \text{ of calculated NSRL at } 1:1E5 \text{ risk level}$$

To calculate the % D_{≤5um} value that yields a weighted NSRL of 110 and following the highly conservative approach of mapping:

- mass fraction reported by Liu (2019) for %D ≤5μm → NSRL ultrafine UART of 97 ug/day
- mass fraction reported by Liu (2019) for %D >5μm → NSRL fine UART of 910 ug/day

$$x \% D_{\leq 5um} \times \frac{97 \text{ ug UART}}{\text{day}} + (1 - x \%) D_{>5um} \times \frac{910 \text{ ug UART}}{\text{day}} = \frac{110 \text{ ug UART}}{\text{day}}$$

x = 98.4% which represents the maximum percentage of ultrafine particles (MMAD = 0.8 μm) in a powder-form OTC product which equates to a lifetime excess cancer risk of 1 in 1 million over a lifetime of use considering a maximum use scenario defined as 4 applications per day, every day, for 70 years.



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**STUDY TITLE: ANALYTICAL DETERMINATION OF RETAINED POWDER SUNSCREEN
FORMULA FOLLOWING 80 MINUTE WATER IMMERSION**

SPONSOR: Colorescience, Inc.
2141 Palomar Airport Road
Suite 200
Carlsbad, CA 92011

SPONSOR FORMULA NUMBER: 00N14761-1M

DATE RECEIVED: April 10, 2019

LOT NUMBER: 20071010

SAMPLE NUMBER: 19-453

DATE COMPLETED: April 17, 2019


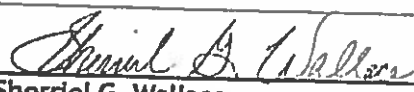
SUMMARY:

The sponsor test product sample, Colorescience Powder Sunscreen Formula (Formula Number 00N14761-1M, Lot Number 20071010), was tested for product retention to human skin following 80 minute water immersion in accordance with FDA, 21 CFR Sec. 201.327, subpart (i), SPF Test Procedure, Sunscreen Drug Products for Over-the-Counter Human Use, Final Monograph, Federal Register, Vol. 76, No. 117, June 17, 2011.

The average retained dosage of test product sample was determined to be 0.542 mg/cm² based on an initial applied dose of 2 mg/cm², representing approximately 27% retention.

The results of this study may be used to deduce that an average retained dose of 0.542 mg/cm² test product resulted in a mean 80 minute Water Resistant SPF Value of 56.35 (Label SPF 52) for this same test product in a previous study conducted in accordance with FDA, 21 CFR Sec. 201.327, subpart (i), SPF Test Procedure, Sunscreen Drug Products for Over-the-Counter Human Use, Final Monograph, Federal Register, Vol. 76, No. 117, June 17, 2011.

APPROVAL:

 Harry W. Sarkas, PhD Investigator	<u>6/13/19</u> Date
 Sherriel G. Wallace FSTI Clinical Director	<u>6/13/19</u> Date

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I. OBJECTIVE

To analytically determine the amount of retained sunscreen formula applied to subjects in accordance with FDA, 21 CFR 201.327, subpart (4) (iii) following an 80 minute water immersion sequence conducted in accordance with FDA 21 CFR 201.237, subpart (i) (7) (ii) [SPF Test Procedure, Sunscreen Drug Products for Over-the-Counter Human Use, Final Monograph, Federal Register, Vol. 76, No. 117, June 17, 2011].

II. STUDY TYPE

Three (3) subject study, with a final report furnished to the sponsor, which includes the analytically determined mean value of retained sunscreen formula following an 80 minute water immersion sequence based on a completed 3 subject test panel. Study Protocol was developed jointly by Solésence LLC and Florida Skin Care Testing (FSTI), 101 N. Bay Street, Bunnell, Florida 32110. Water immersion testing and analytical determinations were conducted on premises at FSTI.

III. SAMPLE DESCRIPTION

SPF 50 Powder Formula # 00N14761-1M, Lot # 20071010, FSTI Sample # 19-453

IV. TEST MATERIAL HANDLING

The Colorescience sample labeled Formula # 00N14761-1M, Lot # 20071010, was assigned FSTI sample number 19-453 and entered into the FSTI SPF test submission log.

V. ARCHIVING

All original protocols, raw data sheets, and copies of final reports are maintained on the premises of FSTI, in limited access storage files in accordance with FSTI SOP# 2008-10. A duplicate copy of all final reports is kept on a secured, password-protected computer hard drive.

VI. PANEL DESIGN

Number of Subjects enrolled	3
Number of Subjects completing study	3
Age Range	27-62
Sex	
Male.....	1
Female.....	2



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VII. PANEL COMPOSITION

A. Fair-skinned subjects, male and female, eighteen years of age or older, of skin types I, II, or III as defined in FDA, 21 CFR, Sec. 201.327, subpart (i), SPF Test Procedure, (3) Test Subjects, (ii) Medical History, (B) Skin Type, June 17, 2011.

Type I - Always burns easily; never tans (sensitive)

Type II - Always burns easily; tans minimally (sensitive)

Type III - Burns moderately; tans gradually (normal)

B. The test panelists were selected based on the following criteria:

a. Inclusion Criteria

1. Individuals eighteen years of age or older.
2. Individuals with fair, uniformly-colored skin on the lower area of the back which would allow a discernable erythema.
3. Individuals free of any dermatological or systemic disorder which, in the opinion of the testing personnel, would interfere with the results of the study.
4. Individuals in good health who have completed a preliminary medical history.
5. Individuals who have read, understood and signed a consent document in compliance with 21 CFR 50.

b. Exclusion Criteria

1. Individuals with any visible skin disease at the study site, which in the opinion of the investigative personnel would, interfere with the study results.
2. Individuals taking medications which might affect study results, e.g., Photosensitizers, antihistamines, analgesics or anti-inflammatory drugs.
3. Females who are pregnant, planning a pregnancy or nursing a child
4. Individuals with a history of skin cancer.
5. Individuals with a history of hepatitis or other blood disease.
6. Individuals with a known sensitivity to cosmetics, skin care products or topical drugs as related to product(s) being evaluated.
7. Individuals with recent sun exposure on the areas to be tested.

VIII. INFORMED CONSENT

An Informed consent was signed by each volunteer prior to initiating the study describing the purpose of the study, the test procedure, potential risks and benefits of participating, as well as the limits of liability. Each subject completed an extensive medical history form and was assigned a subject identification number. These forms are available for inspection on the premises of FSTI only.

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IX. GENERAL TESTING PROCEDURE

Subject Enrollment

The test subjects reported to the testing laboratory and received a complete explanation of the study procedures. Those who participated signed a written, witnessed consent form, and a permission to release personal health information form and provided a brief medical history. The technician did a final examination of the subject's back, between the belt-line and shoulder blades and determined their suitability to participate in this study.

Application of Product for Retention Determination

Five test areas (10 cm x 5 cm), 50 square centimeter rectangles, were drawn in the designated locations on each subject's back (between the beltline and shoulder blade) using a template and an indelible marker. Test formula was applied by the technician by spotting the product across the test area and gently spreading using a finger cot (as specified in FDA, 21 CFR 201.327, subpart (4) (iii) until a uniform film was applied to the entire test area. A product density of 2 mg/cm² was delivered to the test area. To accomplish this, the technician weighed an amount in excess of 100 mg to allow for the residual amount left on the finger cot (approximately 10%). The test product was allowed to stand for a minimum of 15 minutes prior to the 80 minute water immersion of the test formula.

80 Minute Water Immersion Sequence

1. An indoor fresh water Jacuzzi maintained at 23 to 32 deg. Celsius was used in this testing procedure. Fresh water is clean drinking water that meets the standards in 40 CFR part 141.
2. The pool and air temperature as well as relative humidity was recorded prior to testing.
3. The retention of test product submitted by the sponsor was determined after 80 minutes of water immersion using the following procedure as specified in FDA 21 CFR 201.237, subpart (i) (7) (ii), Determination of Water Resistance:
 4. Apply sunscreen product. (Followed by a minimum 15 minute waiting period after application)
 5. Twenty minutes of moderate activity in the water.
 6. Fifteen minute rest period (Do not towel test sites).
 7. Repeat steps b. and c. until a total of 80 minutes water immersion is achieved.
 8. Conclude water test. (Air dry test sites completely without towel)
 9. Begin collection and analytical quantification of retained test product.



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Recovery and Analytical Determination of Retained Product Post Water Immersion

1. Kimtech Science™ Kimwipes™ Delicate Task Wipers were utilized to collect and recover product on retained each test site for each subject following 80 minutes water immersion.
2. Prior to product recovery, each Kimwipe™ was placed on a plastic weigh boat and the gross weight was determined using a calibrated analytical balance with 0.0001g resolution and recorded.
3. Prior to retained product collection on each site on each test subject, each Kimwipe™ was soaked in Isopropyl alcohol.
4. For each test site on each subject, the isopropyl alcohol soaked Kimwipes™ were used to remove all product via repeated rubbing until no visible product was apparent to the technician.
5. Complete removal of retained product was confirmed on each site on each test subject by examining each site using a handheld UV test lamp.
6. Following retained product collection, each Kimwipe was placed back onto the original weigh boat used in Step 2 and allowed to dry completely.
7. The gross weight of each Kimwipe™ with retained product placed on the corresponding plastic weigh boat from Step 2 was determined using a calibrated analytical balance with 0.0001g resolution and recorded.

X. CALCULATION OF RETAINED PRODUCT AND EFFECTIVE DOSE POST WATER IMMERSION

The amount of retained product following water immersion for each test site on each subject is determined by subtracting the initial weight of each Kimwipe™ used for product recovery from its corresponding final weight following product recovery from the test site. The percentage of retained product is then calculated from the ratio of the recovered product mass ratio to that of the applied dose mass. The effective dose following 80 minute water immersion is then calculated noting that the initial dosing was held at 2 mg/cm² in accordance with FDA, 21 CFR 201.327, subpart (4) (iii).

XI. RESULTS

A total of three (3) healthy subjects who fulfilled the test panel participation criteria were inducted into this investigation. The effective doses of retained powder sunscreen Colorescience Formula # 00N14761-1M, Lot # 20071010 following 80 minute water immersion were determined for all test sites for all subjects in this study.



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The mean effective dose following 80 minute water immersion determined from all test sites on all test subjects in this study *is considered to be the equivalent effective dose of this powder sunscreen used to yield a mean 80 minute Water Resistant SPF Value of 56.35 (Label SPF 52) previously in FSTI Study 17-569 on the same test product of the same lot number.* All data is presented in Table I.

XII. ADVERSE EXPERIENCES

No adverse experiences were reported in this study.

References:

1. U.S. Food and Drug Administration, Sunscreen Drug Products for Over-The-Counter Human Use; Final Monograph, 21 CFR Sec. 201.327, subpart (i), SPF Test Procedure, Sunscreen Drug Products for Over-the-Counter Human Use, Federal Register, Vol. 76, No. 117, June 17, 2011.
2. FSTI Study Number 17-569. Data on file at FSTI.



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TABLE I

Study Number	19-453
Formula Number	00N14761-1M
Lot Number	20071010

Subject A ID#2641

Site	Wt. of Product Applied by Technician (g)	Weigh Boat + Kimwipe Wt. (g)	Post 80 Min WR Wt. (g)	Wt. of Product Left on Skin (g)
1	0.1104	4.2267	4.2594	0.0327
2	0.1101	4.0798	4.1086	0.0288
3	0.1113	4.3442	4.3818	0.0376
4	0.1120	4.5071	4.5358	0.0287
5	0.1105	4.4336	4.4596	0.0260
Average				0.0308

Subject B ID#2672

Site	Wt. of Product Applied by Technician (g)	Weigh Boat + Kimwipe Wt. (g)	Post 80 Min WR Wt. (g)	Wt. of Product Left on Skin (g)
1	0.1108	4.4628	4.4889	0.0261
2	0.1099	4.4114	4.4258	0.0144
3	0.1107	4.4390	4.4456	0.0066
4	0.1100	4.4549	4.4723	0.0174
5	0.1109	4.5108	4.5242	0.0134
Average				0.0156

Subject C ID#2023

Site	Wt. of Product Applied by Technician (g)	Weigh Boat + Kimwipe Wt. (g)	Post 80 Min WR Wt. (g)	Wt. of Product Left on Skin (g)
1	0.1087	4.4221	4.4685	0.0464
2	0.1082	4.5719	4.615	0.0431
3	0.1102	4.6670	4.7149	0.0479
4	0.1088	4.5138	4.5505	0.0367
5	0.1097	5.1234	5.1651	0.0417
Average				0.0432

* Weight of Weigh Boat, Kimwipes and powder remaining on the skin

Study Summary

Average Applied Dose (g)	0.1101
Average Applied Dose (mg/cm ²)	2.003
Standard Deviation Applied Dose (g)	0.0010
Standard Deviation Applied Dose (mg/cm ²)	0.0183

Average Retained Dose (g)	0.0298
Average Retained Dose (mg/cm ²)	0.542
Standard Deviation Retained Dose (g)	0.0127
Standard Deviation Retained Dose (mg/cm ²)	0.231

Estimated Post 80 Minute Water Immersion Dose: FSTI Study 17-569	0.542 mg/cm ²
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Powder Sunscreen Use Study 1: A Consumer Application Study

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May 1, 2019

Background

The objective of this study was to estimate the amount of powder applied by consumers under real-world conditions.

Methods

To estimate the amount of time typically applied by consumers,¹ 136 female subjects were asked to indicate the amount of time they spend applying the powder sunscreen product (Sunforgettable[®] Total Protection[™] Brush-On Shield SPF 50; Colorescience, Inc., Carlsbad, CA). Subjects were asked to choose one of five time duration categories: 30-60 sec, 1-2 min, 2-3 min, 3-4 min or >4 min.

Subsequently, 10 applications from five different subjects were evaluated using the following protocol:

- A) Product and container were weighed on a calibrated balance
- B) Product was initially primed according to product labeling
- C) Product was applied to the face in 15-sec increments
- D) Product and container were reweighed to determine amount of product applied
- E) Steps A-D were repeated four times.
- F) The total amount of product applied was obtained by summing the four 15-sec applications

To be conservative, the study investigator applied the low-end of the range (30 seconds) for the first and the mid-point of the range for all other time intervals. For instance, if a responder indicated 30-60 seconds, it was assumed that the product was applied for 30 seconds. For responses of 1-2 min, 2-3 min and 3-4 min, it was assumed that they applied for 1.5 min, 2.5 min and 3.5 min, respectively. For those subjects indicating >4 min application time, it was assumed they only applied for 4 min.

Results

The weighted mean application time was 60.4 seconds. Using mid-points of the first range, the weighted average of application time would be over 70 seconds. Reported application times are summarized in Table 1. The mean application time for the 136 responders was >60 seconds.

Table 1. Reported Application Time (N=136)

Application Time Interval	n (%)
30-60 sec	95 (70)
1-2 min	24 (18)
2-3 min	8 (6)
3-4 min	8 (6)
>4 min	1 (1)

Subjects applied a mean of approximately 0.24 g of sunscreen product. Using the size estimate of 360 cm² for the female's face,² it was calculated that the mean dose application was approximately 0.65 mg/cm² (Table 2).

Table 2. Powder Application in 60 sec

n=10	gm	mg/cm ²
Median	0.24	0.65
Mean	0.24	0.65
Min, Max	0.08, 0.35	0.22, 0.97

References

1. Young AR, Claveau J, Rossi AB. Ultraviolet radiation and the skin: photobiology and sunscreen photoprotection. *J Am Acad Dermatol*. 2017;76:S100-S109
2. Yoon S-H, Lee J. Computing the surface area of three-dimensional scanned human data. *Symmetry*. 2016;67:1-14.

Powder Sunscreen Use Study 2: Survey of Consumer use patterns

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June 5, 2019

Background

The objective of this study was to survey consumers about their use of a powder product under real-world conditions.

Methods

An online survey service using cloud-based software was used to gather data (SurveyMonkey, Inc., San Mateo, CA). Links to the survey were sent via email to two groups of respondents. The first group (n=33) comprised health care professionals who were identified among Colorescience consumers and the second group comprised lay consumers (n=104) who replied to at least 90% of survey questions. Only those responses considered relevant to this report are included here. Questions 1, 2 and 5 were included only in the second group survey to lay consumers while questions 3 and 4 were included in both surveys.

Results

Overall, survey respondents were very familiar with the product they were being questioned about (Sunforgettable Mineral Brush-on Sunscreen SPF 50). Most (92.2%) considered themselves to be regular users and had used the product for a least 1 (12.9%) or 2 (19.8%) years and almost half (45.5%) had used the product for 3 or more years. Survey results are summarized below.

1. Do you feel that you are able to apply the brush evenly around your face? (n=104)

Yes 75.9%
No 24.1%

The majority of respondents believe they can apply the product evenly on and around their face.

2. How much time do you typically use to apply the Sunforgettable Brush thoroughly? (n=103)

30-60 sec	69.9%
60-120 sec	17.6%
120-180 sec	5.9%
180-240 sec	5.9%
>240 sec	0.7%

The average amount of time that a consumer spends applying product is approximately 1 minute. If mid-points of each range is applied by the percentage of response, the weighted the average time is 70.6 seconds of application. A more conservative assumption assumes the lowest point of the first range and mid-points of all other ranges. This equates to an average application time of 60.1 seconds.

3. On a day when you're out and about, how many times typically would you apply/reapply Sunforgettable brush? (n=136)

1-2 times	61.4
2-3 times	25.0
3-4 times	9.8
4-5 times	2.3
>5 times	1.5

Based on a weighted average, respondents reapplied the product 2.1 time daily. *In a separate study based on health care professional use log data, product users (n=19) recorded an average of 2.7 daily applications over a 4-day period).*

4. Where do you apply the Sunforgettable Brush? Please check all that apply.

	n=104, %	n=21, %
Face	100.0	100.0
Neck	75.0	100.0
Ears	46.2	76.2
Shoulders	11.5	38.1
Hands	36.5	57.1
Arms	17.3	33.3
Part in Hair	16.4	38.1
Other	7.7	28.6

A total of 125 respondents between the two surveys answered this question. All respondents from both survey populations apply the product to the face and most (75-100%) apply it to the neck. A substantial number of respondents also apply the product to other areas, such as the ears, hands and arms.

5. Is powder sunscreen easier to reapply compared to other formats of sunscreen such as lotion? (n=102)

Yes	84.3%
No	4.9%
About the same	10.8%

For approximately 95% of respondents, reapplication of powder sunscreen is as easy or easier than reapplying other sunscreen products.

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Powder Sunscreen Use Study 3: A Consumer Log of Application over 4 day period

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May 12, 2019

Background

The objective of this study was to estimate the number of times a brush-on sunscreen product was applied daily by consumers under real-world conditions based on a log-book of use from 19 different health care professionals over a 4-day period.

Methods

To estimate the number of times the product was applied each day, 19 adult female healthcare professionals were asked to record the number of times they applied the powder sunscreen product (Sunforgettable® Total Protection™ Brush-On Shield SPF 50; Colorescience, Inc., Carlsbad, CA).

Results

The results are summarized in Table I. The mean number of daily applications ranged from 2.63 to 2.79. The overall 4-day mean was 2.67 daily applications.

Subject	Day 1	Day 2	Day 3	Day 4
1	3	3	3	5
2	2	2	2	2
3	4	3	4	4
4	5	1	1	3
5	2	1	1	1
6	3	3	2	3
7	3	2	2	3
8	3	2	3	3
9	5	8	8	6
10	1	2	2	1
11	4	3	4	2
12	2	3	1	3
13	1	4	3	1
14	2	3	3	2
15	3	2	3	2
16	1	1	1	1
17	3	3	3	2
18	2	1	1	1
19	4	3	3	5