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Subject: Draft Guidance on Maximal Usage Trials for Topical Active Ingredients Being Considered for Inclusion in an Over-the-Counter Monograph: Study Elements and Considerations; Docket No. FDA-2018-D-1456; 83 Federal Register 23918 (May 23, 2018)

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 Comment in response to the Food and Drug Administration's (FDA's) Guidance on Maximal Usage Trials for Topical Active Ingredients Being Considered for Inclusion in an Over-the-Counter Monograph: Study Elements and Considerations, published at 83 Fed. Reg. 23918 (May 23, 2018).

We appreciate FDA's willingness to seek input from industry and other stakeholders so that the Draft Guidance is reflective of current and sound scientific approaches in this field. Additionally, we also acknowledge the Agency's work in providing industry with its current thinking on certain scientific protocols and methods, and we understand that the Agency believes this work is intrinsic to its mission of protecting public health. While this Draft Guidance is intended to provide considerations for all topical active ingredients being considered for inclusion in an over-the-counter (OTC) monograph, this Comment primarily addresses the issues as applied in the context of sunscreen products, though many of the arguments contained herein are broadly applicable. Further, as guidance documents "do not create or confer any rights for or on any person and do not operate to bind FDA or the public [and

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 137-year-old 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 \$6-\$7, contributing a total of \$102 billion in savings each year. CHPA is committed to empowering consumer self-care by preserving and expanding choice and availability of consumer healthcare products. Visit www.chpa.org.

where], an alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both,”³ we urge FDA to consider and implement the recommendations contained in this Comment.

Overview of Industry Comments

In previous Comments⁴ pertaining to the FDA Guidance ‘Nonprescription Sunscreen Drug Products - Safety and Effectiveness Data’, we recommended FDA include alternative approaches as part of the toxicological risk assessment and determination of an acceptable margin of safety (MOS). We advocated for the FDA to consider the input from experts and utilize modern toxicological approaches when assessing the risk of a particular ingredient, noting that *in silico* and *in vitro* techniques together with traditional *in vivo* testing provide a robust and quantitative risk assessment for ingredients and products. To aid in maintaining current awareness of the state of the science and expert opinion, we suggested participation in venues such as The Society of Toxicology or the Toxicology Forum.

We continue to strongly believe that valid and scientifically-rigorous exposure assessments together with predictions of internal dose could be readily used as an alternative to the Maximal Usage Trial (MUsT) study, and encourage the Agency to consider the approaches that we have outlined in our earlier Comments. Specifically, we previously provided a detailed discussion of approaches for determining internal dose of sunscreen active ingredients using *in vitro/in silico* data coupled with physiologically-based pharmacokinetic (PBPK) modeling⁵. The outcome of the modeling would be a conservative estimate of internal dose that could be compared to equivalent data from animal studies to understand dosimetry, as part of the overall safety assessment. In this regard, models of dermal penetration and estimates of internal dose are intentionally conservative for purposes of risk assessment (i.e., protective of health by tending to overestimate exposure), and amenable to experimental manipulations that otherwise would be prohibitive. Although we readily acknowledge limitations using, for example, *in vitro* skin penetration such as repeated dosing, such studies provide a robust determination of skin penetration of a compound and when combined with existing data often are supportive of human safety, i.e., high MOS.⁶

If the MOS is unacceptable, additional data may be needed to refine such a conservative estimate. In such cases, a MUsT study could be conducted for refining and measuring internal dose. To

³ <https://www.fda.gov/Drugs/20GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

⁴ 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.

⁵ 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, Appendix I

⁶ We contend that FDA should consider and clarify the situations under which a MUsT for topical actives could be waived given the ample amount of existing data on a particular ingredient. For example, where a drug substance can be administered orally as well as applied topically (such as diphenhydramine, menthol) and the oral systemic exposure limits are well established, we envision that is a situation where FDA could determine that additional clinical evaluation of vehicle influences to systemic absorption for a topically applied drug would be unnecessary because of the well-established oral exposure limits.

this end, we respectfully submit the following comments on the Draft Guidance related to MUSt Study Elements and Considerations (Section B of the Draft Guidance), specifically:

- Amount applied
- Frequency of Dosing
- Formulation Considerations

Lines 166-211: Amount of test article applied and frequency of dosing is not representative of actual consumer use

Under the Draft Guidance, the amount of test article applied and the frequency with which subjects are dosed likely do not correspond with actual consumer usage or the directions of use indicated on current sunscreen monograph products. While we agree with FDA that determination of internal dose is important, if eventual regulatory or policy actions are or could be developed based on the results of a MUSt study, the protocols for the maximal usage trial study need careful consideration.

Under the Draft Guidance, the “amount of test article applied should be consistent with existing or proposed directions for use in the applicable OTC monograph.”⁷ For sunscreen drug products, 21 CFR 201.327 (i)(D)(4)(iii) outlines the labeling requirements for the amount of testing material applied when conducting a SPF test (2 mg/cm²). Despite this recommendation in the Draft Guidance, we note that this *is not* the amount of test article that FDA proposed in its requirement for contractor services to conduct a two-part clinical study (MUSt) on sunscreen.⁸ Instead, “Attachment A, *Detailed Study Description*,” to FDA-18- RFQ-1192863 provides that, “[a]pproximately 1 mg/cm² body surface (calculation according to Dubois) of sunscreen will be evenly applied to areas of the body typically exposed to the sun including face, ears, neck, torso, arms and legs (at least 75% of the body surface area).”

While an application of 1 mg/cm² body surface differs from the directions for use in the sunscreen monograph, 1mg/cm² may correspond more to actual consumer use amounts as supported in data obtained from some consumer use studies of cosmetic products, including sunscreen products.⁹ As the *Ficheux et al.* study observes, cosmetic products are to be safe for consumer health when they are applied under normal or reasonably foreseeable conditions of use, and “current and relevant data concerning the amount of product applied and the frequency of use are essential information for a correct exposure assessment.”¹⁰ In this study, participants were invited to use the test products in the closest possible way to their personal usage patterns. The amount of each cosmetic used was

⁷ Lines 166-170 FDA Draft Guidance for Industry - Maximal Usage trials for Topical Active Ingredients Being Considered for Inclusion on an Over-the-Counter Monograph: Study Elements and Considerations, May 2018

⁸ See FDA-18- RFQ-1192863, available at <https://govtribe.com/project/sunscreen-clinical-study> (last accessed Jul. 23 2018)

⁹ Ficheux, A.S., et.al, 2016 Consumption of cosmetic products by the French population second part: Amount data, *Food and Chem. Toxicol.*, 130-141

¹⁰ *Id.* at 130.

determined by differential weighing before and after use, and all tested products were purchased from French supermarkets.¹¹

Ficheux et al. found that generally, the amount of sunscreen per cm² was inversely correlated to the skin surface area for adult men and women and for babies (Table 7). For example, 1.5 mg/cm² (small area), 0.8 mg/cm² (intermediate area) and 0.9 mg/cm² (large area) of cream/milk were on average applied by adult women. Critically, for sunscreen products, use was examined in both a laboratory and beach setting with “no differences . . . observed between the amount data obtained in the laboratory under test conditions and real consumption data obtained on the beach.”¹² We also note the results of previous studies conducted in Europe¹³ and Australia¹⁴ which measured application amounts. In those studies, the median thickness of sunscreen applied was found to be 0.39 mg/cm², and 0.48 mg/cm², respectively.

Thus, if flexibility from monograph labeling requirements is permissible with respect to the amount of test article applied, flexibility ought to be considered in other areas, too—for example, the frequency of dosing. We believe that the requirement of dosing every 2 hours, four times a day deserves further consideration. Presently, the Draft Guidance states that “if the potential monograph labeling recommends re-application after specific intervals or activities, the subjects should be redosed accordingly . . . dosing in a MUsT for sunscreens should use the same dosing interval as directed in OTC sunscreen labeling, every 2 hours.”¹⁵ 21 CFR 201.327 (e), which provides for the directions of use labeling of sunscreen products based on effectiveness data, reads in relevant part:

(e) *Directions.* The labeling of the product contains the following statements, as appropriate, under the heading “Directions.” . . . (3) *For products that satisfy the water resistance test in paragraph (i)(7) of this section.* The labeling states “[bullet] reapply: [Bullet] after [select one of the following determined by water resistance test: ‘40 minutes of’ or ‘80 minutes of’] swimming or sweating [bullet] immediately after towel drying [bullet] at least every 2 hours”.(4) *For products that do not satisfy the water resistance test in paragraph (i)(7) of this section.* The labeling states “[bullet] reapply at least every 2 hours [bullet] use a water resistant sunscreen if swimming or sweating”.¹⁶

While sunscreen reapplication should be encouraged, there are few studies that have investigated the proper frequency of application and little if any data to say that application every 2 hours is warranted. In general, the studies looking at consumer habits and practices suggest they do not

¹¹ *Id.*

¹² *Id.* at 138.

¹³ Autier, P., et al. (2001) Quantity of sunscreen used by European students. *British Journal of Dermatology*, Vol.144:288-291.

¹⁴ Diaz, A., et al. (2012) The Children and Sunscreen Study. *Arch Dermatol*, Vol. 148 (5):606-612.

¹⁵ Lines 211-212 FDA Draft Guidance for Industry - Maximal Usage trials for Topical Active Ingredients Being Considered for Inclusion on an Over-the-Counter Monograph: Study Elements and Considerations, May 2018 (citing 21 CFR 201.327)

¹⁶ 21 CFR 201.327

reapply every two hours.¹⁷ For instance, Wang and Dusza reported in a survey of 423 participants that only 30% knew that sunscreen should be reapplied every 2 hours. Similarly, *Holman et al.* examined sunscreen consumer use patterns among adults aged 18 years and older and concluded that the amount of sunscreen use is less than it should be, with consumers failing to apply it over all exposed body areas, and other consumers not using sunscreen at all.¹⁸ Most consumers do not apply sunscreen regularly or reapply every 2 hours. Clearly, there needs to be additional data to understand how consumers use such products.

Similarly, the *Odio et al.* study shows that sunscreen reapplication every two hours over a 6-hour, 13 MED sun exposure does not provide greater protection than a single application. When the sun exposure was increased – 8 hours, 21 MED – 5 applications protected study subjects against erythema better than a single application in some study subjects.¹⁹ It's probable that consumers reapply less frequently than the recommended every two hours if the lack of erythema reflects consumer real-world experience. Consequently, flexibility with respect to the frequency of dosing should be considered so that the study design more closely aligns consumer experience.

Lines 238-280: Formulation Considerations

The Draft Guidance discusses formulation considerations and recommends that sponsors “evaluate multiple formulations in MUsTs” and “that in the absence of mitigating safety data or other bioavailability-related information . . . [test] at least four formulations.”²⁰ Additionally, the paragraph advocates that the formulations selected for MUsTs “should be *market image* formulations with the highest potential for absorption of the active ingredients . . . and not, for example, a simple extemporaneous formulation (i.e. a dispersion in a vehicle) that was created without regard to such factors as deployability, spreadability, and shelf-life.”²¹ We expect that topical sunscreen active ingredients submitted for inclusion under the OTC monograph will have available data on both bioavailability and safety, which may mitigate testing of four formulations.

We also note that there are direct conflicts with Paragraphs B8 and B9 (*Combinations of Active Ingredients*). Specifically, the Draft Guidance recommends that “[i]n general, the formulation being evaluated in the MUsT should contain the active ingredient being evaluated for inclusion in an OTC monograph as the only active ingredient.”²² Many if not most currently marketed sunscreen products

¹⁷ See *Holman, et al., 2015, Patterns of Sunscreen Use on the Face and Other Exposed Skin Among US Adults; Odio M., et. al. 1994, Comparative Efficacy of Sunscreen Reapplication Regimens in Children Exposed to Ambient Sunlight. Wang, S.Q. and Dusza, S.W. 2009, Assessment of sunscreen knowledge: a pilot survey. BJD 161:28-32.*

¹⁸ *Holman, at 9.*

¹⁹ *Odio, at 122-124.*

²⁰ Lines 254-255, FDA Draft Guidance for Industry - Maximal Usage trials for Topical Active Ingredients Being Considered for Inclusion on an Over-the-Counter Monograph: Study Elements and Considerations, May 2018

²¹ *Id.* at lines 263-265(emphasis in original)

²² *Id.* at lines 233-234

feature a combination of active sunscreen ingredients. Utilization of a 'market image' formulation²³ containing a single active ingredient poses a challenge to sponsors not only in terms of the specific formulation to be tested, but also with respect to the analytical procedures used in the evaluation of the data.²⁴ Additionally, testing a "market image formulation" demonstrating the highest permeability in an *in vitro* test should be sufficient rather than having to test multiple formulations.

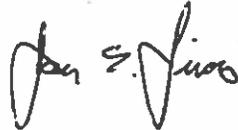
Conclusion

We believe that the framework provided for assessing systemic exposure to topically-applied active ingredients in the Draft Guidance should allow for flexibility as it relates to considerations of dosing and formulation selection. Further, we recommend FDA incorporate alternative approaches for estimating internal dose for sunscreen active ingredients.

We greatly appreciate the opportunity to provide comments.



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²³ Additionally, the requirements for an Investigational New Drug Application (IND) as set forth in 21 CFR 312 are not addressed or referenced in this Draft Guidance. We request clarification on whether the FDA considers 21 CFR 312 applicable to the topical active ingredients that are being considered for inclusion in an OTC monograph (for example, would an IND be needed each time a different market formulation was tested?)

²⁴ See *id.* generally at pg. 9