U.S. FOOD & DRUG ADMINISTRATION

Rapid Precision Testing Laboratories
8225 Rockcreek Parkway
Cordova, TN 38016

Re: Docket No. FDA-2013-P-0323

FEB 2 1 2019

Dear Sir or Madam:

This responds to the citizen petition (Petition) submitted by Robert Sayre, President of Rapid Precision Testing Laboratories, which was received by the Food and Drug Administration (FDA) on March 18, 2013 and assigned Docket No. FDA-2013-P-0323.

The Petition requests that FDA:

(1) "formally withdraw approval of the anti-inflammatory sunscreen ingredients Dioxybenzone, Oxybenzone, Trolamine salicylate, Homosalate, and Octisalate" from the list of over-the-counter (OTC) sunscreen active ingredients in § 352.10 (21 CFR 352.10); and

(2) "reassess [FDA's approach to sun protection factor (SPF) testing] to include sunscreen testing methodology to prescreen products that decrease the erythemal response, falsely inflating SPF values determined in SPF testing" by amending 21 CFR 201 and 21 CFR 310.

Petition at 1.

We interpret the requested actions as asking FDA to (1) exclude the listed active ingredients from an effective final OTC sunscreen drug monograph because of their purported anti-inflammatory properties;[1] (2) amend the sunscreen testing and labeling regulation (21 CFR

[1] As a matter of regulatory terminology, FDA could not "withdraw approval" of the active ingredients at issue as the Petition asks because active ingredients that are listed in an OTC drug monograph are not "approved" by FDA. Rather, FDA does not require drug products that contain only specified active ingredients and otherwise comply with an applicable monograph and other OTC drug regulations to have an approved application. In this case, there is no effective applicable monograph for sunscreen drug products; the monograph referenced in the Petition, located at 21 CFR Part 352, is not and has never been in effect. FDA addressed the circumstances under which it intends to exercise its enforcement discretion with respect to certain marketed OTC sunscreen products in the period before a final monograph becomes effective in the *Guidance for Industry: Enforcement Policy – OTC Sunscreen Drug Products Marketed Without an Approved Application* (May 2018).

201.327) to require an additional test to identify "anti-inflammatory agents capable of attenuating UV [ultraviolet] radiation response" (Petition at 3); and (3) amend part 310 to require an approved application for any sunscreen product containing the purported anti-inflammatory ingredients listed in the Petition or identified using the requested test.[2]

For the reasons discussed below, the Petition is denied.

I. FDA REGULATION OF OTC SUNSCREENS

An OTC drug monograph is a final FDA regulation that identifies active ingredients and other conditions for OTC drugs in a given therapeutic category. An OTC drug is generally recognized as safe and effective and is not misbranded if it meets each of the conditions contained in 21 CFR part 330, as well as each of the conditions contained in an applicable monograph.[3]

A final OTC sunscreen monograph was published in 1999, but its original effective date, planned for May 21, 2001, was extended and then stayed until further notice to permit FDA to address outstanding regulatory issues.[4] In 2011, we published a final rule codified in § 201.327 that established labeling and testing requirements for OTC sunscreen products marketed without approved applications and containing the ingredients specified in the 1999 stayed sunscreen monograph. Today, FDA issued a proposed rule (Sunscreen Proposed Rule) that, if finalized, would amend the currently stayed 1999 final monograph and enable FDA to lift the stay and put into place an effective final sunscreen monograph.[5]

In 2018, FDA published a final guidance for industry *Enforcement Policy — OTC Sunscreen Drug Products Marketed Without an Approved Application* addressing the circumstances under which FDA intends to exercise its enforcement discretion with respect to certain marketed OTC sunscreen products in the period before a final OTC sunscreen monograph becomes effective.[6]

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[2] The Petition asks that FDA "specifically amend 21 CFR Parts 201 and 310, Subpart VI." Petition at 1. Neither part 201 nor part 310 contains a subpart VI. We assume that the Petition means to refer to § 201.327, a final sunscreen labeling and testing regulation, and part 310, subpart E, which (among other things) identifies active ingredients that have been excluded from specific OTC monographs and therefore may be used only in products within those therapeutic categories that have approved applications.

[3] See footnote 1.

[4] 64 FR 27666 (May 21, 1999) (final rule); 65 FR 36319 (June 8, 2000) (extension of effective date); 66 FR 67485 (December 31, 2001) (stay of effective date).

[5] 2019-03019 available at www.federalregister.gov.

[6] Available at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm259001.pdf. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

The guidance also provides a more detailed description of the history and status of the sunscreen monograph rulemaking. Pertinent *Federal Register* Notices can be viewed at

II. DISCUSSION

As detailed in § 201.327, the SPF level displayed on OTC sunscreen product labels is determined by comparing the degree of erythema (redness) observed on treated and untreated skin following a series of UV exposure doses. The actions requested in the Petition are premised on the argument that by decreasing the inflammatory response, the ingredients at issue could falsely inflate the SPF values determined in SPF testing. As noted in the Petition, this concern was addressed by FDA in 2011 in connection with a public comment on proposed § 201.327 and found not to be confirmed by supporting data (Petition at 2).[7] Accordingly, FDA does not currently require sunscreen products to be tested for the presence of purportedly anti-inflammatory ingredients. We have reassessed this position as the Petition requests and have concluded that the evidence provided remains insufficient to demonstrate a need for the requested actions.

The Petition relies primarily on an in vivo SPF study of a single human subject by Sayre, Dowdy, and Rosenberg, which the Petition claims "clearly shows . . . that at four hours all early sunscreen treated UV erythemic responses were eliminated" and "when examined at 24 hours, showed erythema only on the 4 highest doses compared to more intense erythema in all 6 on the untreated side" (Petition at 2-3 (Reference 6)). The study apparently has not been published or peer reviewed. The product tested was a marketed sunscreen with a labeled SPF value of 100 that included three of the five sunscreen active ingredients you request we exclude from a final effective sunscreen monograph, as well as the active ingredients avobenzone and octocrylene. Notably, the sunscreen in the study was applied after UV exposure. The Petition claims that the study shows that the sunscreen product tested, when applied to skin that was already irradiated, had an anti-inflammatory effect on the skin that reduced the erythema response.

In considering the results of this study, FDA has also examined a published study with ten subjects that also involved application of the same SPF 100 sunscreen product to skin that had been previously irradiated. This study demonstrated no significant difference in erythema between skin that had been treated with the sunscreen test product and skin that had not been treated with the sunscreen test product, both when visually assessed by the ISO 24444 SPF protocol and when instrumentally assessed.[8] This clinical study directly contradicts the unpublished single-subject study submitted as supporting evidence for the requests made in this Petition.

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https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/over-the-counterotcdrugs/statusofotcrulemakings/ucm072134.htm.

[7] 76 FR 35649 (June 17, 2011).

[8] Staton J, Feng H. "Anti-inflammatory Effects of Sunscreens – Wonder or Science." The Science of Beauty. 2015;4(6), available at www.dermatest.com.au/Scientific/Anti-inflammatory%20effects.pdf.

You further suggest that any sunscreen active ingredient in the salicylate class may have anti-inflammatory properties and should be excluded from a final effective sunscreen monograph,[9] but you provide no evidence to support this implication. In addition, a peer-reviewed report of an in vivo human study using a solar simulator to produce erythema did not show significant differences in erythema, DNA damage, and sunburn cell formation as compared to control after repeated daily application of 2 percent salicylic acid on human skin over 3.5 weeks.[10] In a second study, 0.5 to 10 percent salicylic acid applied immediately after sunburn-inducing UVB exposure also did not affect erythema.[11] These results, indicating that salicylic acid does not reduce erythema when applied to skin before or after UV radiation exposure, contradict your hypothesis that salicylates as a class[12] may affect erythema by anti-inflammatory action when used in sunscreen products.

Finally, the Petition raises safety concerns regarding the potential for sunscreen active ingredients to be systemically absorbed through the skin. As discussed in the Sunscreen Proposed Rule, FDA is carefully evaluating these concerns as it considers whether sunscreens containing the active ingredients listed in the 1999 stayed final sunscreen monograph—including the five at issue in this Petition—would be generally recognized as safe and effective.[13] You are encouraged to submit your concerns regarding systematic absorption of sunscreen active ingredients as comments on the Sunscreen Proposed Rule.

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[9] See Petition at 2.

[10] Kornhauser A, Wei RR, Yamaguchi Y, et al. "The effects of topically applied glycolic acid and salicylic acid on ultraviolet radiation-induced erythema, DNA damage and sunburn cell formation in human skin." J Dermatol Sci. 2009;55:10-17.

[11] Kristensen B, Kristensen O. "Topical salicylic acid interferes with UVB therapy for psoriasis." Acta Derm Venereol. 1991;71(1):37-40. See also Sayre RM, Dowdy JC, Rosenberg EW. "Sun-protection factor confounded by anti-inflammatory activity of sunscreen agents." J Am Acad Dermatol. 2013;69(3):481 (comment on Ou-Yang H, Stanfield J, Cole C, Appa Y, Rigel D. "High SPF sunscreens (≥70) may provide ultraviolet protection above minimal recommended levels by adequately compensating for lower sunscreen user application amounts." J Am Acad Dermatol. 2012;67(6):1220-1227.)

[12] Trolamine salicylate, homosalate, and octisalate are all members of this class.

[13] For further discussion of this issue, please see the Sunscreen Proposed Rule (2019-03019 available at www.federalregister.gov).

III. CONCLUSION

Based on the limitations of the submitted study, as well as the existence of contradictory evidence and views in the scientific literature, we conclude that there is insufficient evidence to demonstrate a need for the actions requested in the Petition. Accordingly, the Petition is denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research