RPTL
Rapid Precision Testing Laboratories

15 March 2013

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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, rm. 1061
Rockville, MD 20852.

CITIZEN PETITION

A. Action requested

The undersigned submit this petition concerning the Food and Drug Administration's ongoing review of GRASE sunscreen active ingredients as stated in **21 CFR Parts 201 and 310-Labeling and Effectiveness Testing; Sunscreen Drug Products for Over-the-Counter Human Use, Subparts I.B and I.C.**

We request the Commissioner of Food and Drugs specifically to amend approval for the sunscreen agents, listed in **21 CFR Part 352-Sunscreen Drug Products For Over-The-Counter Human Use, Subpart-B §352.10 Sunscreen active ingredients (58 FR 28195)** and any additional regulations, to formally withdraw approval of the anti-inflammatory sunscreen ingredients Dioxybenzone, Oxybenzone, Trolamine salicylate, Homosalate, and Octisalate.

We also request the Commissioner of Food and Drugs to reassess **21 CFR Parts 201 and 310, Subpart VII. SPF Test Issues (Other than Test Parameters), D. Anti-Inflammatory Ingredients** and specifically amend **21 CFR Parts 201 and 310, Subpart VI. SPF Test Parameters** to include sunscreen testing methodology to prescreen products that decrease the erythemal response, falsely inflating SPF values determined in SPF testing.

2013-1970

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FDA-2013-P-0323

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B. Statement of grounds

Oxybenzone and dioxybenzone, currently approved sunscreen agents, should be delisted because both have been identified in US patents as anti-inflammatory agents: see US patents to Dewhirst and also to Smerbeck and Pittz.[1, 2]. Subsequently oxybenzone was identified in another study to inhibit the inflammatory mediator NO synthase [3] and more recently by Couteau, et al [4] as a potent topical anti-inflammatory agent. Smerbeck and Pittz's work is particularly important as they demonstrated attenuation of UV induced erythema in guinea pigs by applying these agents post UV exposure.

In addition we recommend that both Octisalate and Homosalate as well as Trolamine Salycilate, an approved sunscreen agent since before 1978, should also be removed from the list of approved sunscreen agents. Couteau has also identified the approved sunscreen agent Homosalate as a topical anti-inflammatory.[4]. Trolamine Salycilate is also the active ingredient used in Aspercreme, a topical anti-inflammatory products marketed in the USA. Review of the Fourteenth Edition of The Merck Index, "Analgesic (non-narcotic)" indicates that of some 110 analgesic compounds, more than 20% are salicylates.[5] We suggest that if more than 20% of the salicylates are marketed as anti-inflammatory drugs, perhaps none of the remainder in the salicylate family, including Octisalate should be allowed as sunscreen agents. An additional concern, is that particularly all the salicylate sunscreen agents may also be anti-coagulants. Factoring the intended and probable sunscreen product application rates, use of a topical product containing maximum allowed percentages of octisalate and homosalate over a body absorbing ~21% of the applied topical dose, the potential amount absorbed into the body ranges from ~0.325 to ~8 grams or the equivalent of 4 to 100 baby aspirins. This would doubtless be of interest to cardiologists prescribing daily aspirin therapy in conjunction with other drugs.

Suppression of UV-induced erythema by means other than attenuation of radiation clearly masks sunburn without preventing cellular/genomic damage. Clearly such a mechanism, if persistent for a sufficient time, may confound the monograph SPF test. FDA dismissed this concern in 2011 (Subpart VII, D. Anti-Inflammatory Ingredients) asserting that "It seems unlikely that anti-inflammatory ingredients will affect SPF values because their anti-erythemic effect is relatively short-lived compared to the 16–24 hour interval between UV exposure and erythema observation in the SPF test." Our n=1 study using an SPF 100 product clearly shows, as did Smerbeck and Pittz [2], that at four hours all early sunscreen

treated UV erythemic responses were eliminated. While we used a similar UV source to Smerbeck and Pittz we additionally used two graded series of UV doses, that 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. [6] We also observed that all 6 exposed sites on the no-sunscreen control series were tanned on day 18, but on the post exposure sunscreen treated series only the same four higher UV doses were tanned. Clearly the sunscreen product altered not only both early and delayed erythemic responses but also longer term pigmentation responses.

However, given sufficient exposure, sunburn symptoms may in fact appear earlier and early signs of overexposure masked by anti-UV-erythemic effect would in fact be less evident absent the normal prompt. Such UV anti-inflammatory agents are inappropriate for use topical in sun protection products. Considering the potential implications of hidden UV injury upon skin cancer rates may in part explain why skin cancers are ever increasing despite increasing public health messages to rely on sunscreens with ever increasing SPF values.

We request the Commissioner require that all sunscreens irrespective of the current GRASE status of active agents be tested to determine if they might contain any unidentified anti-inflammatory agents capable of attenuating UV response. A simple test following the guidelines of the Smerbeck-Pittz patent [2, 6] would require a human subject to be exposed to a paired series of perhaps 6 UV of exposures each, ranging from ~2,0 SED to 6 SED and after irradiation the sunscreen of interest be applied over the area of one exposure series and both exposure series compared at 4-5 and 22 -24 hours post exposure and possibly a day or so later. See the attached study using the same source as the Smerbeck and Pittz patent.

Finally, we wish to remind the Commissioner that sunscreens currently are tested after a single application of 2 mg/cm^2. In actual use application rates are probably lower resulting in lower concentrations of applied actives. However consumers are instructed to reapply sunscreen often. The FDA currently requires label instructions for reapplication of sunscreens every two hours. Unlike topical anti-inflammatory products, which are designed to be used on specific sites of inflammation, sunscreen users are advised to apply the product to the entire exposed body so that the user may be applying to as much as 1-2 square meters of skin resulting in considerable transdermal delivery of these agents with unknown consequences.

C. Environmental impact

This petition claims applicable exclusion(s) under §§25.30, 25.31, 25.32, 25.33, or §25.34.

D. Economic impact

It is uncertain that there is any fair way to compare the economic impact of skin cancer with the cost of redesigning and retesting sunscreen products. Given that sunscreen products are formulated with active ingredients deemed GRASE, any additional tests required to insure that the ingredients in the products were not otherwise harmful seems justified.

E. Certification

The undersigned certify, that, to our best knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Robert M. Sayre 3/15/13

Robert M. Sayre, Ph.D., President
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Date

References

1. Dewhirst, F.E., *2-Hydroxybenzophenones and their use in treating inflammation*, in *U.S. Patent 4244970*. 1981, Forsyth Dental Infirmary for Children: USA. p. 5.
2. Smerbeck, R.V. and E.P. Pittz, *Synergistic nonsteroidal anti-inflammatory compounds and their compositions*, in *U.S. Patent 4562194*. 1985, Warner-Lambert Co.: USA. p. 5.
3. Chiang, T.M., et al., *Sunscreen ingredients inhibit inducible nitric oxide synthase (iNOS): a possible biochemical explanation for the sunscreen melanoma controversy.* Melanoma Res, 2005. **15**(1): p. 3-6.
4. Couteau, C., et al., *UV Filters, Ingredients with a Recognized Anti-Inflammatory Effect.* PLoS One, 2012. **7**(12): p. e46187.
5. O'neil, M.J., ed. *The Merck Index: An Enclcopedia of Chemicals, Drugs, and Biologicals*. 2006, Merck & Co. Inc/: Whitehouse Station, NJ. Ther-2&3.
6. Sayre, R.M., J.C. Dowdy, and E.W. Rosenberg, *Sunscreens do more than block harmful UV*. Unpublished 1 Person Study, 2012.

Reference Material Provided

1. Dewhirst, F.E., *2-Hydroxybenzophenones and their use in treating inflammation*, in *U.S. Patent 4244970*. 1981, Forsyth Dental Infirmary for Children: USA. p. 5.

Full text pdf may be downloaded free:

http://www.google.com/patents/US4244970

2. Smerbeck, R.V. and E.P. Pittz, *Synergistic nonsteroidal anti-inflammatory compounds and their compositions*, in *U.S. Patent 4562194*. 1985, Warner-Lambert Co.: USA. p. 5.

Full text pdf may be downloaded free:

http://www.google.com/patents/US4562194

3. Chiang, T.M., et al., *Sunscreen ingredients inhibit inducible nitric oxide synthase (iNOS): a possible biochemical explanation for the sunscreen melanoma controversy.* Melanoma Res, 2005. **15**(1): p. 3-6.

Attached

4. Couteau, C., et al., *UV Filters, Ingredients with a Recognized Anti-Inflammatory Effect.* PLoS One, 2012. **7**(12): p. e46187.

Open Source Journal, pdf may be downloaded free:

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0046187

5. O'neil, M.J., ed. *The Merck Index: An Enclcopedia of Chemicals, Drugs, and Biologicals*. 2006, Merck & Co. Inc/: Whitehouse Station, NJ. Ther-2&3.

A recognized medical or scientific textbook that is readily available to the agency.

6. Sayre, R.M., J.C. Dowdy, and E.W. Rosenberg, *Sunscreens do more than block harmful UV.* Unpublished 1 Person Study, 2012.

Attached

From: (901) 386-0175 Origin ID: HKAA
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