

13 February, 2003

CITIZEN PETITION

0594 '03 FEB 14 P12:55
The undersigned submits this petition under 21 CFR §10.25 and §10.30. This petition requests the Commissioner of Food and Drugs to amend, 21 CFR Part 352 Sunscreen Drug Products For Over-The-Counter Human Use: Specifically the failure to establish product labeling and provide tests for products intended for recommendation by physicians for the particular needs of dermatological patients.

A. Action Requested

The petitioners request the Commissioner to amend 21 CFR Part 352, to include a provision to establish prescription sunscreen product category whose labeling is directed to physicians and to their patients. Testing and test procedures specific to clinical conditions for the different patient needs. Use and direction for use specific to specific clinical conditions are also required.

As premarket review will be necessary for each product in this category, it is strictly speaking, not part of the OTC Review process. However, establishing such a category removes issues of UVA and the need for general high SPF protection from OTC consideration, as physicians can prescribe such products for their patients. Further as sunscreens to be used in this category are used at OTC (GRAS) levels, there are no serious safety concerns to be addressed as part of a normal IND/NDA process. Because of the diversity of clinical conditions and more importantly the variety in response spectra of diverse patients, simple tests, like the SPF and SPF water-resistant tests, are not feasible to define in advance. Among the chronic clinical conditions suitable for physician labeling are products intended for: melanoma and non-melanoma skin cancer including patients with hereditary high risk, skin wrinkles, actinic keratoses, lupus erythematosus, and polymorphous light eruptions. There are also numerous acute situations requiring specialized sunlight protection: drug photosensitivity conditions, photosensitivity risks from physician administering of potentially photosensitizing drugs, potential photosensitization from PDT drugs, surgery including plastic surgery patients. This proposal would provide a vehicle to provide super sunsensitive patients with products labeled with SPFs higher than 30.

B. Statement of grounds

CURRENT SITUATION:

There are no prescription sunscreens. There is no provision for either testing or labeling a sunscreen product for any dermatological condition or clinical need. Consequently there is little or no testing of sunscreen products for any clinical need even though there is ample documentation of millions of melanoma and non-melanoma skin cancer patients, many patients suffering from polymorphic

03P-0067

CPI¹

light eruptions, actinic reticulosis, lupus erythematosus, photosensitivity of patients post surgery and plastic repair, patients taking photosensitizing drugs, or who have developed a drug induced photosensitivity, porphyria cutanea tarda, other photosensitive porphyric patients, etc.

The current OTC drug and cosmetic sunscreen system is simply defective. There are no standardized tests for OTC testing of sunscreens for defined clinical uses. All sunscreen tests are mandated using normal individuals. In fact both the static and water resistance SPF use only normal individuals. Today all label claims are only for normal individuals not for dermatological and other patients. The water resistance tests provided by the proposed monograph lead to claims only for normal individuals engaged in normal vacation type outdoor activities. It is easily documented that the action spectra and response spectra for many dermatological conditions are different from normal erythema. Many dermatological conditions have response spectra, with much greater emphasis to the UVA part of the spectrum than for normal individual's sensitivities.

Most importantly patient's insurance will not pay for any sunscreen product irrespective of the patient's condition or whether a prescription is written for its use by the patient because all OTC sunscreen products are intended for normal individuals with normal sunlight sensitivities.

BASIC SCIENCE:

The FDA has specifically recognized the action or response spectrum for erythema and for delayed pigmentation in normal individuals (McKinlay-Diffey Delayed Erythema Action Spectrum and Parrish, Anderson-Gange Delayed Pigmentation Action Spectrum)(1, 2). In addition the FDA has recently proposed using the mouse non-melanoma action spectrum (SCAUP) for labeling UV bulbs used in tanning units(3, 4). All of these action spectra including the Kligman-Sayre mouse photoelastosis action spectrum have similar wavelength responses(5). In fact a product providing protection against one of these spectra presumably will provide protection against the others. These are shown in APPENDIX I, attached. We should note that there is literature suggesting that neither mouse based action spectrum would apply to patients who already have developed either initial skin aging changes or who have been diagnosed with non-melanoma skin cancer.

Action spectra for various conditions requiring physician labeling and suitable for the proposed prescription category are significantly different generally from the action or response spectra of simple over exposure to sunlight, enumerated above, also see Murphy(6). Erythropoietic protoporphyria patients are specifically sensitive to longer UVA and visible wavelengths. Polymorphous light eruption patients are specifically sensitive to longer UVA wavelengths to a greater extent than normal sensitivities. Solar Urticaria patients also react to longer UVA wavelengths and sometimes to visible light. Lupus erythematosus patients vary from heightened UVB/UVA sensitivities to also visible light sensitivity in some

patients. A few of these action spectra are compared to the erythema action spectrum in APPENDIX II.

Drug induced photosensitivities not only include UVA wavelengths but visible as well. None appear similar in shape to wavelength distributions of conditions of normal risk.

SUNSCREEN INDUSTRY PROPOSALS:

Members of the sunscreen industry have primarily focused on relatively simple sunscreen tests including in vitro and non-invasive in vivo(7-11). The in vivo test proposed to validate UVA protection involves preventing normal development of pigmentation from single acute exposures on normal individuals(12).

AAD:

The AAD's letter to FDA posted to the docket on September 7, 2000: (<http://www.fda.gov/ohrms/dockets/dailys/00/Sep00/090700/c000576.pdf>) regarding the need for high SPF products, specifically noted that 10 to 20% of otherwise healthy individuals suffer from polymorphous light eruptions (PMLE) that has both UVB and UVA and sometimes visible light sensitivities. The AAD specifically noted that sometimes broad-spectrum sunscreens with SPFs greater than 60 may be useful. They also noted that "the limited number formulations sunscreen available in this country has not been very useful for PMLE patients." They broaden their comments to include lupus erythematosus patients, "photoprotection measures, such as the use of high SPF, broad-spectrum sunscreens have proved useful for patients with lupus, but as with PMLE, the sunscreens currently available in the U.S. are inadequate to the task." Finally they observe that "Indeed, patients with special needs, such as a lupus patient, will be unable to determine from the label whether her sunscreen will be able to protect her from photosensitivity reactions."

FDA:

The FDA has heard the sunscreen industry and dermatological society proposals for the need for high SPF labeling and for UVA testing and labeling for sunscreen products. As the current testing and labeling of sunscreen products since the 1978 Sunscreen Report and Monograph deal with use of sunscreen drug products by normal individuals and for normal outdoor activities, the FDA might well separate specific claims and needs. Conceivably high SPF products could be a prescription use of sunscreens for individuals who have normal spectral sensitivities to sunlight that physicians had recognized with specific sensitivities and specific risks to UV injury including the many melanoma and non-melanoma skin cancer patients. Similarly such products could benefit surgery and plastic surgery patients with heightened risk of photosensitivity.

General UVA sensitivity and risks from sunlight, theoretically at least are considered within the framework of the current SPF tests. All solar simulators are claimed within the standards for such devices to resemble, if not mimic, the

solar spectrum and its risks, particularly for normal individuals. If the solar simulators do not provide an adequate spectrum for testing all sunlight risks in normal individuals, that is easily corrected by specifying the standards correctly.

Petitioners' Conflict of Interest:

Neither petitioner has any financial interest in any company or product that might benefit from this proposal. Neither petitioner has received any payment nor expects to receive any payment from making this petition.

Information possibly unfavorable to this petition:

The authors are aware of no information unfavorable to this petition. Sometimes patients response satisfactorily to OTC sunscreen products, often the products do not provide the protection required by patients.

C. Environmental impact

The agency has established categorical exclusion under §§ 25.31 (see: 21 CFR Parts 310, 352, 700 and 740 Sunscreen Drug Products For Over-The-Counter Human Use; Final Monograph, Supplementary Information IX. Environmental Impact, Federal Register / Vol. 64, No. 98 / Friday, May 21, 1999 / Rules and Regulations, page 27686) that action of this type, does not individually or cumulatively have significant effect on the human environment and therefore neither an environmental assessment nor an environmental impact statement is required.

D. Economic impact

The petitioners understand that an assessment of economic impact is required to be submitted only when requested by the Commissioner following review of the petition. However, it is the opinion of the petitioners that, since none of the companies now selling sunscreens under current FDA guidelines have tested and labeled any product for patient use there is now no cost for such testing. Clearly there will be costs associated with meeting patient's needs. We believe that there will be only moderate (1) cost (and price) increases to industry, government, and consumers; (2) productivity of wage earners, businesses, or government; (3) competition; (4) supplies of important materials, products, or services; (5) employment; and (6) energy supply or demand, beyond that already detailed in 21 CFR Parts 310, 352, 700 and 740 Sunscreen Drug Products For Over-The-Counter Human Use; Final Monograph, Supplementary Information VII. Analysis of Impacts, Federal Register / Vol. 64, No. 98 / Friday, May 21, 1999 / Rules and Regulations, page 27683.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, 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.

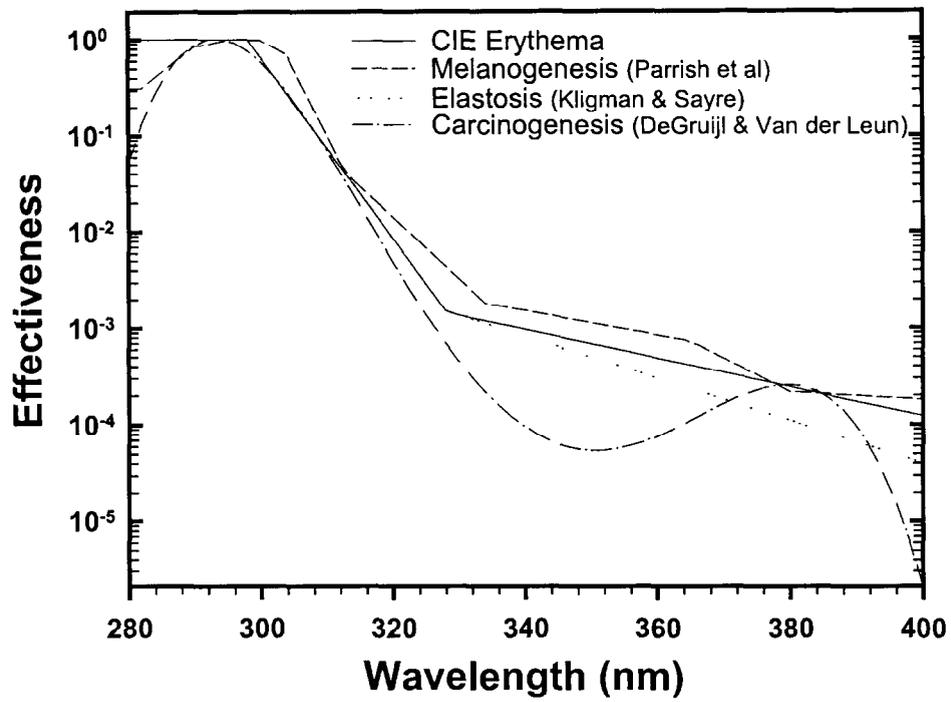
(Signature) Robert M Sayre
(Name of petitioner) Robert M. Sayre, Ph.D.
(Mailing address) 8621 Loxley Fairway
Cordova, TN 38018
(Telephone number) (901) 386-0175
(Fax number) (901) 386-7218
(E-Mail) RPTL@AOL.COM

(Signature) Ramon M Fusaro
(Name of petitioner) Ramon Fusaro, M.D., Ph.D.
(Mailing address) 984360 Nebraska Medical Center
Omaha NE 68198-4360
(Telephone number) 402-559-4399
(Fax number) 402-599-4104
(E-Mail) rmfusaro@creighton.edu

References:

1. McKinlay A F, Diffey B L. A reference action spectrum for ultraviolet induced erythema in human skin. In: Passchier WF, Bosnjakovic BFM, editors. Human exposure to ultraviolet radiation: Risks and regulations. Proceedings of a seminar held in Amsterdam, 23-25 March 1987. Amsterdam: Excerpta Medica; 1987. p. 83-87.
2. Parrish J A, Jaenicke K F, Anderson R R. Erythema and melanogenesis action spectra of normal human skin. *Photochem Photobiol* 1982; **36**: 187-191.
3. de Gruijl F R, van der Leun J C. Action spectra for carcinogenesis. In: Urbach F, editor. Biological Responses to ultraviolet A radiation. Overland Park, Kansas: Valdenmar Publishing Company; 1992. p. 91-97.
4. de Gruijl F R, Sterenborg H J, Forbes P D, et al. Wavelength dependence of skin cancer induction by ultraviolet irradiation of albino hairless mice. *Cancer Res* 1993; **53**: 53-60.
5. Kligman L H, Sayre R M. An action spectrum for ultraviolet induced elastosis in hairless mice: quantification of elastosis by image analysis. *Photochemistry and Photobiology* 1991; **53**: 237-242.
6. Murphy G M. Diseases associated with photosensitivity. *Journal of Photochemistry and Photobiology B: Biology* 2001; **64**: 93-98.
7. Diffey B L, Tanner P R, Matts P J, Nash J F. In vitro assessment of the broad-spectrum ultraviolet protection of sunscreen products. *J Am Acad Dermatol* 2000; **43**: 1024-1035.
8. Sayre R M, Agin P P. A method for the determination of UVA protection for normal skin. *J Am Acad Dermatol* 1990; **23**: 429-440.
9. Cole C. Sunscreen protection in the ultraviolet A region: how to measure the effectiveness. *Photodermatol Photoimmunol Photomed* 2001; **17**: 2-10.
10. Diffey B L. Sunscreens and UVA protection: a major issue of minor importance. *Photochemistry and Photobiology* 2001; **74**: 61-63.
11. Diffey B. Sunscreen protection in the ultraviolet A region: how to measure effectiveness. *Photodermatol Photoimmunol Photomed* 2001; **17**: 200.
12. Lim H W, Naylor M, Honigsmann H, et al. American Academy of Dermatology Consensus Conference on UVA protection of sunscreens: *summary and recommendations*. Washington, DC, Feb 4, 2000. *J Am Acad Dermatol* 2001; **44**: 505-508.
13. Magnus I A. *Dermatological photobiology: Clinical and experimental aspects*. Oxford: Blackwell Scientific Publications; 1976.
14. Young A R, Magnus I A. An action spectrum for 8-MOP induced sunburn cells in mammalian epidermis. *Br J Dermatol* 1981; **104**: 541-548.

APPENDIX I



Legend:

Human erythema(1)

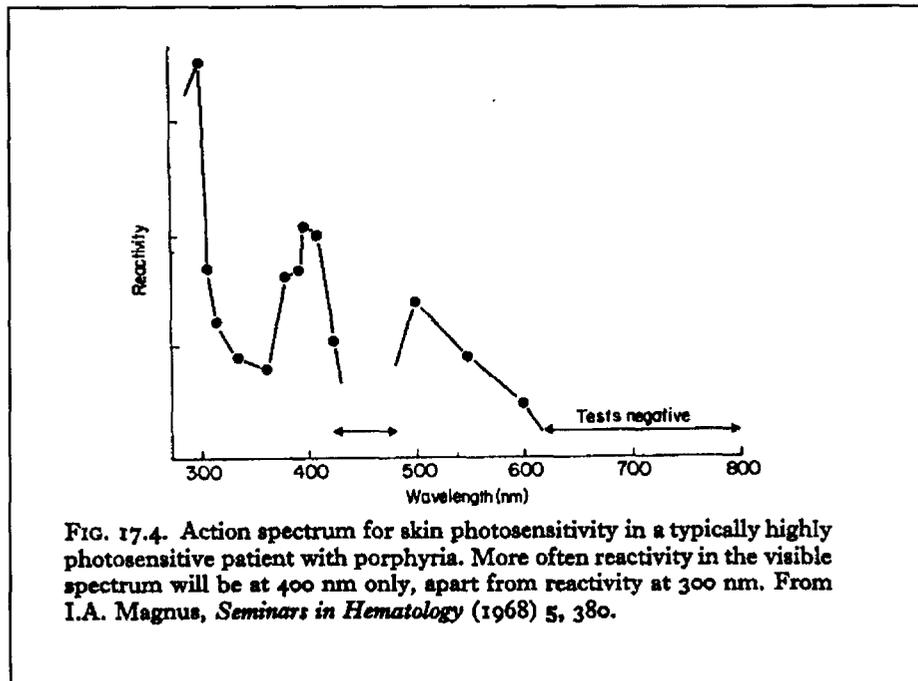
Human melanogenesis(2)

Mouse phtotocarcinogenesis(3, 4)

Mouse photoelastosis(5)

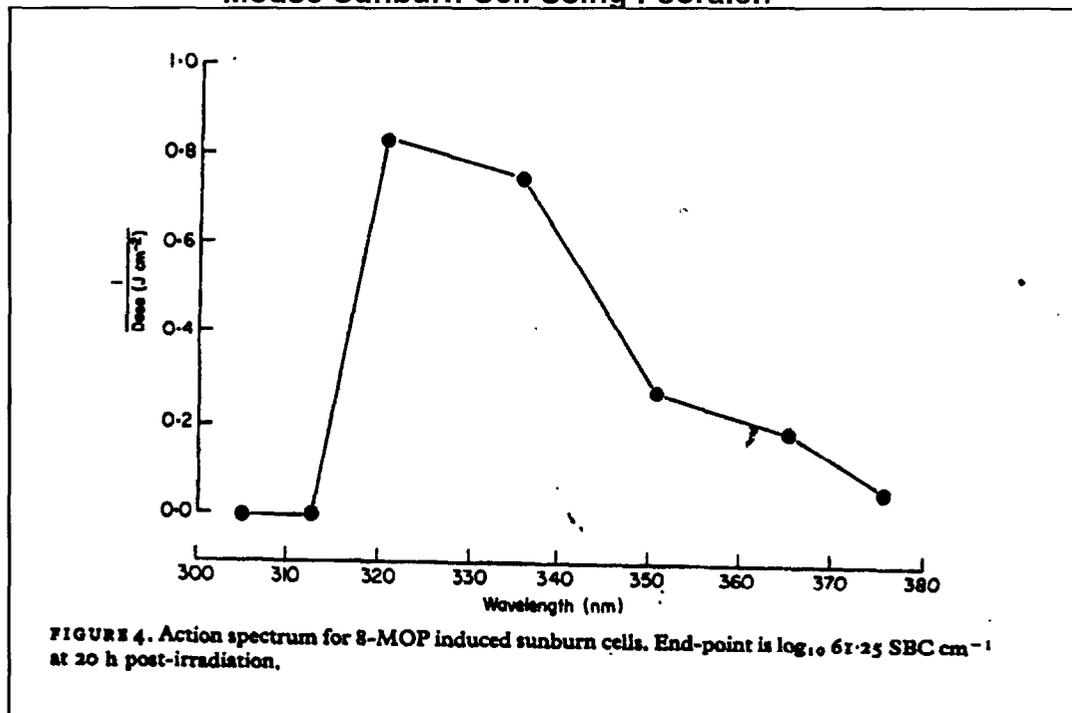
APPENDIX II

PORPHYRIA PATIENT RESPONSE



Human porphyria action spectrum provided in Magnus(13), p. 239.

Mouse Sunburn Cell Using Psoralen



Study by Young and Magnus(14).

Rapid Precision Testing Laboratories

P.O. Box 1342

Cordova TN 38088-1342

Telephone: (901) 386-0175, Fax: (901) 386-7218

E-mail: RPTL@aol.com, Website: WWW.RapidPrecision.com

February 13, 2003

To: Dockets Management Branch
Room 1061 (301)827-6860
5630 Fishers Lane
Rockville, MD 20852

From: Robert M. Sayre

Subject: Citizens Petition

Accompanying this memo are two copies of a Citizens Petition submitted by myself and Dr. Ramon Fusaro.

Thank you.

Robert M. Sayre