

Procter & Gamble

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Sunscreen Drug Products for Over-the-Counter Human Use; Monograph; Extension of Effective Date; Reopening of Administrative Record, FDA Docket No. 78N-0038

Dear Sir/Madam:

This provides three (3) copies of comments to the administrative record of the Sunscreen Drug Products for Over-the Counter Human Use, Final Rule, which was reopened on June 8, 2000.

The comments presented in this submission specifically address the concern that the Critical Wavelength calculated from absorbance curves using *in vitro* substrate spectrophotometry, does not have any biological merit. We tested this hypothesis using two sets of three products and determining the critical wavelength and an *in vivo* UVA protection factor (UVA-PF), controlling for the SPF of the products. We found a straight line correlation between the critical wavelength and UVA-PFs for products with an SPF of about 10 and for a set of products with an SPF of about 20. These data support the critical wavelength and provide evidence of a quantitative biological protection based on the determination of a UVA-PF.

Importantly, in this study we demonstrate that if the product SPF is not controlled for, as expected the relationship between critical wavelength and UVA-PF no longer holds. Thus, this obvious but critically important point must be accounted for.

Presently there is no agreed to method to evaluate long wave UVA protection of sunscreen products. Many methods, mostly *in vivo* generating UVA-PF, have been advocated. We believe these methods do not assess long wave UVA protection of sunscreen products. It is our view that there is no *in vivo* method that presently is capable of evaluating long wave UVA protection.

We strongly recommend the Agency consider the Critical Wavelength method as the only means of evaluating UVA efficacy of sunscreen products. This simple, reproducible method will ensure consumers are protected against the breadth of the UV spectrum.

Respectfully,
The Procter & Gamble Company



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APPENDIX 5 PFA Study Clinical Report

1. **Executive Summary**

There have been questions regarding the "biological relevance" of the critical wavelength method as a means of evaluating long wave UVA efficacy of sunscreen products. Moreover, detractors of the critical wavelength have attempted to discredit the method by evaluating products with disparate SPF values to show that critical wavelength does not correlate with *in vivo* measures of UVA protection.

To add clarity and systematically address these concerns, the Procter & Gamble Co. conducted a study which is the basis for this submission. Specifically, we designed a study to test the hypothesis that a positive correlation exists between critical wavelength and an *in vivo* UVA protection factor for products in which the SPF has been controlled for.

To test this hypothesis, we created 2 sets of 3 sunscreen products. The first set of 3 products had SPF values approximately equal to 10 and the second set had SPF values approximately equal to 20. Within each set of products, we had a low, medium and high UVA protection. This was achieved by formulating the products with UVB sunscreens for the low, and adding oxybenzone to the medium and the long wave UVA filter, avobenzone to the high product. We determined SPF and the UVA protection factor (UVA-PF), using the method of Cole and VanFossen (ref. 15), and critical wavelength for all 6 products. As well, we included 2 commercial products to determine where they fell in the data set.

We found that when SPF was not controlled for, the relationship between PFA and critical wavelength was not strong and if anything there was no predictivity. In contrast, when the SPF was controlled for, there was a highly significant positive correlation between the UVA-PF and critical wavelength. In addition, the commercial products fell within the correlation for each level of SPF.

These data support the hypothesis and demonstrate the positive relationship between the *in vitro* derived critical wavelength and the *in vivo* determined UVA protection factor for a set of sunscreen products in which the amplitude and breadth of UVA protection were systematically increased.

Together with our earlier submissions supportive of the critical wavelength method, we strongly recommend the agency adopt the Critical Wavelength method as the only means of assessing UVA efficacy of sunscreen products. The data presented herein address concerns regarding the biological relevance of the critical wavelength and demonstrate the quantitative nature of this measure. Thus, it is our considered view that the combination of SPF and Critical Wavelength provide a complete description of UV efficacy of sunscreen products and communicate an uncomplicated message to consumers thereby preserving and advancing public health campaigns advocating the routine use and appropriate application of sunscreen products as part of a strategy to reduce skin damage produced by sun exposure.

2. **Abstract**

The objective of this study was to demonstrate what relationship if any there was between *in vivo* and *in vitro* measures of sunscreen photoprotection against ultraviolet (UV) A (320 - 400 nm). It was hypothesized that a positive correlation exists between the *in vivo* measure of UVA protection, using the method of Cole and VanFossen (1992), and the Critical Wavelength for products with the same Sun Protection Factor (SPF). Six model sunscreen products, 3 low SPF and 3 high SPF, were prepared. Within the low and high SPF groups, the level of UVA photoprotection was increased by the addition of the short and longwave UVA filters, oxybenzone and avobenzone, respectively. For each product, SPF and UVB-APF were determined. The absorbance of each model sunscreen was determined using substrate spectrophotometry, from which the critical wavelength was calculated.

There was a direct correlation between the *in vivo* UVA protection factor and critical wavelength for the low SPF ($r^2 = 0.99$, $p < 0.0001$) and the high SPF products ($r^2 = 0.99$, $p < 0.0001$). There was no statistically significant correlation between critical wavelength and PFA if the SPF of the products was not controlled for. These data illustrate the quantitative nature of the Critical Wavelength measure and demonstrate the UVA photoprotection afforded using this index. Because there are so many concerns regarding *in vivo* UVA test methods including human relevance of endpoint measures, reproducibility, consumer relevance, etc., the Critical Wavelength evaluation provides a uniform, singular means of accessing sunscreen product efficacy which, together with SPF, provide a complete description of the product.

3. BACKGROUND

The spectral distribution of solar UV radiation reaching the surface of the earth encompasses wavelengths between 290 and 400 nm. Commonly defined ranges for specific bands of the terrestrial UV spectrum are UVB (290 - 320 nm) and UVA (320 - 400 nm). In addition, the UVA waveband is often further divided into UVA II (320 - 340 nm) and UVA I (340 - 400 nm), generally reflecting the higher erythemogenic efficiency of shorter UVA wavelengths (1). Importantly, the division between these UV wavebands is arbitrary and may differ depending how it is defined; human skin is exposed primarily to solar UV, which includes all UV wavebands.

It has been demonstrated that long wavelengths of solar UV (i.e., > 340 nm) can contribute to skin damage. This assertion is based on both clinical evidence and theoretical considerations. The studies by Lavker *et al.* (2,3), Lavker and Kaidby (4), and Lowe *et al.* (5) provide evidence that repeated exposure to an artificial source of long wavelength UVA produces morphological changes in human skin indicative of photodamage. These data corroborate studies in animals where exposure to UVA was reported to accelerate photodamage (6,7) and the induction of skin tumors (8). Since the overwhelming majority of sunscreen products available to consumers provide protection primarily limited to UVB and short wavelength UVA II (320 - 340 nm), it has even been hypothesized that the use of such products may paradoxically increase exposure to long wavelength UVA I (340 - 400 nm) (9) by selectively changing the spectrum of solar sunlight received by the skin (10).

A particularly meaningful aspect of the damage produced by UVA was identified in the study by Lavker *et al.* (2). In this study the skin damage produced by the light source occurred even though the subjects applied a sunscreen product containing oxybenzone. These data clearly emphasize the need for protection at wavelengths beyond the short UV AII spectrum.

Given the consumer need for long wavelength UVA protection and the absence of meaningful information regarding such protection on currently-marketed sunscreen products, there is an urgent demand for a reliable, versatile and universally-applicable method that provides purposeful, SPF-independent information regarding UVA photoprotection. Several *in vivo* methods using human subjects have been proposed (for review see 11-13) but not widely accepted. Although there are several reasons for this, the limitation of all proposed human studies of UVA photoprotection is the absence of an endpoint measure that is a true surrogate marker for long wavelength (i.e., > 340 nm) UVA-induced skin damage, especially melanoma and photoaging. From a more practical perspective, the existing human studies utilize endpoints that: (i.) are redundant with SPF testing, i.e. erythema (14,15), (ii.) are oxygen and, by definition, UV dose-rate dependent (16-18); (iii) are skin-type dependent; (iv.) have a high degree of variability, and (v.) may require extraordinary exposures to an artificial UVA source, the human health consequences of which are unknown.

Several *in vitro* methods to evaluate UVA photoprotection have been designed. One such method proposed by Prof. B.L. Diffey (19) makes no assumptions regarding the action spectra for UVA-induced acute or chronic skin damage and obviates the need for human subjects utilizing clinical endpoints with indeterminate value in relation to protection from sunlight. This proposed *in vitro* method is based on the absorption spectrum of a sunscreen product, which is obtained using UV substrate spectrophotometry. The absorption spectrum is reduced to a single index termed *Critical Wavelength*, defined as the wavelength where the integral of the spectral absorbance curve reached 90% of the integral from 290 to 400 nm. Importantly, the critical wavelength value is based on the inherent shape of the absorbance curve not its amplitude and, therefore, is independent of application thickness and other undesirable variables characteristic of *in vitro* calculations of absolute protection factors. As well, it should also be noted that the critical wavelength determination does not promote the false notion of UVB and UVA as separate entities, but rather as part of a continuous electromagnetic spectrum.

The specific aim of this study was to demonstrate the relationship between critical wavelength and an *in vivo* measure of UVA protection. It is hypothesized that

- there is a positive correlation between the critical wavelength and *in vivo* UVA protection factor for products with the same SPF.

4. **Methods and Materials**

a) **Product Samples**

Six (6) sunscreen products, 3 low SPF & 3 high SPF, were prepared as simple oil in water emulsions (for details see Appendix I). The products were comprised of the following UV filters:

Table 1. Composition of Six Model Sunscreens

Code	Target Efficacy		UV Filter (% w/v)						
	UVB	UVA	PBSA	HSAL	OSAL	OMC	OCTO	OXY	AVO
E	low	low	1.5			4			
F	low	mid	1.5					3	
G	low	high	1.5						3
B	high	low		15	5	7.5	10		
C	high	mid		15	5		10	6	
D	high	high		4			5	4	3

PBSA: 2-phenylbenzimidazole-5-sulfonic acid; HSAL: homosalate; OSAL: octyl salicylate; OMC: octylmethoxycinnamate; OCTO: octocrylene; OXY: oxybenzone; AVO: avobenzone

As well, two (2) commercial products were purchased in Cinc. OH, with labeled SPF's of 8 and 25 (Study Code I and J, respectively) for evaluation in this study.

b) **Substrate Spectrophotometry And Determination Of Critical Wavelength**

The critical wavelength was determined using the method described by Diffey (), with a slight modification. Briefly, the absorbance of the reference substrate was determined. Then products were applied uniformly at a rate of 1 mg/cm² to the substrate with a finger cot. The product film was allowed to dry under ambient conditions (22 ± 2 °C) for 15 minutes. Samples were pre-irradiated with broad band UV radiation filtered to simulate a solar UV spectrum (290 - 400 nm). The total pre-irradiation UV dose in J/cm² was numerically equal to 2/3rd the product SPF, e.g. for a SPF 15 product, pre-irradiation was 10 J/cm². Immediately after pre-irradiation, the UV absorbance of the product film was measured. The measurement performed on the product sample was corrected for the untreated reference and the resulting absorbance curve used to calculate the critical wavelength. The protocol is presented in APPENDIX 2.

c) **Calculation of the Critical Wavelength**

The critical wavelength was calculated using the following equation:

$$\lambda_c = \frac{\int_{290}^{400} A(\lambda) d\lambda}{\int_{290}^{400} A(\lambda) d\lambda} = 0.9 \int_{290}^{400} A(\lambda) d\lambda$$

where A is absorption and λ wavelength. For each absorption spectrum, the integrals, which represent the area under the product absorbance curve, were estimated using trapezoidal integration. The final critical wavelength value for each model sunscreen was the 95% lower confidence limit computed from the individual replicates. The average absorbance for each product tested is provided in APPENDIX 3.

d) Determination of *in vivo* SPF

The *in vivo* SPF values were determined using the methods specified in the FDA's Proposed Rule: Sunscreen Drug Products For Over-The-Counter Human Use (May 12, 1993) for SPF¹. A detailed protocol is included with the study report in **APPENDIX 4**

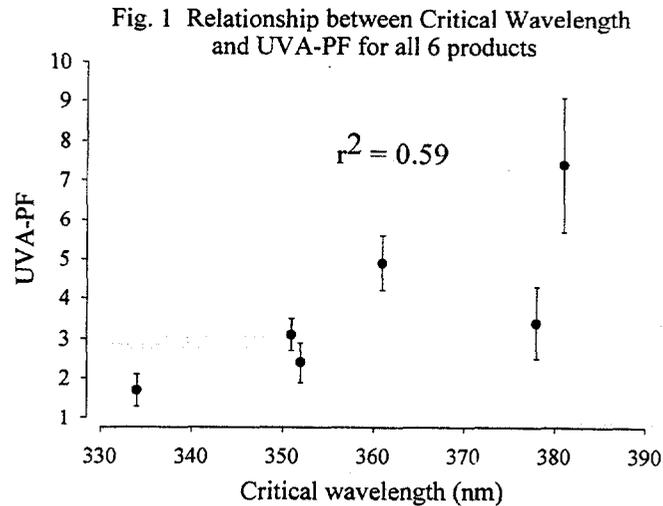
e) Determination of *in vivo* UVA photoprotection

The UVA-PF was determined for each subject in each treatment group using the method of Cole and VanFossen (15). A detailed protocol is included with the study report in **APPENDIX 5**.

¹ Food and Drug Administration. May 12, 1993. Establishment of a Monograph; Notice of Proposed Rulemaking. Sunscreen Drug Products For Over-The-Counter Human Use. Federal Register. 50 (90): 28194-28302.

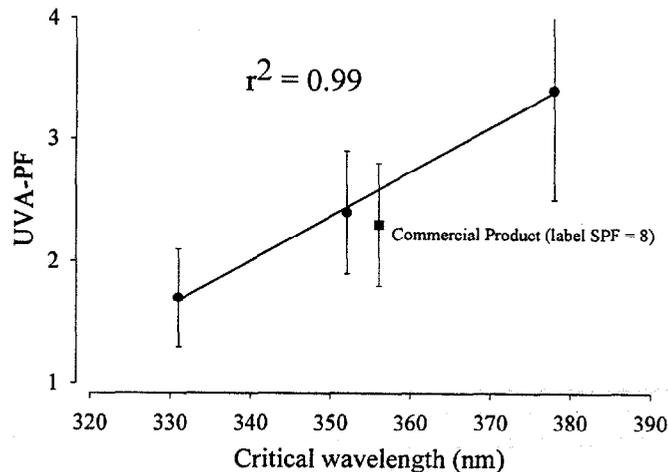
5. Results

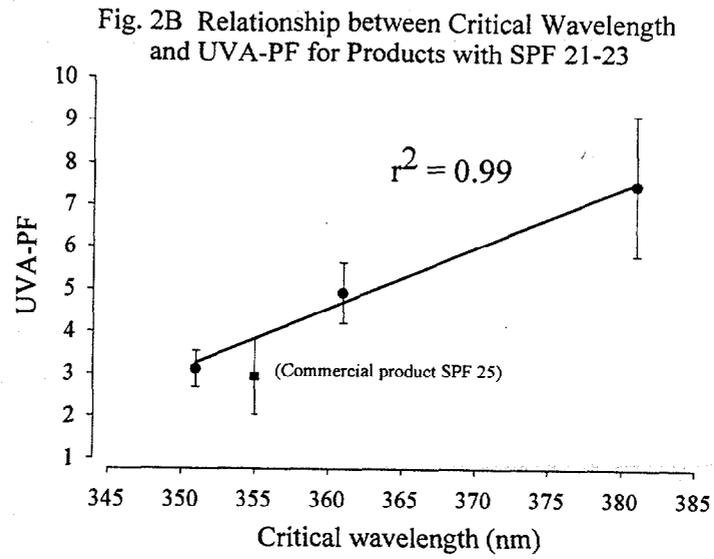
The relationship between the critical wavelength and the UVA protection factor (UVA-PF) for all 6 products is presented in Fig. 1. There was no statistically significant relationship between the critical wavelength and UVA-PF when the product SPF was not controlled for.



In contrast, when the SPF of the product was controlled for, there was a statistically significant ($p < 0.0001$) straight line, positive correlation between the critical wavelength and the UVA-PF relationship (Fig. 2A and 2B).

Fig. 2A Relationship between Critical Wavelength and UVA-PF for Products with SPF 10-11





As well, the two commercial products, were within the deviation of the line.

6. Discussion and Conclusion

A positive relationship between the critical wavelength and the *in vivo* measure of UVA photoprotection further establishes the biological predictivity of the *in vitro* test. The critical wavelength is based on the absorption spectrum of a sunscreen product and is independent of the amount of product applied. This is of considerable importance since the determination of any protection factor is product dose/application dependent. The thickness of product application determines in part the amplitude of the absorption curve which in turn affects the determination of protection factors. Thus, if the protection factor such as SPF, is not controlled for the relationship with critical wavelength is meaningless. Moreover, as we demonstrate, if SPF is not controlled for, there will be no relationship between critical wavelength and, in this case, the UVA-PF.

In conclusion, we believe a combination of *in vivo* SPF and critical wavelength provides a complete description of a product's inherent photoprotective characteristics - SPF describes the amplitude of protection (at a given application rate) and critical wavelength provides a reliable measure of the product's spectral absorption capability. No other efficacy measures are needed.

7. **References**

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