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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.

Avon Products, Inc "Avon" is a leading manufacturer and distributor of quality cosmetic and over-the-counter drug products in the United States. Avon's mission is to deliver quality products that improve the lives of our consumers. We believe that consumers should be offered products which facilitate informed choice with regard to the degree and scope of sun protection against the full spectrum of harmful UV radiation. To that end, Avon was one of the first cosmetic companies to market an aesthetic, daily wear sunscreen product incorporating Parsol 1789TM that provides full spectrum coverage against UVA I and UVA II.

In comments published in the *Federal Register* the FDA reopened the administrative record for the rulemaking for OTC sunscreen drug products. 65 Fed Reg 36319 (June 8, 2000). In a feedback letter from FDA to CTFA of July 16th and during feedback meetings of January 27th, and October 26th, FDA requested additional information on UVA testing and labeling. It is our intent by this letter to present our general comments on labeling and testing requirements for UVA protection.

We believe that two principles are paramount in formulating a decision on this issue. First, there must be a clear nexus between test method endpoint and type of UVA claim; second, UVA labeling must be easily understandable and must not mislead the consumer regarding extent of protection across all relevant wavelengths:

- Exposure to UVR has many acute and chronic consequences including; erythema, sunburn, dyspigmentation, carcinogenesis, immune suppression, photoaging and photodermatoses. Both UVB (290nm -320nm) and UVA (320nm - 400nm) contribute to the damaging effects of exposure to UVR. In contrast to UVB, the action spectra of UVA-mediated effects are not well understood. Existing *in vivo* methods are inappropriate measures of UVA protection because they rely on measurement of effects of exposure to a narrow range of UVA

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wavelengths. In the absence of physiologically relevant markers of photodamage, the absorption spectrum of a sunscreen offers the most rational and objective measure of protection in the wavelengths of interest. To this end, we advocate the use of the modified Diffey/Critical Wavelength (CW) method in determining the extent of UVA protection afforded by a sunscreen. The method is simple, reproducible, and absorption spectra are relatively independent of sample preparation artifacts (e.g., variations in film thickness). Importantly, the CW method accounts for any lack of photostability of the final product form. Establishment of a CW cutoff of ≥ 370 nm ensures that sunscreens claiming broad spectrum protection provide adequate protection across *all* relevant UVR regions of interest.

- Label claims should not be misleading, confusing or provide the consumer with a false sense of security. We support a single pass/fail labeling of “broad spectrum protection”. When combined with SPF labeling, the term “broad spectrum” offers a complete description of a product’s ability to protect the consumer from the damaging effects of UVR. Furthermore, it offers simple and concise information that allows the consumer to make informed choices regarding sunscreen protection.

In summary, we support the use of the modified Diffey/critical wavelength method for measuring UVA protection. In combination with SPF testing, the CW method provides the basis of labeling which communicates a complete description of the ability of a sunscreen product to block UVR. The claim “broad spectrum protection” constitutes a simple and accurate labeling statement that is easily understandable by consumers.

Both UVA And UVB Contribute To The Damaging Effects Of Exposure To UVR (Although The Action Spectra Of UVA-Mediated Photobiologic Effects Are Not Well Understood)

Both UVA and UVB contribute to UVR-induced carcinogenesis. There is considerable epidemiologic evidence supporting a role for UVR in skin carcinogenesis (e.g., the strong association of skin cancer with a history of sun exposure in children and, in particular, sunburn (1-3); certain forms of skin cancer are much more predominant on sun exposed sites as compared with sun protected sites (4-7); individuals affected by xeroderma pigmentosum [i.e. who have impaired DNA repair capacity] are exquisitely sensitive to UVR and develop numerous nonmelanoma skin cancers early in life (8)).

DNA is the primary target for UVR-induced damage leading to genetic mutations and non-melanoma skin cancers (9). The action spectrum for many forms of DNA damage (including pyrimidine dimer formation) correlates closely with that of erythema and resides primarily in the UVB range (10). This close correlation has provided evidence for an association of UVB with carcinogenesis. Mouse models have also implicated UVB in the development of squamous cell carcinomas (11-13). However, the lack of suitable animal models for other human cancers, i.e. melanoma and basal cell carcinoma, have hindered the determination of the dose and wavelength dependencies of these forms of cancer.

In contrast to the available wealth of information establishing a role for UVB in the etiology of skin cancer, the role of UVA is less well understood. Nonetheless, UVA has been

implicated in the development of melanoma (14) and it has been suggested that an increased risk of melanoma may be present in individuals frequenting suntan parlors (whose light sources typically emit as much as 95% UVA) (15 and ref therein). In an opossum model UVA radiation induced the formation of melanoma precursors (18). UVA induced melanoma formation in a fish model (although the relevance of this model is unclear) (19). Wolf *et al.* showed that UVB sunscreens do not prevent the progression of transplanted melanomas (20).

Although UVA is not appreciably absorbed by DNA, absorption by other molecules is important and studies indicate that UVA-induced generation of singlet oxygen within human skin appears to be a key biological mediator of damage. Reactive oxygen species generated following UVA exposure leads to DNA damage such as oxidation of guanine bases (16). *In vitro* studies using skin cells also show that mitochondrial DNA mutations arise from UVA irradiation (17). These studies indicate that the potential for UVA to contribute to melanoma and non melanoma skin cancers cannot be ruled out (and even appears likely). Nonetheless, much more work is needed to determine the relative contribution of UVA wavelengths to carcinogenesis.

UVA induces suppression of the immune response. UVR has a direct suppressive effect on the immune response in human and animal models (15,21,22), which may also contribute to the carcinogenic potential of UVR. Suberythemal doses of solar simulated light prevent the induction of contact hypersensitivity in humans (23). However, the action spectrum of this phenomenon is far from certain. UVB and UVA II have both been shown to induce a tolerizing effect on the skin's immune response. However, combinations of UVB and UVA have demonstrated lower suppression rates as compared to isolated UVB or UVA, indicating an antagonist effect of combined radiation (24). While UVA I failed to induce tolerance to contact allergens it was effective at inducing Langerhans cell depletion (21).

The failure of sunscreens to protect against immune suppression to the same extent as erythema suggests that the action spectrum for the immune response may lie in the UVA range (25). Further, the dose relationship between UVR and immunosuppression differs from that of UVR and erythema (26). Transplantation patients receiving immunosuppressive drugs develop numerous skin cancers (27) on sun exposed sites indicating a clear association between immunosuppression and development of cancer. The direct effect of UVR on the immune response is likely to have a similar negative impact on health. In the absence of a defined action spectrum for immunosuppression, complete sun protection of UVR *must* include protection against all wavelengths.

Broad spectrum UVA has been implicated in photoaging. Both UVB and UVA appear to contribute to photoaging of skin although the relative contribution of UVA *vis-a-vis* UVB is debated (21, 28-31, 43, 44). UVA has been implicated in photoaging, especially solar elastosis and skin wrinkling. Using the hairless mouse model, Kligman has demonstrated that repeated UVA exposures lead to dermal changes associated with photoaging (30). Lavker and others, have shown that repeated suberythemal doses of UVA result in significant changes in skin including inflammation, lysozyme deposition and hyperplasia. These changes were produced equally by UVA I and broadband UVA suggesting a role for longer wavelength UVA in skin damage (32-34). In the U.S. (where the average life expectancy is increasing dramatically), the appearance of skin and maintenance of youthful appearance has created a genuine consumer

need for means of effectively preventing photodamage. A complete program of sun protection should include protection from both UVA I and II in order to prevent dermal photoaging.

There Should Be A Clear Nexus Between UVA Methodology And Label Claims

The lack of information on action spectra requires use of full-spectrum sunscreen systems to protect against photodamage. The association of UVA exposure with various forms of photodamage demonstrates the need for true, broad-spectrum protection. While the relative importance of UVA I versus UVA II remains to be determined, there exists ample evidence to suggest that UVR protection should include the entire spectrum of UVA wavelengths. UVR in the range of UVB, UVA I and UVA II are all present in sunlight at ground level. While UVB has higher erythemogenic potential, UVA is far more abundant and can, therefore, contribute appreciably to photodamage. Moreover, because UVA penetrates deeper into the skin than UVB, a greater number of cells may be affected. The studies cited above highlight the need for a greater understanding of UVR action spectra for photobiologic phenomena especially carcinogenesis. In the absence of such data, a comprehensive protection program should include the use of broad-spectrum sunscreens that block UVR in the UVA I and UVA II regions.

Existing in vivo methods are inappropriate measures of UVA protection because they rely on measurement of effects of exposure to a narrow range of UVA wavelengths. Several *in vivo* methods have been proposed for evaluating the UVA protection afforded by sunscreens. These include the phototoxic protection factor (PPF), immediate pigment darkening (IPD), persistent pigment darkening (PPD), and the UVA erythema/pigmentation method (PFA). The validity of PPF (36) and IPD (35) have generally been questioned due to concern over the relevance of the endpoints and the impracticality of the assays themselves. PPD (37) and PFA (38) rely on generation of tanning and/or erythema as a biologic endpoint. Both methods are weighted heavily towards shorter UVA wavelengths (UVA II). SPF already accounts, at least in part, for UVA II-induced erythema and (importantly) PPD and PFA do not adequately assess the breadth of UVA protection. The relevance of these *in vivo* methods is thus questionable as no correlation exists between erythema, pigment darkening and the biologic endpoints that UVA sunscreens are meant to protect against. The dose response for tanning and erythema do not correlate with the dose relationship for many forms of photodamage such as erythema. The light sources employed are filtered to eliminate most UVB radiation and represent a form of radiation that is rarely encountered in nature. *In vivo* UVA test methods require long irradiation times and employ wavelengths that the skin will never be exposed to under natural conditions hence the response of skin may be quite different as compared to natural light. As discussed previously, the biologic effects of full spectrum UVR may differ significantly from that of isolated wavelengths, hence the relevance of protection factors generated using these methods is further called into question. Finally, the photochemical reaction of sunscreens to full spectrum UVR may differ significantly from that observed with UVA only, hence photodegradation of sunscreens cannot be accounted for in these assays (49).

There is no compelling reason why a UVA test method should be in vivo. One argument proposed in favor of *in vivo* methods is that they account for interactions between product and skin (e.g., degradation by enzymes, absorption into skin, etc). In fact, sunscreen products are

specifically designed to have minimal interaction with the skin. In order to be effective, a sunscreen system must remain as a film on the skin surface. Any sunscreen which fails this requirement would likely fail its targeted SPF value. Hence in the battery of testing sunscreen products must undergo, any skin interaction will be detected.

Critical Wavelength is the most appropriate method for assessing UVA protection of sunscreens. Sunscreens were originally intended to prevent sunburn and erythema. We now know that "complete" sun protection requires protection against multiple endpoints not correlated with erythema. Ideally sunscreens should protect against all damaging wavelengths. In the absence of detailed action spectra and surrogate markers for relevant biologic endpoints it is more meaningful to assess a sunscreen's ability to function as a screening agent across the range of UVR wavelengths.

The Critical Wavelength (CW) method proposed by Diffey (40) is an *in vitro* method that defines the wavelength below which 90% of a sunscreen's UV absorbance occurs. The attenuation of light by a sunscreen film on an artificial substrate is measured at each wavelength using a light source that produces a continuous output over the terrestrial UVR spectrum. In 1996, CTFA recommended a modification of Diffey's method that includes a preirradiation step and use of one of several substrates such as Transpore tape or Vitro skin (41).

CW has several important advantages over other proposed methods. In particular, the method involves a preirradiation step that accounts for photodegradation of the test product and is relatively unaffected by application rate. Importantly, CW measures the screening ability of a sunscreen product over the entire range of relevant wavelengths (i.e. 320-400 nm). Because the action spectrum for the biological effects of UVA are unknown, it is imperative that protection is afforded in all UVA wavelengths. Finally, by establishing a minimum level of absorption in the longer UVA wavelengths, the method can be used to establish broad-spectrum sunscreen protection. Any sunscreen which meets the criteria for $CW \geq 370$ nm will provide significant protection against both UVA I and II.

CW has several advantages over the "Boots ratio method". The Boots ratio method (50) simply compares the relative absorption in UVB *versus* UVA and does not provide a qualitative or quantitative measure of the breadth of coverage throughout the UVA spectrum. Hence a sunscreen can conceivably fail to provide adequate UVA I protection while achieving a relatively high UVA:UVB ratio. CW assures protection coverage throughout both UVA I and II wavelengths. Second, the ratio method relies upon absolute spectral absorbency and is subject to variations in sample preparation. Because CW is a measure of *relative* absorption over a range of wavelengths and not an *absolute* measurement, the value is relatively independent of sample variables, e.g., product film thickness. Finally, in offering several arbitrary levels of UVA protection the Boots rating system offers little value to consumers in selecting an appropriate level of UVA protection and may serve to confuse and mislead the consumer. In contrast, CW analysis and a simple pass/fail definition of broad-spectrum protection offers accurate and easily understandable information to the customer.

A combination of CW and SPF addresses proportionality issues better than PFA. Concern over UVA:UVB proportionality arises from the compensation hypothesis (45). This

hypothesis states that sunscreens may be used to extend the length of time in the sun, thus exposing consumers to greater amounts of damaging UVA rays. Concern for UVA: UVB proportionality has been used to argue in favor of *in vivo* UVA testing (46). We contend that this argument is flawed based on the fact that SPF testing already accounts for a minimum UVB:UVA II proportionality and therefore measurement of PFA is duplicative:

- Approximately 15% of the erythral effective energy of sunlight is UVA radiation. Thus, in order to obtain an SPF of roughly 7 or greater, some level of UVA protection must be afforded in the UVA II region. This minimal level represents approximately $0.15 \times \text{SPF}$. This theoretical relationship has also been demonstrated experimentally (37). As the SPF of a sunscreen increases from 8 to 30, the percent of UVA blocked increases from 16% to nearly 78%. Hence UVB: UVA II proportionality is inherent to the SPF test.

Further, *in vivo* UVA testing does *not* account for proportionality in the UVA I region:

- *In vivo* UVA test methods are an inappropriate means of establishing UVA:UVB proportionality because they are weighted heavily towards UVA II. Hence they can be used only to establish UVB:UVA II proportionality while neglecting UVA I protection. In contrast, because CW analysis relies upon calculation of the area under the curve, UVA:UVB proportionality is maintained (i.e., in order for a sunscreen to maintain a given Critical Wavelength, both UVA I and UVA II protection must increase as UVB protection increases).

Label Claims Should Not Be Misleading, Confusing Or Provide A False Sense Of Security

UVA protection claims should provide concise, simple and meaningful information to consumers. The claims should correlate closely with the endpoint that is to be measured. Ideally, UVA test methodology would measure endpoints related to UVA-induced damage (i.e. endpoints that UVA sunscreens are meant to protect against) and the claims would reflect that testing. As no *in vivo* method currently exists that fulfills this criterion, we have advocated the use of an *in vitro* method that reflects the ability of a sunscreen to attenuate UVA throughout the entire spectrum and describes this ability with a simple pass/fail designation. UVA claims that reflect the pass/fail criterion with a simple “broad spectrum” claim provide the most relevant information to consumers.

In contrast to this simple, easily understood and biologically relevant labeling criterion, some proposed labeling claims are based on test methods (e.g., PFA) that can be used to generate “protection factors”. As the Agency and leading dermatologists and academicians have acknowledged, protection factors suffer from many disadvantages (9). In converting a logarithmic measurement to a linear scale, protection factors do not necessarily reflect the actual magnitude of a sunscreen's protection and tend to be misleading to consumers (42). For example, a sunscreen with an SPF value of 30 does not provide twice as much protection as a SPF 15 sunscreen. More importantly, protection factors based on measurement of attenuation of a

narrow region of UVA will lead consumers into a false sense of security that their sunscreen is effectively blocking all solar light when, in fact, they are being exposed to UVA I.

We believe that SPF will continue to be the primary source of information used by the consumer in choosing sunscreen products. That being so, we believe that the designation of a second protection factor for UVA protection would serve only to confuse consumers. We strongly urge FDA to adopt a simple statement on UVA claims based on CW analysis - i.e., any product with $CW \geq 370$ nm should be labeled as a "broad spectrum" sunscreen. The proliferation of a numerical or categorical claim of UVA protection would lead to innumerable combinations of SPF and UVA protection factors from which consumers would need to select a sunscreen. This situation would leave the consumer to decide what combination and ratio of UVB and UVA is appropriate. Such a policy would be confusing at best and, at worst, may lead consumers to make inappropriate choices of UVR protection.

Summary

UVA test methodology should be simple, accurate, reproducible and utilize a relevant endpoint (one that sunscreens are meant to protect against). Similarly, claims should be relevant, easy to understand and reflect the endpoint that is measured. Unfortunately, the action spectra of most photobiologic phenomena, especially those related to UVA, are poorly understood. However, there exists sufficient evidence to suggest that complete sun protection should include protection from both UVA I and II. Use of the modified Diffey method/Critical Wavelength analysis provides the most relevant means of determining UVA protection.

Similarly, use of a pass/fail criteria for a broad spectrum claim provides the most meaningful information to the consumer. A broad spectrum claim based on Critical Wavelength analysis provides information on balanced protection throughout all relevant UVA wavelengths and establishes an appropriate UVA:UVB proportionality. A broad spectrum claim in conjunction with SPF provides a measure of the breadth and amplitude of UVR protection. We urge the FDA to consider adoption of the modified Diffey/critical wavelength method and broad spectrum UVA claim for incorporation in the OTC Sunscreen Monograph.

Thank you for your consideration.

Sincerely,



Stephen D. Gettings

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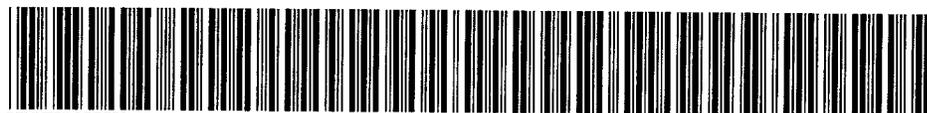
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