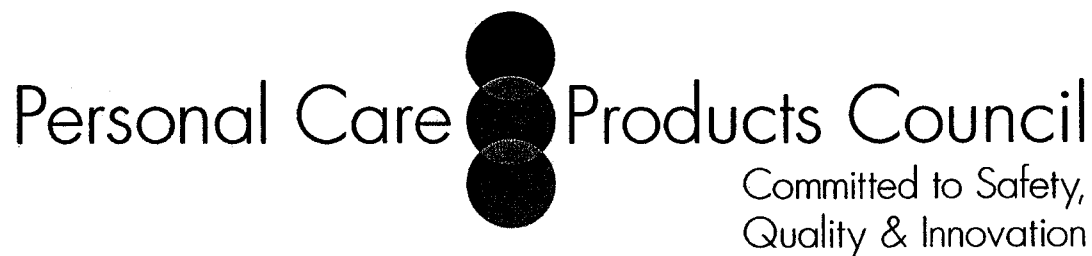


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COMMENTS SUBMITTED BY



Sunscreen Drug Products for Over-the-Counter Human Use; Proposed
Amendment of Final Monograph
Docket No. 1978N-0038, Regulatory Information No. 0910-AF43

December 26, 2007

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December 26, 2007

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD, 20852

Re: Sunscreen Drug Products for Over-the-Counter Human Use;
Proposed Amendment of Final Monograph; Docket No.
1978N-0038, Regulatory Information No. 0910-AF43

The Personal Care Products Council (the Council) (formerly the Cosmetic, Toiletry, and Fragrance Association) and the Consumer Healthcare Products Association (CHPA) are pleased to provide these comments in response to the Food and Drug Administration's (FDA's) proposed amendment to the final monograph for over-the-counter (OTC) sunscreen drug products for human use (the Proposed Rule). 72 Fed. Reg. 49070 (August 27, 2007).

Based in Washington, D.C., the Council is the leading national trade association representing the \$250 billion global cosmetic and personal care products industry. Founded in 1894, the Council's more than 600 member companies manufacture, distribute, and supply the vast majority of finished personal care products marketed in the U.S. As the makers of a diverse range of products that millions of consumers rely on everyday, from sunscreens, toothpaste and shampoo to moisturizer, lipstick and fragrance, personal care products companies are global leaders committed to product safety, quality and innovation.

CHPA, founded in 1881, is a national trade association representing the leading manufacturers of OTC, non-prescription medicines and dietary supplements. Members of CHPA are responsible for over 90 percent of the retail sales of OTC drug products in the United States. CHPA member products include sunscreen drug products.

Together, the Council and CHPA members market or manufacture the vast majority of sunscreen products sold in the U.S., as well as a large number of OTC drugs and cosmetic-drugs (products that are regulated as both cosmetic-drugs). The Council and CHPA members export sunscreen products throughout the world, and many members have manufacturing facilities located outside the U.S.

We believe sunscreens are important to public health in helping to prevent not only sunburn, but also skin cancer and many other significant and detrimental effects of UV radiation. On August 27, 2007, FDA published the Proposed Rule. The Agency has

requested comments on a number of testing and labeling issues related to sunscreen products. FDA has extended the comment period by 30 days; allowing for a 120-day comment period. 72 Fed. Reg. 67264 (November 28, 2007).¹

Contained herein are comments on the Proposed Rule that address key issues relating to the testing, labeling and safety of products that offer sun protection. We have developed commentary and data addressing FDA's questions and issues relating to the testing and labeling of sunscreen products including: (I) Sun Protection Factor (SPF); (II) UVA; (III) Anti-aging; (IV) Labeling; (V) Ingredients; (VI) Implementation; (VII) Economic Impact; (VIII) Sunscreens Containing AHAs; and (IX) Nanotechnology and Sunscreens.

We believe the recommended changes outlined in these comments are necessary to ensure that FDA's final monograph reflects sound science and policy and complies with the First Amendment of the United States Constitution, the Administrative Procedure Act (APA), the Federal Food, Drug, and Cosmetic Act (FDCA), and its corresponding regulations. We look forward to an open dialogue with FDA on these issues, which are of critical importance to our members.

I. Sun Protection Factor

We support the decision to allow sunscreen products to be labeled with SPFs up to SPF 50+ and understand that higher SPF levels may be considered if the Agency's review of data and methods supports a decision that current methods are valid and supporting data are acceptable to the Agency. We request the following changes to the Proposed Rule, which are discussed in more detail below:

- The Agency should return to panels of 20-25 subjects for SPFs of 30 through 50 and also, consistent with the International SPF Test Method (which is currently under consideration to become an ISO standard), consider adopting SPF panels of "at least ten" subjects, while retaining the current statistical treatment of the data. In addition, we believe that all sunscreen product forms, including newer forms, should be tested by existing standard methods that require application to the test site by weight at 2 mg/cm.
- The term "sunburn" should be used rather than the term "UVB sunburn" on the Principal Display Panel (PDP) and in the Uses section of the Drug Facts box. We submit that the term "UVB Sunburn" is scientifically incorrect. While SPF can be described as the "sunburn protection factor," SPF (and sunburn) is not a function of UVB alone.

¹ Deadline for comment submission is December 26, 2007.

- FDA should return to the “at least annually” measurement schedule calibration of solar simulators.
- The Agency should adopt the updated solar simulator specifications that are now recognized globally and which will support more harmonized outcomes of SPF testing internationally.
- FDA should amend the finger cot application requirement to allow for the application of powder products to allow for use of a sponge applicator.
- The Agency should shorten the duration of testing because it is possible to use a multiport type solar simulator rather than a single port style solar simulator. The multiport simulator (equipped with liquid light guides) is also suitable for easily accommodating different dosage forms. We therefore request that the current proposal allow for multiport simulators with test subsite areas of 0.5cm² that are separated by 0.8cm.
- FDA should allow for all sunscreen products to be delivered to the test site by weight, and spread over the test site evenly, regardless of the form or final package delivery method. Application by weight (2 mg/cm²) enables all products to be compared based on the same methodology.

A. SPF Cap

We support the Agency’s decision to allow sunscreen products to be labeled with SPFs up to SPF 50+ and understands that higher SPF levels may be considered if supporting data are submitted to the Agency for review.

B. Sunscreen SPF Testing

1. General Comments: a panel of 20-25 subjects for expected SPFs of 30 and above is sufficient. We urge FDA to adopt an SPF panel size of “at least ten” to harmonize with the international SPF test method.

The Council previously supplied the Agency with data to support the accuracy and reproducibility of sunscreen testing methods. We support the changes in the SPF test method proposed by the Agency, with the exception of the need for an increased number of subjects for products with SPFs of 30 and above. To that end, we are submitting SPF results on two high SPF formulations tested at two laboratories which illustrate that higher SPF products can be tested within current statistical requirements with panels of 20-25 subjects. A report on that testing and the final reports from the laboratories are attached as Appendix 1. We believe that based on the available data, sunscreen products with SPFs up to 50 do not exhibit undue variability using current methods and do not require extra subjects to obtain valid results. The statistical treatment of the data will penalize poorly formulated products that exhibit wide variability in results by lowering the calculated SPF versus the mean. We ask that the Agency return to panels of 20-25 subjects for SPFs of 30 through 50.

The International SPF Test Method requires panels of “at least ten” subjects for valid SPF results, along with statistical control.² In the interest of harmonization, the Council is providing SPF testing results from six formulations that demonstrate that, using the 1999 FDA SPF methodology, the results of either the first ten subjects or ten randomized results from panels of 20 subjects will result in the same SPF mean value. These data are attached as Appendix 2. Therefore, we recommend that FDA consider also adopting SPF panels of “at least ten” subjects, while retaining the current statistical treatment of the data. This change would be a major step towards international harmonization of SPF methods, while maintaining data quality. While there is a calculation of the confidence interval based on the 20 subjects for labeling purposes (Mean -A) in the FDA method, in the International test method there is a statistical criterion for validating the mean value obtained on at least 10 subjects. In the International method the 95% confidence interval should be no more than 17% of the mean, otherwise the number of subjects is increased until the criterion is fulfilled, but with no more than 20 subjects.

The Agency has asked for comments on newer forms of sunscreens not available during the time of the original Advisory Panel. When testing for SPF, the key requirement is that every product (regardless of form) is delivered to the test site by weight, and then spread over the test site evenly, regardless of the product form. This application by weight (2 mg/cm²) enables all products to be compared based on the same standardized methodology. We believe that all sunscreen product forms should be tested by existing standard methods that require application to the test site at 2 mg/cm². We are not aware of any product type that cannot be tested by the existing FDA methods.

2. SPF Is Not Solely “UVB”: SPF is an indicator of combined UVA/UVB effectiveness against sunburn

The action spectrum for sunburning ultraviolet radiation extends from the UVB well into the UVA.³ Figure 1 below clearly shows the contribution to sunburn in human skin from UVA (320-400 nm) as well as UVB (290-320 nm). Sunburn produced by solar radiation is a biological response to the UVA and UVB radiation received by the skin concomitantly.⁴ To achieve SPFs of above 12, both UVB and UVA protection must

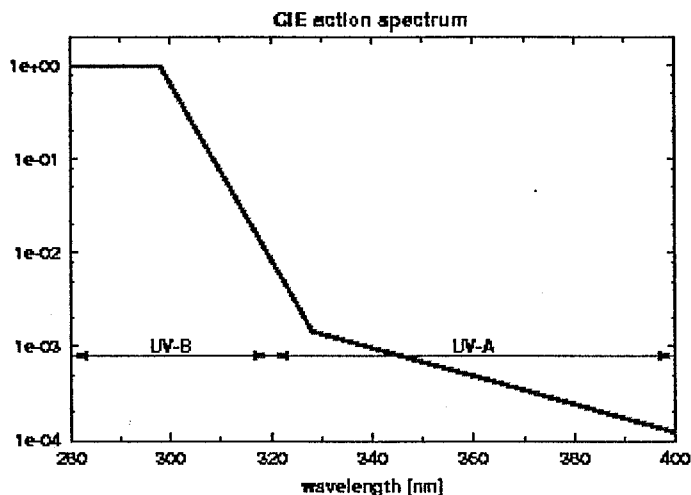
² International Sun Protection Factor Test Method, Colipa, 2005.

³ McKinlay AF, Diffey BL. A reference action spectrum for ultra-violet induced erythema in human skin. In: Human Exposure to Ultraviolet Radiation: Risks and Regulations. WF Passchier and BFM Bosnjakovic, eds. Elsevier Science Publishers, 1987, pp. 83-87; Parrish JA, Jaenicke KF, Anderson RR. Erythema and melanogenesis action spectra of normal human skin. Photochem Photobiol 1982;36: 187-191.

⁴ Urbach F. Ultraviolet A transmission by modern sunscreens: is there a real risk? Photodermatol Photoimmunol Photomed 1992/1993;9:237-241; Sunscreen Drug Products for Over-the-Counter Human Use. Federal Register 43: No. 166, August 25, 1978:38206-38269; Shaath N. Encyclopedia of UV absorbers for sunscreen products. Cosmetics and Toiletries (continued...)

be included in a sunscreen product to inhibit the sunburn response caused by UVA.⁵ A product with a single UVB sunscreen active ingredient will rarely have an SPF above 8-10 because of its failure to provide the necessary UVA spectrum protection required to block the full range of the sunburn response.⁶ The SPF, therefore, cannot be solely described as “UVB”. To do so is both scientifically inaccurate and misleading.

Figure 1: CIE Action Spectrum⁷



While the skin's sunburn response is caused approximately 80% by UVB, the 20% contributed by UVA is significant and cannot be overlooked or discounted in order to make SPF “simple”. When we are out in the sun, we are exposed to UVA and UVB together. Urbach has elegantly explained the effect of wearing a sunscreen on the transmission of UV energy to the skin in terms of the erythral action spectrum and the

1987;102:21-39; Sayre RM, Agin PP. A method for the determination of UVA protection for normal skin. *J Am Acad Dermatol* 1990;23:429-440.

⁵ Cole CA, Van Fossen R. Testing UVA Protective Agents in Man. In: Urbach F, ed., *Proceedings of the Second International Conference on the Biological Effects of UVA Radiation*, June 1991. Valdenmar Publishing Co., Overland Park KS, 1992, pp 335-345; Cole C. Multicenter evaluation of sunscreen UVA protectiveness with the protection factor test method. *J Am Acad Dermatol*. 1994 May; 30(5 Pt 1):729-36.

⁶ Agin, PP. UVA protection percent: a versatile method for determining the UVA efficacy of sunscreens. In: Urbach F, ed., *Proceedings of the Second International Conference on the Biological Effects of UVA Radiation*, June 1991. Valdenmar Publishing Co., Overland Park KS, 1992, pp 347-362.

⁷ The CIE action spectrum is a model for the susceptibility of skin to sunburn (reddening of the skin; erythema). Proposed by McKinlay & Diffey (1987), it was adopted as a standard by the Commission Internationale de l'Eclairage (CIE). CIE (International Commission on Illumination) Research Note 1987, A reference action spectrum for ultraviolet induced erythema in human skin, *CIE J.* 6, pp. 1722.

skin cancer action spectrum, and in terms of the potential UVA and UVB contribution to these biological effects.⁸

The contributions to efficacy from the combined active ingredients utilized in higher SPF products form the basis for the products' overall effectiveness against sunburn, which is expressed as the SPF, and which can be expressed as the percentage of the burning UVA and UVB energy blocked by the product. To prevent sunburn, sunscreen products higher than about an SPF 10 must provide UVA sunburn protection in order to be effective.

While the specifications for solar simulators in the 1978 OTC Sunscreen Monograph; Advanced Notice of Proposed Rulemaking only described the required content of UVB radiation, xenon arc solar simulators filtered as described in the monograph have always contained UVA radiation in addition to the UVB, simulating sunlight from 290 to 400 nm. 43 Fed. Reg. 38206 (August 25, 1978). In fact, these solar simulators, used since 1978, contain over 90% of their output in the UVA part of the total UV spectrum. This fact can easily be seen in the requirements for the waveband energy specifications shown below in Table 1, as now updated by the European Cosmetics, Toiletry and Perfumery Association (COLIPA) in the International Harmonized SPF Method,⁹ as well as in the solar simulator light source emission spectra published by Sayre.¹⁰ The updated solar simulator specifications (which FDA should adopt, as discussed below) clearly show that the lamp used contains UVA as well as UVB energy. The UVA energy present in the solar simulator significantly contributes to the skin's sunburn response seen in the SPF test. The SPF (which measures sunburn protection from UV exposure) is therefore not solely a "UVB" designator, but describes the **overall sunburn protection** provided by the sunscreen product against UVA as well as UVB.

The SPF test provides a reliable method for evaluating a sunscreen product's performance against sunburn. 43 Fed. Reg. 38206 (August 25, 1978); 58 Fed. Reg. 28194 (May 12, 1993). The SPF determined against full spectrum solar ultraviolet as delivered by solar simulator measures the effectiveness of the sunscreen product against all wavelengths (UVA and UVB combined) which contribute to sunburn in one useful measurement. The SPF test itself provides the visible evidence on the skin of product efficacy against sunburn induced by UVB and UVA energy. While the term

⁸ Urbach F. Ultraviolet A transmission by modern sunscreens: is there a real risk? *Photodermatol Photoimmunol Photomed* 1992/1993;9:237-241.

⁹ International Sun Protection Factor Test Method, Colipa, 2005.

¹⁰ Sayre RM, Dowdy JC. Spectral Standardization of Sources Used for Sunscreen testing: 5 Years of Compliance. In: *Sunscreens, Regulations and Commercial Development*, Third editions. Edited by N.A. Shaath. Taylor and Gump Publishers, Boca Raton, FL, 2005. Pp. 843-851.

“Sunburn Protection Factor” is accurate, the sunburn response is undeniably not due to simply “UVB.”

In addition to the table of RCEE values below, the International SPF Test Method also includes the following requirement for the solar simulator’s UVA energy:

To ensure that appropriate amounts of UVA radiation are included in the spectrum of the solar simulator throughout the entire UVA range, the total radiometric proportion of the UVA II (320-340 nm) irradiance of the simulator must equal or exceed 20% of the total UV (290-400 nm) irradiance. Additionally, the UVA I region (340-400 nm) irradiance must equal or exceed 60% of the total UV irradiance.

Modifications were made to the % RCEE values reported in the 1993 proposed OTC Sunscreen Tentative Final Monograph and were incorporated into both the COLIPA Guidelines for SPF testing as well as the International Harmonized Sunscreen SPF Test Method. 58 Fed. Reg. 28194 (May 12, 1993). The purpose of these modifications was to narrow the allowed ranges of values to lower the potential impact of lamp variabilities on the outcome of the SPF test results between testing laboratories.

Table 1: Updated %RCEE acceptance limits for the UV solar simulator output¹¹

Spectral Range (nm)	Measured %RCEE	
	Lower limit	Upper limit
250-290		<0.1%
290-300	1.0	8.0
290-310	49.0	65.0
290-320	85.0	90.0
290-330	91.5	95.5
290-340	94.0	97.0
290-400	99.9	100.0

The International Harmonized SPF Method also includes specifications for the required amount of UVAII and UVAI that must be included in the lamp output spectrum to assure appropriate UVA radiation is provided to best simulate solar radiation quality. These UVA requirements are: UVAII \geq 20% of total UV radiation and UVAI radiation must be \geq 60% of the total UV.

¹¹ International Sun Protection Factor Test Method. Colipa, 2005.

In addition to the comments above, it is also clear that UVA alone can induce sunburn (erythema) in skin based on the light source and endpoint of the PFA (Protection Factor A) test method.¹² The Agency has commented in the Proposed Rule that the PFA UVA test results in erythema, similar to the SPF test. Yet the UV source is the same solar simulator as described above, filtered to contain only its UVA wavelengths. Therefore, the conclusion that UVA in sunlight is capable of inducing erythema (sunburn) can be supported by these as well as other peer review publications.¹³ Again, UVA as well as UVB induce and contribute to sunburn in human skin as part of the SPF test. Ascribing sunburn to UVB alone is scientifically inaccurate and misleading.

In summary, sunscreen's SPF value does not solely reflect the protection offered against UVB radiation. Instead, it provides information about the overall sunburn protection that the product provides against both UVA and UVB rays. See below for our comments regarding "UVB SPF" labeling.

3. Calibration of Solar Simulators: the required measurement and calibration schedule can be reduced to "at least annually"

We request that FDA return to the "at least annually" measurement schedule. According to Sayre, multiple solar simulators in use at six SPF testing laboratories were studied over a period of 5 years.¹⁴ Sayre concluded that the devices were not only compliant with both FDA and COLIPA specifications over that time, but also that they "changed very little" over that timeframe. His report showed that the solar simulator

¹² Cole CA, Van Fossen R. Testing UVA Protective Agents in Man. In: Urbach F, ed., Proceedings of the Second International Conference on the Biological Effects of UVA Radiation, June 1991. Valdenmar Publishing Co., Overland Park KS, 1992, pp 335-345; and Cole C. Multicenter evaluation of sunscreen UVA protectiveness with the protection factor test method. J Am Acad Dermatol. 1994 May;30(5 Pt 1):729-36.

¹³ McKinlay AF, Diffey BL. A reference action spectrum for ultra-violet induced erythema in human skin. In: Human Exposure to Ultraviolet Radiation: Risks and Regulations. WF Passchier and BFM Bosnjakovic, eds. Elsevier Science Publishers, 1987, pp. 83-87; Parrish JA, Jaenicke KF, Anderson RR. Erythema and melanogenesis action spectra of normal human skin. Photochem Photobiol 1982;36: 187-191; Urbach F. Ultraviolet A transmission by modern sunscreens: is there a real risk? Photodermatol Photoimmunol Photomed 1992/1993;9:237-241; Cole CA, Van Fossen R. Testing UVA Protective Agents in Man. In: Urbach F, ed., Proceedings of the Second International Conference on the Biological Effects of UVA Radiation, June 1991. Valdenmar Publishing Co., Overland Park KS, 1992, pp 335-345; and Cole C. Multicenter evaluation of sunscreen UVA protectiveness with the protection factor test method. J Am Acad Dermatol. 1994 May; 30 (5 Pt 1):729-36.

¹⁴ Sayre RM, Dowdy JC. Spectral Standardization of Sources Used for Sunscreen testing: 5 Years of Compliance. In: Sunscreens, Regulations and Commercial Development, Third editions. Edited by N.A. Shaath. Taylor and Gump Publishers, Boca Raton, FL, 2005. Pp. 843-851.

instruments were maintained to “a rather tight and reproducible solar profile over a period of years”. He concluded that “during this period, solar simulators with proper laboratory maintenance have met the standards and have continued to do so from year to year even when used daily.” Based on the data published by Sayre, and the high level of reproducibility of the spectral characteristics of the lamps over time, we believe that the required measurement and calibration schedule can be reduced to once yearly and when lamps or other key components are changed.

Note also that the solar simulator spectra shown in Table 42.1 of the Sayre reference include significant UVA energy over the 320-400 nm waveband. In fact, the vast majority of the energy in the solar simulator output lies in the UVA portion of the spectrum, as indicated by the International Harmonized SPF Test Method’s %RCEE acceptance limits and specifications that we recommend.

4. Updated Solar Simulator Energy Limits

We urge the Agency to adopt the updated solar simulator specifications that are now recognized globally, and that will support more harmonized outcomes of SPF testing internationally. These specifications are included in the proposed %RCEE values within the ISO SPF Test methodology being developed.

Table 1 above lists the updated International/Colipa %RCEE ranges for solar simulators used in SPF testing.¹⁵ These ranges have been expanded to now include a 290-300 nm waveband, and have also been updated to maintain tighter control on the energy limits for the remaining wavebands.

In addition to the RCEE ranges in, the International SPF Test Method also includes (as stated above) the following requirement for the solar simulator’s UVA energy:

To ensure that appropriate amounts of UVA radiation are included in the spectrum of the solar simulator throughout the entire UVA range, the total radiometric proportion of the UVA II (320-340 nm) irradiance of the simulator must equal or exceed 20% of the total UV (290-400 nm) irradiance. Additionally, the UVA I region (340-400 nm) irradiance must equal or exceed 60% of the total UV irradiance.

C. Applying Alternate Dosage Forms: use of sponge applicator, not finger cot

FDA has proposed requiring the application of all test products “by spreading a product using a finger cot [rather] than by spreading with a glass or plastic rod.” 72 FR

¹⁵

International Sun Protection Factor Test Method, Colipa, 2005.

49070 at 49101. We request that this requirement be amended to include the application of powder products using a sponge applicator.

For powder products, a sponge applicator is preferable to a finger cot for even application to the test site. An example of a sponge applicator available from a scientific supply source is the "Fisherbrand® Non-Sterile Swabs, Foam Tipped/5" Polypropylene Handle, Cat. No. 14-960-3L". Numerous similar sponge swabs are commercially available. Appendix 3.

To compare the effectiveness in producing an even distribution of a powder test product on the test site, two powder products were spread by use of a finger cot and also with a sponge applicator. A technician trained in the application of sunscreen products performed the applications. The attached photographs clearly show the superior evenness of application using a sponge applicator [labeled as SP in the photo] *versus* a finger cot [labeled as FC in the photos]. Appendix 4. Using a sponge applicator also replicates consumer use. We note that many powder cosmetics are packaged with a sponge applicator.

D. Test Subsite: use of multiport style of solar simulators

The test subsite discussion in the Proposed Rule only considers the use of singleport type solar simulators (for example, as manufactured by Solar Light Company, Inc.). FDA has proposed increasing the labeling of specific SPF values to 50 and has revised the collective term to "50+." While singleport solar simulators are used successfully for high SPF testing, there are concerns about the increased burden on the test subjects spending long hours in the laboratory to complete the necessary testing.

To shorten the test duration, it is possible to also use a multiport solar simulator. In addition, the multiport simulator (equipped with liquid light guides) is suitable for accommodating different dosage forms. For example, powder specimens can be applied easily to test sites on test subjects lying face down, which is the posture used for many measurements made with multiport simulators.

For the reasons explained above, we suggest including the use of multiport solar simulators in the proposed testing method outlined by FDA. To allow this, the following specifications for multiport simulators should be included: test subsite areas of 0.5cm² separated by 0.8cm.

Therefore, 21 C.F.R. 352.70 (G)(c)(4)(ii) *Test subsite* should read as:

Test subsites are the locations to which ultraviolet radiation is administered within a test site. At least 5 test subsites will receive UV doses within each test site. Test subsites will be at least 0.5 square centimeter (cm²) in area and will be separated from each other by at least 0.8 cm. Mark the location of each test subsite with indelible ink.

E. Presaturated Finger Cot

FDA is proposing to revise the application requirement in 21 C.F.R. 352.72(e) (proposed section 352.70(c)(5)) to read: "Pretreat the finger cot by saturating with the sunscreen and then wiping off material before application." *Id.* Application by weight has been standardized since 1978 and an added requirement of an unspecified "saturation" amount is unnecessary and would introduce an unwelcome variability in the amount (by weight) of the application. We request that FDA eliminate the proposed presaturation finger cot requirement.

An unspecified amount of "saturation" would introduce variability in the amount of material applied which is specified as application by weight, at 2 mg/cm². We submit the following information and data in Appendix 5 to demonstrate the lack of significance of the residual amount left on the finger cot after product application (with no pre-treatment):

- eleven members of the Harrison Research Laboratory technical staff, trained in the application of sunscreen products, weighed finger cots prior to use for application of various sunscreen products. One hundred finger cots were used, and no technician supplied more than 10. All weights are in grams.
- the weights of the residual on the finger cots varied from 0.0 to 0.041 g; the mean difference is 0.01043 g; the mode difference is 0.006 g, and the mode percent difference is 2.13%. To elucidate the significance of the residual material on the finger cot, a one-sample-summary statistical test was performed (Difference of the Mean over the Standard Error, Pre- and Post-Application).
- the data were examined to elucidate the effect of the "outlier" application (#40); the scoring of post-irradiation MED was not negatively affected, and the score attained for this application is within the Modal value achieved by the test material.

Because the application by weight has been standardized since 1978, and because a requirement of an unspecified "saturation" amount would introduce an unwelcome variability in the amount, by weight, of the application, we respectfully request that this requirement be eliminated as unnecessary.

II. **UVA**

We acknowledge FDA for addressing UVA testing and labeling in the Proposed Rule, given the significant public health benefits that sunscreens with UVA protection provide and the importance of communicating that benefit to consumers. As the national trade association representing the personal care products industry, we believe it is important for us to provide comprehensive and meaningful comments regarding UVA testing and labeling. To that end, the Council submits information on aspects of UVA (mainly UVA water resistant testing) that reflect our overall membership position

(i.e., “Harmonized Industry UVA Position” in Section II A). Additionally, and because our members hold two differing positions with respect to the Agency’s proposed UVA testing and labeling, we have included both industry positions within this comment (i.e., “Industry UVA Position A” in Section II B and “Industry UVA Position B” in Section II C).

A. Harmonized Industry UVA Position

1. Sunscreen UVAPF Testing: number of subjects to produce valid data should be “at least 10.”

The JCIA Test Method¹⁶ and the Afssaps modified JCIA protocol¹⁷ recommended by the European Commission in Europe for UVA protection assessment require panels of “at least ten” subjects for valid UVAPF results, along with a statistical control.¹⁸ Inter-laboratory studies have shown that reproducible results can be obtained between laboratories using at least 10 subjects.¹⁹ In the interest of harmonization, the Council is providing UVAPF testing results from different formulations demonstrating the sufficiency and reproducibility of results from a panel of 10 subjects when using the JCIA methodology. The statistical criteria used show a low variability on 10 subjects without a need to increase the number of subjects. Comparisons between laboratories for the same products also demonstrate good reproducibility of results with a panel of 10 subjects.²⁰

Therefore, since the FDA’s proposed *in vivo* UVA methodology parallels the JCIA methodology, we recommend that the FDA adopt the similar language and requirement of “at least ten” subjects for UVAPF panels and to add a statistical criteria as used in the JCIA method to ensure a sufficient number of subjects to obtain relevant results. According to JCIA “with respect to variation, it was decided that the mean UVAPF value

¹⁶ Japan Cosmetic Industry Association (JCIA) Technical Bulletin. Measurement standards for UVA protection efficacy. Issued November 21, 1995 and effective as from January 1 1996.

¹⁷ Agence Française de sécurité sanitaire des produits de santé (Afssaps) Determination of the UVA protection factor based on the principles recommended by the JCIA. January 13, 2006.

¹⁸ European Commission Recommendation on the efficacy of sunscreen products and the claims made relating thereto. *OJL* 265/39, (26.9.2006).

¹⁹ Moyal D, Wichrowski K, Tricaud C. *In vivo* persistent pigment darkening method: a demonstration of the reproducibility of the UVA protection factors results at several testing laboratories. *Photodermatol Photoimmunol Photomed*; 22; 124-128 (2006); and Moyal D, Pissavini M, Boyer F, Perier V, JH Frêlon. *In vivo* Persistent Pigment Darkening method: proposal of a new standard product for UVA protection factor determination. *Intern J of Cosm Sci*, 29,443-449,2007.

²⁰ Moyal D, Wichrowski K, Tricaud C. *In vivo* persistent pigment darkening method: a demonstration of the reproducibility of the UVA protection factors results at several testing laboratories. *Photodermatol Photoimmunol Photomed*; 22; 124-128 (2006).

is valid if the Standard error (SE) is kept within 10% of the measured UVAPF value. If however the SE exceeds 10% the number of subjects shall be supplemented so that the SE falls within 10% and a highly reliable UVAPF may be determined". This change would be a major step towards international harmonization of PPD UVAPF method.

2. Subjects Skin Types: adopt skin type IV in addition to skin types II and III

The FDA requires selection of subjects with skin type II or III for UVA *in vivo* testing procedure. The JCIA Measurement standards for UVA protection efficacy allows inclusion of subjects belonging to skin types II, III or IV.²¹ These skin types are described in 12 C.F.R. 352.72. According to the JCIA standards (**Annotation 1) Selection of Subjects**, no significant differences were found between PFA values of standard sample obtained from skin types II, III and IV. Therefore skin types II, III and IV have been stipulated. All reported data indicate that skin types II to IV yield equivalent protection factors.²² Therefore, we recommend that FDA consider adopting skin type IV in addition to skin types II and III for UVAPF panels. This change would be a step towards international harmonization of PPD UVAPF method.

3. Standard sunscreen: harmonize with JCIA Test Method and Afssaps modified JCIA protocol

The control product used in the JCIA Test Method²³ and the Afssaps modified JCIA protocol²⁴ is different from the FDA control proposal. The JCIA control product has been used for UVA test method since 1996 and contributed to the implementation of the UVA testing method by helping produce reliable and reproducible results.²⁵

²¹ Japan Cosmetic Industry Association (JCIA) Technical Bulletin. Measurement standards for UVA protection efficacy. Issued November 21, 1995 and effective as from January 1 1996.

²² Moyal D, Wichrowski K, Tricaud C. *In vivo* persistent pigment darkening method: a demonstration of the reproducibility of the UVA protection factors results at several testing laboratories. *Photodermatol Photoimmunol Photomed*; 22; 124-128 (2006); Stanfield JW, Edmonds SH, Agin P. An evaluation of methods for measuring sunscreen Ultraviolet A protection factors. In *Sunscreens Development, Evaluation, and Regulatory aspects*. NJ Lowe, NA Shaath, MA Pathak Eds, Marcel Dekker, 537-558, 1997; and Cole C. Sunscreen protection in the ultraviolet A region: how to measure the effectiveness. *Photodermatol Photoimmunol Photomed*; 17; 2-10 (2001).

²³ Japan Cosmetic Industry Association (JCIA) Technical Bulletin. Measurement standards for UVA protection efficacy. Issued November 21, 1995 and effective as from January 1, 1996.

²⁴ Agence Française de sécurité sanitaire des produits de santé (Afssaps) Determination of the UVA protection factor based on the principles recommended by the JCIA. January 13, 2006.

²⁵ Moyal D, Wichrowski K, Tricaud C. *In vivo* persistent pigment darkening method: a demonstration of the reproducibility of the UVA protection factors results at several testing (continued...)

This UVA control product ("JCIA Standard") contains 3% ethylhexylcinnamate (USAN name "octinoxate") and 5% avobenzone. The complete quantified formulation and manufacturing instructions are enclosed in the reference below published by the JCIA.²⁶ While it is understood that the current Sunscreen Final Monograph (1999) specifies that the maximum allowed concentration of avobenzone is 3%, the use of this formulation as an alternate laboratory control reference material should be considered for the purposes of validating laboratory test procedures.

Testing of this control formulation in a 7 laboratory ring test has established that the UVA protection factor provided is 4.2 with a standard deviation of 0.2.²⁷ These were within the expected value as published by the JCIA of 3.75 with standard deviation of 1.01.²⁸

Considering the historical background and validation available on this formula and its use as an internationally recognized reference/control material, we feel it is important to have this control available as an alternate to the UVA control formula proposed by the FDA to be used for products that are to be marketed in international markets. We strongly urge the Agency to adopt this reference formulation as an additional option for use as a control product to validate *in vivo* UVA testing.

4. Water Resistant UVA testing: because the SPF on the label is the "post-water" protection measurement of combined UVA/UVB sunburn protection, water resistant UVA testing is unnecessary

We are concerned that the proposed *in vivo* method for performing Water Resistant or Very Water Resistant UVA Protection (PPD) testing has not been validated or published in any clinical trials to our knowledge. In particular, the influence of water immersion on the PPD skin response is unknown. Furthermore, in discussing this possible testing requirement with several leading testing laboratories, it has been revealed that for a high SPF/high UVA protection sunscreen product, conducting such a test could take more hours than the laboratory is open for business each day (e.g., in

laboratories. *Photodermatol Photoimmunol Photomed*; 22; 124-128 (2006); and Moyal D, Pissavini M, Boyer F, Perier V, JH Frêlon. *In vivo* Persistent Pigment Darkening method: proposal of a new standard product for UVA protection factor determination. *Intern J of Cosm Sci*, 29,443-449,2007.

²⁶ Japan Cosmetic Industry Association (JCIA) Technical Bulletin. Measurement standards for UVA protection efficacy. Issued November 21, 1995 and effective as from January 1, 1996.

²⁷ Moyal D, Wichrowski K, Tricaud C. *In vivo* persistent pigment darkening method: a demonstration of the reproducibility of the UVA protection factors results at several testing laboratories. *Photodermatol Photoimmunol Photomed*; 22; 124-128 (2006)..

²⁸ Japan Cosmetic Industry Association (JCIA) Technical Bulletin. Measurement standards for UVA protection efficacy. Issued November 21, 1995 and effective as from January 1, 1996.

excess of 12 hours). Moreover, the proposed test would be exceedingly arduous and exhausting for test subjects. We propose to the Agency that UVA water resistance testing would not only be overly demanding for subjects, but also that it is not necessary to assess UVA water resistance performance as part of the Agency's labeling plan.

For water resistant or very water resistant sunscreen products, sunscreen formulations are specifically designed to keep the suncreening ingredients on the surface of the skin as a substantive film. The film-forming ingredients used to make a product water resistant or very water resistant and substantive to skin keep the UVA as well as the UVB absorbers on the skin.

We have conducted experiments by *in vitro* methods illustrating that both the UVA and UVB absorbance are retained post-water exposure for formulations designed to resist removal by water. Appendix 6. These formulations are composed of a variety of UVA and UVB sunscreen active ingredients commonly used in sunscreen products sold in the U.S. In these figures, we show that after 80 minutes of water exposure on Vitro-Skin® (a skin equivalent, IMS Inc.), both the UVA and UVB sunscreen absorbance for SPF 15, 30 and 50 sunscreen formulas are still present in formulations that have been specifically designed to be "very water resistant". It is our conclusion that the UVA protection does not preferentially wash off from a "very water resistant" sunscreen product. Because the SPF on the label is the "post-water" protection measurement of combined UVA/UVB sunburn protection, there is no need to also conduct a clinical substantivity test for UVA protection alone. While some water resistant or very water resistant sunscreen formulations could experience some loss of absorbance from the skin after water exposure, the loss is still accounted for as part of the water resistant or very water resistant SPF measurement.

Water Resistant or Very Water Resistant SPF methods already account for the performance of the UVA as well as the UVB sunscreens in the formulation. The UVA protection is not preferentially lost after 80 minutes of water exposure.

In addition, the proposed new directions for sunscreen product use will instruct the user of a water resistant or very water resistant sunscreen product to reapply the product after 40 or 80 minutes of water exposure, or at least every two hours. Because the product will be reapplied, the UVA protection as well as the SPF will be renewed frequently, thus further obviating the need for separate water resistance UVA testing.

B. Industry UVA Position A²⁹

The Council's member companies that support Industry UVA Position A (UVA Group A) have reviewed the proposed UVA testing method and labeling scheme. After

²⁹ Council member companies that support Industry UVA Position A include the following [in alphabetical order]: Avon; Beauty Avenues; Estee Lauder; Johnson & Johnson; L'Oreal USA; Mary Kay; Revlon; Schering-Plough; and Shiseido.

conducting several evaluations, UVA Group A is opposed to the *in vitro* test methodology proposed by the FDA. There are numerous reasons why it feels that the proposed *in vitro* test methodology is inappropriate, and contrary to the primary purpose of providing meaningful UVA protection to consumers as stated below. This group proposes to substitute the Critical Wavelength computation as the substitute analysis of *in vitro* UVA absorbance spectrophotometric data.

1. *The UVAI/UV proportionality test method assumes that UVAI radiation is of equal biological consequence to UVB and UVAIL radiation. The proposed UVAI/UV computation forces manufacturers to design "flat" spectrum filters to achieve higher UVA ratings at the cost of lowered UVB protection at equivalent SPF values.*

If manufacturers wish to have high/highest UVAI ratings on their products at a given SPF level, the UVB and UVAIL levels **must be lowered** in order to achieve the desired "flatness" mandated by the UVAI/UV proportionality test. In fact, to achieve the "highest" UVA level, the absorbance spectrum must be deliberately skewed to weight the longest UVA I wavelengths. Action spectrum studies for human non-melanoma³⁰ and murine³¹ skin cancer, malignant melanoma³², elastin damage³³, and immune suppression³⁴ all indicate that the majority of chronic damage is primarily mediated through the shorter wavelengths of the UVB, and UVAIL, but not UVAI. The test method ignores the significant contribution of UVAIL protection provided in products, which provides a constituent part of overall UVA protection. Based on the published action spectra

³⁰ CIE 138/2 Action spectrum for photocarcinogenesis (non-melanoma skin cancer) CIE Central Bureau, Kegelgasse 27, A-1030 Vienna, Austria.

³¹ De Gruijl F., Henricus J., Sterenborg C.M., Forbes P., Davies R., Cole C., Kelfkens G., van Weelden H., Slaper H., van der Leun J. (1993) The wavelength dependence of skin cancer induction by ultraviolet irradiation of albino hairless mice. *Cancer Research*, 53:53-60; and Kelfkens G., de Gruijl FR, van der Leun, JC. Tumorigenesis by shortwave ultraviolet A: papillomas versus squamous cell carcinomas. *Carcinogenesis*, 12:8. 1377-1382, 1991.

³² Kligman L.H., Sayre R.M., An action spectrum for ultraviolet induced elastosis in hairless mice: Quantification of elastosis by image analysis. *Photochem. Photobiol.* 52:2, pp237-242, 1991.

³³ DeFabo EC, Noonan FP, Fears, T, Merling G. Ultraviolet B but not Ultraviolet A radiation initiates melanoma. *Cancer Research* 64:18, 6372,6376, 2004.

³⁴ Nghiem DX, Kazimi N, Clydesdale G, Ananthaswamy HN, Kripke, MK, Ullrich SE. Ultraviolet A suppresses an established immune response: Implications for sunscreen design. *J. Invest. Dermatol.* 117:1193-1199, 2001; and Longstreth JD, de Gruijl F.R., Kripke M.L. Takizawa Y. van der Leun J.C. Effects of increased solar ultraviolet radiation on human health. Environmental Effects of Ozone Depletion: 1994 Assessment. <http://sedac.ciesin.org/ozone/UNEP/chap2.html#imm>; www.ciesin.org/docs/001-535c/001-535c.html

data, the UVA II wavelengths are clearly the more damaging portion of the UVA spectrum. By requiring a flat or UVAI-skewed spectrum with the UVAI/UV proportionality test to reach the “best” UVA ratings, we are forced to diminish the protection in the part of the spectrum most documented to be responsible for chronic and pathologic damage. Because this is inappropriate, we ask that a different evaluation computation be considered to insure appropriate protection across the UVA spectrum to accurately qualify UVA ratings for products while being able to maintain critical UVB and UVAll protection for the consumer.

2. *The proposed in vitro UVAI/UV proportionality test method has not been validated and contains several technical elements that are inappropriate for accurate measurement.*

Substrate: The proposed test method stipulates the use of “roughened quartz plates” without further definition of the quality or level or roughness applied to these plates. Most industry sunscreen manufacturers have not included use of quartz plates in currently available methods due to lack of standardization. When used in Australia as an optional part of the testing requirements there, quartz plates are purchased and are roughened by “hand” with carborundum to achieve a “roughened” surface. There is no standardized roughness achieved, and plates must be “re-roughened” after multiple uses. Additionally, there is no specification for the roughness of the quartz plates and literature reveals that the roughness of the plates can play a significant role in the outcome of the testing.³⁵ Standardization and validation of a specific roughness parameter is needed for product testing substrates.

More recently disposable polymethylmethacrylate plates (PMMA) that are purchased with a roughened surface have been used extensively in Europe and more recently in the U.S. with notable success. Disposability of the substrate is particularly meaningful and guarantees that there is no residual sunscreen from previous testing. Data is provided in attachment using roughened PMMA plates showing their utility in *in vitro* testing for Critical Wavelength assessments. Appendix 7.

Application quantity: The proposed test method stipulates the use of 2 mg/cm² of the sunscreen product on the test substrate for spectroscopic examination. While this quantity correlates directly with the application dose used on human skin, the amount is excessive for all but the most sophisticated and sensitive spectrophotometric instruments that are capable of measuring optical density in excess of 3 – 4 absorbance units (AU). Spectrophotometric equipment utilized by the majority of industry manufacturers have a maximum range of 2 – 2.2 AU.

³⁵ Ferrero L., Pissavini M., Dehais A., Margueire S., Zastrow L. Importance of Substrate Roughness for *In Vitro* Sun Protection Assessment. *IFSCC Magazine*, 9:2, 2-13, April/June, 2006.

When excessive quantities of sunscreen product are measured with this equipment, the instruments will “flat-top” and underestimate the higher absorbance bands of the product, typically in the UVB portion of the spectrum where absorbance is highest. The result is to overestimate the amount of the UVA protection provided relative to the UVB and UVAII portions of the spectrum. This directly affects the accuracy of the proposed UVAI/UV proportionality test, as well as every other computation devised for product evaluation. If measurements are not contained within the validated linearity range of the spectrophotometer, the results are simply invalid.

Previous testing with 2.0 mg/cm^2 in a round robin test conducted by the Council resulted in overestimation of the UVA protection of the 7 test products by a factor of 2 because the spectrophotometric instruments used in the test were measuring beyond the linearity limits of the instruments. Appendix 7.

Alternatively, industry has determined that use of lower quantities, on the order of 0.75 to 1.0 mg/cm^2 results in absorbance values within the linearity range of most laboratory spectrophotometers and provides a valid measure of the proportional absorbance of the sunscreen products across the spectrum. Ring tests conducted both in Europe and by the Council in the U.S. have shown that results from testing with application doses within this range, combined with scalar adjustment of the spectral absorbance curve determined by the product SPF value, yield direct correlation with *in vivo* UVA PPD test results, validating the appropriate spectral distribution measurement derived from the lower application density. Thus, there is no need to use the same amount as is used in human SPF testing, as the outcome is based strictly on the inherent shape of the absorbance spectrum obtained.

Requiring special, highly expensive spectrophotometric equipment in order to measure the absorbance of products at the prescribed 2.0 mg/cm^2 level is both unnecessary and burdensome, when alternate application density has been shown to be adequate and less error-prone. Methods for qualifying spectrophotometer ranges are included in the COLIPA and Council submissions for alternate *in vitro* testing methodology. Appendix 7.

Pre-irradiation dose: With a lower application amount, a lower UV exposure dose should also be used. A reduced application quantity, which greatly reduces the film thickness, allows more ‘exposure’ of the filters in the products to UV, magnifying any photo-instability characteristics. The Agency’s suggested pre-irradiation for 2 mg/cm^2 application (with a dose of UV energy in MEDs that equal $2/3$ the products’ labeled SPF) requires extremely large doses of UV energy for high SPF products. For example, an SPF 50 would require a dose of 33.3 MEDs. If the flux of the light source is chosen so that it approximates solar flux, the length of time needed to deliver the pre-irradiation dose could require 8 hours or more of continuous UV exposure per sample. These pre-irradiation doses are excessive, and expose samples to greater UV exposure than most individuals would receive in one day, due to the changing solar UV flux throughout the day.

as the angle of the sun varies. We ask the Agency to modify the pre-irradiation conditions to a lower UV exposure dose more appropriate to a reduced application amount.

Variability: The proposed UVAI/UV proportionality test gives high variability for products with lower levels of UVA protection. Evaluations of products containing primarily UVAII and only minimal amounts of UVAI protection results in a highly variable value for the UVAI/UV proportion as repeated runs yield variability in the “tail” portion of the absorbance curve. A test with one product with minimal UVAI protection yielded a variability of over 40% because the amount of measured UVAI was essentially in the “noise” portion of the spectral measurement. We feel that this is a serious flaw in the proposed methodology.

The UVAI/UV ratio index is more variable than Critical Wavelength and more operator dependent.

The UVAI/UV ratio and the Critical Wavelength λ_c are relative absorbance indices. Relative absorbance indices are expected to be very robust. However, it has been observed by Ferrero et al.³⁶ that the ratio UVA/UVB also known as Boots ratio can vary from 0.54 to 0.62 depending on the roughness of the plates (for the same amount of sunscreen product applied (1mg/cm² and with the roughness varying from 1.88 to 6.76 μ m) whereas Critical Wavelength only varies from 375 to 377 nm under the same conditions. These authors have concluded that the lowest variation (4%) is obtained with the Critical Wavelength endpoint and higher variability (13%) is obtained when a ratio of absorbance is calculated.

In addition, work done by the German Society of Cosmetic Chemists (DGK) in their comments to the Proposed Rule have confirmed that the Critical Wavelength method is less sensitive to the measurements conditions compared to the UVAI/UV ratio. The DGK has studied the influence of the pressure (strong versus low) for the application of the product on quartz plate. As shown in Table 2 below, the mean Critical Wavelength values obtained within the laboratories in the two conditions of application are close (375 versus 376 nm) and the extreme values are 374 nm and 377.2 nm with only a difference of 3 wavelength units. However, for the UVAI/UV ratio the mean values obtained are 0.78 and 0.83 and the extreme values 0.75 and 0.85. This again demonstrates that the ratio of absorbance is an index more variable than the Critical Wavelength index and that the Critical Wavelength measurement is a more repeatable and reliable measure of the breadth of sunscreen protection in the UVA.

³⁶ Ferrero L., Pissavini M., Dehais A., Margueire S., Zastrow L. Importance of Substrate Roughness for *In Vitro* Sun Protection Assessment. *IFSCC Magazine*, 9:2, 2-13, April/June, 2006.

Table 2: Critical Wavelength Values Obtained Within Laboratories

	UVAI/UV ratio	UVAI/UV ratio	Critical Wavelength	Critical Wavelength
Lab	Application with strong pressure	Application with low pressure	Application with strong pressure	Application with low pressure
A	0.78	0.82	375.4	376.6
B	0.78	0.85	375	375.4
C	0.79	0.84	376	377.2
D	0.76	0.82	374	377
E	0.8	0.84	376	376
F	0.8	0.85	376	376
G	0.75	0.78	373.8	374.8
Mean	0.78	0.83	375.2	376.1

Measurement instrumentation and light source: 21C.F.R. 352.71a. specifies the use of a solar simulator similar to the source used for clinical SPF testing for evaluating absorbance properties of the sunscreen products *in vitro*. This source would however be inappropriate for measurement of spectral absorbance as the energy output of this source is very low in the region below 300nm. For determining *in vitro* absorbance value, the light source should be full spectrum with no filtration to maximize instrument transmission properties with full sensitivity. Industry utilizes spectrophotometric instruments for absorbance/transmission measurements of sunscreen products and incorporates UV lamps appropriate for these measurements. The spectrophotometers contain spectral dispersion elements appropriate for wavelength discrimination. A separate specification for the light source for absorbance/transmission properties is unnecessary.

Light source for sample irradiation: We would propose that the light source used for exposure of the sunscreen samples be the same as that used for clinical testing as specified in 21 C.F.R. 351.7(b) as well as other sources that comply with the lamp specifications for the UV portion of the lamp output.

Number of measurements needed: The industry-proposed Critical Wavelength methodology yields a very low level of variance in the assessed Critical Wavelength value as evident in the multi-center ring testing. Appendix 7. Given the high repeatability and low variance within and between test laboratories, we recommend that n=5 plates is sufficient to establish the Critical Wavelength value for a sunscreen product.

3. *The proposed UVAI/UV in vitro test methodology and computation analysis would be unique and would not be in harmonization with internationally recognized in vitro testing parameters.*

The European Commission has recommended utilization of the *in vivo* PPD test method for determination of the magnitude of the UVA protection, and the Critical Wavelength³⁷ *in vitro* computation for determination of the breadth of the UVA protection. The Critical Wavelength *in vitro* methodology and computation has been recommended by industry (previous Council filings with the sunscreen docket), the Skin Cancer Foundation (SCF), as well as the American Academy of Dermatology (AAD). While no test method is perfect, the Critical Wavelength evaluation and computation method provides assurance that UVA protection across the spectrum and can provide graduated efficacy assessments according to the breadth of UVA spectrum.

To add yet another and different and un-validated testing method and computation analysis to the already disparate field of *in vitro* UVA test methods, labeling schemes and criteria will simply add additional confusion to consumers.

4. *The proposed success criteria for the in vitro UVAI/UV proportions are arbitrary, and disproportionate with the in vivo PPD ratings. In fact, it is virtually impossible to achieve the 0.95 **** rating for the in vitro test method for all but the lowest SPF protection products.*

In order to achieve the 0.95 UVAI/UV proportionality rating, it is mathematically impossible to achieve that rating unless a product provides protection in the 380-400nm range. Only one of the U.S. monographed filters absorbs above 380nm, large particle size titanium dioxide (TiO₂). However, in this range the protection provided by TiO₂ is minimal in comparison to the other monographed UVB, UVAII, and other UVAI filters, and the use of high quantities of TiO₂ in products is undesirable as it makes products highly visible with poor aesthetic qualities. In addition, combinations of TiO₂ and avobenzone are prohibited in U.S. formulations, so this combination cannot be used.

In a survey amongst U.S. products as well as many European products, there have been no products identified that can meet this arbitrary 0.95 ratio proposed by the FDA for UVAI/UV proportionality. Given the limited palate of filters and combinations of filters available for product formulation in the U.S., as well as a lack of filters capable of providing UVAI protection in the 380-400nm range on a global scale, we find it difficult to justify the setting of the "highest" UVA rating at this impossibly high level.

While it is desirable to have encouragement for innovation to meet this high standard, it is unreasonable to believe that this can be achieved in the foreseeable future due to the sheer nature of UV filter technology needed to do this. Filters have broad spectral absorption characteristics, and to provide

³⁷ Diffey BL, Tanner PR, Matts PJ, Nash JF, *In vitro* assessment of the broad-spectrum ultraviolet protection of sunscreen products. J. Am. Acad. Dermatol. 2000; 43: 1024-35.

protection in the 380-400nm range will result in absorbance that extends into the range above 400nm, resulting in “visible” sunscreen products, that are well known to be unacceptable to the vast majority of sunscreen users (make-up and foundation type products being a unique exception). As noted above, this will cause sunscreen products’ absorbance spectra to be tilted unnaturally toward the long UVA, where there is no known biological need for the overpowering protection mandated by this requirement, at the expense of the products’ UVB protection profile.

Because of the proposed requirement to label products with the lower of the two test results (*in vitro* and *in vivo*), the result is that products with exceptional UVAII and UVAI protection as measured *in vivo* using the PPD or PFA test methods (at levels of 12+ and even 20+) must be labeled as if they were only PPD 8 with *** ratings, because they fail to achieve the impossible 0.95 UVAI/UV rating for the *in vitro* test. The result is that the *in vivo* PPD results are “capped” for labeling at PPD 8, and there is no incentive for manufacturers to provide UVA protection at or above this level as the highest rating is not achievable. The consumer will be unable to distinguish products that provide the highest protection because of the inappropriate 0.95 proportionality hurdle set for the *in vitro* UVAI/UV test method. We believe this forces inappropriate labeling, mislabels the true UVA protection provided by the product and does a great disservice to the consumer seeking the best possible protection.

We strongly request that the Agency reconsider use of the proposed UVAI/UV *in vitro* test method and labeling scheme in order to protect the rights and health of the consumer who seeks to find and use the best-balanced protection products.

5. *As an alternate to the proposed UVAI/UV proportionality in vitro test, we request that the Agency reconsider the use of the Critical Wavelength computation with an alternate rating scale to achieve a more appropriate labeling scheme.*

The primary purpose of the *in vitro* test to be used in conjunction with the *in vivo* PPD test method is to assure breadth of protection across and deep into the UV1 spectrum. We feel that the Critical Wavelength computation adequately achieves these goals providing that assurance.

Critical Wavelength computation has been used within industry for over a decade, and has been shown to be highly reproducible within and between laboratories. In addition to published test results, we include in this submission a document containing inter-laboratory *in vitro* testing including computation and analysis of Critical wavelength for seven test products representing a wide range

of UVA filtering characteristics.³⁸ These results show high inter-laboratory correlation on the Critical Wavelength computation.

As mentioned before, the Critical Wavelength computation is also recognized and recommended by the European Commission for labeling of sunscreen products within the European Community. It has also been recognized and recommended for use by the AAD, and the SCF as an appropriate measure for the breadth of sunscreen protection.

COLIPA in conjunction with the Council has recently completed inter-laboratory testing on a new *in vitro* test method that provides for determination of an "absolute" UVA absorbance characterization. Appendix 7. This test method provides many additional technical specifications that are more appropriate for *in vitro* testing than those proposed by the Agency. The test results show a high level of correlation across the various testing laboratories, with only a small number of replicate determinations, as variability is remarkably low.

Critical specifications for Critical Wavelength *in vitro* test methodology:

- a. lower application density – 0.75 – 1.0 mg/cm² - this eliminates the possibility to "overload" the commercial spectrophotometers and keeps the measurement parameter within the validated linearity range of the instruments.
- b. use of disposable roughened PMMA plates - use of standardized disposable plates eliminates variability of roughness and any errors resulting from inadequate plate cleaning from "reusable" substrates. Acceptable roughness factors for PMMA plates is within the range of Sa = 2.0 to 5.0 um.
- c. A lower UV exposure dose (equivalent to 1.2 * projected PPD value in J/cm² UV). This dose of UV exposure evaluates and compensates the resulting absorbance curve for any photo-instability. This dose has been chosen based on correlation studies of multiple exposure doses and found to provide the closest correlation to *in vivo* PPD test results. The lower dose (compared with the Agencies' proposed UV exposure dose of $\frac{2}{3} * \text{SPF} * 2 \text{ J/cm}^2$) is appropriate as the application density is significantly lower than the 2.0 mg/cm² quantity proposed by the Agency. Using a thinner application quantity, which greatly reduces the film thickness, there is more 'exposure' of the filters in the products and any photo-instability characteristics are magnified.

³⁸ Diffey BL, Tanner PR, Matts PJ, Nash JF, *In vitro* assessment of the broad-spectrum ultraviolet protection of sunscreen products. J. Am. Acad. Dermatol. 2000; 43: 1024-35.

- d. A test to establish the linearity range of spectrophotometers is also supplied in Appendix 7. Standardized PMMA plates doped with absorbent filters are available for single and double thickness measurements to establish the absorbance levels at which spectrophotometers deviate from linear (accurate) absorbance readings. Readings above this deviation point in any part of the spectrum invalidate the accuracy of the measurement, and lower quantities of sunscreen must be used to determine the spectral absorbance characteristics of the sunscreen.
- e. The first step of the Critical Wavelength computation requires determination of the total area under the absorbance curve for each test sample. The area is then integrated from 290 nm to 400nm adding the absorbance value at each individual wavelength to the sum and dividing the sum by the total area under the absorbance curve. The wavelength at which 90% of the total UV absorbance area under the curve is reached represents the "Critical Wavelength" for the test sample.
- f. It is proposed to use Critical Wavelength values as determinants of the *in vitro* star ratings for the labeling of products. The following values are proposed for labeling purposes:

Critical Wavelength

<325 nm	No UVA protection
325 - <335	*
335 - <350	**
350 - <370	***
≥ 370	****

We propose that the lower of the Critical Wavelength rating and the *in vivo* PPD test rating be used to determine the UVA protection rating for labeling of products, similar to the Agency's proposal.

Table 3: UVA Group A Proposed Labeling³⁹

<i>In vitro</i> Critical Wavelength	Rating	<i>In vivo</i> PPD Test Result	Rating
< 325	no required labeling	< 2	no required labeling
325- < 335 nm	low	2 - < 4	low
335 - <350	medium	4 - < 8	medium
350 - < 370	high	8 - < 12	high
≥ 370	highest	≥12	highest

Perform both UVA tests and label with lower rating of the two results.

C. Industry Position B⁴⁰

The Council's member companies that support Industry UVA Position B (UVA Group B) support the FDA proposal for UVA testing and labeling as it is published in the Proposed Rule according to the table below:

Method		Label	
<i>In vivo</i> PPD	<i>In vitro</i> UVAI/UV	stars	Category
0-2	0 – 0.2		No UVA protection
2-4	0.2 – 0.39	★☆☆☆	Low
4-8	0.4 – 0.69	★★☆☆	Medium
8-12	0.7 – 0.95	★★★☆☆	High
> 12	> 0.95	★★★★★	Highest

Whereas we believe that international harmonization on UVA testing and labeling would provide significant benefits to the consumer, government, and industry, the unilateral UVA framework that FDA has proposed is a principles-based approach that is, at a minimum, unbiased and fair. As such, **we believe the Agency should adopt this without any delay or modification.**

³⁹ UVA Group A believes FDA should eliminate the UVA star rating system and instead only require category descriptors for UVA protection. See Section IV(C) below.

⁴⁰ Council member companies that support Industry UVA Position B include the following [in alphabetical order]: Ciba Specialty Chemicals; Procter & Gamble; and Unilever.

1. Background

The need for protection against solar ultraviolet (UV) radiation is well established. Whereas the Sun(burn) Protection Factor or SPF provides a measure of efficacy against short wavelengths of UV, there has been no standard of measure or communication of sunscreen product efficacy against long wavelength UV. The Proposed Rule addresses this need.

2. Support for FDA Proposal

In the absence of international harmonization, we support the UVA test method and labeling proposed by FDA. The FDA scheme employs compulsory *in-vitro* and *in-vivo* methods to establish a UVA efficacy rank. The lower result of the (two) compulsory tests determines the rank, which is then communicated to the consumer via a Product Category Descriptor (Low, Medium High, Highest) and corresponding stars (symbols). The UVA ranking is thus semi-independent of the SPF.

3. UVA Methodologies

We support the *in vivo* UVA Protection Factor (PF) determination as proposed by FDA. We acknowledge however, that this measure does not correspond or serve as a surrogate for any known biological damage attributed to chronic UVA exposure. As FDA indicates:

- “the PPD method could result in some products yielding high UVA radiation protection factors without having broad absorbance throughout the UVA radiation spectrum due to strong absorbance in the UVA II region.”

To this end, FDA comprehends the inherent shortcomings of current *in vivo* UVA-PF (PPD) testing, and, as such, *in vitro* testing is also needed for an appropriate measure of the effect of UVA radiation when applying a rank. The FDA proposed *in-vitro* method is based on thin layer substrate, spectrophotometric determination of sunscreen product absorbance.

Whereas we support the *in vitro* proposal, we recommend the FDA consider the following modifications:

- Use of roughened polymethylmethacrylate (PMMA) plates instead of quartz plates. PMMA plates are more readily available and are used in the Colipa thin layer substrate spectrophotometric method for *in vitro* PPD determination.⁴¹ In addition, PMMA plates are cheap and disposable ensuring no residual sunscreen product in the event of reusing the substrate.

⁴¹ Method for the *in vitro* determination of UVA protection by sunscreen products. <http://www.colipa.com/site/index.cfm?SID=15588&OBJ=28546&back=1>.

On the other hand, roughened quartz plates as stipulated by the Agency have several problems including (1) standardization for roughness and, after multiple uses, the plates must be “re-roughened”, and (2) sourcing of such plates which, at present, requires “roughening” be done by the purchaser of the plates. Most sunscreen manufacturers have not used quartz plates again due to lack of standardization.

- Use of a dose of 1.0 mg/cm² be used for the *in vitro* determination of absorbance of sunscreen products. The proposed application of 2.0 mg/cm² surpasses the dynamic range of many instruments especially for high protection factor products. That is, many of the currently available spectrophotometric instruments are not capable of measuring the absorbance units associated with a 2.0 mg/cm² dose of sunscreen product. The accuracy of the proposed UVAI/UV proportionality test, and any other *in vitro* UVA metric, is compromised if measurements are not contained within the linearity range of the spectrophotometer, which can occur if the dose used exceeds the capability of the equipment.

Alternatively, a dose of 0.75 mg/cm² has been proposed for the Colipa *in vitro* UVA test method⁴² based on several round-robin studies and would seem an appropriate dose for the current thin-layer substrate spectrophotometric method.

- Use a pre-irradiation exposure adjusted to the dose of product applied. At present, the pre-irradiation dose suggested by the Agency is impractical and excessive. For example, using a standard Suntest CPS+ light source, the pre-irradiation times for sunscreen products with SPF between 20 – 50 range from 4 – 11 hours, based on the FDA proposal (SPF x 200 J/m²-eff x 2/3). Such excessive exposures result in product drying out and unreliable measures.

We recommend the Agency use half of the dose, i.e., SPF x 100 J/m²-eff x 2/3, which accounts for lower dose of product applied to the substrate.

Alternatively, in Colipa *in vitro* UVA method, a lower UV exposure dose equivalent to 1.2 x projected PPD value in J/cm² has been shown to account for any photo-instability.³

In summary, the proposed method calculates a simple mathematical ratio of UV1 (340-400 nm) to Total absorbance, UVA + UVB, (290-400 nm). The ratio is then interpreted against a four-tier ranking model. We support this approach because the calculation is mathematically sound and is unbiased with regard to UVA-induced skin damage, for which the action spectrum has yet to be elucidated.

We acknowledge that this method, with the ratio and four-tier ranking model, will likely result in few products with four stars (the highest UVA protection), and, that

⁴² Method for the *in vitro* determination of UVA protection by sunscreen products.
<http://www.colipa.com/site/index.cfm?SID=15588&OBJ=28546&back=1>

effectively, for most products, that the *in-vitro* method will be the limiting method when assessing UVA protection. We accept these facts, over modifications to the proposed methodology that impinge on soundness. We also acknowledge and accept that the proposed method leaves room for innovation, whereby 'highest' levels of UVA protection can be obtained, as demonstrated by some currently-available international products.

Comments in support of UVAI/UV ratio

- The top category presented by FDA is attainable. The Agency acknowledges the challenge in obtaining the top category for both *in vivo* AND *in vitro* criteria. This would require a "flat" spectrum and relatively high absorbance for UVA II, e.g., PPD > 12, and UVA I, akin to clothing. Sunscreen products attaining a Boots 5-star rating (UVA/UVB > 0.95) in Europe are, in essence, a flat spectrum which is what the highest FDA *in vitro* category, 0.95 UVAI/UV, provides. Moreover, these currently marketed products in Europe are SPF up to 50. The limiting factor would be the *in vivo* UVA-PF, which would be the limiting category descriptor. Moreover, as noted by FDA, the argument that the top category is unattainable is not a reason to change it. The Agency has applied principles-based criteria and it may be challenging but the cosmetics industry is driven by innovation and this is simply another incentive to make better products. We believe that a suggestion to change FDA's proposed UVA calculation metric and 'highest' labeling criterion are attempts to build commercial bias into the process, rather than options for future innovation, and should be discounted.
- UVA I is damaging and consumers need to be protected. As the Agency rightly points out, there is no data to clearly identify which UVA wavelengths are more damaging as we move to longer wavelengths. In fact, there are studies showing in humans that exposure to UVAI produces immune suppression⁴³ and an increase in p53-positive cells.⁴⁴ In fact, based on the results of Dumay *et al.* the authors' state "This should prompt manufacturers to increase efficacy of sunscreen products by reinforcing protection against UVAI radiation, especially in those containing UVB filters with high SPF values." In fact, this is precisely what the Agency is proposing. We need to protect across the full UVA spectrum and this is being proposed by FDA as follows: the PPD method provides a measure of short wavelength UVA II and the UVA I /UV ratio ensures protection against UVAI. Collectively, the FDA proposal of SPF + *in vivo* UVA-PF (PPD) +

⁴³ Dumay, O, Karam, A, Vian, L, Moyal, D, Hourseau, C, Stoeber, P, Peyron, JL, Meynadier, J, Cano, JP, Meunier, L (2001) Ultraviolet AI exposure of human skin results in Langerhans cell depletion and reduction of epidermal antigen-presenting cell function: partial protection by a broad-spectrum sunscreen. *Br J Dermatol* **144**:1161-1168.

⁴⁴ Seite, S, Moyal D, Verdier, MP, Hourseau, C, Fourtanier, A (2000) Accumulated p53 protein and UVA protection level of sunscreens. *Photodermatol Photoimmunol Photomed* **16**:3-9.

in vitro UVAI/UV provides efficacy measures against wavelengths from 290-320, 320-340 and 340-400 nm, respectively.

- Thin layer substrate spectrophotometry is a “validated” method for determining absorbance/transmittancy of sunscreen products. Calculation of UVA I /UV or any other metric based on the data obtained in using *in vitro* thin layer substrate spectrophotometry is simply a mathematical expression describing the absorbance/transmittance of the sunscreen product. The method is validated and has been tested extensively as evidenced by publications in the peer-reviewed literature. The metric proposed by FDA, namely UVAI/UV is a modification of the Boot’s star UVA/UVB ratio, which has been used for nearly twenty years.
- The FDA has rejected Critical Wavelength in the Proposed Rule. P&G and others submitted data and, after due consideration, FDA chose not to support this metric. FDA has decided this is not an appropriate means of designating UVA protection for labeling purposes. The data contained in Comments C572 and C567 submitted by L’Oreal and considered by the Agency in rejecting Critical Wavelength were cited in support of this recommendation.

We believe any attempt to replace the current FDA proposal, i.e., UVA I/UV ratio, with Critical Wavelength or any other metric would be contrary to the Agency’s desire for “. . . [a] test, [that] in combination with the PPD method, provides a better assessment of overall UVA radiation protection”. In addition, changing the UVA I / UV ratio and corresponding category designations would not be in the interests of consumers or public health since the proposed method and labeling criteria when taken together with *in vivo* SPF (UVB) and PPD (UVA II), provide measures against all segments of solar UV from 290-400 nm.

In conclusion, we believe the FDA proposal for UVA testing and labeling is unbiased and fair. In the absence of international harmonization, we support the FDA proposal as written without any modifications.

International Harmonization: European Commission Recommendation

The European Commission (EC) published a “**Recommendation on the efficacy of sunscreen products and the claims made relating thereto**” on 22 September 2006.⁴⁵ This recommendation establishes the minimum efficacy standard for sunscreen products in order to ensure a high level of protection of public health using a simple, understandable label. The EC recommendation uses an *in-vivo* test or a validated in-vitro method to establish UVA efficacy. There are no UVA categories; rather UVA efficacy is a dependent component of the SPF claim thereby ensuring

⁴⁵ Commission Recommendation of 22 September 2006 on the efficacy of sunscreen products and the claims made relating thereto (*notified under document number C (2006) 4089* <http://eur-lex.europa.eu/JOHtml.do?uri=OJ:L:2006:265:SOM:EN:HTML>)

commensurate protection. Specifically, UVA efficacy is required in a 1 to 3 ratio (UVA to SPF) ratio. This presents significant benefits to the consumer. Communication to the consumer is simple and consistent, the consumer is not forced to choose a UVA efficacy level that is independent of SPF, and, consumers receive a consistent message regarding the dangers of sun exposure. As stated by the EC "Legally speaking, a recommendation is not binding. However, the Commission – who has worked closely with consumer associations as well as industry⁴⁶ on this file - expects industry to take steps so that the recommendation becomes "visible" for the consumer in summer 2007."

Harmonization with the EU scheme would benefit industry by reducing testing requirements, and by reducing the volume of possible product-claim combinations. Moreover, harmonization with Europe would benefit FDA by sending the important message that FDA is willing to fully participate in the recently established International Cooperation on Cosmetic Regulation (ICCR).

III. PREMATURE SKIN AGING, SKIN CANCER, AND SKIN DAMAGE CLAIMS

We propose claims that sunscreen helps protect against premature skin aging, skin cancer, and skin damage. Specifically, we recommend that FDA permit the following optional indication: "with regular [or continued] use helps protect against premature skin aging [or "skin damage" or "certain types of skin cancer"] caused by the sun."

In the preamble to its Proposed Rule, FDA tentatively concluded that the previously proposed indications regarding premature skin aging, skin cancer, or skin damage would be false or misleading in that such claims "would be inherently misleading to consumers by suggesting that sunscreen use alone may help prevent" such conditions. 72 Fed. Reg. at 49079 (emphasis added). In particular, FDA found that claims that a sunscreen "helps prevent" premature skin aging, skin cancer, and skin damage "would be inherently misleading to consumers by suggesting that sunscreen use alone may help prevent" the conditions. Id. (emphasis added).

We respectfully disagree with this conclusion and requests that FDA reconsider its position. Claims that sunscreen "helps prevent" or "helps protect against" premature skin aging, skin cancer, and skin damage are not claims that sunscreen "alone" prevents or protects against these conditions. Moreover, the data support claims that sunscreen helps prevent and protect against premature skin aging, skin cancer, and skin damage. Accordingly, such claims are truthful and nonmisleading. We thus believe that our members have a First Amendment right to utilize these claims.

⁴⁶ European Cosmetics, Toiletry and Perfumery Association (COLIPA): The European trade association comprised of sunscreen manufacturers including most multinational companies.

A. Claims that Sunscreen “Helps Prevent” or “Helps Protect Against” Premature Skin Aging, Skin Cancer, and/or Skin Damage Are Not Claims That Sunscreen Alone Prevents or Protects Against These Conditions

FDA’s contention that “helps” claims suggest that sunscreen use alone may help prevent against premature skin aging, skin cancer, and skin damage conflicts with the everyday meaning of the word “helps.” Using the term “helps” does not set up the expectation that the protection offered by sunscreens is absolute. It also does not suggest to consumers that sunscreens alone prevent and protect against skin damage, skin cancer, or premature skin aging. On the contrary, this language communicates that sunscreen use contributes to the prevention of these conditions. It also alerts consumers that complementary measures are necessary to assure adequate sun protection and sunscreens alone are not enough.

Further, in the context of the sun educational statement (see our proposed statement below in Section IV(D)), the meaning of the phrases “helps prevent” or “helps protect against” are even more clear. The educational statement tells consumers that sunscreen is only one part of a comprehensive sun protection program and that wearing protective clothing and limiting time in the sun are also important steps in preventing sun damage. Thus, important information that clarifies the labeling claims “helps prevent” or “helps protect against” claims will always and automatically be available to consumers.

The regulations require FDA to evaluate product efficacy based on whether there is a “reasonable expectation” that the product “will provide clinically significant relief of the type claimed.” 21 C.F.R. 330.10(a)(4)(ii) (emphasis added). In evaluating claims that sunscreens “help prevent” and “help protect against” premature skin aging, skin cancer, and skin damage, FDA must consider whether the data support the conclusion that sunscreens have a contributory impact in preventing these conditions as part of a comprehensive skin protection program. This inquiry is separate from whether sunscreens alone prevent these conditions.

B. Sound Science Supports Claims that Sunscreens Help Prevent and Help Protect Against Premature Skin Aging, Skin Cancer, and Skin Damage Claims

The data submitted to the docket show that there is a “reasonable expectation” that sunscreen helps prevent and helps protect against skin damage, premature skin aging, and skin cancer. Indeed, FDA has concluded that sunscreens are effective in protecting the skin from UV exposure and sunburn. Based on the well-established link between UV exposure and skin damage, premature skin aging, and skin cancer and the established efficacy of sunscreens in providing protection from UV exposure, there is a reasonable expectation that sunscreen helps prevent and helps protect against skin damage, premature skin aging, and skin cancer. Thus, such claims meet the applicable standard for efficacy and should be permitted.

Although the complete action spectrum for photocarcinogenesis and photoaging remains to be studied, the harmful effects of UV radiation are well known.⁴⁷ Studies in mouse models have shown that histologic and biochemical changes occur in response to specific UV wavelength irradiation. For example, UVB (290-320 nm) irradiated hairless mouse skin treated with 5% PABA prior to exposure showed elevated DNA synthesis, hyperplastic epidermis and hypergranulosis in unprotected areas, with lower levels in protected areas.⁴⁸ Further, multiple studies in humans have provided molecular models of premature skin aging.⁴⁹ Moreover, UV is a known carcinogen according to U.S. Department of Health and Human Services, Public Health Service, and the eleventh edition of the National Toxicology Program Report on Carcinogens.⁵⁰

A number of studies not referenced in FDA's literature review support the conclusion that using sunscreen helps prevent and helps protect against skin cancer, including studies showing the following:

1. Murine models exposed to chronic UV develop squamous cell carcinoma;⁵¹
2. Regular use of SPF-17 sunscreen with both UVB and UVA protection prevents actinic keratoses in humans;⁵²
3. Actinic keratoses is reduced in human patients applying active sunscreen compared with vehicle;⁵³ and

⁴⁷ Lim, HW et al. American Academy of Dermatology Consensus Conference on UVA protection of sunscreens: Summary and recommendations. J Am Acad Dermatol 44:505-8, 2001.

⁴⁸ Snyder, DS, May M. Ability of PABA to protect mammalian skin from ultraviolet light-induced skin tumors and actinic damage. J Invest Dermatol. 65:543-546, 1975.

⁴⁹ Fisher, GJ et al. Molecular basis of sun-induced premature skin ageing and retinoid antagonism. Nature 379:335-339, 1996; Fisher, GJ et al. Pathophysiology of premature skin aging induced by ultraviolet light. N Engl J Med 447: 1419-1428, 1997; Bernstein, EF. Et al. Ultraviolet radiation activates the human elastin promoter in transgenic mice: a novel *in vivo* and *in vitro* model of cutaneous photoaging. J Invest Dermatol 105:269-273, 1995; Garmyn, M et al. The effect of acute and chronic photodamage on gene expression in human keratinocytes. Dermatol 190:305-308, 1995.

⁵⁰ <http://ntp.niehs.nih.gov/ntp/roc/eleventh/profiles/s183uvrr.pdf>.

⁵¹ de Gruijl, FR, Forbes, PD. UV-induced skin cancer in a hairless mouse model. Bioessays 17:651-660, 1995.

⁵² Thompson, SC, Jolley, D, Marks, R. Reduction of solar keratoses by regular sunscreen use. N Engl J Med 329: 1147-1151, 1993.

⁵³ Naylor, MF, Boyd, AS, Smith, DW et al. High sun protection factor (SPF) sunscreens in the suppression of actinic neoplasia. Arch Dermatol 131:170-175, 1995.

4. Daily application of sunscreen decreased the rate of actinic keratosis acquisition among adults by 24%.⁵⁴

It is simply not rational to reject the effectiveness of sunscreens on sunburn as a surrogate marker for the damage caused by UV radiation, particularly in light of the significant body of preclinical work that supports sunscreen's effectiveness as one important preventative measure for skin cancer and premature skin aging. Furthermore, FDA's dismissal of the preclinical work on this topic contravenes its own heavy reliance on preclinical data in the IND process.

FDA asserts that the data are not adequate to support the described claims because the cited studies did not examine the chronic, long-term consequences of UV radiation exposure in human skin and therefore it is not possible for FDA to extrapolate the data to longer time points at which the short-term histological changes may cumulate to produce skin damage. 72 Fed. Reg. at 49089.⁵⁵ Long-term data are now available. As the AAD notes, "well-designed randomized controlled trial data, involving over 1400 subjects studied over a period of 12.5 years, have indicated that daily use of sunscreen can decrease the incidence of squamous cell carcinoma by 40%."⁵⁶ Moreover, if significant changes can be documented in short-term studies, this should be of sufficient importance to encourage the use of sunscreen by consumers through use of truthful and nonmisleading claims that sunscreen helps prevent and helps protect against premature skin aging, skin cancer, and skin damage.

⁵⁴ Darlington S, Williams G, Neale R, Frost C, Green A. A randomized controlled trial to assess sunscreen application and beta carotene supplementation in the prevention of solar keratoses. *Arch Dermatol* 139:451-5, 2003.

⁵⁵ As part of the Agency's support for their conclusion, it cites several references. Garland (rule Ref. 25) indicates that "[n]o epidemiological studies were identified that showed a protective effect of use of chemical sunscreen on the risk of melanoma or other cutaneous malignancies in humans." It should be noted, however, that this reference is from 1997 and that any data included in it would have been from before 1997. At that time in the U.S., commonly available sunscreen products did not contain sunscreen ingredients that effectively blocked UVA rays. In fact, the first significantly effective UVA blocking sunscreen ingredient, avobenzone, was not permitted for use in the U.S. until 1996. Thus, while Garland's statement may have been accurate at that point in time, it likely does not correctly reflect the current state of the U.S. marketplace with the wide availability of effective UVA blocking sunscreen products. A second reference cited by the Agency, Gasparro (Ref. 24), indicates that blocking UVA rays can protect the skin from sun-induced damage. Gasparro references Thompson et al., which shows that "regular use of a high potency sunscreen (sun protection factor [SPF] -17 containing both UVB and UVA absorbing ingredients) could prevent solar keratoses..."

⁵⁶ Comments of AAD, Docket No. 1978N-0038, at 4 (November 2, 2007) (citing van der Pols. et al., Prolonged Prevention of Squamous Cell Carcinoma of the Skin by Regular Sunscreen Use, *Cancer Epidemiol Biomarkers Prev* 2006; 15: 2546-8).

Large-scale long-term clinical trials on the effect of sunscreen use on skin cancer and premature aging of the skin are extremely challenging to complete and may not even be fully instructive based on the following:

1. Clinical studies are generally performed on adults. Yet more than one-half of a person's lifetime UV exposure occurs during childhood and adolescence.⁵⁷ Thus, it would be impossible to collect a comprehensive history of exposure, including use of sunscreen for each significant past exposure. It would also be impossible to determine whether sun exposure during a clinical trial or previous to the clinical trial caused an adverse skin outcome.
2. One severe sunburn can lead to skin damage many years in the future. Even if someone completely avoided sun exposure during a long-term clinical trial, skin cancer and skin damage could still appear many years later, without a person ever recalling the incident (especially if it occurred in early childhood).
3. Ethics Committees would be averse to exposing subjects to a known carcinogen without protection. Subjects would be difficult to enroll if they are informed that they may be exposed to a level of radiation that could cause cancer or skin damage.
4. It would be difficult for a long-term study to control out-of-study sun exposure, thereby compromising the data.
5. Development of skin cancer and/or sun damage is a decades-long process. It is likely that follow-up would require surveys based on information recall, a form of data collection which is known to be unreliable.

Given the body of scientific data already available and the practical and ethical implications of conducting the type of testing FDA has requested, it is plainly not in the public interest to require that such testing be conducted before allowing truthful and nonmisleading labeling claims regarding the role of sunscreen in helping prevent and protect against premature skin aging, skin cancer, and skin damage.

⁵⁷ Glanz K et al. Guidelines for School Programs to Prevent Skin Cancer. Recommendations and Reports Vol. 51/RR-4, National Center for Chronic Disease Prevention and Health Promotion; Division of Cancer Prevention and Control; Division of Adolescent and School Health; April 26, 2002.

C. Sound Public Policy Supports Claims that Sunscreens Help Prevent and Help Protect Against Premature Skin Aging, Skin Cancer, and Skin Damage Claims

To be comprehensive and effective, a public health message about skin health and sun exposure must contain information about the reasonable expectation that sun exposure can lead to skin damage and information about the reasonable expectation that using a sunscreen can help protect skin from this damage. Anything less is a disservice to the public; the more that people can do to protect themselves from these harmful effects, the better.

Sunscreens are, in many instances, the most practical means of protection from UV rays. For example, there are parts of the body (such as hands and tops of feet) that will be exposed to the sun, especially during the summer months. In addition, even if one wears a hat and sunglasses, the remainder of the face and neck must be protected from UV exposure. Furthermore, there will be circumstances where sunscreen will be the only feasible option on much of the body, e.g., while swimming. Also, in many situations, avoiding sun or seeking shade will not be possible.

Moreover, sunscreen is often the most practical and reliable means of protecting a child, for example, through application of a sunscreen by a parent before school or camp. Indeed, schools have recognized that outdoor activities during the school day are important to the healthy development of children. Accordingly, policies must encourage the use of sunscreens to protect against UV radiation during these foreseeable exposures.⁵⁸

Informing people that there is a reasonable expectation that sunscreens may help prevent and protect against UV-induced premature skin aging, skin cancer, and skin damage could provide the incentive they need to seek out, purchase, and regularly use effective sunscreens.⁵⁹ In particular, ethnic populations who do not tend to experience sunburn are unlikely to use a sun protection product that is only labeled for sunburn protection. Truthful and nonmisleading claims that sunscreen helps prevent and helps protect against premature skin aging, skin cancer, and skin damage are likely to motivate these individuals to use sunscreens, while the rest of FDA's proposed labeling will not.

⁵⁸ Glanz K et al. Guidelines for School Programs to Prevent Skin Cancer. Recommendations and Reports Vol. 51/RR-4, National Center for Chronic Disease Prevention and Health Promotion; Division of Cancer Prevention and Control; Division of Adolescent and School Health; April 26, 2002.

⁵⁹ Mahler IM, Kulik JA, Gerrard M, Gibbons FX. Long- Term Effects of Appearance-Based Interventions on Sun Protection Behaviors, *Health Psychology*, Vol 26, No. 3 350-360, 2007.

D. The First Amendment Requires FDA to Allow Truthful and Nonmisleading Claims that Sunscreens Help Prevent and Help Protect Against Premature Skin Aging, Skin Cancer, and Skin Damage Claims

1. Overview

FDA initially seeks to justify its proposed limitation on claims that sunscreen “helps prevent skin damage and premature skin aging” by claiming that the Proposed Rule merely establishes the outer boundary of effectiveness claims that FDA determined to be justified by available scientific evidence. FDA argues that it has imposed no restriction on speech so long as NDA procedures are available to those manufacturers seeking a “helps prevent” or “helps protect” indication. 72 Fed. Reg. 49080. Absent an NDA, FDA contends that “helps” claims not conforming to the wording of the Proposed Rule would promote the unlawful distribution of an unapproved product and thus warrant no First Amendment protection. *Id.* at 49078. These FDA contentions do not withstand First Amendment scrutiny.

First, FDA’s contention that the filing of a sunscreen NDA is a “significant available option to manufacturers for proposing alternative labeling statements” is wholly unrealistic. The cost and delay of securing an NDA are massive and, indeed, a principal justification for regulating by monograph. Thus, any claim that the availability of NDA procedures avoids the need to test monograph speech restrictions under First Amendment standards is unavailing. See Zauderer v. Office of Disciplinary Counsel, 471 U.S. 626, 651 (1985) (“unduly burdensome” requirements effectively foreclose speech).

Second, FDA argues that it must preclude skin cancer, premature aging and skin damage claims in the Proposed Rule because “helps prevent” and “helps protect” claims misleadingly imply that sunscreens “alone” afford protection against these conditions. Even leaving aside the scientific evidence fully supporting these “helps” claims which is presented earlier in these comments, FDA’s approach is constitutionally flawed. The courts have made it clear that FDA cannot find statements relating to drug efficacy false or misleading by *ipse dixit*. Washington Legal Foundation v. Friedman, 13 F.Supp. 2d 51, 72-74 (D.D.C. 1998). Here, FDA does not dispute that the UV rays of the sun are a significant risk factor for skin cancer, premature skin aging and other skin damage.” Nor does FDA dispute that sunscreens block, to a measurable degree, UV ray impact on human skin. Thus, like reducing total sun time exposure and using protective clothing, sunscreens are risk limiting and telling consumers that they “help” prevent or “help” protect against the sun’s potentially adverse effects gives consumers valuable information which they can use to benefit their health. FDA’s claim that *some* consumers may misuse this sunscreen information to limit other precautions may justify an effort to reiterate the need for additional exposure and protective clothing precautions as we have proposed in this submission. It cannot, however,

constitutionally justify precluding the dissemination of truthful and non-misleading information about the health benefits of sunscreens. Thompson v. Western States Med. Ctr., 535 U.S. 357 (2002).⁶⁰

FDA's effort to justify its restriction of "helps" claims on grounds other than the mistaken assertion that they are false or misleading has no merit. FDA makes the circular argument that by precluding "helps" claims by a prescriptive final OTC monograph, it can render them part of the unlawful activity of promoting an unauthorized drug. If, however, FDA has no constitutional basis to restricting such claims, its attempt to limit them through the allegedly affirmative restrictions of a prescriptive final OTC monograph must also fail. Washington Legal Foundation clearly teaches that the outer boundaries of FDA approval are not necessarily the outer boundaries of truthful, non-misleading statements.

We now turn to a detailed presentation on the relevant First Amendment precedent.

2. First Amendment Commercial Speech Safeguards Limit FDA's Authority to Regulate Sunscreen Claims

The First Amendment protects "commercial speech," including product labeling, from certain restrictions. Under the governing Central Hudson test, FDA can only prohibit speech that relates to an illegal activity, is false, or is "inherently misleading." Cent. Hudson Gas & Electric Corp. v. Pub. Serv. Comm'n of N.Y., 447 U.S. 557, 566 (1980); In re R.M.J., 455 U.S. 191, 202-03 (1982). FDA bears the burden of demonstrating that the speech meets any of these criteria. Ibanez v. Fla. Dep't. of Bus. and Prof'l Regulation, Bd. of Accountancy, 512 U.S. 136, 144, 146 (1994). To meet its burden to show that speech is "inherently" misleading, the government must prove that the speech cannot be cured of its misleading quality with disclaimers, qualifying language, warnings, or other speech. See In re R.M.J., 455 U.S. at 203-07. The bar is set high: "[f]or a particular mode of communication to be inherently misleading, it must be incapable of being presented in a way that is not deceptive." Revo v. Disciplinary Bd. of N.M., 106 F.3d 929, 933 (10th Cir. 1997) (emphasis added).

If the speech does not concern illegal activity and is not false or inherently misleading, FDA must not restrict it. Ibanez, 512 U.S. at 142. Instead, FDA must justify any limitation on the speech under the remainder of the Central Hudson test. This test requires FDA to show that the speech restriction: (1) addresses a "substantial"

⁶⁰ FDA's contention that "helps" claims can be read to assert that sunscreen "alone" can prevent skin cancer, skin aging or skin damage is, to say the least, strained. Under FDA's logic, the statement "Yeast helps make a light and fluffy cake" should be read as an assertion that a cake could be made from yeast "alone." In any event, FDA should have considered – and did not consider – additional disclaimers to avoid a possible misunderstanding of "helps" before barring such a claim. Pearson v. Shalala, 164 F.3d 650 (D.C. Cir. 1999).

governmental interest; (2) directly advances this interest; and (3) is not more extensive than necessary to serve this interest. Cent. Hudson, 447 U.S. at 566.

To show direct advancement of a governmental interest, the government must demonstrate that the “harms it recites are real and that its restriction will in fact alleviate them to a material degree.” Edenfield v. Fane, 507 U.S. 761, 770-771 (1993). In Edenfield, the Court found a restriction on a CPA’s solicitation of clients did not “directly advance” the state’s interest in maintaining ethical conduct among accountants. Id. at 771. The Court reasoned that the state presented no evidence – such as studies or anecdotal evidence – to show that the restriction furthered its interests. Id. However, in Went For It, the Court found direct advancement where the state submitted a 106-page two-year study and anecdotal evidence. Fla. Bar v. Went For It, 515 U.S. 618, 628-29 (1995). Thus, the Court upheld the state’s prohibition on soliciting legal services from accident victims within thirty days of the relevant accident. Id. at 635.

In order to demonstrate that a restriction of speech is not more extensive than necessary to serve a governmental interest, the government must show that it cannot “achieve its interests in a manner that does not restrict speech, or that restricts less speech.” Western States, 535 U.S. 357, 371 (2002). Courts must consider whether there are “numerous and obvious less-burdensome alternatives” to the government’s regulation to determine whether the speech restriction is more extensive than necessary. City of Cincinnati v. Discovery Network, Inc., 507 U.S. 410, 418 n.13 (1993).

Several cases from the food and drug context are particularly relevant to the instant case. First, Western States involved a challenge to section 503A of the Food and Drug Administration Modernization Act (FDAMA), which exempted compounded drugs from the new drug approval requirements if their manufacturers refrained from particular forms of advertising and promotion for the compounded products. Western States, 535 U.S. at 360. The provision was designed to prevent pharmacies from mass manufacturing compounded drugs in circumvention of the new drug approval provisions. The Supreme Court held that the speech restriction was invalid because it was more extensive than necessary” to achieve this interest. Id. at 371. Further, FDA could not justify its restriction based on the contention that the advertising was “inherently misleading because the drugs could be labeled with a disclaimer to address any potential to mislead. Id. at 376.

In Washington Legal Foundation, the D.C. federal district court considered the constitutionality of FDA’s off-label speech policy for drugs and devices. The policy prohibited certain Continuing Medical Education programs discussing off-label uses and some distribution of reprints that mentioned such uses. The court applied Central Hudson to determine if the commercial speech restriction was permissible. Washington

Legal Found, 13 F. Supp. 2d 51 (D.D.C. 1998).⁶¹ FDA contended that off-label speech related to an illegal activity because the Agency considered the product to be misbranded if the manufacturer disseminated information about an off-label use. Id. at 66. The court rejected this argument, finding it “tautological.” Id. It found that the “proper inquiry” is whether the underlying activity to which the speech relates – there, off-label prescriptions – is illegal. FDA could not find that the restricted speech related to illegal activity because physicians were not barred from off-label prescribing. Id. The court also dismissed FDA’s contentions that off-label speech was inherently misleading, reasoning that a disclaimer could cure any misleading quality of the speech. Id. at 67-69. Applying the remainder of Central Hudson, the court concluded that the disclaimer policy was a less restrictive means to accomplishing the government’s substantial interest in providing incentives to obtain approval of off-label uses. Thus, the court found that the off-label rules were “more extensive than necessary.” Id. at 72-74.

In the dietary supplement context, the D.C. Circuit found that FDA could not prohibit certain health claims, even if they were not supported by significant scientific agreement, and instead must require disclaimers. Pearson v. Shalala, 164 F.3d 650, 654 (D.C. Cir. 1999). The court rejected FDA’s contention that the proposed health claims were inherently misleading. Id. at 655. The speech restriction was found to be more extensive than necessary because FDA had not shown that “disclosure would not suffice to cure [any] misleadingness.” Id. at 657-58. The court did, however, find that disclaimers would be inappropriate and a total ban permissible if “credible evidence” did not support the claim or if the government “demonstrate[d] with empirical evidence” that disclaimers would not convey the intended message and would instead lead to consumer confusion. See id. at 659-660; see also Whitaker v. Thompson, 248 F. Supp 2d 1, 10-11 (D.D.C. 2002) (finding that only claims supported by zero or “one or two old studies” cannot meet the credible evidence standard, and holding that the standard was met where one-third of available studies supported claim).

3. Claims that Sunscreens Help Prevent and Help Protect Against Premature Skin Aging, Skin Cancer, and Skin Damage Cannot be Restricted Under the First Amendment.

In light of these governing principles, claims that sunscreen helps prevent and helps protect against premature skin aging, skin cancer, and skin damage on sunscreen

⁶¹ The D.C. District Court subsequently considered the propriety of FDAMA’s off-label speech policy, which allowed such speech only in certain narrow circumstances. Using very similar reasoning to that articulated in its initial opinion, the court again rejected the speech restriction as violative of the First Amendment. Washington Legal Found. v. Henney, 56 F. Supp. 2d 81, 87 (D.D.C. 1999). The D.C. Circuit reviewed this opinion on appeal. It vacated the judgment on other grounds, but stated: “[i]n disposing of the case in this manner, we certainly do not criticize the reasoning or conclusions of the district court. As we have made clear, we do not reach the merits of the district court’s First Amendment holdings.” Washington Legal Found. v. Henney, 202 F.3d 331, 337 n.7 (D.C. Cir 2000).

products are protected under the First Amendment. These claims do not concern illegal conduct and are truthful and nonmisleading. Though the Agency has a substantial interest in ensuring safe and effective OTC drugs, it has not supplied the necessary empirical evidence to demonstrate that restricting these claims for sunscreens advances this government interest. It has also failed to prove that its Proposed Rule is not more extensive than necessary.

Claims that sunscreen helps prevent and helps protect against premature skin aging, skin cancer, and skin damage do not relate to illegal conduct. The underlying activity that these claims concern is sale of an OTC drug that is generally recognized as safe and effective for sunburn protection, which is obviously legal. FDA's arguments to the contrary are untenable in light of Washington Legal Foundation. In the preamble, the Agency asserts that these claims for sunscreens relate to illegal activity. It reasons that the claims themselves would promote the drug for an unapproved use, which would render sale of the drug illegal, and therefore, the speech relates to an illegal activity. 72 Fed. Reg. at 49079-80. As discussed above, FDA's nearly identical argument to this effect was rejected in Washington Legal Foundation as tautological. FDA's contentions suffer from the same flaws here. The issue is whether a speech restriction is constitutional. FDA cannot circumvent this analysis by defining the speech itself as illegal. On the strength of Washington Legal Foundation, then, this circular argument fails.

The claims are also not inherently misleading, for numerous reasons. First, FDA has not affirmatively demonstrated that the claims are inherently misleading, as is constitutionally required. The Agency did not show that consumers cannot understand the claims, nor did it show that the claims cannot be rendered nonmisleading through the addition of disclaimers or qualifying language. Instead, it expressed "concern" because it is "not aware" of sufficient data supporting the claim that "sunscreen use alone prevents skin cancer or premature skin aging." 72 Fed. Reg. at 49079. These findings do not discharge the Agency's weighty constitutional burden for restricting commercial speech.

Second, a large body of scientific evidence supports the claims, as discussed above and in numerous comments filed to the docket. FDA's own statements and the statements of other government agencies also sustain the claims. These data and studies certainly rise to the level of "credible evidence."⁶² Thus, under Pearson, the

⁶² The "credible evidence" standard applies to OTC drugs. FDA argues that one lone footnote in Pearson, which stated that "drugs appear to be in an entirely different category" from dietary supplements in terms of potential harm, renders the entire Pearson analysis inapplicable. 72 Fed. Reg. at 49080. The Pearson opinion does not support this conclusion. The footnote was contained in the direct advancement portion of the opinion. 164 F.3d at 656 n.6. The court did not state that a product's drug status would impact any other part of the Central Hudson analysis, nor did it indicate how particularly direct advancement analysis would be different for drugs. Thus, it is not plausible to conclude that Pearson is irrelevant to the instant issues. Further, even if FDA is correct that the Pearson analysis is inapplicable to drugs, (continued...)

claims are not inherently misleading. Additional language could be used to cure any potentially misleading qualities and to reflect the level of scientific evidence supporting the claims. We recommend one such disclaimer in these comments. Consequently, FDA cannot implement its proposed restrictions unless it shows that the claims, with any appropriate disclaimers, actually mislead consumers.

Third, as discussed above, the Agency is incorrect that “helps” claims – claims that sunscreen helps prevent or helps protect against premature skin aging, skin cancer, and skin damage – are inherently misleading. FDA reasons that such claims “suggest that sunscreen use alone” prevents or protects against these conditions. Id. (emphasis added). As discussed above, consumers are highly unlikely to interpret these claims to mean that the product alone can prevent skin cancer, premature skin aging, and skin damage. The presence of the sun alert/educational statement (such as the one we propose below) makes this interpretation particularly unlikely, since it emphasizes that other measures besides sunscreen are needed to prevent and protect against premature skin aging, skin cancer, and skin damage. FDA also has produced no consumer comprehension tests to support its unlikely assumption.

FDA alternatively attempts to justify its speech restriction based on the remainder of the Central Hudson test. It argues that it has a substantial interest in ensuring that OTC drugs are safe and effective, that its speech restriction directly advances this interest based on the “available evidence,” and that this restriction is not more extensive than necessary. 72 Fed. Reg. at 49079-80. The Agency does not, however, present any evidence that truthful and nonmisleading claims that sunscreens help prevent and help protect against premature skin aging, skin cancer, and skin damage present “real” harms, as required by Edenfield. FDA has offered no evidence that these claims will prompt consumers to spend more time in the sun or to forego other sun protective measures. Instead, it points only to a controversial study that showed use of high SPF sunscreens – not sunscreens with any premature skin aging, skin cancer, or skin damage claims – increased time spent in the sun. 72 Fed. Reg. at 49090-91.

FDA also has not shown that its speech restriction will “alleviate” these purported harms “in a material way,” as Edenfield also requires. The Agency has proffered no evidence demonstrating that restricting these claims will reduce time spent in the sun or encourage the use of other sun-protective measures. In fact, the evidence it does present cuts the other way. The study FDA cites used unlabeled packages, so it arguably demonstrates that use of sunscreens without such claims increases the time spent in the sun. Id.; Philippe Autier et al., Sunscreen Use and Duration of Sun Exposure: a Double-Blind, Randomized Trial, 91(15) Journal of the National Cancer Institute 1304 (1999). Unlike in Went For It, then, FDA has not presented any evidence showing that its proposal directly advances its interests.

the governing principles of commercial speech analysis remain the same. Western States – a Supreme Court opinion – shows that the Central Hudson framework discussed in these comments applies to drugs.

Finally, the Agency has not demonstrated that its proposed restriction is not more extensive than necessary to serve its interests. FDA considered alternatives, including a public education campaign and a voluntary labeling regime, and found that these methods would not further its interests as effectively. 72 Fed. Reg. 49080. FDA also noted that manufacturers can pursue alternative labeling through the NDA approval process. *Id.* However, FDA failed to consider the most obvious less restrictive alternative: an appropriate disclaimer, which is already present in the form of the Sun Alert. The Supreme Court has exhorted and endorsed this alternative from *In re R.M.J.* to *Western States*. In all of these cases, the Court has made clear that a disclaimer or explanatory statement is always constitutionally preferable to outright suppression of speech. Because FDA failed to consider this obvious, less burdensome alternative, its proposed restriction is unconstitutional.

Further, FDA's identification of the NDA process as a viable alternative for making these claims is flawed in light of *Western States*. There, the Court found the speech restriction was more extensive than necessary even though compounded drug manufacturers could have pursued approval of their drugs if they wished to advertise their products. *See Western States*, 535 U.S. at 369-70, 372-73. The Supreme Court recognized in that case that "it would not make sense to require compounded drugs created to meet the unique needs of individual patients to undergo the testing required for the new drug approval process." *Id.* at 369. Similarly, it does not make sense to require sunscreens, which can generally be marketed pursuant to the streamlined OTC monograph system, to undergo such testing in order to make useful and informative claims. In sum, FDA's policy on claims that sunscreen helps prevent and helps protect against premature skin aging, skin cancer, and skin damage is more extensive than necessary.

Our proposal for these claims is a concrete example of a less restrictive alternative to FDA's proposal. We recommend the use of a modified sun alert as a disclaimer for products with its proposed skin damage, premature skin aging, and skin cancer claims.⁶³ This would enable consumers to understand that sunscreen is one part of a multifaceted sun protection program, and that sunscreen alone does not prevent and protect against the mentioned conditions. It would thus accomplish FDA's goals in a more narrowly tailored manner. We urge FDA to adopt this proposal.

IV. LABELING

We believe that FDA must amend its proposed sunscreen labeling requirements in several respects. First, FDA cannot require sunscreens to be labeled with the term

⁶³ As discussed in other parts of these comments, the proposed disclaimer reads: "It is important to protect against both UVB and UVA rays from the sun since they increase the risk of skin cancer, premature skin aging, and other skin damage. Decrease UV exposure by limiting time in the sun, wearing protective clothing and using a sunscreen."

“UVB SPF,” because this phrase misleadingly suggests that sunscreens with SPF protect against UVB rays only. Second, the Agency may not adopt the proposed “no UVA protection” disclaimer requirement, because this statement would be false and misleading as to both (1) sunscreens that offer a minimal but not zero level of UVA protection; and (2) products that have not undergone UVA testing but that nonetheless do provide UVA protection. Third, FDA should eliminate the star rating system for UVA protection levels because consumers will likely think the stars represent overall product quality (as in similar rating systems for movies, hotels, and restaurants). The star system is therefore likely to prompt consumers to ignore the SPF value and select sunscreens solely on the star rating, contrary to FDA’s intentions and public health interests. Fourth, the Agency should combine its proposed PDP educational statement and sun alert warning into one succinct, required educational statement. It should locate this statement in the Other Information section of the Drug Facts panel, since the sun alert is not a warning under statutory, regulatory, and Agency usage of the term. Fifth, FDA should modify the proposed reapplication directions to reflect that scientific evidence does not support a 2 hour reapplication direction and to clarify the proper reapplication method.

FDA also should adopt our proposals to streamline the labeling requirements for regular-size and small-size sunscreens alike. It should delete unduly burdensome labeling requirements, such as (1) the unnecessary water resistant indication statement; (2) directions for child use in products unlikely to be used on children; and (3) use of the term “skin rash” rather than “rash” in the warnings section. FDA should permit our proposed, optional indications statement: “With regular [or continued] use helps protect against premature skin aging [or “skin damage” or “certain types of skin cancer”] caused by the sun.”

Finally, FDA’s proposed small package rules violate the APA because they allow labeling relief for some small package sunscreens (those labeled for use on small areas of the face) but not others. FDA should adopt our small package labeling proposal or a similar scheme that does not suffer from this flaw.

A. FDA should abandon the terminology “UVB SPF” in sunscreen labeling and continue to utilize only the term “SPF”

We believe that FDA cannot require sunscreens to be labeled as providing “UVB SPF” protection. In light of the science discussed in section I(B)(2), this description is false and misleading in violation of the FDCA and its accompanying regulations. We thus believe that the Agency must eliminate this labeling requirement from the proposed monograph.

Under the FDCA, FDA cannot require OTC drug labeling that is false or misleading in any way. See FDCA 502(a). The corresponding regulations similarly provide that labeling for OTC drugs, including sunscreens, “shall be clear and truthful in all respects and may not be false or misleading in any particular.” 21 C.F.R. 330.10(a)(4)(v).

The Proposed Rule mandates the following indications statements for sunscreens, depending on their SPF:

- For sunscreens of SPF 2 to under 15, the indications statement must read “low UVB sunburn protection;”
- For sunscreens of SPF 15 to 30, the indications statement must read “medium UVB sunburn protection;”
- For sunscreens of SPF 30 to 50, the indications statement must read “high UVB sunburn protection;” and
- For sunscreens of SPF over 50, the indications statement must read “highest UVB sunburn protection.”

72 Fed. Reg. at 49087, 49113. The “UVB” designation is also required on the PDP in association with the SPF. *Id.* at 49112.

While we agree that the term SPF should represent “Sunburn Protection Factor,” we believe that FDA must abandon the terminology “UVB SPF” in sunscreen labeling. This language strongly suggests that SPF is a measure of the product’s protection against UVB radiation only. However, as discussed above in detail in section I(B)(2), a sunscreen’s SPF is not solely representative of the product’s protection against UVB radiation. SPF is a measure of the sunscreen’s ability to prevent sunburn, and the CIE action spectrum shows that sunburn is in part due to UVA radiation. Thus, SPF depends on the percentages of burning UVA and UVB radiation blocked by the product. In fact, sunscreens with an SPF of above 12 must have UVA protection to be effective at preventing sunburn. Further, SPF values have always been tested using solar simulators emitting both UVA and UVB radiation, and therefore the SPF level derived from this test represents the product’s protection against both types of rays. In sum, SPF denotes the product’s overall sunburn protection against UVB and UVA radiation. Consequently, use of the term “UVB SPF” is false and misleading because it implies that sunscreen with SPF provides no protection against UVA radiation. This phrase therefore violates the FDCA and its corresponding regulations.

We thus urge the Agency to drop “UVB” as a descriptor for SPF both on the PDP and in the indications section of the Drug Facts panel. We also recommend that FDA return to the scientifically correct “SPF” (as the abbreviation for “Sunburn Protection Factor”) on the PDP. The Agency need not add additional information to the indications statement to compensate for the loss of the term “UVB,” as the revised indications clearly state the level of protection that the product provides.

The following represent the appropriate revised indications:

- “low sunburn protection” for sunscreens of SPF 2 to under 15;
- “medium sunburn protection” for sunscreens of SPF 15 to under 30;
- “high sunburn protection” for sunscreens of SPF 30 to 50; and

- “highest sunburn protection” for sunscreen of SPF over 50.

B. The Agency Should Abandon Its Proposal to Require a “No UVA Protection” Disclaimer on SPF-Bearing Sunscreen Products.

FDA cannot mandate that SPF-bearing products be labeled with the statement “No UVA protection.” This proposed disclaimer would render the labeling of SPF-bearing products false and misleading, since these products do offer some UVA protection.

As discussed above, the FDCA and its accompanying regulations forbid FDA from requiring labeling that is false or misleading in any way. See FDCA 502(a); 21 C.F.R. 330.10(a)(4)(v). As stated in the Proposed Rule, “FDA is proposing that a sunscreen product that [has not been shown to] provide at least a ‘low’ level of UVA protection include the following statement . . . : ‘no UVA protection.’” 72 Fed. Reg. at 49083. Specifically, FDA plans to require this disclaimer on sunscreen products that have not undergone UVA testing, and on those tested products that offer a UVA protection level of less than 2. Id. at 49108, 49121.

FDA’s proposed disclaimer would cause the labeling of SPF-bearing products to be false and misleading. As described above, SPF is a measure of the products’ overall sunburn protection. Sunburn derives from both UVA and UVB rays, both in nature and in SPF testing procedures, so SPF represents the products’ protection against sunburn from both UVA and UVB rays. Thus, SPF products cannot be said to have “no” UVA protection. Further, where untested products provide a significant amount of UVA protection, it is false to say they provide “no” such protection. Sunscreen products that offer UVA protection of > 2 but more than level 0 also cannot correctly be said to provide “no” UVA protection. Instead, FDA’s required statement would be factually false and misleading as to all of these sunscreen products. The Proposed Rule would therefore violate the FDCA and its corresponding regulations.

To avoid these serious legal problems, FDA should eliminate the requirement to label SPF-bearing products with the statement “No UVA protection.” The absence of UVA labeling on these products will adequately signal to consumers that the products do not provide significant UVA protection or else have not been tested to determine UVA protection.

C. FDA Should Eliminate the UVA Star Rating System and Instead Only Require Category Descriptors for UVA Protection

We believe that the Agency should abandon its proposal to require that a sunscreen’s UVA protection level be conveyed through use of a star rating system. We believe that the proposed star rating system will confuse and mislead consumers.

Under FDA’s proposal, a sunscreen’s tested UVA protection level must be conveyed through both a textual category descriptor and a star-based graphic. For

example, the PDP of products providing the highest level of UVA protection must state “UVA **** Highest.” 72 Fed. Reg. at 49112. The star graphic for these highest protection UVA products must be composed of four filled stars. For products providing less than the highest UVA protection level, the star-based graphic is composed of one, two, or three darkened stars from the left (for low, medium, and high levels of protection, respectively), and three, two, or one empty unfilled stars, respectively. *Id.* The unfilled stars are intended to communicate that the star rating is out of a possible four stars.

FDA selected the combination of textual category descriptors and graphic descriptors for UVA protection for several reasons. First, according to FDA, this labeling scheme will be accessible to consumers. It reasoned that “consumer familiarity with similar star rating systems (e.g., movies, hotels, and restaurants) used for many years in the United States provide a basis for consumers’ understanding of [the proposed star system].” 72 Fed. Reg. at 49084. It also stated that the two-pronged UVA labeling scheme will assure that consumers “consider UVB and UVA radiation protection equally in selecting an OTC sunscreen drug product,” *id.* at 49083, since it will mirror use of the SPF value and category descriptor for sunburn protection labeling. FDA concluded that the star system will not overshadow the SPF value “because [the Agency is] proposing a required statement to inform consumers about the importance of both UVA and UVB protection.” *Id.* at 49084.

We believe FDA should abandon the star system for UVA labeling because it is likely to mislead consumers. As FDA recognizes, consumers are familiar with the star rating systems used for films, restaurants and hotels. However, in these situations, the star rating is used to convey overall product quality. If consumers rely on their experience with the movie, restaurant and hotel rating systems to interpret sunscreen labeling – as FDA assumes they will – they are likely to conclude that the UVA star system is the sole representation of the sunscreen’s overall quality. Furthermore, based on their knowledge of the government’s star-based rating for crashworthiness of motor vehicles, consumers might think that the use of a star rating means the government – not the manufacturer – performed the sunscreen testing.⁶⁴ Finally, consumers could confuse filled and empty stars. FDA acknowledges this point. It reasons that it should use a “no UVA protection” disclaimer rather than four empty stars because consumers might confuse four empty stars for four filled stars. *Id.* at 49083. This concern is equally applicable when filled and empty stars are next to one another on a package for low, medium, or high UVA protection sunscreen. Consumers are likely to find the empty/filled star graphics incomprehensible. In short, the star system would likely mislead consumers.

⁶⁴ The National Highway Traffic Safety Administration conducts crash testing of motor vehicles and formulates star ratings. National Highway Traffic Safety Administration, Buying a Safer Car, at 2-3 (2007), available at <http://www.safercar.gov/BASC2007/images/BSC2007.PDF>. Consumers are likely familiar with this process from car advertising.

The star system could also cause consumers to believe that the product's star rating is more important than its SPF value. The risk of this interpretation is particularly acute if consumers believe the star rating signifies overall quality – a likely interpretation given FDA's expectation that they will rely on their experiences with movie, restaurant and hotel star ratings. Consumers might simply ignore the SPF value and choose a sunscreen based on the UVA star rating, contrary to FDA's goal that the two values be given equal weight in purchasing decisions. Furthermore, FDA's cited consumer research supports the conclusion that consumers will think the star graphic is more important than the product's SPF value. One cited study shows that including both an SPF value and UVA star rating on the label confuses consumers. Specifically, this study found that "symbols (i.e., stars) misled consumers into giving equal or greater importance to the UVA radiation rating compared to the SPF value." Id. at 49082 (emphasis added). The study concluded that "a descriptive approach [to UVA labeling] better conveyed to consumers the added benefit of UVA protection without detracting from the SPF value." Id.

This study also shows that FDA's proposal is against the weight of consumer labeling research. Though FDA states that "none of the [consumer comprehension] studies combined labeling systems as [FDA proposes]," id. at 49084, the studies discussed in the previous paragraph – and cited by FDA – investigated the effect of adding a UVA star system to labeling that already included an SPF value. This study provides firm support for our expectation that consumers will misunderstand the star rating system when used in conjunction with the SPF value on sunscreen labeling.

To address these problems, we recommend elimination of the UVA star rating system. Under our proposal, UVA labeling on the PDP would simply include the category descriptor along with the term "UVA," e.g. "UVA low." We believe FDA should maintain the proposed UVA labeling for the indications section: "[low/medium/high/highest] UVA protection." Because the SPF rating and sunburn protection category descriptor on the PDP will remain in the same size font and same location as the corresponding UVA category descriptor, consumers will still receive information on both SPF and UVA protection on the PDP. Further, the our proposed modified sun alert will also inform consumers that protection from both UVA and UVB rays is critical. We believe this proposal avoids the consumer confusion issues that the star rating system presents. It also accomplishes FDA's goals of providing information about the magnitude of UVA protection and giving UVA protection prominence on the PDP. Finally, it resonates with the study recommendation described above for "a descriptive approach [to UVA labeling]." Id. at 49082.

In sum, we believe that FDA should omit the UVA star system labeling requirement for sunscreen PDPs and simply use a category descriptor to convey the sunscreen's level of UVA protection.

D. The Sun Alert Is Not a Warning, and FDA Should Condense and Relocate the Educational Content of the Labeling

FDA's proposal to deem the "sun alert" a Warning is inconsistent with the FDCA, the regulations, and the Agency's long-standing interpretation of the term "warning."

Under the Proposed Rule, FDA requires sunscreen manufacturers to label their products with the following warning statement: **"UV exposure from the sun increases the risk of skin cancer, premature skin aging, and other skin damage. It is important to decrease UV exposure by limiting time in the sun, wearing protective clothing, and using a sunscreen."** 72 Fed. Reg. at 49113. FDA previously required that the sun alert be located in the "Other Information" section of the Drug Facts panel. Id. at 49072. According to FDA:

the statement is [now] most appropriate in the "Warnings" section because it warns consumers that effective protection from the sun does not involve only the application of sunscreens, as many consumers believe. In addition, it warns consumers that UV radiation not only increases the risk of sunburn but also increases the risk of skin cancer and premature skin aging, which many consumers may not know. FDA believes the new warning will encourage consumers to use sunscreen, limit time in the sun, and wear protective clothing to reduce UV exposure.

Id. at 49090. In particular, FDA believes that "this new proposed warning will decrease the likelihood of consumers spending more time in the sun when using a sunscreen," by "educating consumers about a sun protection program." Id. at 49091 (emphasis added).

The FDCA, regulations, and Agency policy show that "warnings" are statements describing the risk associated *with use of a given product*. The statute requires drug warnings "against use in those pathological conditions or by children where its use may be dangerous to health." FDCA 502(f) (emphasis added). The general OTC Drug Review procedural regulations require OTC drug labeling to include "warnings against unsafe use, side effects, and adverse reactions." 21 C.F.R. 330.10(a)(4)(v) (emphasis added). Similarly, the regulations delineating warning statements for OTC drugs provide for warnings relating the product's risks, such as the risks of ingestion and prolonged use, side effects, and contraindications. 21 C.F.R. 369.20, 369.21. These regulations do not require generalized educational statements informing the reader about the underlying condition that the product treats or prevents or about alternative treatments. See id. Thus, the statute and regulations show that the term "warning" does not encompass general education statements.

Long-standing Agency policy also shows that the term "warning" refers to statements about a product's specific risks. In adopting the generally governing OTC drug labeling and formatting rule, FDA noted "The 'Warnings' section . . . contains information regarding when the product should absolutely not be used, drug-drug and

drug-food interactions, when to consult a doctor or pharmacist before taking the product, possible side effects, and when to stop use and contact a doctor after taking the product.” 64 Fed. Reg. 13254, 13259 (March 17, 1999). FDA has repeatedly emphasized -- and emphasizes in the Proposed Rule at issue, the following:

[W]arnings are necessary to ensure that these OTC drug products continue to be safe and effective for their labeled indications under ordinary conditions of use as those terms are defined in the [FDCA]. This judgment balances the benefits of these drug products against their potential risks.

72 Fed. Reg. at 49107 (emphasis added). The Agency’s statements thus also show that warnings communicate information about the risks of a particular product.

The proposed Sun Alert does not disclose any risks, side effects, adverse events, or contraindications specific to using sunscreen. Instead, it discusses the risks of sun damage from UV sources, and the use of sunscreen as part of an overall sun protection plan. Thus, it is not “warning” under the statute, regulations, and customary FDA usage. Instead, by FDA’s own terminology, this statement is “educati[onal]” in nature. Though FDA is correct that it is helpful to provide consumers with general educational information at the point of sale, the warning panel of drug labeling is not the appropriate vehicle. Indeed, under the principle FDA advocates in the Proposed Rule, virtually any educational statement could be required in the warnings section. This is clearly not the result contemplated by Congress or by the regulations. Consequently, FDA should modify its Proposed Rule to require a sun alert-type educational statement in the “other information” section of the Drug Facts labeling.

We recommend combining the proposed sun alert with the proposed PDP educational statement and relocate the condensed version.⁶⁵ We propose that the following appear in the “Other Information” section of the Drug Facts labeling:

It is important to protect against both UVB and UVA rays from the sun since they increase the risk of skin cancer, premature skin aging and other skin damage. Decrease UV exposure by limiting time in the sun, wearing protective clothing and using a sunscreen.

⁶⁵ The Proposed Rule requires that one of the following two educational statements appear on the PDP of all sunscreen products: (1) “UV rays from the sun are made of UVB and UVA. It is important to protect against both UVB & UVA rays;” or (2) “UV rays from the sun are made of UVB and UVA. It is important to protect against both UVB & UVA rays to prevent sunburn and other skin damage.” 72 Fed. Reg. at 49113.

We believe that condensing these two educational statements is advisable. As proposed, the educational statements are repetitive. Our streamlined version is less burdensome and conveys the same message to consumers.

FDA proposes to exempt lip products from the sun alert requirement but not the PDP educational statement requirement. In view of these Agency preferences, we propose the following statement appear in the “Other Information” section of the Drug Facts labeling for lip products:

It is important to protect against both UVB & UVA rays from the sun since they increase the risk of skin cancer, premature skin aging and other skin damage.

E. The Agency Should Modify the Proposed Reapplication Directions and Eliminate the Additional Required Indication for Water Resistant Products.

FDA should change the proposed reapplication directions to reflect sound science concerning reapplication frequency. It should also streamline the reapplication directions and indications statements to omit unnecessary labeling text and avoid consumer confusion.

FDA’s proposed reapplication directions vary based on whether the product meets the water resistant/very water resistant criteria. For water resistant and very water resistant products, the Agency proposes to require the following reapplication directions: “reapply after [40 or 80 minutes, respectively] of swimming or sweating [or perspiring] and after towel drying. Otherwise, reapply at least every 2 hours.” 72 Fed. Reg. at 49113. For products that do not satisfy these criteria, FDA proposes to require the following reapplication directions: “reapply at least every 2 hours and after towel drying, swimming, or sweating [or perspiring].” *Id.* Sunscreen products, whether water resistant or not, would also be required to be labeled with the direction “apply and reapply as directed to avoid lowering protection.” *Id.* The Agency’s proposed directions for very water resistant, water resistant, and non-water resistant products are summarized in Table 4 below.

Table 4: Proposed Rule Very Water/Water Resistant Directions

Very Water Resistant Directions	Water Resistant Directions	Non-Water Resistant Directions
<ul style="list-style-type: none"> • apply liberally [or generously] [(<i>optional</i>) and evenly] (time, if required) before sun exposure • apply and reapply as 	<ul style="list-style-type: none"> • apply liberally [or generously] [(<i>optional</i>) and evenly] (time, if required) before sun exposure • apply and reapply as 	<ul style="list-style-type: none"> • apply liberally [or generously] [(<i>optional</i>) and evenly] (time, if required) before sun exposure • apply and reapply as

<p>directed to avoid lowering protection</p> <ul style="list-style-type: none"> • children under 6 months of age: ask a doctor • reapply after 80 minutes of swimming or sweating [or perspiring] and after towel drying. Otherwise, reapply at least every 2 hours. 	<p>directed to avoid lowering protection</p> <ul style="list-style-type: none"> • children under 6 months of age: ask a doctor • reapply after 40 minutes of swimming or sweating [or perspiring] and after towel drying. Otherwise, reapply at least every 2 hours. 	<p>directed to avoid lowering protection</p> <ul style="list-style-type: none"> • children under 6 months of age: ask a doctor • reapply at least every 2 hours and after towel drying, swimming or sweating [or perspiring].
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In the preamble of the Proposed Rule, the Agency explained its basis for concluding that 2 hours should be the directed reapplication time frame. It reasoned that a 2001 study by Wright et al. showed that “subjects who reapplied sunscreen every 1 to 2 hours and after swimming did not report sunburn.” *Id.* at 49092. The Agency also relied upon a number of AAD sources in supporting its position (References 38, 57, 58, and 59). The Agency indicated that its reapplication directions are intended to combat loss of protection due to rubbing, swimming, or sunscreen degradation over time.⁶⁶

Separately, the Agency proposed to mandate additional indications statements for water resistant and very water resistant products, beyond the basic indications statements required for non-water resistant products. The Proposed Rule provides that water resistant and very water resistant products must be labeled with the indication: “retains SPF after [40 or 80, as appropriate] minutes of activity in the water [or swimming or sweating or perspiring or swimming/sweating or swimming/perspiring].” 72 Fed. Reg. at 49092.

We believe that FDA’s proposal to direct reapplication every 2 hours is not supported by adequate science. The AAD now recognizes that “little scientific data exists on the topic” of reapplication, “making it difficult to universally recommend a specific reapplication time interval for all sunscreens.”⁶⁷ AAD supports a direction that sunscreens be reapplied “often” and after rubbing, swimming, or perspiring. *Id.* In other words, a source FDA relies upon heavily now agrees that the available studies do not justify a 2 hour reapplication time frame for all sunscreens. The component of the reapplication directions mandating reapplication after rubbing, swimming, or sweating

⁶⁶ FDA, Questions and Answers on the 2007 Sunscreen Proposed Rule, <http://www.fda.gov/cder/drug/infopage/sunscreen/qa.htm#14>.

⁶⁷ Comments of AAD, Docket 1978N-0038, at 3 (November 2, 2007), available at http://www.aad.org/pm/temp/alerts_Dec12007.html.

will address FDA's concerns about loss of sunscreen due to these activities. Furthermore, sunscreen technology has evolved so that the stability of sunscreen formulations is no longer a concern, independent of rubbing, swimming, or sweating.

The use of the 2 hour reapplication text could also confuse consumers. When the water resistant and non-water resistant directions are viewed side-by-side, consumers may think that they need to reapply non-water resistant products every 2 hours and water resistant products every 40/80 minutes. In other words, consumers may get the incorrect impression that non-water resistant products need to be reapplied less often than water resistant products. In view of the scientific conclusions of the AAD and the potential for the current 2 hour reapplication directions to mislead consumers, we believe that FDA should modify its proposed reapplication directions to eliminate the 2 hour time frame and instead mandate reapplication "often."

Further, to avoid redundant and confusing labeling regulations, FDA should streamline its current proposed directions and eliminate the additional required indications statements for water resistant products. The Agency's requirements that sunscreen directions statements contain both (1) a direction to reapply "as directed" to avoid lowering protection and (2) a direction to reapply after a prescribed time frame or after toweling, swimming, or sweating are repetitive. Also, consumers are likely to find the direction to reapply "as directed" confusing when it is contained in a separate bullet from the actual reapplication intervals.

The proposal to mandate an additional indications statement for water resistant products is also problematic. These required indications statements – "retains SPF after [40/80] minutes of" water activity or sweating – would be completely duplicative of the reapplication directions for these products, which read as follows under the FDA proposal: "reapply after [40/80] minutes of swimming or sweating [or perspiring] and after towel drying." This labeling requirement is therefore redundant and unduly burdensome.

We recommend that FDA delete the additional required indications statement for water resistant products (proposed 21 C.F.R. 352.52(b)(1)(vii)&(viii)). The Agency should also mandate the following reapplication directions in place of the two current proposed bullets regarding reapplication. For water resistant and very water resistant products, the directions section should read: "To maintain protection, reapply after [40/80] minutes of swimming or sweating [or perspiring] and after rubbing." For other products, the directions should read "To maintain protection, reapply often and after rubbing, swimming, sweating [or perspiring]."

We believe its proposal will serve FDA's goals. It will communicate to consumers that frequent reapplication is necessary to avoid lowering protection, particularly when the consumer swims, sweats, or rubs the skin with a towel. It will avoid consumer confusion between the reapplication time frames for water resistant and non-water resistant products, by eliminating a specific time frame from the non-water resistant directions. It will also reduce confusion by omitting the hard-to-understand "reapply as

directed” bullet. It accords with the recommendations of the AAD. Finally, it eliminates redundant and unduly burdensome labeling requirements.

F. The Agency Must Change Its Proposed Labeling Requirements for “Regular-Sized” Sunscreen Packages

This section summarizes our recommended alterations to FDA’s proposed sunscreen labeling rules for “regular-sized” packages.⁶⁸ Our suggestions are represented in chart and graphical form for the Agency’s convenience.

First, we recommend a streamlined PDP regulation that implements necessary rule changes described above. We suggest the Agency abandon its proposals to require (1) the phrase “UVB SPF” on the PDP; (2) the UVA star rating labeling; and (3) the statement “no UVA protection” on sunscreens that are not tested for UVA protection or do not meet the threshold for the “low” UVA protection category. The rationales for these proposed changes are outlined above. FDA also should condense its proposed PDP educational statement and proposed sun alert in one required statement in the “Other Information” section of the Drug Facts panel, as discussed.

With respect to the Drug Facts panel, FDA should permit the following optional indications statement: “With regular [or continued] use helps protect against premature skin aging [or “skin damage” “certain types of skin cancer”] caused by the sun.” The rationale for this claim is described above in section III. We also propose that the phrase “skin rash” in the warnings section be modified to read simply “rash.” Consumers will understand this term, as it is commonly used. Therefore, FDA should utilize this less burdensome labeling requirement. We also recommend streamlined reapplication directions as aforementioned and omission of the additional indications statement for water resistant and very water resistant products. Finally, we request that FDA implement our suggested PDP changes in the Drug Facts panel, including (1) elimination of the requirements to label with the phrases “UVB SPF” and “no UVA protection;” (2) prohibition of any UVA claims for sunscreens not tested for UVA protection or not meeting the threshold for the “low” UVA protection category; and (3) combination of the sun alert and PDP educational statements and relocation of this new statement to the Other Information section.

These suggestions are summarized in table (Table 5) and graphic (Figures 2 and 3) form to illustrate the differences between FDA’s proposal and our recommended labeling.

⁶⁸

Sunscreen products that are not either: (i) in small-size packages; or (ii) are lip products.

Table 5: “Regular-Size” OTC Sunscreen Label

PDP Labeling		
FDA Proposed Rule	Industry Recommendation	Comments
UVB SPF [numeric value] (low/medium/high/highest) (e.g., “UVB SPF 15 Medium”)	SPF [numeric value] (low/medium/high/highest) (e.g., “SPF 15 Medium”)	Delete “UVB”
UVA (star symbol) (low/medium/high/highest) protection (e.g., “UVA **** Highest”) or “no UVA protection”	UVA (low/medium/high/highest) protection (e.g., “UVA Highest”).	Delete star (“****”) symbol requirement Delete “no UVA protection” labeling requirement
“UV rays from the sun are made of UVB and UVA. It is important to protect against both UVB & UVA rays.” or “UV rays from the sun are made of UVB and UVA. It is important to protect against both UVB & UVA rays to prevent sunburn and other skin damage.”		Delete this required PDP statement [Combine with proposed FDA warning and require in “Other Information” (see below)]
“water resistant” [or “water/sweat resistant” or “water/perspiration resistant”] OR “very water resistant” [or “very water/sweat resistant” or “very water/perspiration resistant”] (if applicable)	“water resistant” [or “water/sweat resistant” or “water/perspiration resistant”] OR “very water resistant” [or “very water/sweat resistant” or “very water/perspiration resistant”] (if applicable)	[No proposed change]
Back Panel Labeling		
<i>Uses:</i> • (low/medium/high/highest)	<i>Uses:</i> • (low/medium/high/highest)	Delete “UVB”

<p>UVB sunburn protection</p> <p>Additional Indications (select one or both) –</p> <ul style="list-style-type: none"> • “provides (low/medium/high/highest) protection against [select one of the following: ‘sunburn’ or ‘sunburn and tanning’]” • “for skin that sunburns (minimally/moderately)” (for low/medium SPF levels) OR “for skin (highly/extremely) sensitive to sunburn” (for high/highest SPF levels) • (low/medium/high/highest) UVA protection or “no UVA protection” • retains SPF after 40/80 minutes of [select one or more of the following: ‘activity in the water’, ‘swimming’, ‘sweating’, ‘perspiring’, ‘swimming/sweating’ or swimming/perspiring]” (only include if water/very water resistant) <p>Manufacturers who wish to combine the “Uses” statements about UVA protection and UVB sunburn protection may do so if the descriptors (i.e., levels of protection) are the same (e.g., “medium UVB sunburn/UVA protection”).</p>	<p>sunburn protection</p> <p>Additional Indications (select one or both) –</p> <ul style="list-style-type: none"> • “provides (low/medium/high/highest) protection against [select one of the following: ‘sunburn’ or ‘sunburn and tanning’]” • “for skin that sunburns (minimally/moderately)” (for low/medium SPF levels) OR “for skin (highly/extremely) sensitive to sunburn” (for high/highest SPF levels) • (low/medium/high/highest) UVA protection, if applicable • With regular [or continued] use helps protect against premature skin aging [or “skin damage” or “certain types of skin cancer”] caused by the sun. (optional) <p>Manufacturers who wish to combine the “Uses” statements about UVA protection and sunburn protection may do so if the descriptors (i.e., levels of protection) are the same (e.g., “medium sunburn/UVA protection”).</p>	<p>If “no UVA protection” (as FDA defines it) is met, then label will be silent with respect to UVA</p> <p>Delete additional required indication for water resistant and very water resistant products.</p> <p>Allow optional indication related to skin aging, skin damage, and certain types of skin cancer.</p> <p>Delete “UVB” in uses combination provision. Please see our comments regarding “UVB SPF”</p>
<p>Warnings:</p> <p>UV exposure from the sun</p>	<p>Warnings:</p> <p>For external use only</p>	<p>Combine sun alert with</p>

<p>increases the risk of skin cancer, premature skin aging, and other skin damage. It is important to decrease UV exposure by limiting time in the sun, wearing protective clothing, and using a sunscreen.</p> <p>For external use only</p> <p>When using this product keep out of eyes. Rinse with water to remove.</p> <p>Stop use and ask a doctor if skin rash occurs</p> <p>Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center immediately [or right away].</p>	<p>When using this product keep out of eyes. Rinse with water to remove.</p> <p>Stop use and ask a doctor if rash occurs</p> <p>Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center immediately [or right away].</p>	<p>proposed PDP educational statement and move to Other Information section (see below).</p> <p>Omit "skin" from rash warning.</p>
<p><i>Directions:</i></p> <ul style="list-style-type: none"> • apply liberally [or generously [(optional) and evenly] (time, if required) before sun exposure • apply and reapply as directed to avoid lowering protection <p>As an option, the labeling may state:</p> <ul style="list-style-type: none"> • apply to all skin exposed to the sun • children under 6 months of age: ask a doctor • reapply at least every 2 hours and after towel drying, swimming, or sweating [or perspiring] <p>OR if water/very water</p>	<p><i>Directions:</i></p> <ul style="list-style-type: none"> • Apply liberally [or generously] [(optional) and evenly] (time, if required) before sun exposure. • To maintain protection, reapply often and after rubbing, swimming, sweating [or perspiring]. <p>OR if water/very water resistant, replace the above statement with the following statement:</p> <ul style="list-style-type: none"> • To maintain protection, reapply after 40/80 minutes of swimming or sweating [or perspiring] and after rubbing. • Children under 6 months: 	<p>Condense reapplication directions and replace "at least every two hours" with "often"</p>

<p>resistant, replace this statement with the following statement:</p> <ul style="list-style-type: none"> • reapply after 40/80 minutes of swimming or sweating [or perspiring] and after towel drying. Otherwise, reapply at least every 2 hours. 	<p>ask doctor.</p> <p>As an option, the labeling may state:</p> <ul style="list-style-type: none"> • apply to all skin exposed to the sun 	
	<p><i>Other Information</i></p> <p>It's important to protect against the sun's UVB & UVA rays as they increase the risk of skin cancer, premature skin aging and other skin damage. Decrease UV exposure by limiting time in the sun, wearing protective clothing and using a sunscreen.</p>	<p>Add condensed version of sun alert and proposed PDP educational statement to Other Information section.</p>

These suggestions are summarized in table (Table 5) and graphic (Figures 2 and 3) form to illustrate the differences between FDA's proposal and our recommended labeling.

Figure 2:
FDA Proposed Rule "Regular-Size" OTC Sunscreen



This Figure is intended to provide an illustrative example for demonstration purposes and for ease of visualizing the proposed/recommended label.

Figure 3:
Industry Recommended "Regular-Size" OTC Sunscreen



This Figure is intended to provide an illustrative example for demonstration purposes and for ease of visualizing the proposed/recommended label.

G. FDA Must Alter Its Proposed Labeling Requirements for Small-Sized Packages

FDA should modify its small package sunscreen labeling proposal in several significant respects. First, under the APA, FDA must revise its small package labeling requirements to apply to all containers meeting the small package criteria under 21 C.F.R. 201.66(d)(10), rather than limiting this relief to products labeled for use on small areas of the face. Second, we recommend modified and streamlined sunscreen labeling to aid consumer comprehension, prevent undue burdens, and conform the labeling to the FDCA. These suggestions are summarized in table and graphic form to illustrate the differences between FDA's proposal and our recommended labeling.

1. FDA Cannot Treat Small Packages Labeled for Use on Small Parts of the Face Differently Than Other Small-Sized Packages.

FDA's Proposed Rule contravenes the APA because it provides labeling relief for some small package sunscreens but not others, without adequately justifying this disparate treatment. FDA must amend the rule to provide similar relief from labeling requirements for all sunscreen products in small packages.

The APA provides that a reviewing court must "hold unlawful and set aside" Agency rules that are "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. 706(2)(A). Courts have interpreted this statutory language to prohibit Agency actions that "treat similarly situated people differently." Bracco Diagnostics, Inc. v. Shalala, 963 F. Supp. 20, 27-28 (D.D.C. 1997). More specifically, the Agency cannot "permit two sets of similar products to run down two separate [regulatory] tracks, one more treacherous than the other, for no apparent reason." Id. at 28. The Agency must articulate a "rational basis" for treating two similar products distinctly. Id. In Bracco Diagnostics, the D.C. federal district court found that FDA acted arbitrarily and capriciously when it regulated one ultrasound contrast agent as a device and another, similar agent as a new drug. Id.

In the Proposed Rule, FDA states its plan to regulate small-packaged sunscreens for use on the lips or small areas of the face differently than all other sunscreens in small packages. Specifically, the Agency proposes to allow a modified indication statement and limited warnings for cosmetic-drug products labeled for use on small areas of the face if they meet the small package definition. 72 Fed. Reg. at 49114. Additionally, labels for lip protectants and lipsticks with sunscreen need not contain the "sun alert" and can have condensed directions, warnings, and indications statements. Id. FDA asserted that it provided these exemptions because the Agency "believes that sunscreen products labeled for use only on small areas of the face, including lip products containing sunscreen, serve an important public health need and FDA does not want to discourage manufacturers from marketing these products." Id. at 49075. It provided even more relief for lip products because these "are sold in even smaller packages" than the other sunscreen products. Id.

However, FDA refused to extend this labeling relief to other sunscreen products in small packages. It noted that “most” other makeup products with sunscreen “are not sold in small packages.” Id. at 49077. It also reasoned that manufacturers of these products would continue to market their products despite the requirement for full Drug Facts labeling, whereas manufacturers of lip and small area products would be “discourage[d]” from marketing their products if they had to meet the full Drug Facts labeling requirements. Id. FDA reasoned that the sun alert was necessary for all larger area face products because “FDA believes that consumers are at great risk for UV-induced skin damage, including cancer, on the face.” Id. FDA also stated that it would have “concerns” with labeling flexibility being applied to non-lip/non-small area products because these products “may be applied to a large area of the face or other areas of the body” and may serve as consumers’ everyday sunscreen. Id. at 49092.

We believe that FDA has not adequately justified its more lenient treatment of lip and small area sunscreen manufacturers. All sunscreen manufacturers who package their products in small packages face similar economic burdens in complying with labeling requirements. Their products are all OTC drug sunscreens for use on human skin, raising similar safety and efficacy concerns. Hence, FDA must treat these products similarly unless it can articulate a rational basis for regulating them differently.

FDA has not met its burden to support disparate treatment in this case. The Agency assumes that “most” non-lip and non-small face area sunscreen products are not sold in small packages. This reasoning does not justify disparate treatment of such products that are sold in small packages. The Agency’s other proffered justifications for treating such products differently also are not “rational bases” under Bracco. Consumers may rely on lip and small area products for everyday protection, just like other small package products. FDA has pointed to no medical evidence that consumers are at greater risk for skin damage or cancer on their faces as opposed to their lips, eyes, ears, and noses. Small package makeup products – such as concealers and foundations – are unlikely to be used all over the body, just like lip and small face area products. Finally, FDA’s economic justification is unconvincing. It has no basis to conclude that lip and small face area sunscreen manufacturers will suffer a greater economic impact from the full labeling rules than other manufacturers of small package sunscreens. Instead, all small package sunscreen manufacturers will be “discouraged” from manufacturing sunscreen products in view of FDA’s lengthy labeling requirements. Given that FDA assumes makeup products are more likely to serve as consumer’s primary sun protection, it is hard to understand why a disincentive to make these products would be more tolerable than a disincentive to make lip and small area sunscreens. Overall, FDA’s purported reasons for treating lip and small face area products differently are not compelling.

In summary, the Agency has not provided a rational basis for treating lip and small area sunscreen products differently than other small package sunscreen products. Instead, the Agency is forcing manufacturers of non-lip, non-small area sunscreens to run down a separate, more treacherous regulatory track than manufacturers of lip and small area sunscreens, for no apparent reason. The Proposed Rule is thus arbitrary and capricious in violation of the APA. Our proposed small package policy is supported

by the “rational basis” of actual product size. It proposes the most lenient requirements for the smallest products (lip products) and treats other small package sunscreens meeting the criteria of 21 C.F.R. 201.66(d)(10) similarly. The only proposed labeling distinction that is not based on package size – allowing omission of the “children under 6 months of age: ask a doctor” direction from color cosmetics and lipstick/lip gloss/color lip balm/lip color extender products – is based on a rational justification. These products, unlike others, will not foreseeable be used on children under six months of age, while parents may use sunscreen lip protectants and small package non-color cosmetic sunscreens on these children. FDA should adopt our proposal to avoid the identified legal problem.

2. The Agency Should Make Other Changes to the Small Package Labeling Requirements to Meet the FDCA’s Requirements and Streamline the Label.

We believe other labeling changes are also necessary for small package sunscreens.

With respect to PDP labeling for small package products, we believe FDA should make three primary changes, all of which are described above. The Agency should: (1) delete the “UVB” term from the required SPF value statement; (2) abandon the star rating system for UVA labeling; and (3) eliminate the requirement to include the “educational material” on the PDP. For non-lip products, this PDP educational statement should be combined with the proposed sun alert, condensed, and relocated to the Other Information part of the Drug Facts panel. For lip products (on which the sun alert is not required) FDA should utilize our proposed streamlined version of the PDP educational statement, and locate it in the Other Information section as well. Our proposed lip educational statement actually integrates components of the proposed sun alert and, in this regard, is more comprehensive than FDA’s corresponding proposal.

With respect to the back panel Drug Facts labeling, we propose that FDA allow the optional indications statement related to skin aging, skin damage, and certain types of skin cancer described in the “regular-sized” package section. We also propose several changes to streamline the labeling requirements. As explained above, the rash warning should refer to a “rash” rather than a “skin rash.” This requirement is less burdensome and consumers will still understand it. The reapplication directions should be condensed and the directed 2 hour reapplication time should be changed to “often” for the reasons outlined above. With respect to color cosmetics and lipstick/lip gloss/color lip balm/lip color extender products, we recommend deletion of the “children under 6 months of age: ask a doctor” direction, since these products are unlikely to be used on children. Finally, as explained, we believe these proposed changes should apply to small package products whether they are labeled for use on small parts of the face or not.

These suggestions are summarized in table (Tables 6 – 7) and graphic (Figures 4 – 11) form to illustrate the differences between FDA’s proposal and our recommended labeling.

Table 6: Lip Protectant

PDP Labeling		
FDA Proposal Rule	Industry Recommendation	Comments
UVB SPF [numeric value] (low/medium/high/highest) (e.g., "UVB SPF 15 Medium")	SPF [numeric value] (low/medium/high/highest) (e.g., "SPF 15 Medium")	Delete "UVB"
UVA (star rating) (low/medium/high/highest) protection (e.g., "UVA **** Highest") or "no UVA protection"	UVA (low/medium/high/highest) protection (e.g., "UVA Highest").	Delete star ("****") symbol requirement Delete "no UVA protection" labeling requirement
<p>"UV rays from the sun are made of UVB and UVA. It is important to protect against both UVB & UVA rays."</p> <p>or</p> <p>"UV rays from the sun are made of UVB and UVA. It is important to protect against both UVB & UVA rays to prevent sunburn and other skin damage."</p>		<p>Delete this required PDP statement</p> <p>[Require modified version in "Other Information" (see below)]</p>
"water resistant" [or "water/sweat resistant" or "water/perspiration resistant"] OR "very water resistant" [or "very water/sweat resistant" or "very water/perspiration resistant"] (if applicable)	"water resistant" [or "water/sweat resistant" or "water/perspiration resistant"] OR "very water resistant" [or "very water/sweat resistant" or "very water/perspiration resistant"] (if applicable)	[No proposed change]
Back Panel Labeling		
<p><i>Use:</i></p> <ul style="list-style-type: none"> helps prevent sunburn 	<p><i>Use:</i></p> <ul style="list-style-type: none"> helps prevent 	Allow optional indication related to skin aging, skin

and chapped lips	<p>sunburn and chapped lips</p> <ul style="list-style-type: none"> • with regular [or continued] use helps protect against premature skin aging [or “skin damage” or “certain types of skin cancer”] caused by the sun. <i>(optional)</i> 	damage, or certain types of skin cancer
<p><i>Warning:</i></p> <p>Stop use if skin rash occurs.</p>	<p><i>Warning:</i></p> <p>Stop use if rash occurs.</p>	Omit “skin” from rash warning
<p><i>Directions:</i></p> <ul style="list-style-type: none"> • apply liberally [or generously] [(optional) and evenly] (time, if required) before sun exposure • apply and reapply as directed to avoid lowering protection • children under 6 months of age: ask a doctor • apply liberally and reapply at least every 2 hours for sunburn protection 	<p><i>Directions:</i></p> <ul style="list-style-type: none"> • Apply liberally [or generously] [(optional) and evenly] (time, if required) before sun exposure • To maintain protection, reapply often and after rubbing, swimming, sweating [or perspiring] • Children under 6 months: ask doctor 	Condense reapplication directions and replace “at least every two hours” with “often”
	<p><i>Other Information:</i></p> <p>It is important to protect against both UVB & UVA rays from the sun since they increase the risk of skin cancer, premature skin aging and other skin damage.</p>	Add modified version of proposed PDP educational statement to Other Information section

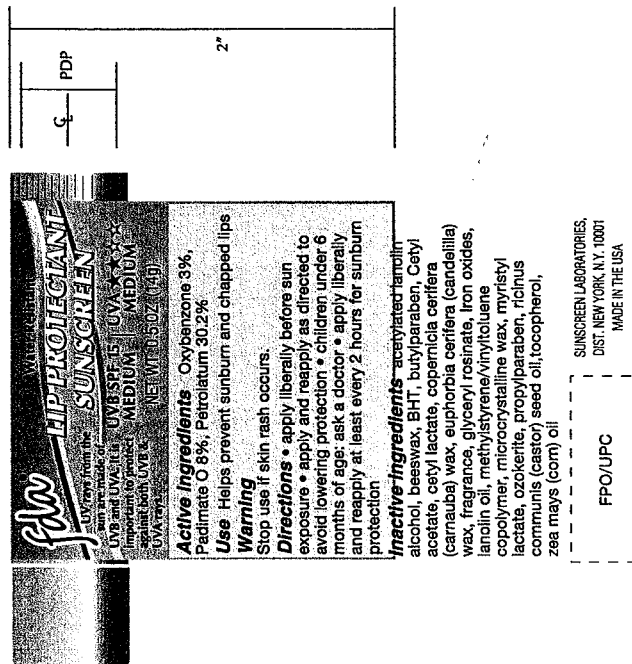
Figure 4:

Type Specs

DFF Headers: Helv. Med 7pt/6.5pt TR:-10
DFF Info: Helv.Med.Con 6pt/6.5 TR:-10
Address: Helv. Med Con 5pt
SOL: Optima BI 9pt/9pt
UVA/UVB: Optima BL 6pt/6pt
NET WEIGHT: Helv. Med Con 7pt TR:25

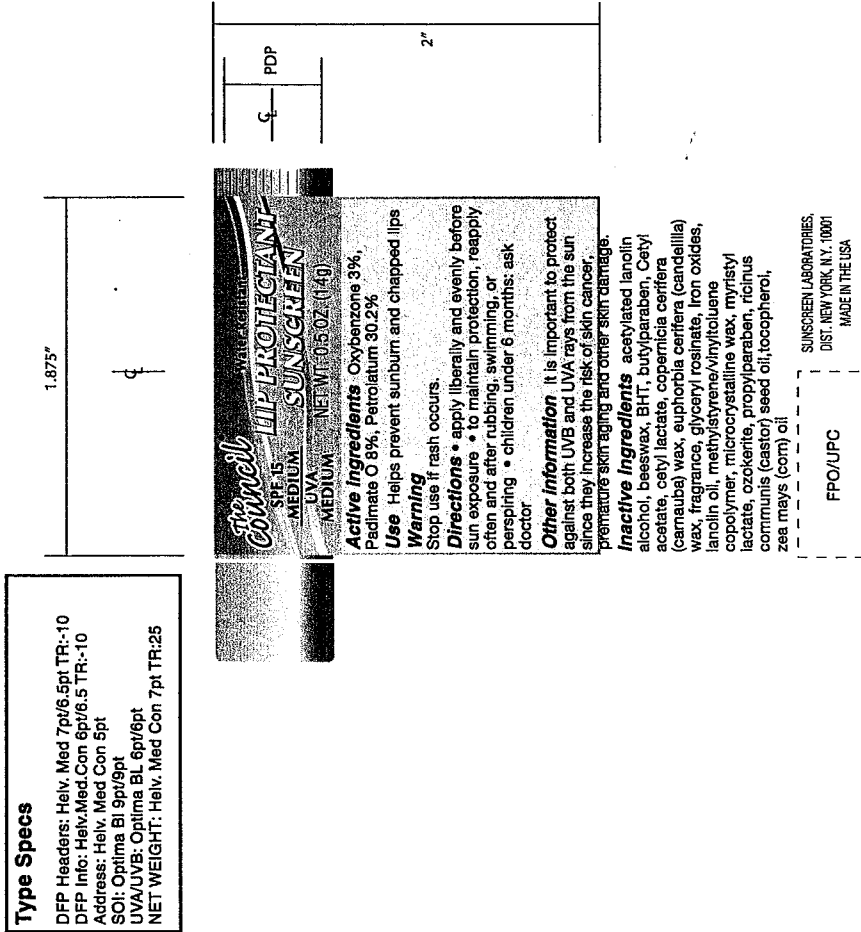
1.875"

—



This Figure is intended to provide an illustrative example for demonstration purposes and for ease of visualizing the proposed/recommended label.

Figure 5:
Industry Recommended Lip Protectant



This Figure is intended to provide an illustrative example for demonstration purposes
 and for ease of visualizing the proposed/recommended label.

Table 7: Lipstick, Lip Gloss, Color Lip Balm, Lip Color Extenders

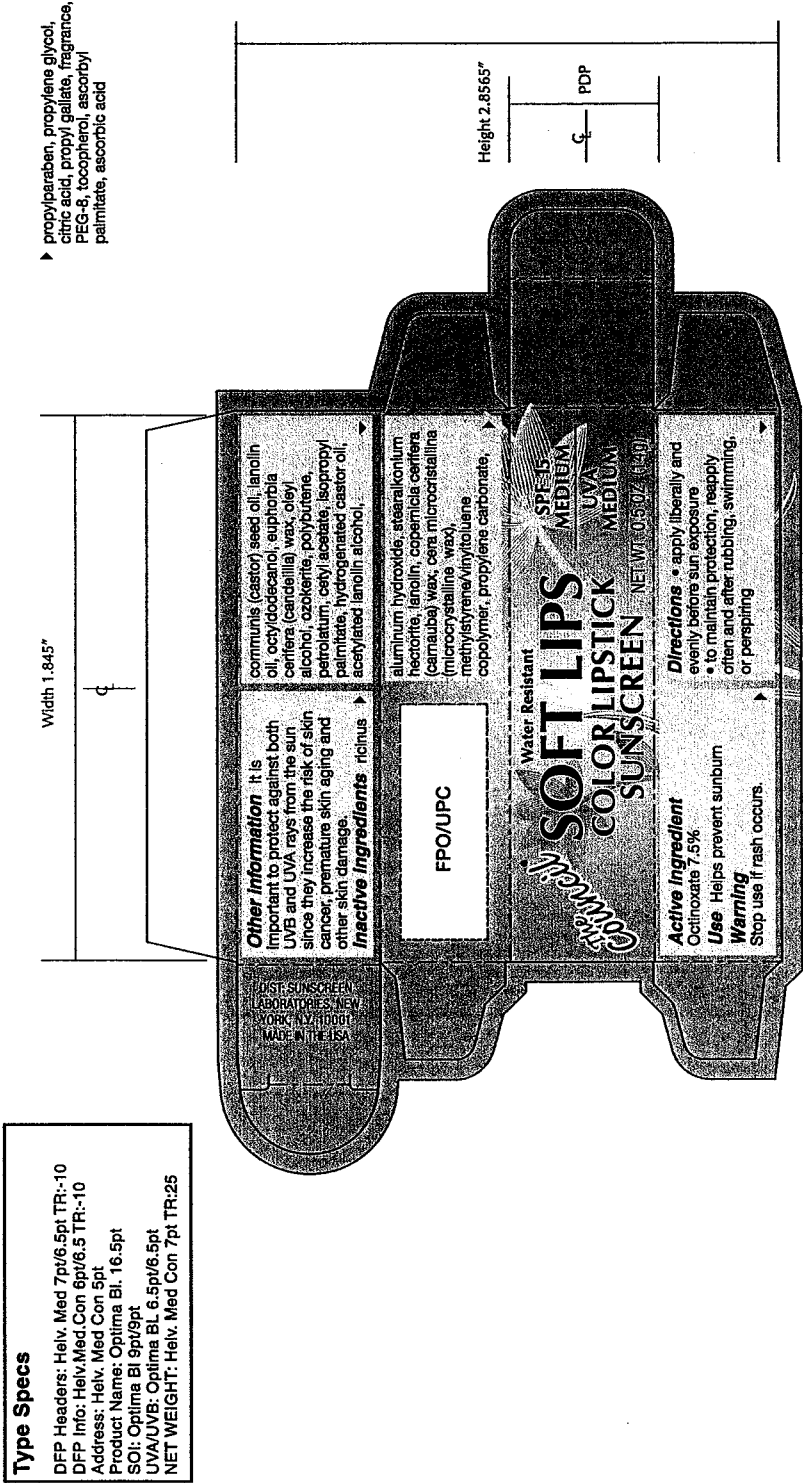
PDP Labeling		
FDA Proposed Rule	Industry Recommendation	Comments
UVB SPF [numeric value] (low/medium/high/highest) (e.g., “UVB SPF 15 Medium”)	SPF [numeric value] (low/medium/high/highest) (e.g., “SPF 15 Medium”)	Delete “UVB”
UVA (star rating) (low/medium/high/highest) protection (e.g., “UVA **** Highest”) or “no UVA protection”	UVA (low/medium/high/highest) protection (e.g., “UVA Highest”).	Delete star (“****”) symbol requirement Delete “no UVA protection” labeling requirement
“UV rays from the sun are made of UVB and UVA. It is important to protect against both UVB & UVA rays.” or “UV rays from the sun are made of UVB and UVA. It is important to protect against both UVB & UVA rays to prevent sunburn and other skin damage.”		Delete this required PDP statement [Require modified version in “Other Information” (see below)]
“water resistant” [or “water/sweat resistant” or “water/perspiration resistant”] OR “very water resistant” [or “very water/sweat resistant” or “very water/perspiration resistant”] (if applicable)	“water resistant” [or “water/sweat resistant” or “water/perspiration resistant”] OR “very water resistant” [or “very water/sweat resistant” or “very water/perspiration resistant”] (if applicable)	[No proposed change]
Back Panel Labeling		
<i>Use:</i> helps prevent sunburn	<i>Use:</i> <ul style="list-style-type: none"> helps prevent sunburn with regular [or 	Allow optional indication related to skin aging, skin damage, or certain types of skin cancer

	continued] use helps protect against premature skin aging [or “skin damage” or “certain types of skin cancer”] caused by the sun. <i>(optional)</i>	
Warning: Stop use if skin rash occurs.	Warning: Stop use if rash occurs.	Omit “skin” from rash warning
Directions: <ul style="list-style-type: none"> • apply liberally [or generously] [(optional) and evenly] (time, if required) before sun exposure • apply and reapply as directed to avoid lowering protection • children under 6 months of age: ask a doctor • apply liberally and reapply at least every 2 hours for sunburn protection 	Directions: <ul style="list-style-type: none"> • Apply liberally [or generously] [(optional) and evenly] (time, if required) before sun exposure • To maintain protection, reapply often and after rubbing, swimming, sweating [or perspiring] 	Condense reapplication directions and replace “at least every two hours” with “often” Omit child direction
	Other Information: It is important to protect against both UVB and UVA rays from the sun since they increase the risk of skin cancer, premature skin aging and other skin damage.	Add modified version of proposed PDP educational statement to Other Information section

Type Specs



Figure 7:
Industry Recommended Lipstick



This Figure is intended to provide an illustrative example for demonstration purposes and for ease of visualizing the proposed/recommended label.

Table 8: Small-Size Package OTC Sunscreen

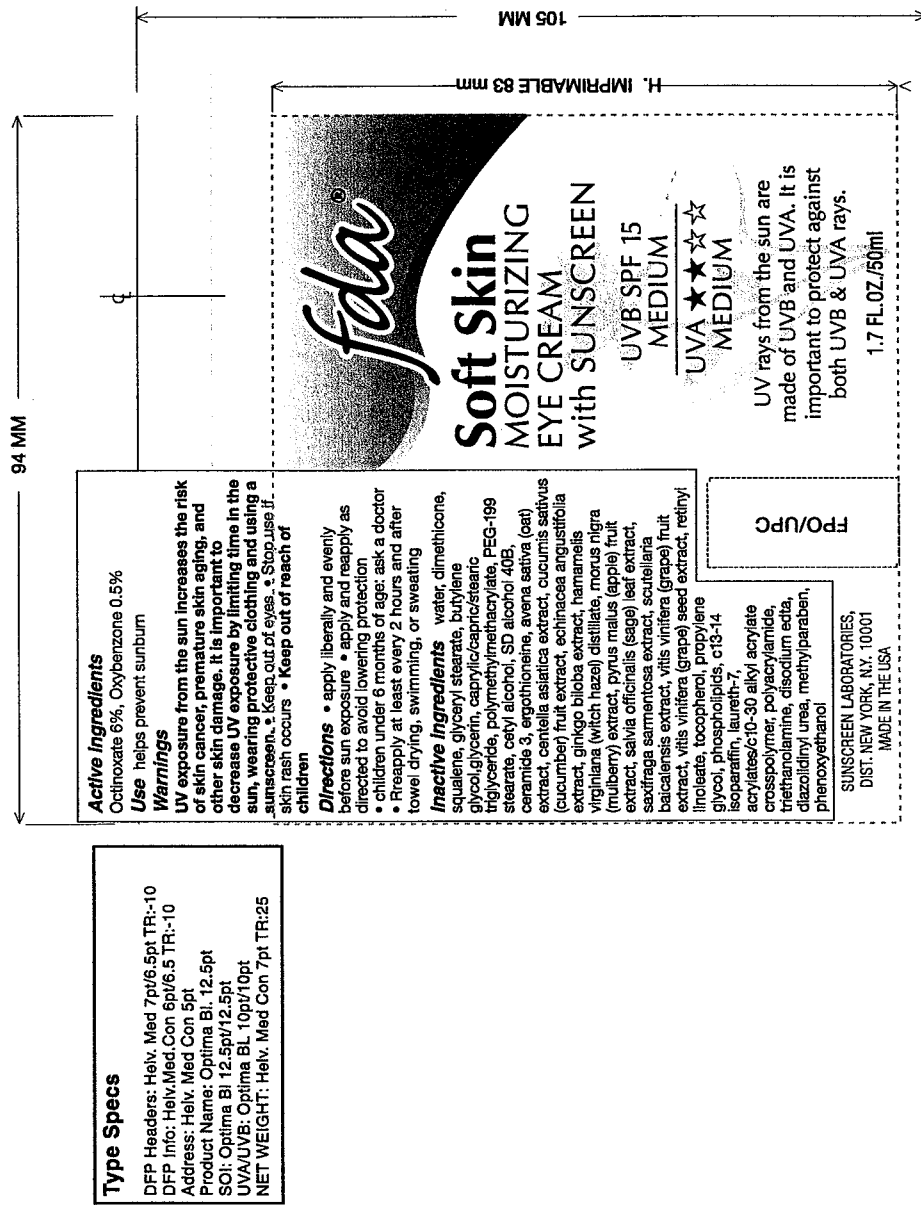
PDP Labeling		
FDA Proposed Rule	Industry Recommendation⁶⁹	Comments
UVB SPF [numeric value] (low/medium/high/highest) (e.g., “UVB SPF 15 Medium”)	SPF [numeric value] (low/medium/high/highest) (e.g., “SPF 15 Medium”)	Delete “UVB”
UVA (star rating) (low/medium/high/highest) protection (e.g., “UVA **** Highest”) or “no UVA protection”	UVA (low/medium/high/highest) protection (e.g., “UVA Highest”).	Delete star (“****”) symbol requirement Delete “no UVA protection” labeling requirement
<p>“UV rays from the sun are made of UVB and UVA. It is important to protect against both UVB & UVA rays.”</p> <p>or</p> <p>“UV rays from the sun are made of UVB and UVA. It is important to protect against both UVB & UVA rays to prevent sunburn and other skin damage.”</p>		<p>Delete this required PDP statement</p> <p>[Combine with proposed FDA warning and require in “Other Information” (see below)]</p>
<p>“water resistant” [or “water/sweat resistant” or “water/perspiration resistant”] OR “very water resistant” [or “very water/sweat resistant” or “very water/perspiration resistant”] (if applicable)</p>	<p>“water resistant” [or “water/sweat resistant” or “water/perspiration resistant”] OR “very water resistant” [or “very water/sweat resistant” or “very water/perspiration resistant”] (if applicable)</p>	[No proposed change]

⁶⁹ As discussed, we believe that these suggestions should apply to small packages under 21 C.F.R. 201.66(d)(10), regardless of whether labeled for use on small parts of the face.

Back Panel Labeling		
<p><i>Use:</i></p> <p>helps prevent sunburn</p>	<p><i>Use:</i></p> <ul style="list-style-type: none"> • helps prevent sunburn • with regular [or continued] use helps protect against premature skin aging [or “skin damage” or “certain types of skin cancer”] caused by the sun. <i>(optional)</i> 	<p>Allow optional indication related to skin aging, skin damage, or certain types of skin cancer</p>
<p><i>Warnings:</i></p> <p>UV exposure from the sun increases the risk of skin cancer, premature skin aging and other skin damage. It is important to decrease UV exposure by limiting time in the sun, wearing protective clothing, and using a sunscreen.</p> <ul style="list-style-type: none"> • keep out of eyes • stop use if skin rash occurs. • keep out of reach of children. 	<p><i>Warnings:</i></p> <ul style="list-style-type: none"> • keep out of eyes. • stop use if rash occurs. • keep out of reach of children. 	<p>Omit proposed sun alert requirement.</p> <p>[Combine with proposed FDA warning and require in “Other Information” (see below)]</p> <p>Omit “skin” from rash warning</p>
<p><i>Directions:</i></p> <ul style="list-style-type: none"> • apply liberally [or generously] [(optional) and evenly] (time, if required) before sun exposure • apply and reapply as directed to avoid lowering protection • children under 6 months of age: ask a 	<p><i>Directions:</i></p> <ul style="list-style-type: none"> • Apply liberally [or generously] [(optional) and evenly] (time, if required) before sun exposure • To maintain protection, reapply often and after rubbing, swimming, sweating [or perspiring] 	<p>Condense reapplication directions and replace “at least every two hours” with “often”</p>

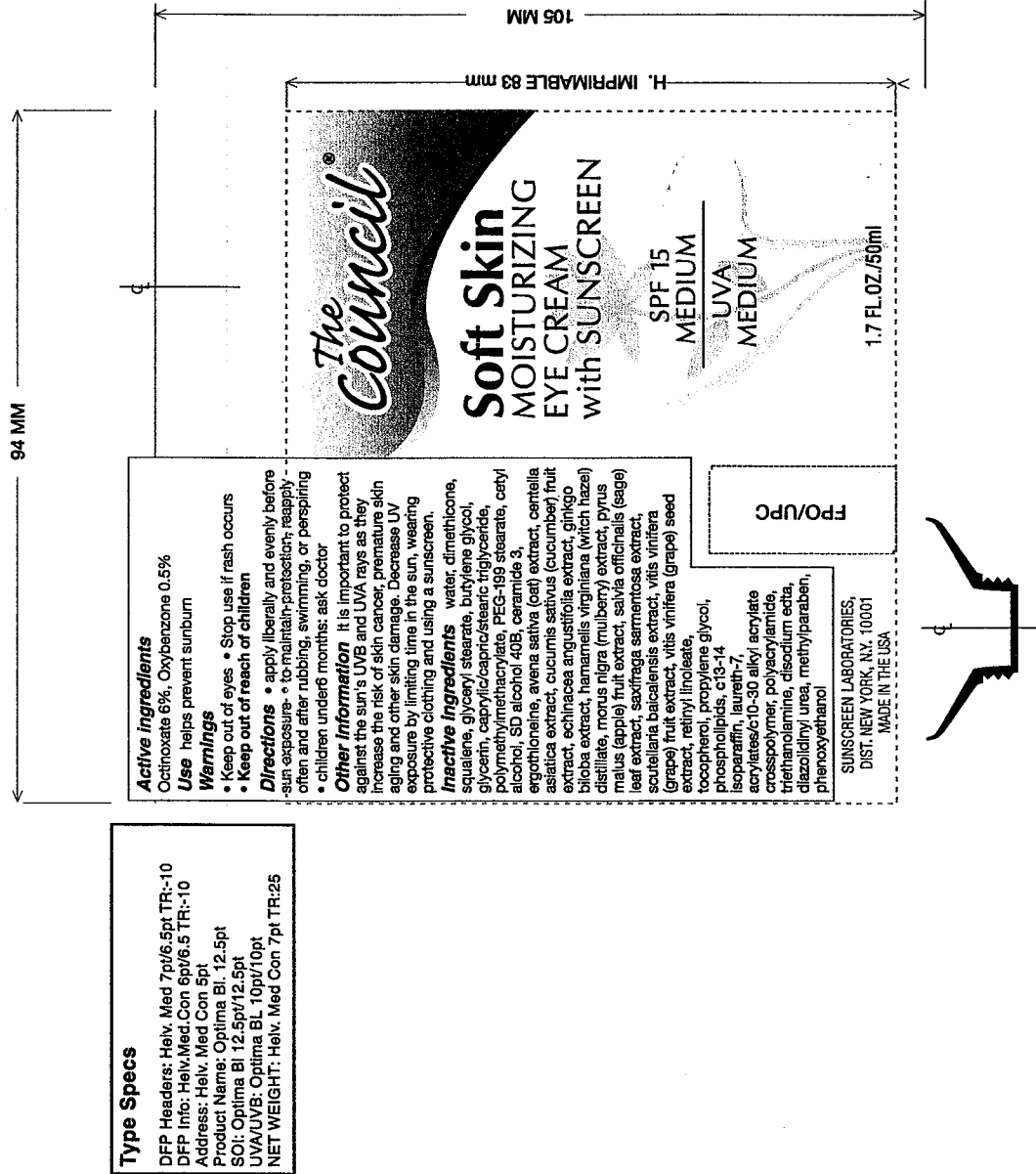
<p>doctor</p> <ul style="list-style-type: none"> • reapply at least every 2 hours and after towel drying, swimming, or sweating [or perspiring] <p>OR if water/very water resistant, replace this statement with the following statement:</p> <ul style="list-style-type: none"> • reapply after 40/80 minutes of swimming or sweating/perspiring and after towel drying. Otherwise, reapply at least every 2 hours. 	<p>OR if water/very water resistant, replace the above statement with the following statement:</p> <ul style="list-style-type: none"> • To maintain protection, reapply after 40/80 minutes of swimming or sweating/perspiring and after towel drying. • Children under 6 months: ask doctor 	
	<p><i>Other Information:</i></p> <p>It's important to protect against the sun's UVB & UVA rays as they increase the risk of skin cancer, premature skin aging and other skin damage. Decrease UV exposure by limiting time in the sun, wearing protective clothing and using a sunscreen.</p>	<p>Add condensed version of sun alert and proposed PDP educational statement to Other Information section</p>

Figure 8:
FDA Proposed Rule Small Package OTC Sunscreen



This Figure is intended to provide an illustrative example for demonstration purposes and for ease of visualizing the proposed/recommended label.

Figure 9:
Industry Recommended Small Package OTC Sunscreen



This Figure is intended to provide an illustrative example for demonstration purposes and for ease of visualizing the proposed/recommended label.

Table 9: Small-Size Package OTC Sunscreen (with Color Cosmetic)

PDP Labeling		
FDA Proposed Rule	Industry Recommendation⁷⁰	Comments
UVB SPF [numeric value] (low/medium/high/highest) (e.g., “UVB SPF 15 Medium”)	SPF [numeric value] (low/medium/high/highest) (e.g., “SPF 15 Medium”)	Delete “UVB”
UVA (star rating) (low/medium/high/highest) protection (e.g., “UVA **** Highest”) or “no UVA protection”	UVA (low/medium/high/highest) protection (e.g., “UVA Highest”).	Delete star (“****”) symbol requirement Delete “no UVA protection” labeling requirement
<p>“UV rays from the sun are made of UVB and UVA. It is important to protect against both UVB & UVA rays.”</p> <p>or</p> <p>“UV rays from the sun are made of UVB and UVA. It is important to protect against both UVB & UVA rays to prevent sunburn and other skin damage.”</p>		<p>Delete this required PDP statement</p> <p>[Combine with proposed FDA warning and require in “Other Information” (see below)]</p>
<p>“water resistant” [or “water/sweat resistant” or “water/perspiration resistant”] OR “very water resistant” [or “very water/sweat resistant” or “very water/perspiration resistant”] (if applicable)</p>	<p>“water resistant” [or “water/sweat resistant” or “water/perspiration resistant”] OR “very water resistant” [or “very water/sweat resistant” or “very water/perspiration resistant”] (if applicable)</p>	[No proposed change]

⁷⁰ As discussed, the Council believes that these suggestions should apply to small packages under 21 C.F.R. 201.66(d)(10), regardless of whether labeled for use on small parts of the face.

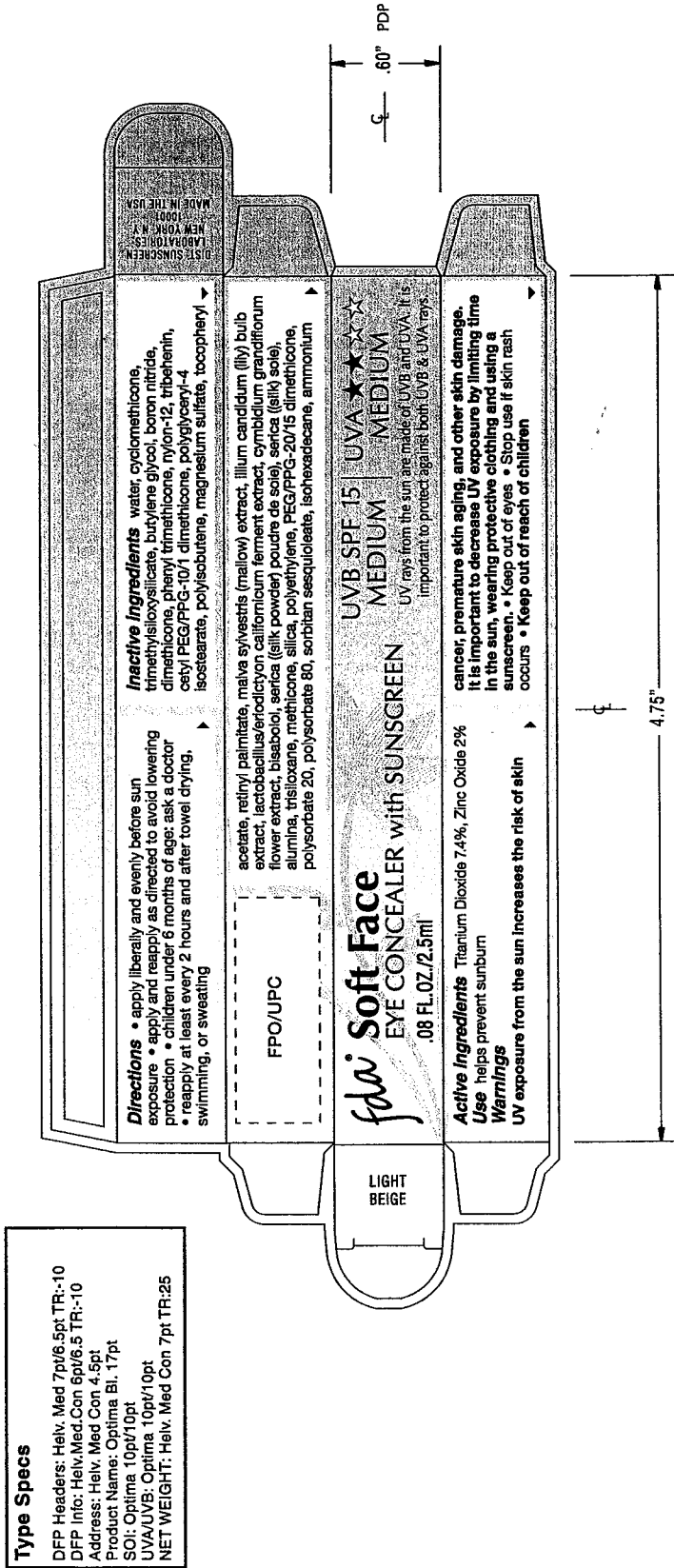
Back Panel Labeling		
<p>Use:</p> <p>helps prevent sunburn</p>	<p>Use:</p> <ul style="list-style-type: none"> • helps prevent sunburn • with regular [or continued] use helps protect against premature skin aging [or “skin damage” or “certain types of skin cancer”] caused by the sun. <i>(optional)</i> 	<p>Allow optional indication related to skin aging, skin damage, or certain types of skin cancer</p>
<p>Warnings:</p> <p>UV exposure from the sun increases the risk of skin cancer, premature skin aging and other skin damage. It is important to decrease UV exposure by limiting time in the sun, wearing protective clothing, and using a sunscreen.</p> <ul style="list-style-type: none"> • keep out of eyes • stop use if skin rash occurs. • keep out of reach of children. 	<p>Warnings:</p> <ul style="list-style-type: none"> • keep out of eyes. • stop use if rash occurs. • keep out of reach of children. 	<p>Omit proposed sun alert requirement.</p> <p>[Combine with proposed FDA warning and require in “Other Information” (see below)]</p> <p>Omit “skin” from rash warning</p>
<p>Directions:</p> <ul style="list-style-type: none"> • apply liberally [or generously [(optional) and evenly] (time, if required) before sun exposure • apply and reapply as directed to avoid lowering protection • children under 6 months of age: ask a 	<p>Directions:</p> <ul style="list-style-type: none"> • Apply liberally [or generously] [(optional) and evenly] (time, if required) before sun exposure • To maintain protection, reapply often and after rubbing, swimming, sweating [or perspiring] <p>OR if water/very water resistant, replace the above</p>	<p>Condense reapplication directions and replace “at least every two hours” with “often”</p> <p>Omit child direction</p>

<p>doctor</p> <ul style="list-style-type: none"> reapply at least every 2 hours and after towel drying, swimming, or sweating [or perspiring] <p>OR if water/very water resistant, replace this statement with the following statement:</p> <ul style="list-style-type: none"> reapply after 40/80 minutes of swimming or sweating [or perspiring and after towel drying. Otherwise, reapply at least every 2 hours. 	<p>statement with the following statement:</p> <ul style="list-style-type: none"> To maintain protection, reapply after 40/80 minutes of swimming or sweating/perspiring and after rubbing. 	
	<p><i>Other Information:</i></p> <p>It is important to protect against both UVB and UVA rays from the sun since they increase the risk of skin cancer, premature skin aging and other skin damage. Decrease UV exposure by limiting time in the sun, wearing protective clothing and using a sunscreen.</p>	<p>Add condensed version of sun alert and proposed PDP educational statement to Other Information section</p>

Figure 10:

FDA Proposed Rule Small-Size Package OTC Sunscreen (with Color Cosmetic)

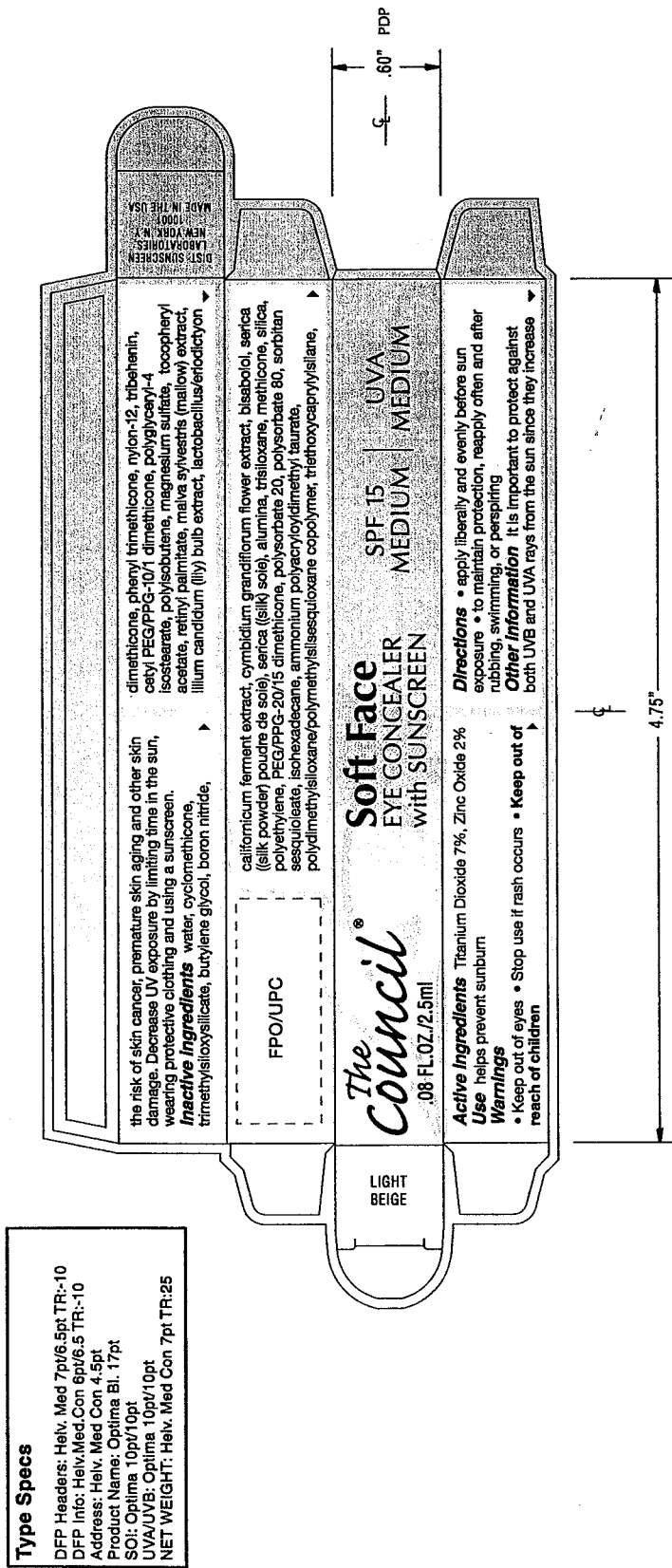
► polyacryloyldimethyl taurate, polydimethylsiloxane/polymethylsilsesquioxane copolymer, triethoxycaprylsilane, tetrasodium EDTA, phenoxethanol, methylparaben, ethylparaben, propylparaben



This Figure is intended to provide an illustrative example for demonstration purposes and for ease of visualizing the proposed/recommended label.

Figure 11:
Industry Recommended Small-Size Package OTC Sunscreen (with Color Cosmetic)

► tetrasodium EDTA, phenoxyethanol, methylparaben, ethylparaben, propylparaben



This Figure is intended to provide an illustrative example for demonstration purposes and for ease of visualizing the proposed/recommended label.

H. Conclusion

In summary, FDA must eliminate the following components of its Proposed Rule: (1) the mandated “UVB SPF” terminology, which is false and misleading; (2) the “no UVA protection disclaimer,” which will be factually false and misleading in many cases; and (3) the UVA star labeling system, which will confuse consumers and is therefore misleading. The term “SPF” should be used instead of “UVB SPF.” FDA should simply allow for products that are not tested for UVA or that have a UVA level of less than 2 to remain silent on UVA protection. FDA should use only the category descriptors for UVA protection.

We urge FDA to combine its proposed sun alert and PDP educational statement and relocate the condensed statement in Other Information section of the Drug Facts panel. This change will reflect that the sun alert is not a “warning” in the statutory or regulatory sense or under previous Agency usage. FDA should modify the reapplication directions because the directed 2 hour reapplication interval is not scientifically supported. It should streamline these directions and the rash warning. It should also eliminate the additional water resistant indication statement and unneeded child directions to avoid unduly burdensome labeling requirements. FDA should permit the optional indications statement relating to skin damage, skin cancer, and premature skin aging. Finally, FDA should modify its proposed small package rules. The APA prohibits FDA from treating small area and lip products differently than other small package products. The Agency should therefore adopt a small package labeling regime like the one we recommend, which draws distinctions based on package size and practical considerations.

V. **INGREDIENTS**

We support the addition of the combination of avobenzone with ensulizole and avobenzone with zinc oxide (ZnO), and urges the Agency to give interim approval for these combinations prior to issuance of a final monograph.

VI. **IMPLEMENTATION**

FDA should allow for a 36-month implementation period. The proposed 18-24 month implementation period does not provide sufficient time for industry to comply with the Proposed Rule. The Agency noted that “estimating the number of products affected is difficult because we lack data on the number of products currently marketed.” 27 Fed. Reg. at 49108. However, FDA estimates that the number of sunscreen products on the market is approximately 3000; of which about 75% would be retested for UVA protection. For the record, we disagree with both of these estimates.

We believe that the number of products on the market is greater than 3000 and that the percentage of products that will need to be retested for UVA is at least 90%.

However, assuming *arguendo*, FDA's estimate of the number of products (i.e., 3000) is accurate, the time period required to conduct the testing and execute necessary relabeling would be at least 36 months, as discussed below.

A. FDA Has Underestimated the Number of Products that Would Require Testing and Should Extend the Implementation Period Accordingly

We believe FDA has not accurately estimated the increased amount of required UVA testing. The number of products that will need to be tested is much more than what is anticipated by FDA (i.e., approximately 90%). Because a significant number of current sunscreen formulations already provide UVA protection – and since companies would be required to relabel anyway – it is highly likely that they will wish to include UVA claims on their relabeled products. This will result in a substantially larger demand for UVA testing than FDA has anticipated.

Furthermore, the Agency has not adequately considered the limited capacity of individual testing labs. The increased UVA testing demand will overwhelm the limited number of clinical laboratories (approximately 5-6 laboratories), making testing and data generation an even more lengthy process; with every sunscreen manufacturer affected by the new requirements. The proposed water resistant UVA testing will also be very time consuming. Moreover, these test labs will also need to continue conducting SPF testing and begin PFA testing for new products during this period. FDA's suggested time frame is not realistic given the magnitude of the testing that would be required.

In total, the proposed requirements will likely more than double the amount of clinical testing that the industry conducts. For example, if we assume for the purposes of a straw man calculation that there are 6 test labs that would be able to perform the *in vivo* UVA test and that they could each run 5 full panels of 20 subjects for water resistant PFA testing per week, then:

$$\frac{3000 \text{ products}}{30 \text{ panels per week}} = 100 \text{ weeks (approximately 2 years)}^{71}$$

However, before UVA testing can even begin, commercial clinical test laboratories must order, install, calibrate and test the required equipment. Trials must then be conducted to insure that the methodology and protocols can be properly carried out, and that laboratory technicians are familiar with the changes. Thus, before laboratories can even begin testing current formulations, we estimate that at least 5 months will have elapsed.

71

Approximately 2 years minimum to benchmark all current products.

B. FDA Has Underestimated the Amount of Required Relabeling and Should Extend the Implementation Period Accordingly

FDA has stated that the majority of products on the market are sold primarily in tubes or plastic bottles without a secondary carton. This is not correct. Facial and body moisturizers as well as facial cosmetics, which include foundations, powders and concealers and some lip products, are sold with primary *and* secondary graphics. These products represent a large number of cosmetic sunscreens on the market. Every package, primary and secondary, will need relabeling and the *in vivo* and *in vitro* test data would need to be available before label artwork modification could be completed. In addition, many product packaging forms have extended lead times due to the types of printing and other decoration methods involved.

For these reasons, we request that FDA extend the time frame for implementation of the Final OTC sunscreen monograph to a time period of at least 36 months in order for manufacturers to prepare, complete and execute changes in labeling and/or product design.

VII. ECONOMIC IMPACT

We agree with FDA that retesting of current SPF values is unnecessary. Also, we agree that when generating an economic impact estimate, it is necessary to make assumptions in the absence of precise data. The Agency has estimated that the one-time incremental cost of the Proposed Rule is \$53 million.⁷² We, however, believe this is a significant underestimation. We estimate that the economic impact of the Proposed Rule is approximately \$124.7 million.

A. FDA's Underestimation of the Amount and Cost of UVA Testing has Contributed to an Underestimation of the Economic Impact of the Proposed Rule

FDA estimated the total one-time cost to industry of retesting products for UVA protection at approximately \$5.4 million (\$2,400 per product). We disagree, and submit a more accurate estimate of approximately \$32.9 million (\$12,000 per product).

As explained in Section VI above, we believe that approximately 2,700 products would require UVA testing. A number of leading contract laboratories estimate that the cost of UVA testing is \$12,200 per product (*in vitro* UVAI/UV testing at \$800 + *in vivo* testing at \$11,400). Thus, 2,700 products tested at \$12,200 per product, in aggregate, equals \$32.9 million cost to the industry for retesting.

⁷²

72 Fed Reg 49070 at 49108.

B. FDA's Underestimation of the Amount and Cost of Relabeling Has Contributed to an Underestimation of the Economic Impact of the Proposed Rule

FDA has estimated that the total one-time cost to industry for relabeling individual stock keeping units (SKUs) is approximately \$47.5 million (\$7,600 per SKU). We disagree. The cost to relabel products per the Proposed Rule is approximately \$90 million (\$15,000 per SKU).

For an SKU requiring the addition of a new carton or expanded labeling (e.g., tri-fold label), the total cost would be \$15,000 – 17,000. If the product is currently marketed with secondary labeling, then the cost to relabel would be \$10,000 – \$12,000. Additionally, all SKUs, including both primary and secondary labeling and/or packaging would also require redesigning work that we modestly estimate at \$5,000 per SKU. Thus, our reasonable estimate of relabeling cost is approximately \$15,000 per SKU. For calculation and comparison sake, if we use FDA's 6,000 (i.e., 50%) SKU number, the total relabeling cost per SKU is \$90 million.

Applying the revised cost estimates for retesting and labeling, the one-time incremental cost of the Proposed Rule is \$124.2 million.⁷³

VIII. SUNSCREENS CONTAINING AHAS

FDA is considering an additional warning or direction for sunscreen drug products containing AHAs similar to the warning for the cosmetic products⁷⁴ described in the guidance for industry. Given the body of existing evidence on AHAs and skin sensitivity we do not believe that voluntary or mandatory labeling on OTC sunscreen drug products containing AHAs regarding possible risks of increased sun damage (e.g., sunburn) is warranted. Recently, the effect to the skin from sunscreen products containing AHAs was evaluated by the SCCNFP. According to the SCCNFP, two clinical studies examined the effects of several commercially available moisturizers containing a sunscreen and an AHA, and exposures to 1 MED did not increase sunburn cells (or "SBCs") significantly.⁷⁵ Furthermore, such a warning is confusing and nonsensical, especially in light of FDA's guidance regarding cosmetics containing AHAs.

⁷³ \$34.2 million (retesting) + \$90 million (relabeling) = \$124.2 million.

⁷⁴ FDA Guidance for Industry, Labeling for Topically Applied Cosmetic Products Containing Alpha Hydroxy Acids as Ingredients (January 10, 2005) (For cosmetics containing AHAs, FDA recommends, "Sunburn Alert: This product contains an alpha hydroxy acid (AHA) that may increase your skin's sensitivity to the sun and particularly the possibility of sunburn. Use a sunscreen and limit sun exposure while using this product and for a week afterwards.")

⁷⁵ Updated Position Paper Concerning Consumer Safety of Alpha-Hydroxy Acids, SCCNFP/0799/04, adopted by SCCNFP on May 25, 2004.

IX. NANOTECHNOLOGY AND SUNSCREENS

FDA requested comment on TiO₂ formulated in particle sizes as small as a few nanometres and referred to a previous assessment of micronized TiO₂ and the conclusion that there was no evidence of a safety concern from use of this material in sunscreen products.

In brief there is significant evidence that commercial forms of TiO₂ and ZnO, used as UV filters, are safe for intended use.

A. Properties

The small particle size of sunscreen grades of TiO₂ and ZnO is essential in order to deliver effective UV protection in a form which is acceptable to the consumer. Larger size materials give poor UV protection and are opaque and white on skin.

Inorganic sunscreens are very mild on skin, provide broad spectrum protection, and work synergistically with organic sunscreens. This makes them particularly valuable in high SPF formulations or products for sensitive skin and/or children.

B. Safety of Inorganic Sunscreens

1. General

There is a significant amount of research showing that inorganic UV filters are safe for intended use. Recently, both European and Australian⁷⁶ experts have summarized the extensive data and found no reliable evidence that TiO₂ or ZnO present any concern for their intended use as UV filters in sunscreens and cosmetic products. Further another review of available data on the safety on nanotechnology and nanoparticles in cosmetics, and in particular sunscreens, also concluded that there is no evidence that insoluble ZnO or TiO₂ nanoparticles used in sunscreens penetrate into or through human skin or may produce human local or systemic exposure and/or adverse health effects.⁷⁷

This growing consensus among experts was well summarized by the American Health Foundation in its 1996 report reviewing of all *in vitro* and *in vivo* safety and

⁷⁶ SCCNFP opinion concerning titanium dioxide:- http://ec.europa.eu/health/ph_risk/committees/sccp/documents/out135_en.pdf; and Australian Therapeutic Goods Administration review on the safety of sunscreens containing nanoparticles of titanium dioxide or zinc oxide:- <http://www.tga.gov.au/npmuds/sunscreen-zotd.htm>

⁷⁷ G.J.Nohynek, J.Lademann, C.Ribaud, M.S.Roberts; *Grey Goo on the Skin? Nanotechnology, Cosmetic and Sunscreen Safety. Critical Reviews in Toxicology* **37**:251-277, 2007.

toxicity studies which had been conducted with fine particle TiO₂ and ZnO. This review concluded that:

- There is no evidence of any negative biological impact of topical TiO₂ or ZnO, alone or in combination with other UV absorbers;
- Theoretical concern to the photocatalytic activity of TiO₂ is not supported by numerous studies using multiple methods and endpoint measures designed to detect such effects; and
- The risks of potential photooxidative effects of TiO₂ and ZnO in sunscreen formulations have been demonstrated to be negligible.

2. Skin Penetration

The small particle size of inorganic sunscreens has led to a theoretical concern that these particles may penetrate the skin. There has been considerable research on skin penetration of TiO₂, and this issue was specifically addressed by the SCCNFP in their opinion on TiO₂.⁷⁸ The weight of evidence demonstrates that these particles remain on the surface of the skin.⁷⁹

A review by Fitzgerald,⁸⁰ submitted to the European Commission's Scientific Committee on Consumer Products in 2005, concluded:

Neither established *in vitro* and *in vivo* dermal penetration methods, nor other sophisticated experimental methods, such as the ion beam analytical methods used in the NANODERM project, have found any meaningful penetration of titanium dioxide through the skin. Menzel et al (2004) reported that "it has been proved that micronized TiO₂ ...penetrated...into the living stratum granulosum" but their published data do not support this conclusion. The consensus among all other investigators is that there is no measurable penetration of ultrafine titanium dioxide through the stratum

⁷⁸ SCCNFP opinion concerning titanium dioxide:-
http://ec.europa.eu/health/ph_risk/committees/sccp/documents/out135_en.pdf

⁷⁹ F. Pflücker, V. Wendel, H. Hohenberg, E. Gärtner, T. Will, S. Pfeiffer, R. Wepf, H. Gers-Barlag; *Skin Pharmacology & Applied Skin Physiology* 2001:14 (suppl1), 92-97; Schulz J, Hohenberg H, Pflücker F, Gärtner E, Will T, Pfeiffer S, Wepf R, Wendel V, Gers-Barlag H, Wittern KP (2002); Distribution of sunscreens on skin. *Adv Drug Deliv Rev.* 2002 Nov 1;54 Suppl 1:S157-63; and Gelis C, Miquel C, Mavon A (2004). *In vivo* and *ex vivo* study of the skin penetration of mineral and organic sunscreens and assessment of the efficiency of this photoprotection on a reconstituted human epidermis. Poster no. 111 presented at 23rd IFSCC (International Federation Societies of Cosmetical Scientists) International Congress, Orlando, Florida, 24-27 Oct 2004.

⁸⁰ R. Fitzgerald, Review of recent literature on safety of nanomaterials in cosmetics with special references to skin absorption and resorption of ultrafine titanium dioxide and zinc oxide, 26 September 2005.

corneum in animal or human skin either *in vitro* or *in vivo*... The data for penetration of ultrafine zinc oxide are limited to animal skin *in vitro*, but are consistent with those for titanium dioxide: there is no measurable passage of ultrafine zinc oxide through the stratum corneum.

Referring specifically to new studies which had been carried out after the SCCNFP opinion on TiO₂,⁸¹ Fitzgerald further concluded:

None of these new nanoparticulate skin penetration data affect the conclusions reached by SCCNFP for titanium dioxide or zinc oxide on the basis of data obtained from standard guideline studies of dermal penetration, i.e. the current test guidelines for skin penetration still appear to be the optimal method for assessing exposure, irrespective of particle size.

In January 2006, the Australian Therapeutic Goods Administration (ATGA) conducted a review of the scientific literature in relation to the use of nanoparticulate ZnO and TiO₂ in sunscreens.⁸² They noted the results from isolated cell experiments indicate that ZnO and TiO₂ can induce free radical formation in the presence of light. However the ATGA recognised this would only be a concern for people using sunscreens if there was penetration into viable skin cells. They concluded on weight of evidence that this is not the case.

The most recent review by Nohynek *et al* referenced the SCCNFP opinion and the skin penetration studies discussed within it, and also discussed other studies which have been conducted more recently.⁸³ Once again, the authors concluded that:

At present, there is no evidence that insoluble ZnO and TiO₂ nanoparticles used in sunscreens penetrate into or through human skin or may produce local or systemic exposure and/or adverse health effects.

Nohynek *et al* also considered the possibility of penetration via hair follicles:

...although insoluble nanoparticles, such as TiO₂, were shown to be present in the hair follicle orifices; they remained outside the living skin and no evidence for local (living skin) or systemic exposure via follicular penetration was found.

⁸¹ SCCNFP opinion concerning titanium dioxide:
http://ec.europa.eu/health/ph_risk/committees/sccp/documents/out135_en.pdf.

⁸² Australian Therapeutic Goods Administration review on the safety of sunscreens containing nanoparticles of titanium dioxide or zinc oxide:-
<http://www.tga.gov.au/npmeds/sunscreen-zotd.htm>

⁸³ G. J.Nohynek, J.Lademann, C.Ribaud, M.S.Roberts; *Grey Goo on the Skin?* Nanotechnology, Cosmetic and Sunscreen Safety. *Critical Reviews in Toxicology* 37:251-277, 2007.

3. Toxicity

In addition to a demonstrated lack of systemic exposure through the topical application of sunscreen-grade TiO₂ and ZnO, including nano-sized particles, the toxicity, phototoxicity, genotoxicity, photo-genotoxicity, and carcinogenicity of these ingredients have been evaluated. After reviewing these studies, the SCCNFP stated “Numerous tests for mutagenicity and clastogenicity have been carried out, and consistently show negative results.”⁸⁴

Investigations have shown that the commercial forms of TiO₂ used in sunscreens are not photomutagenic or capable of inducing photo mediated chromosomal effects.⁸⁵ In their review, Nohynek et al concluded:

Overall, whilst TiO₂ or ZnO micro- or nano-sized particles may cause cytotoxicity in the presence of UV irradiation, they do so at relatively high concentrations and in in-vitro systems only. It is unlikely that, given the low concentrations epidermal cells will be exposed to, either ZnO or TiO₂ NP pose a phototoxic, genotoxic, or photo-genotoxic risk; on the contrary, there is robust evidence that these substances applied topically protect human skin against UV-induced adverse effects, including DNA damage and skin cancer.⁸⁶

A very recent paper reports on the study of the photo-clastogenic potential of 8 different types of TiO₂ nanoparticles.⁸⁷ The authors concluded:

The studies presented in this paper, which were performed in a rigorous and carefully controlled manner, indicate that eight different rutile and anatase forms of titanium dioxide with different surface treatments (five

⁸⁴ SCCNFP opinion concerning titanium dioxide:-
http://ec.europa.eu/health/ph_risk/committees/sccp/documents/out135_en.pdf.

⁸⁵ SCCNFP opinion concerning titanium dioxide:-
http://ec.europa.eu/health/ph_risk/committees/sccp/documents/out135_en.pdf; G. J.Nohynek, J.Lademann, C.Ribaud, M.S.Roberts; *Grey Goo on the Skin? Nanotechnology, Cosmetic and Sunscreen Safety. Critical Reviews in Toxicology* 37:251-277, 2007; and E. Theogaraj, et al., An investigation of the photo-clastogenic potential of ultrafine titanium dioxide particles, *Mutat. Res.: Genet. Toxicol. Environ. Mutagen* (2007), <http://dx.doi.org/10.1016/j.mrgentox.2007.08.002>

⁸⁶ G. J.Nohynek, J.Lademann, C.Ribaud, M.S.Roberts; *Grey Goo on the Skin? Nanotechnology, Cosmetic and Sunscreen Safety. Critical Reviews in Toxicology* 37:251-277, 2007.

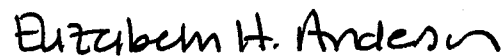
⁸⁷ E. Theogaraj, et al., An investigation of the photo-clastogenic potential of ultrafine titanium dioxide particles, *Mutat. Res.: Genet. Toxicol. Environ. Mutagen*. (2007), <http://dx.doi.org/10.1016/j.mrgentox.2007.08.002>

surface-treated and three without surface treatment) are not activated to photogenotoxins by solar simulated (UVA+ UVB) light.

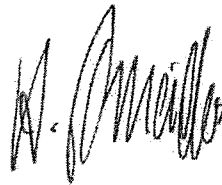
X. CONCLUSION

We consider the recommended changes outlined in these comments necessary to ensure that FDA's final monograph reflects sound science and policy and complies with the First Amendment of the United States Constitution, the APA, FDCA, and its corresponding regulations. We look forward to an open dialogue with the Agency on these issues, which are of critical importance to our members. If you have any questions, please contact Farah K. Ahmed, Assistant General Counsel, Personal Care Products Council at 202-331-1770.

Sincerely,



Elizabeth H. Anderson
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Counsel
Personal Care Products Council



Heinz Schneider, Dr. Med., Vice President,
Regulatory & Scientific Affairs
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