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Division & Dockets Management (HFA-35)
Food & Drug Administration
Room 1061
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USA

Comments on :
OTC Sunscreen Drug Products Proposed Amendment of Final Monograph
FDA Docket No. 1978N-0038 (formerly Docket No. 78N-0038)
RIN number 0910-AF43
72 Fed. Reg. 49070 (August 27, 2007).

Dear Sir/Madam,

The German Society of Cosmetic Chemists (DGK), a member of the International Federation of Societies of Cosmetic Chemists, would like to thank the FDA for publishing the proposed amendment to the OTC Sunscreen Drug Products Final Monograph and we would like to take this opportunity to make comments about some aspects related to the proposed in-vitro UVA test methodology.

The DGK established a sun protection task force in 1993 composed of expert scientists from finished goods manufacturers, UV filter suppliers, efficacy testing and dermatology institutions and testing apparatus manufacturers. This task force has been particularly active in evaluating the efficacy of suncare products via in-vivo and in-vitro methods using ring studies.
Some of this work has been published in papers or at scientific conferences:

- Gers-Barlag and members of the DGK Task Force Sun Protection.
  Multicentre comparison of sunscreens by the in-vitro determination of relative parameters
  XXI IFSCC International Congress 2000, Berlin

- Gers-Barlag and members of the DGK Task Force Sun Protection.
  In-vitro testing to assess the UVA protection performance of suncare products
  Int. J. Cosmet. Sci., **23** (2001) 3-14

- Gers-Barlag and members of the DGK Task Force Sun Protection.
  The reproducibility of an in-vitro determination of the UVA INDEX describing the relative UVA protection of suncare products
  IFSCC Magazine, **5**, 3, (2002) 1-6

- Bimczok and members of the DGK Task Force Sun Protection.
  Influence of Applied Quantity of Sunscreen products on the Sun Protection Factor (SPF) – a multi-centre study organised by the DGK Task Force Sun Protection.
  Skin Pharmacol Physiol, **20**, 57-64 (2007)

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The proposed rule has raised substantial new issues with respect to in-vitro methodology of UVA protection (§ 352.71 UVA in vitro testing procedure), an area in which the DGK Sun Protection Task Force has developed a substantial amount of expertise.

The specific areas in which we comment are:

- The light source for the transmission measurements
  - In-vivo sources, complying with the RCEE limits will reduce the dynamic range of instruments measuring relative transmission through a sample, especially in the UVB-region.

- The proposed quartz glass substrate
  - Degree of roughness of a substrate affects the UVAI/UV-Ratio and so has to be defined thoroughly.

- The amount of product applied to the substrate
  - Amounts of 2mg/cm² of sunscreen, as usual in in-vivo tests, result in absorption-values far above 2.5 AU, which cannot be measured reliably by most spectrophotometers. Furthermore such high amounts are difficult to apply homogenous on a roughened substrate.

- The spectrophotometer input optics
  - The specification of input optics should be supplemented to ensure comparable results between different instruments and labs.

- The sunscreen drug product application to the substrate
  - Pressure during application can have a significant effect on the shape of a spectrum and therefore can affect the UVAI/UV-Ratio.

- The pre-irradiation dose to take into account photoinstability
  - In case of reduced application amounts the preirradiation dose has to be recalculated, because the thickness of a sunscreen film influences the photodegradation of a product.

- The calculation of the spectral transmittance at each wavelength interval
  - Modern spectrophotometers usually measure in 1nm-wavelength intervals. Wavelength accuracy control with a holmiumperchlorate solution (NIST-Standard, ASTM-method) requires at least 1nm-steps to be measured.

Detailed Description of our Comments :

§ 352.71 UVA in vitro testing procedure.

(a) Light source for transmittance/absorbance measurements.

In this section it is stated that the light source should satisfy the requirements for solar simulators described in § 352.70(b) (which is summarised in the following table.

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(% RCEE defined in different bands)

W.L. range :	RCEE% :
< 290 nm	< 0.1%
290-310 nm	46.0 – 67.0%
290-320 nm	80.0 – 91.0%
290-330 nm	86.5 – 95.0%
290-340 nm	90.5– 97.0%
290-350 nm	93.5– 98.5%
290-400 nm	93.5 – 100.0%)

Comment.
The FDA solar simulator specification for the light source is the one recommended for the in-vivo testing of the sun protection factor. For transmission/absorbance measurements the conditions are difficult to achieve with current commercial UV transmission devices, for example common detectors (PMT, CPD, CCD and DAD) have a lack of sensitivity in the short UV-range (<300nm). It is therefore not recommended to filter (weaken) the sources in that region to achieve agreement with the RCEE-values and the commercial instruments available today for the measurement of transmission of UV radiation do not use such a filtered source.

These RCEE specifications are unnecessary in case of relative measurements, it is only necessary to define the pre-irradiation source.

Colipa in their recommendations for the determination of UVA protection published in 2007 **(see reference 5)** state that the lamp that is used to measure the transmittance must emit a continuous spectrum over the range 290-400 nm, and the level of irradiance should be sufficiently low, so that the photostability of the product is not unduly challenged. Therefore the UV-dose during one measurement cycle should not exceed 0.2 J/cm². For every wavelength, the irradiance must be at least 100 times higher than the so-called “irradiance” which is measured while the lamp is switched off.

We recommend that the Colipa recommendations for the light source for the transmittance absorbance measurements be used.

(b) Substrate.

In this section it is stated to use optical-grade quartz plate suitable for substrate spectrophotometry that has been roughened on one side.

Comment.
We agree that a roughened surface is necessary to correctly undertake the method. However it is important to note that the substrate used and its degree of roughness have to be standardised in order to obtain consistent results. We have evaluated various substrates with various grades of roughness (grit size) and found that the UVAI/UV ratio varies, depending upon both the substrate used and also upon the degree of roughness of the substrate. For example a European suncare formulation containing 4% Methylbenzylidene Camphor, 2% Ethylhexyl Triazone and 2% Avobenzone applied to quartz glass plates with a FEPA roughness of 220 with an average grit diameter of 58 µm gave a UVAI/UV ratio of a of 0.77 versus 0.85 for quartz glass with a FEPA roughness of 80 which had an average grit size 185µm **(reference 2, page 1).**

This data also demonstrates that the shape of the absorbance curve obtained from the formulation is dependent upon the type of substrate and degree of roughness. This is especially true in the UVB range **(reference 2, pages 3 and 5**). If the absorbance of the substrate varies, then reproducibility of

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the data is compromised. It will be very difficult for one laboratory to obtain the same results as another laboratory unless such potential variability is controlled.

In a separate ring study with 7 laboratories using the same types of quartz glass plates, the average UVAI/UV ratio of strongly roughened quartz (FEPA 80) was 0.83 versus 0.78 from gently roughened plates (FEMA 220) **(reference 1 page 1).**

Ferrero **(reference 4)** published similar data in which the values of relative factors such as UVA/UVB ratio and critical wavelength were roughness dependent.

Colipa in their recommendation for the determination of UVA protection published in 2007 **(see reference 5)** have undertaken extensive work on the choice of substrate for in-vitro efficacy and determined that roughened PMMA prepared according to Appendix 3 of attachment 5 is suitable.

In their document Colipa stated that micro topography measurements can be achieved to characterize the plate surface roughness. They state that contact or non-contact systems are available to provide accurately a surface roughness value (e.g., Sa in µm, according to EUR 15178 EN). The roughness value of the PMMA plates used for the validation of the Colipa method is close to Sa = 2 µm. For such a low roughness value, a sunscreen application rate of 0.75 mg / cm2 is the quantity needed in order to not exceed a spectral absorbance 2.0 in the range 290 nm ≤ λ ≤ 400 nm.

We will come back to this application amount later in our comments.

Colipa uses PMMA-plates coated with a thin layer of glycerine as a reference to obtain a similar refractive index as for sunscreen coated plates.
The optical characteristics of glycerine coated PMMA plates with an optimal roughness for an application amount of 0.75mg/cm² has the following parameters:

Wavelength range (nm)	Minimum transmission (%)	Maximum transmission (%)
290	60	70
300	69	79
320	81	91

In addition there is a considerable economic factor involved in the choice of PMMA plates rather than quartz. Roughened plates that have had formulations containing microfine pigments applied to them are virtually impossible to clean after a single use, so have to be discarded. A 4.5”+-.015” x 4” quartz glass plate in the USA costs US$130, the price for a similar PMMA plate is less than US$10. Thus the use of quartz glass is an extra economic burden.

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We therefore request that the parameters of the substrate used be specifically defined to have specific roughness and absorbance characteristics and that the substrate be roughened PMMA plates. These parameters are adequately described in the Colipa recommendations **(reference 5).**

(d) Spectroradiometer input optics.

In this section it is stated that unless the spectroradiometer is equipped with an integrating sphere, an ultraviolet radiation diffuser should be placed between the sample and the input optics of the spectroradiometer. The diffuser will be constructed from any UV radiation transparent material (e.g., Teflon or quartz). The diffuser ensures that the radiation received by the spectroradiometer is not collimated.
The spectroradiometer input slits should be set to provide a bandwidth that is less than or equal to 5 nanometers.

Comment.
We suggest to supplement these instructions with those recommended by Colipa. A spectrophotometer which uses monochromatic illumination and in which the transmitted radiation is not measured through a monochromator should employ a fluorescence rejection filter. The spectrophotometer input optics should be designed for diffuse illumination and/or diffuse collection of the transmitted irradiance through the roughened PMMA substrate, without and with the sunscreen layer spread on its surface. Smaller fractional port areas compared with total sphere wall area will lead to greater accuracy. In any case, the spatial response should be close to a cosine response (cosine error smaller than ± 5% for incident angles < 70°). To reduce the variability between readings and to compensate for the lack of uniformity in product layer, it is recommended that the area of each reading site should be at least 0.5 cm² (reference 5 page 2) in order to reduce the potential for error.

(e) Sunscreen drug product application to substrate.

In this section it is stated that the accuracy of the test depends upon the application of a precisely controlled amount of sunscreen product with a uniform distribution over the application area of the substrate. The product is applied at 2 milligrams per square centimetre to the substrate. To achieve uniform distribution over the substrate, the sunscreen product should be applied in a series of small dots over the application area of the substrate and then spread evenly using a gloved finger. A very light spreading action for a short period of time (approximately 10 seconds) should be used when distributing the product to ensure complete coverage without excessive build up of product in the troughs of the substrate.

Comment.
Our experience has demonstrated that the amount applied and the way it is applied is the source of large potential variation in the results obtained.

1. Amount Applied
The amount of 2mg /cm^2 which is the amount recommended for in-vivo determination of efficacy is too much to give reproducible results, especially for products with a protection factor of medium or higher. This is because 2mg/cm² is exceeding the dynamic range of most industrial spectrophotometers, especially when using a moderate roughened substrate, where the roughened structure is covered by a thick closed film. Most instruments can only measure sunscreen formulations that have an SPF higher than about 25 with a strongly reduced amount applied to the substrate.

We have demonstrated the effect of varying the amount of product (0.75, 1.50 and 2.00 mg/cm^2) of 3 emulsions (in-vivo SPF 10, 30 and 25 respectively) to the substrate on the UVAI/UV absorbance ratio and on the absorbance spectrum **(Reference 6)**.

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For the SPF 10 formula the UVAI/UV ratio varied from 0.73, to 0.79 to 0.81 for the 0.75, 1.50 and 2.00 mg/cm^2 application amounts respectively. The absorbances were within the dynamic range of the apparatus.

For the SPF 25 and 30 formulations only the absorbance of the 0.75 mg/cm^2 amount was within the dynamic range of the apparatus and UVAI/UV absorbance ratios could only be measured for the two lowest applied amounts.

We therefore recommend to decrease the application thickness to 0.75 mg/cm² on PMMA roughened plates with FEPA grit 120.

2. Application.
It is crucial to have an even application in order to obtain an even thickness and distribution over the support. We agree that the best means to apply this is via small drops but the method recommended by the FDA we believe needs to be improved. With the use of finger gloves (latex) it is difficult to apply small amounts of sample on a roughened rigid surface. In addition, finger gloves have a bigger saturation capacity for emulsions than the fingertip. The use of a saturated finger does not have these shortcomings.

A spreading time of 10 seconds to apply 2 mg/cm^2 is not sufficient to break the emulsion and does not lead to an even film as shown in the photographs in **reference 3** in which we applied the 3 sunscreen formulations discussed in the amount applied section discussed above. The local thickness and surface texture of an overlaid film (2mg/cm²) is predominately determined by the last finger-cot movements and not by the roughness of the substrate. By breaking of an emulsion we mean when the intact structure of the emulsion is broken by shear stress so that the inner and outer phases separate allowing the volatile components to evaporate. This occurs when a sunscreen emulsion is spread onto the human skin under normal usage conditions. The optical properties of an unbroken and broken emulsion will not be equivalent.

No indications of the pressure used to apply the product are given in the proposed amendment. We have data from a ring study of 7 laboratories which indicates that the UVAI/UVabsorbance ratio depends upon the amount of pressure applied to the emulsion during application **(reference 1, page 2).** A ratio of 0.78 was obtained under low pressure and a ratio of 0.83 under high pressure. The pressure was simply measured by putting the substrate on a weighing balance and observing the weight on application of the product, for low pressure a weight of less than 50g was stipulated and for high pressure a weight greater than 200g weight was stipulated.

Application of a high pressure will increase the likelihood that product loss will occur by forcing the product over the sides of the plate.

We therefore recommend a 2 stage application process in which the product is initially applied with very low pressure followed by rubbing in with higher pressure as described by Colipa **(reference 5):**

“After application (and check-weighing, if employed), the sunscreen product is spread immediately over the whole surface using light strokes with a fingertip “pre-saturated” with the product. Spreading should be completed in a two-phase process. First, the product should be distributed over the whole area as quickly as possible (less than 30 seconds) without pressure. Then the sample should be rubbed into the rough surface using pressure. The second phase should also take 20 to 30 seconds. This treated sample should then be allowed to equilibrate for at least 15 minutes in the dark at ambient temperature to help facilitate formation of a standard stabilised product film”.

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Using this method and with an application amount of 0.75mg/cm^2 we evaluated the nature of the film of the 3 test emulsions that had previously been tested by the FDA recommendation. Photographs of the emulsions were then taken which indicated a very even distribution of the products over the roughened substrate **(reference 3).**

(f) Pre-irradiation to account for differences in photostability.

In this section it is stated that to account for potentially varying degrees of photostability between sunscreen drug products, irradiate the sunscreen product on the substrate with a dose of UV radiation equal to the SPF of the sunscreen product multiplied by 200 J/ m$_2$-eff multiplied by 2/3. A UV radiation dose of 200 J/m$_2$-eff is equivalent to one minimal erythema dose (MED). The UV dose to be delivered is determined by multiplying the light source spectral irradiance action spectrum for erythema in ''CIE S 007/E Erythemal Reference Action Spectrum and Standard Erythema Dose,'' at each wavelength, integrating over wavelength, and multiplying the integral by the exposure time. ''CIE S 007/E Erythemal Reference Action Spectrum and Standard Erythema Dose,'' dated 1998, is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from CIE Central Bureau, Kegelgasse 27, A–1030, Vienna, Austria, or may be examined at the Center for Drug Evaluation and Research, 10903 New Hampshire Ave., Bldg. 22, Silver Spring, MD 20993, or at the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC.

Comment.

Pre-irradiation might cause molecular changes of UV filters. By contrast to photobiological effects, photochemistry of UV filters strongly depends on the absolute total UV irradiance rather than on the erythemal weighted irradiance. Since precise erythemal irradiance measurement is complicated, expensive and unnecessary for UVA in vitro testing, it is recommended to give an absolute dose in order to achieve the highest degree of interlaboratory reproducibility.
This dose will be dependent upon the thickness of the sunscreen film applied to the substrate as shown in **reference** 10 (Internal measurements of Beiersdorf AG in Germany in conjunction with the Colipa ring test) in which the UVA absorbance to UVB absorbance ratio increases with film thickness for the same dose of UV radiation (20J/cm^2).

We therefore request that if the FDA take into account our arguments for a reduction in the amount of product to be applied from 2mg/cm^2 to 0.75 mg/cm^2 , then the pre-irradiation dose has to be adjusted accordingly.

(g) Calculation of the spectral transmittance at each wavelength interval.

In this section it is stated that the dynamic range of the measurement system and the intensity of the light source should be sufficiently high that signals measured at all UV wavelengths (290 to 400 nanometers) through a highly absorbing sunscreen product are above the noise level of the measurement system. Spectral irradiance will be measured at 5 nanometer intervals, from 290 to 400 nanometers.

Comment.

We fully concur that the dynamic range of the detecting system and the intensity of the light source be sufficient to allow for reproducible results. With this in mind we would like to recommend two measures that ensure this.

1. The detector should be able to read an absorbance of at least 2.2 and preferably 2.5 for products with a high protection factor. This is easily tested by separately measuring the absorbance from 290 to 400nm of 2 UV absorbing roughened plexiglass plates and adding the spectra together. The resulting absorbance is then compared to the absorbance obtained from the two plates lying on top of each

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other **(reference 8).** Using this method we compared the performance of 13 instruments with the spectra shown in **reference 7.** 8 of the instruments were insufficient for the measurement of high absorbance levels.

2. 5nm-intervals for wavelength measurements are not sufficient for a precise alignment. State of the art photometric instruments are capable of measuring a wavelength-interval of 1nm. Wavelength-calibration of instruments should be possible with a certified Standard (e.g. NIST standard SRM2034, Holmiumperchlorate solution) in 1nm-steps **(reference 11)**. This will allow regular control of the measurement device with standardized procedures because insufficient dynamic, misalignment and/or contamination of the measurement device can lead to systematic measurement errors and make it difficult to compare the result between different laboratories.

We therefore recommend that these two measures be made to ensure that the instrument used is capable of generating realistic results.

We thank the FDA once again for letting us have the opportunity to comment on the proposed amendments and are available for any comments you may have on our proposals.