DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 352, 700, and 740

[Docket No. 78N–0038]

RIN 0905–AA06

Discussion of Ultraviolet A–Protection Claims and Testing Procedures for Over-the-Counter Sunscreen Drug Products; Public Meeting and Reopening of the Administrative Record

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of public meeting and reopening of the administrative record.

SUMMARY: The Food and Drug Administration (FDA) is announcing that a public meeting will be held to discuss testing procedures to demonstrate that an over-the-counter (OTC) sunscreen drug product protects users from ultraviolet A (UVA) radiation. FDA is holding this meeting after considering public comments regarding UVA claims and testing procedures received in response to the agency's notice of proposed rulemaking and letters sent by the agency. In addition, FDA is reopening the administrative record for the proposed rulemaking for OTC sunscreen drug products to allow comment on matters considered at the meeting. FDA intends to invite guests and consultants to address technical matters related to the questions listed in this document. This meeting is part of the ongoing review of OTC drug products conducted by FDA.

DATES: The meeting will be held on May 12, 1994, 8:30 a.m. The agency anticipates that the meeting will last 1 day. However, if there is sufficient interest in participation, the meeting will be extended an additional day at the discretion of the chairperson. Submit relevant data and notice of participation by April 29, 1994. Submit comments regarding matters raised at the meeting by July 31, 1994. The administrative record will remain open until July 31, 1994.

ADDRESSES: Submit relevant data, notice of participation, and written comments to the Dockets Management Branch (HFA–305), rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857. The meeting will be held in conference rm. D, Parklawn Bldg., 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Jeanne Rippere, Center for Drug Evaluation and Research (HFD–813), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–1003.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of May 12, 1993 (58 FR 28194), FDA published a notice of proposed rulemaking for OTC sunscreen drug products. In the proposed rule, the agency discussed OTC sunscreen drug products that claim to provide protection from UVA radiation and the public health significance of UVA radiation (58 FR 28194 at 28232 and 28233). The agency also discussed testing procedures for sunscreens that absorb UVA radiation (58 FR 28194 at 28248 to 28250). The comment period for comments related to UVA ingredients, claims, and testing closed on November 8, 1993.

To ensure that sunscreen drug products having UVA protection claims offer significant UVA protection, the agency proposed that an OTC sunscreen ingredient must have an absorption spectrum extending to 360 nanometers (nm) or above in order to display UVA protection claims in its labeling (58 FR 28194 at 28233). The product would also have to demonstrate meaningful UVA protection by satisfying UVA testing procedures that would be included in the monograph. However, these procedures have yet to be established. The agency requested specific comments on appropriate procedures to be used. Previously, the agency had requested specific information on UVA protection factors (Ref. 1).

In the proposed rule (58 FR 28194 at 28248 to 28250), the agency tentatively suggested that a testing method similar to the one described by Lowe et al. (Ref. 2) could be used to demonstrate that a sunscreen drug product provides protection against UVA radiation. This method uses 48- and 72-hour erythema reactions and 12- to 14-day melanogenesis in skin sensitized with 8-methoxsalen (8–MOP). However, because the agency did not have enough information or data to propose a method for determining UVA protection in the proposed rule, the agency stated that a method should be developed and validated in the same manner as was the sunscreen testing procedure for protection against ultraviolet B (UVB) radiation (i.e., sunscreen protection factor (SPF) testing). Furthermore, the agency requested comments and data regarding an appropriate testing methodology for OTC sunscreen drug products that afford UVA protection.

The agency received a substantial amount of comments, data, and information regarding UVA ingredients, claims, and testing procedures. After evaluating the submitted material, the agency finds that there are two basic interrelated questions regarding testing procedures for determining UVA protection that must be addressed before the agency can complete its assessment of appropriate UVA ingredients and claims. These questions are:

(1) What action spectrum best describes the biological risk of UVA radiation (i.e., which ultraviolet radiation wavelengths are most likely to cause biological damage), and

(2) Which testing procedure best defines the UVA protection provided by a sunscreen drug product?

I. Action Spectra for UVA-Related Skin Damage

Several comments discussed the appropriate action spectrum for biological risk associated with UVA radiation. One comment stated that, in developing a consensus regarding an acceptable assay for determining the UVA protection provided by a sunscreen drug product, the specific UVA effect that is to be blocked must be considered. These effects include UVA erythema, UVA-induced drug photosensitivity, immediate pigment darkening, delayed tanning, or other effects of photodamage.

One comment stated that several action spectra describing different aspects of solar-induced skin damage have been determined in a number of different species and cell types. The comment described these aspects as photocarcinogenesis, DNA damage, photoaging, mutagenicity, and immunosuppression. The comment maintained that each action spectrum for UV-induced damage closely tracks the human erythemal action spectrum. The comment stated that the best summary of the biological risk of UV light has been published by the Commission Internationale de l'Eclairage (CIE) (Ref. 3). The CIE Hazard Spectrum embodies the comprehensive, yet normal, risks to human skin due to full-spectrum UV exposure and reflects the findings of the action spectra biological responses to UV described above. The CIE Hazard Spectrum shows that the damage risk for UVB at 290 nm is 100 times higher than that at 320 nm. The damage risk at 320 nm is 100 times higher than that at 400 nm. The damage risk at 320 nm is at least 10 times greater than the damage risk at 340 nm. This spectrum shows that the most damage potential is in the UVB wavelengths (290 to 320 nm), followed by the shorter UVA wavelengths (320 to 340 nm). The comment cited numerous scientific

articles and submitted action spectra to support its statements (Ref. 4).

Another comment stated that although protection against UVA is important, it is not as important as protection against UVB. The comment argued that, based on the CIE Hazard Spectrum, the UVB wavelengths contribute 80 to 85 percent of the damage risk in sunlight, while UVA contributes 15 to 20 percent of the damage risk.

One comment stated that some known effects on humans caused by UVA radiation include:

(1) Photoaging of the skin,

(2) UVA-induced hypersensitivities,

(3) Augmentation of skin cancers, and

(4) Erythema. However, the comment noted that there is no single known action spectrum to describe which parts of the UVA spectrum are most active in causing these effects. Therefore, the comment maintained that it is not appropriate to use the UVA-erythema action spectrum for testing purposes. The comment stated that UVA protection should be assessed in relation to UVB protection and that the assumption should be made that all wavelengths are equally important.

One comment stated that the "current test for erythema" is inadequate to test for the full spectrum of UVA radiation because erythema is not a valid measurement of UVA exposure. The comment argued that using the erythema action spectrum to test for UVA protection will give consumers a false sense of the extent of UVA protection afforded by a product. The comment added that the immediate pigment darkening (IPD) action spectrum is preferable because it is broad enough to take into account almost all UVA wavelengths. Another comment stated that the IPD action spectrum is indicative of a true broad spectrum UVA response.

One comment noted that the IPD action spectrum was first described to extend from 300 to 420 nm, with a broad peak between 340 and 370 nm (Ref. 5). The action spectrum was later described to extend from 300 to 620 nm, with a peak effectiveness between 400 and 500 nm (visible light) (Ref. 6). Because of the difference between these two reported spectra, the comment reevaluated the action spectrum for IPD between 310 and 400 nm and reported that the IPD action spectrum extends from 320 to 400 nm with a low peak around 340 nm (Ref. 7).

Concurrent with determining which testing procedure is appropriate for use in validating the UVA protection provided by a sunscreen drug product, the agency must determine what portion of the UVA spectrum should be blocked by the product before consumers are effectively protected against the hazards of UVA radiation. The agency would like to consider the following specific questions at the meeting:

1. Which action spectra are the most important with respect to skin damage caused by UVA radiation?

2. Is the erythema action spectrum an adequate surrogate for UVA biological risk, or is some other action spectrum (such as the IPD action spectrum) more appropriate?

3. Can a sunscreen drug product that protects consumers against the shorter UVA wavelengths (320 to 340 nm) but not against longer UVA wavelengths (340 to 400 nm) prevent significant UVA damage?

4. What should consumers expect from a sunscreen drug product that is labeled to provide protection against UVA radiation or as a "broad spectrum" sunscreen?

II. UVA Testing Procedures

The agency did not propose a method for determining UVA protection in the tentative final monograph for OTC sunscreen drug products. The agency stated that a method should be developed and validated in the same manner as the sunscreen testing procedure for protection against UVB radiation (58 FR 28194 at 28250). The agency noted that any such method should clearly demonstrate that a particular product provides significant protection against UVA radiation. The method should include the use of a control sunscreen preparation that absorbs UVA radiation and that can be used to assure the reliability of the testing procedure and equipment. The method should demonstrate that a sunscreen ingredient either does or does not protect against UVA radiation. The agency requested comments and data regarding an appropriate testing method for OTC sunscreen drug products that protect against UVA radiation. In response, the agency received information and data pertaining to several UVA testing procedures, including both in vivo and in vitro test methods.

One comment recommended adoption of an in vitro test method that does not rely upon either photosensitization or nonsolar light sources for determining UVA protection for normal skin (Ref. 8). According to the comment, this method involves:

(1) Determining the UV absorbance spectrum of the sunscreen product,

(2) Calculating a convolution spectrum by multiplying the solar spectrum with the current CIE Hazard Spectrum, and

(3) Incorporating the sunscreen transmission spectrum into the convolution spectrum to obtain a UVA effectiveness ratio which is conveniently expressed as a UVA protection percentage (APP). The comment maintained that, unlike other methods, the APP represents the fraction of full spectrum UVA (320 to 400 nm) removed by a product.

The comment stated that because the original "full spectrum" method produces an SPF value analogous to the clinically determined SPF number, the APP has direct relevance to the SPF determined on human subjects and is a subset of the full-spectrum SPF determination. The comment added that once an SPF has been determined clinically, it is simple to take the full-spectrum absorbance spectrum and calculate the APP based on the clinical test results. Therefore, although the determination of the APP does involve in vitro measurements, it also relies on direct clinical measurements.

The comment contended that there are a number of advantages to using the APP system:

(1) It is a subset of the existing SPF for sunscreen drug products and, therefore, relates to an erythemal endpoint in normal skin;

(2) It does not unnecessarily duplicate clinical testing;

(3) It clearly demonstrates whether a sunscreen drug product provides meaningful protection against UVA radiation, and it is useful in determining comparative UVA protection;

(4) It avoids the deficiencies of nonsolar light sources, photosensitizing chemicals, the failure of dose reciprocity for human UVA exposures, and endpoints which do not relate to known UVA damage to human skin;

(5) It is independent of exposure dose or duration;

(6) It includes all the UVA wavelengths in their direct proportion and intensity as found in natural sunlight; and

(7) It is directly relevant to overall product effectiveness. The comment added that in the absence of a light source specific to the UVA range, APP determination is the best measurement of a product's UVA protection level.

One comment stated that the in vitro APP test is difficult to extend to a human in vivo situation and that the test cannot be used to study substantivity or stability. The comment added that because the APP test uses the erythema action spectrum and a mathematical extraction of the UVA segment of the solar spectrum, it

overestimates the actual amount of UVA radiation blocked by most products. A reply comment argued that the APP technique is derived from well-studied and extensively published in vitro SPF methodology (Refs. 9, 10, and 11), that it is simple to evaluate water resistance using this model, and that data on water resistance have been published. The reply comment added that APP values are derived from the same spectral data (320 to 400 nm) that provide in vitro SPF values. The final SPF value from clinical studies is compared to the in vitro SPF and the absorbance spectrum can be matched to the exact clinical SPF for UVA calculations. The UVA portion of the sunscreen's efficacy can then be calculated from the in vitro SPF data. Therefore, the comment argued that the APP has direct relevance to the clinical effectiveness of the sunscreen product, but does not require the exposure of human subjects to unnecessary UV radiation.

One comment stated that an in vitro method developed by Diffey and Robson (Ref. 12) avoids many of the limitations of in vivo methods (e.g., lack of reciprocity and light sources that produce 5 to 20 times the intensity of the sun) and allows the correct estimation of the attenuating power of a sunscreen drug product. The comment described this method as recording photocurrent in 5 nm steps from 290 to 400 nm and measuring the spectral transmission of UV radiation through a sample of Transpore™ tape with and without sunscreen applied. Transpore™ tape is UV radiation transparent and has a rough surface that distributes sunscreen products in a way similar to the uneven surface of the skin. Any radiation source may be used, providing there is a continuous power distribution between 290 and 400 nm. This method assesses the SPF of a product and the UVA/UVB ratio. The UVA/UVB ratio compares the reduction of UV radiation in the UVA region with that in the UVB region of the spectrum. According to the comment, this ratio can be used as an indicator of the UVA protection properties of a sunscreen drug product.

One comment claimed that the method developed by Diffey and Robson (Ref. 12) has many advantages, as well as being simple, inexpensive, and well correlated with clinical testing. The comment noted that the method does not require a biological endpoint such as erythema, tanning, or immediate pigment darkening. The comment stated that the method provides a basis for the classification of the UVA protection provided by a product and added that a manufacturer planned to utilize the Diffey and Robson method to standardize the UVA claims of its products. Sunscreen products would be labeled with one to four stars depending upon the amount of UVA protection provided by the products as determined by the Diffey and Robson method. The comment concluded that using the "star" rating system for UVA claims and the SPF designation for UVB claims provides a simple method for consumers to determine the protective nature of a sunscreen product. The comment submitted a description of the manufacturer's methodology and "star" rating system (Ref. 13).

Another comment submitted data describing the application of this ratio method to the determination of the SPF and UVA/UVB ratio of titanium dioxide and zinc oxide dispersions (Ref. 14). The comment noted that the accuracy of this method is enhanced by good product application and that the in vitro results obtained by this method show good agreement with in vivo values.

However, another comment contended that the Diffey and Robson method (Ref. 12) has been shown to have poor correlation with clinical results (Ref. 15). The comment stated that the Diffey and Robson method has been used as the basis for "quantifying" UVA protection expressed as "stars" on the package labeling of some sunscreen products sold in Europe (Ref. 16). Without using an action spectrum such as the CIE UV Hazard Spectrum or the erythemal efficacy spectrum for weighting, the "star" method considers all UVA wavelengths as having the same erythemal effectiveness. The "star" value results from an unweighted ratio of the UVA absorbance to the UVB absorbance of the product. Therefore, the comment maintained that a low SPF product with a flat absorbance spectrum could get four "stars" (i.e., the highest rating), while a higher SPF product would get fewer "stars" because the higher SPF product would absorb disproportionately higher levels of UVB, similar to the action spectrum for erythema. The comment stated that the "star" concept is in direct contrast to the accepted concept of formulating sunscreen drug products to provide the most protection in the most damaging portion of the UV spectrum. The comment contended that the "star" method is misleading to consumers and added that the use of the "star" method in England has been criticized by dermatologists, who have asked that the system be withdrawn.

One comment recommended that the agency adopt the current Standards Association of Australia (SAS) UVA (broad spectrum) test method AS–2406 as an objective measure of UVA blocking (Ref. 17). This method measures the percent transmission of the test sunscreen drug product between 320 and 360 nm. If an 8-micrometer layer of appropriately dissolved sunscreen product does not transmit more than 10 percent of UV radiation at any wavelength from 320 to 360 nm inclusive, the product may be considered as providing broad spectrum protection. The comment contended that this method has a number of advantages. UV protection claims are most appropriately substantiated by measuring the blocking of UV directly rather than measuring some consequence of UVA exposure. Thin film spectrophotometric evaluation of sunscreen drug products has reached a level of technical proficiency to permit instrumental evaluation of UVA blocking potential. Adopting an already accepted standard protocol will enhance the ability of the United States sunscreen industry to compete equally in foreign markets. This test will substantially reduce testing costs. No human subjects are used. The comment added that this method provides a strict criterion that serves to identify only the most effective UVA blockers. The comment submitted several UVA scans to demonstrate that the SAS method differentiates between the "poorly effective" oxybenzone-containing sunscreens and an assortment of products containing "excellent" UVA blockers, e.g., titanium dioxide and avobenzone (Parsol 1789) (Ref. 17).

Two comments contended that there are several deficiencies in the SAS method. The results are not correlated to a clinical SPF test. Numerous studies have shown that solution and thin-film spectra are not relevant to actual product performance on skin. The performance of the sunscreen is evaluated only in the limited range of 320 to 360 nm, rather than throughout the entire UVA spectrum (320 to 400 nm).

Two comments recommended that the agency not adopt in vitro methods that rely on measuring the transmission of UVA radiation through either epidermis or a UV-transparent skin cast (Refs. 18 and 19). The comments contended that these methods are inappropriate because they use nonsolar UVA radiation sources and limited range UVA detectors or detectors without an appropriately weighted response. The comments stated that these limitations would cause the results to be nonrelevant to the actual responses of normal skin to full-spectrum natural sunlight. The comments mentioned that one method (Ref. 19) contains a small but significant contamination by UVB

energy below 320 nm that would adversely affect the resulting efficacy values and lead to erroneous measures of UVA efficacy. The comments stated that the other method (Ref. 18) skews results toward the longer UVA wavelengths because of the lamp's deficiencies in the shorter, energy-rich UVA. The comments added that this skewing causes an overestimation of the protection of some products, making those with ingredients that are long wavelength absorbers (such as avobenzone) look unrealistically effective.

One comment concluded that a rigorous and foolproof in vitro test method has not been established or validated. The comment submitted two scientific publications that discuss some of the difficulties associated with in vitro sunscreen testing techniques (Refs. 15 and 20). The comment argued that none of the current in vitro methods adequately evaluate the photostability of sunscreens. It further stated that a validated in vivo human UVA test method must first be established. Then, future in vitro test methods can be tested and validated against this standard.

Several comments urged the agency not to adopt a testing method that utilizes photosensitizing chemicals. The comments presented a number of arguments against this type of testing. It is considered unethical because of the carcinogenic potential of the photosensitizing chemical (such as 8–MOP). The action spectrum (i.e., for 8–MOP induced erythema) is artificial and inappropriate. The values obtained vary with the sensitizing chemical used and the spectrum of the irradiating source used. The values obtained have no relevance to real-life situations. The testing may result in a persistence of pigmentation or blistering reactions. 8–MOP sensitization exaggerates the biological response and presents a risk of causing severe ulcerative acute reactions. 8–MOP puts subjects at risk for phototoxic reactions for up to 6 hours after exposure.

One comment contended that photosensitizing testing methods have a number of benefits, such as short irradiance times, clearly defined endpoints, and reproducible results. The comment added that the results from these test methods are relevant to patients taking 8–MOP or other photosensitizing drugs with similar action spectra. The comment concluded that photosensitizing test methods could be useful to determine photoprotection factors for claims against phototoxic reactions.

Several comments urged the agency to accept the IPD testing method for determining UVA protection. One comment stated that the IPD method is generally recognized by a substantial body of scientists as the preferred UVA testing method. Several comments provided a number of benefits for using the IPD method. They claimed that this test method is the one that is most representative of true conditions because it is an in vivo determination that accounts for biological reactions that can occur on living skin. Unlike the testing procedure using skin photosensitized with 8–MOP, the IPD test is indicative of a true broad spectrum response of normal healthy skin. Unlike erythema that is a response only to the shorter wavelength UVA radiation, IPD is a response to broad spectrum UVA radiation. The IPD method requires the use of considerably lower doses of radiation energy, thus exposing subjects to less risk. The IPD method uniquely compliments the current SPF system by accurately reflecting the actual amount of long wave UVA radiation attenuated by a sunscreen product. The IPD method is reliable, accurate, and reproducible. The IPD test can be performed in a standard sunscreen evaluation laboratory with minimal adaptation of existing equipment. The comments concluded that until well-established action spectra for specific UVA damage are established, IPD is the best method currently available because it reflects broad spectrum UVA protection equally across the entire UVA spectrum.

One comment submitted a testing protocol using IPD as the endpoint (Ref. 21). The comment stated that the suggested testing procedure fulfilled a number of criteria. The resulting protection factor gives the consumer additional information about the sunscreen number, complementing the SPF value. The response variable has a relatively flat action spectrum (i.e., 320 to 400 nm, with a low peak at around 340 nm) throughout the region of interest. Using this spectrum results in UVA protection values that closely reflect the actual amount of radiation reduced. The testing response obeys dose reciprocity over the anticipated irradiance range. The test is practical with minimal risk to subjects. The comment added that an eight-center clinical test has validated this method as acceptable for determining UVA protection over the entire UVA spectrum, including long wavelength UVA (i.e., 340 to 400 nm).

The comment submitted clinical test results from the eight test sites (Ref. 21). Each testing facility completed between 10 and 20 subjects. Subjects with skin types III and IV were used. Four sunscreen formulations and a vehicle control were tested. The sunscreen products contained:

(1) 7-percent padimate O,
(2) 2-percent oxybenzone,
(3) 5-percent oxybenzone, and
(4) 4 percent titanium dioxide.

The protocol used a randomized, complete block design with all subjects at each testing center receiving all five test materials. The comment stated that the studies were conducted similar to an SPF test, but a detailed protocol was not submitted. For example, UVA dosages and application density of the test sunscreens were not noted. Six sites used a 150–Watt (W) Xenon lamp with 3-millimeter (mm) WG335 and 1-mm UG11 filters. One site used a 1,000–W Xenon lamp with 3-mm WG335 and 2-mm UG11 filters. One site used a Krypton lamp (i.e., Dermlite) of unspecified wattage. The comment noted that neither of the last two UVA sources are recommended, and the results obtained using these lamps were included for information purposes only.

The IPD threshold dose of UVA radiation was first measured on unprotected skin, then on protected skin. The ratio of these two doses was then calculated to derive the UVA Protection Factor (UVA-PF). The IPD was graded immediately after UV exposure, allowing complete testing in a single visit.

The comment stated that comparison of test products indicated that the mean UVA-PF of the vehicle (1.7), the 7-percent padimate O product (1.8), and the 2-percent oxybenzone product (1.8) were similar. The 5-percent oxybenzone product (2.1) and the 4-percent titanium dioxide product (3.0) were both significantly greater than the other three products. The titanium dioxide product was significantly greater than the 5-percent oxybenzone product. Although overall statistical analysis detected significant site-by-product interaction, the individual results indicate that this was primarily a quantitative interaction effect. The comment maintained that the consistency of the results was encouraging, considering that this was the first experience in reading the IPD response for most of the participating sites. The comment stated that these data indicate that the IPD procedure can reliably discriminate among products that provide meaningful long wavelength UVA protection. The comment proposed using a base size of 20 subjects per test and a 4-percent titanium dioxide product as a control to be run concurrently with each subject. The comment proposed that the UVA-

PF be the lower 95 percent confidence interval subtracted from the mean.

Three comments recommended using an IPD test based upon two recent publications (Refs. 22 and 23). One study (Ref. 22) used a Xenon lamp equipped with a dichroic mirror filtered with 1-mm WG345, 1-mm WG320, and 1-mm UG11 filters. The exposure increments were programmed in arithmetic increments of 2 Joules per square centimeter (J/cm²). On protected skin, the increments were 3 or 4 J/cm². Application density of the test sunscreen products was 2 milligrams per cm². Visual assessment of pigmentation was done immediately after exposure and was performed on the basis of a homogenous pigmentation with well-defined borders as endpoints. The UVA-PF is determined as the ratio of minimal IPD dose with protection to the minimal IPD dose without protection.

The other study (Ref. 23) recommends the use of xenon or metal halide sources, or a xenon/metal halide combination, with continuous spectra restricted to the UVA spectrum (320 to 390 nm) with filters, such as 3-mm WG335 and 1-mm UG5. Six UVA doses ranging from 4 to about 30 J/cm² are applied in 50 percent increments to subjects with skin types II, III, and IV. The study states that with potential free interpolation, this is actually a 25-percent progression. The doses applied on the protected skin are multiplied by the expected UVA-PF of the product under test. Observation of the responses are delayed for at least 1 hour, and typically 2 hours, after exposure. The study states that results are less variable if read at 2 hours. A simultaneous determination of the minimal IPD doses on protected and unprotected skin is done at the same time in standard room and illumination conditions. Other parameters concerning the test area, size of test sites, product application density, selection of volunteers, etc. follow the same current standards as for the SPF determination.

Several comments objected to the use of the IPD testing method. One comment stated that the action spectrum for the IPD response is flat and quite dissimilar from the action spectrum for damage to the skin from ultraviolet light for erythema, skin cancer, or photoaging of the skin. The comment contended that the IPD response has not been demonstrated to be a direct or surrogate endpoint for biological damage and, therefore, there is no relationship between a product's ability to prevent IPD and to prevent damage to the skin. The comment added that IPD has been shown to be unstable, variable, and nonlinear. Another comment stated that the IPD reaction shows nonreciprocal behavior, i.e., the severity of the reaction depends upon the time taken to deliver a certain dose.

One comment noted that there are two methods of assessing UVA protection that are referred to as IPD. The comment stated that these two methods differ in the amount of energy needed to produce a response and the time after irradiation at which the endpoint is read. In one method, the response is read at 45 seconds after exposure. This response is transient and has been shown to be highly variable and nonreproducible. The response is oxygen-dependent and can only be elicited in darker skin types. In the second method, the response is read at 2 to 4 hours after exposure and uses a much higher dose of UVA. The test causes a persistent pigment response in the skin that may last up to several hours. The comment maintained that the action spectrum for the persistent pigment endpoint has been neither determined nor published.

The comment argued that the threshold problem of not having a truly solar UVA-only light source further complicates the results obtained using either IPD method. The comment contended that even filtered Xenon lamps contain significant amounts of visible radiation which, while not harmful to the skin, may cause the IPD reaction to occur. The comment pointed out that a sunscreen's ability to block visible light should not be confused or combined with its ability to provide UVA protection. In addition, the comment argued that the light sources used for both IPD methods lack significant energy in the shorter UVA wavelengths, which are present in sunlight and which are responsible for the preponderance of UVA damage to the skin.

Stating that there is great demand among the "sunbather" population for a "great looking" tan and for an indicator to predict how good a tan can be obtained with a product, one comment argued that tanning tests like the IPD are not appropriate for measurement of the damage caused by UVA radiation. The comment contended that measures of melanogenesis would be misinterpreted by consumers as indicators of efficacy of tanning and that consumers would soon be choosing products with the lowest IPD rating to help get the deepest tan.

One comment recommended that the agency adopt the Protection Factor in UVA (PFA) test method (Refs. 24, 25, and 26). This method is similar to the SPF testing procedures with a modification to the light source to virtually eliminate UVB radiation and thus expose subjects to UVA radiation (greater than 99 percent). The PFA test uses subjects with skin types I, II, and III. The UVA source is a continuous UVA spectrum (preferably xenon arc) filtered with a 3-mm Schott WG335 filter that eliminates 99 percent of the UVB radiation, with less than 1,500 W per square meter (W/m²) irradiance. UVA exposures are delivered at 25-percent increments to skin above and below the expected UVA protection level of the sunscreen product times the minimal response dose. The endpoints measured in this testing method are delayed erythema or tanning, whichever is present, observed 16 to 24 hours after UV exposure. The comment stated that these acute responses have similar action spectra to the chronic action spectra for nonmelanoma skin cancer (as determined in animals), solar elastosis, and skin wrinkling. The comment added that the data indicate equivalent results with either response parameter. Minimal response doses are elicited with UVA exposure ranging from approximately 80 to 250 J/cm². The PFA is the ratio of the minimal response dose on protected skin to the minimal response dose on unprotected skin.

The comment submitted the results of a multicenter evaluation of sunscreens using PFA methodology (Ref. 25). Sunscreens containing 2 or 5 percent oxybenzone, 7 percent padimate O, and a placebo were tested in five laboratories using a PFA protocol. All the solar simulators had intrinsic UV reflecting/IR absorbing dichroic mirrors and were fitted with Schott 3-mm WG335 and 1-mm UG11 filters. The comment stated that the PFA test method yielded reproducible results between test centers and was capable of distinguishing between the three levels of UVA protection provided by the placebo sunscreen and the sunscreens containing 2- or 5-percent oxybenzone. The test was incapable of distinguishing between the UVA protection provided by the placebo and the 7-percent padimate O (a strong UVB absorber with little UVA absorbency). The comment stated that these results indicate that the PFA test method is not influenced by the presence of a strong UVB blocker in the formulation and is specific in identifying UVA protection. The comment added that the data show that the level of irradiance of the light sources (i.e., 300 to 1,200 W/m²) did not influence the protection factors of the sunscreens.

Two comments stated that testing procedures using modified lamps that produce mostly UVA wavelengths are unsatisfactory for evaluating the UVA

protection afforded by a sunscreen drug product because the filters required for such testing can remove 40 percent or more of the critical, damaging wavelengths between 320 and 340 nm. In addition, the comments pointed out that some of these modified lamps contain UVB wavelengths below 320 nm that can overwhelm UVA effects. However, another comment stated that PFA values obtained using modified lamps and delayed tanning or erythema as endpoints weigh the UVA II (320 to 340 nm) heavily and, for the most part, ignore the contribution of the longer UVA wavelengths (360 to 400 nm). One comment stated that failure of reciprocity may occur with very long exposures and that making each test exactly the same for each differently configured UV source used and its particular energy distribution would be impossible. Another comment stated that dose reciprocity for the endpoints of delayed tanning or erythema has been reported to fail at irradiances between 10 and 50 milliwatts per cm^2 and below. One comment noted that the interval after exposure at which the responses are evaluated can bias the results. The comment added that the infrared energy or heat delivered to the skin during these exposures can affect and alter the results.

The comment stated that no currently existing lamps accurately and fully reproduce the UVA spectrum of sunlight. Pure UVA I lamps, e.g., the UVASUN series, are used primarily for photochemotherapy where only longer wave UVA (above 340 nm) is wanted. Xenon arc lamps modified with a WG345 filter are deficient in UVA energy below 335 nm and do not accurately reflect the energies or damage risk of natural sunlight UVA. According to the comment, such lamps remove too much of the energy at the short end of the spectrum and result in overestimating the UVA effectiveness of sunscreens. Xenon arc lamps filtered with 1- or 2-mm WG335 filters contain UVB wavelengths below 320 nm and thus can greatly affect test results. Thicker WG335 filters cut off too much lower UVA energy to accurately represent UVA risk.

One comment submitted a method that assesses the attenuation of the incident solar radiation on human skin by a sunscreen (Ref. 27). This method utilizes the principles of diffuse reflectance and fluorescence excitation spectroscopy. The method directly measures the optical properties of the skin decoupled from its biological responses. Both procedures are based on the same principle, any modification of the surface of the skin will produce changes in its absorption properties. Application of a sunscreen modifies the surface of the skin by providing an additional barrier through which solar radiation must penetrate before reaching the skin. Measurement of the absorption properties of the skin before and after sunscreen application yields the transmission spectrum of the product and permits calculation of it solar protection value for the wavelength range investigated. The comment stated that, because this method allows repetitive testing, evaluations of substantivity and water resistance are possible. The comment contended that, because the testing is done on human skin, questions of binding, distribution, and photodegradation can be answered. In addition, the comment maintained that this testing procedure, like the Diffey and Robson method (Ref. 12), does not suffer from a lack of dose reciprocity, as observed with UVA-induced acute skin reactions. The comment concluded that this procedure allows for the correct estimation of the attenuating power of a sunscreen; thus, the protection potential of products in sunlight will be correctly estimated.

The agency would like to discuss the advantages and disadvantages of the various recommended testing procedures and the following specific questions regarding these test methods at the meeting:

1. Which of the in vitro test methods described above would be adequate to evaluate the UVA protection provided by a sunscreen drug product? Why would the others not be appropriate?

2. Are the results of in vitro UVA testing methods relevant to the UVA protection provided to consumers by a sunscreen drug product during normal use?

3. Does the APP test method demonstrate whether a sunscreen drug product provides meaningful protection against harmful UVA radiation?

4. Do the data show that the APP test does not overestimate the actual amount of UVA radiation blocked by most sunscreen drug products? Identify the data.

5. Describe the specifications for an appropriate light source for the IPD testing method, e.g., spectral distribution, intensity, etc.

6. What UVA radiation doses are appropriate for use in the IPD test?

7. When should the IPD response be read—immediately, or 1 or 2 hours after UVA exposure?

8. Is the IPD reaction relevant to protection of the skin from UVA damage?

9. Do the available data demonstrate that the IPD test is stable, nonvariable, and reproducible? Identify the data.

10. Do the available data demonstrate that the IPD testing response obeys dose reciprocity over the anticipated irradiance range?

11. Are results of the PFA testing procedure relevant to protection of the skin from UVA damage? Identify the results.

12. Do the data show that the PFA test obeys dose reciprocity? Identify the data.

13. Can the interval after exposure at which PFA responses are read affect the results?

14. Does the heat or infrared energy delivered to the skin during PFA testing exposure affect the results?

15. Describe the specifications for an appropriate light source for the PFA testing method, e.g., spectral distribution, intensity, etc.

The agency has concluded, under 21 CFR 10.65, that it would be in the public interest to hold a public meeting to discuss the many questions and topics associated with UVA testing for OTC sunscreen drug products. The proposed rulemaking involves 21 CFR parts 352, 700, and 740; however, the discussion at the public meeting will be limited to part 352.

The agency requests information regarding UVA protection claims and UVA testing procedures from any interested person. However, the agency requests that only new or additional information not previously included in the rulemaking be submitted. Data should be specifically limited and relevant to the questions asked. Any individual or group may, on or before April 29, 1994, submit to the Dockets Management Branch (address above), comments and data relevant to the questions and topics on UVA protection and testing procedures contained in this document. Two copies of any comments are to be submitted, except that individuals may submit one copy. All comments are to be identified with the docket number found in brackets in the heading of this document. It is not necessary to resubmit data and information submitted previously to this docket.

Any individual or group interested in making a presentation at the meeting should contact Jeanne Rippere (address above). Presentations should only address the questions and topics listed previously. Persons interested in participating in the meeting must also send a notice of participation on or before April 29, 1994, to the Dockets Management Branch (address above). All notices of participation submitted

should be identified with the docket number found in brackets in the heading of this document and should contain the following information: Name, address, telephone number, business affiliation, if any, of the person desiring to make a presentation, summary of the presentation, and the approximate amount of time requested for the presentation.

Groups having similar interests are requested to consolidate their comments and present them through a single representative. Depending on the time available and the number of participants, FDA may require joint presentations by persons with common interests. After reviewing the notices of participation, FDA will notify each participant of the schedule and time allotted to each person.

The administrative record for the OTC sunscreen drug products rulemaking is being reopened to specifically include only the proceedings of this public meeting. The administrative record will remain open until July 31, 1994, to allow comments on matters raised at the meeting.

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(6) Reference 30, Comment No. C128, Docket No. 78N–0038, Dockets Management Branch.

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(17) Comment No. C171, Docket No. 78N–0038, Dockets Management Branch.

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Michael R. Taylor,

Deputy Commissioner for Policy.

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