

Caroline Nutley, PhD
DIRECTOR OF INTERNATIONAL
REGULATORY AFFAIRS



April 10, 2000

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20857

4904 00 APR 10 AM 55

Re: Draft Guidance for Industry on Photosafety Testing; Docket Number 99D-5435; 65
Federal Register 1399; January 10, 2000

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies that are devoted to inventing medicines allowing patients to lead longer, happier, healthier and more productive lives. Investing \$26 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for new cures.

I am writing on behalf of PhRMA Photobiology Working Group to provide comments on the *Draft Guidance for Industry on Photosafety Testing*. PhRMA believes consensus has been reached in key areas. We would like to ensure that remaining differences of opinion are clearly articulated and that they can be resolved through continued dialogue. With these goals in mind, this letter summarizes the working group's concerns about rodent photocarcinogenicity testing to assess the potential risk to humans of non-photosensitizing drugs and drug products. In addition, we propose a clinical approach that, we believe, will yield better scientific data on safety. These are presented in the accompanying attachment.

In general, PhRMA agrees with much of the proposed evaluation of photosensitizing drugs as presented in the Draft Guidance. A photosensitizing drug is one that absorbs light, most commonly ultraviolet radiation (UVR) 290 - 400 nm, and is phototoxic, as determined using any number of *in vitro* or *in vivo* approaches, including human phototoxicity testing. Identification of phototoxic activity represents a relevant acute or potentially chronic human health hazard that requires appropriate labeling advising physicians of this risk. In this way, meaningful concerns can be incorporated into the risk/benefit assessment and communicated to patients to instruct them to minimize exposure to sunlight and take additional measures as appropriate to the individual patient.

PhRMA believes that the available data do not support the use of rodent photocarcinogenicity testing to evaluate drugs and drug products which do not absorb light between 290 - 400 nm or are not acutely phototoxic (i.e., non-photosensitizing drugs and drug products). This conclusion is based on: i) the expressed views of informed scientists

99D-5435

C7

Pharmaceutical Research and Manufacturers of America

and physicians; ii) the absence of scientific justification for assessment of human health risk using data obtained from multivariate experiments evaluating secondary or indirect effects in rodents; and iii) substantial uncertainty about the relevance to humans of rodent photo co-carcinogenicity study results, based on molecular, biochemical, and structural differences between SKH1 (hr/hr) albino hairless mouse and human skin.

Scientific data support the idea that clinical testing of non-photosensitizing drugs of concern is substantially more relevant and meaningful. Specifically, established clinical, noninvasive photobiological endpoints can be used to determine potential changes in UVR dosimetry or skin responsiveness, or both. Results from such studies can be used to develop relevant labeling advising health care practitioners of real risks for use in risk/benefit assessment and patient communications.

The enclosed attachment summarizes PhRMA's comments on this document. We trust that these will be useful to the Agency as this draft Guidance is revised.

Sincerely,

A handwritten signature in black ink, appearing to read "C. Nutley". The signature is written in a cursive, slightly slanted style.

Caroline J Nutley.

Pharmaceutical Rresearch and Manufacturers of America Comments on Draft Guidance for Industry on Photosafety Testing; Docket Number 99D-5435

PhRMA Overview

The best example of a photoactivated drug with substantial phototoxicological consequences, both acute and chronic, is 8-methoxypsoralen (8-MOP). The combination of 8-MOP and UVA (i.e., PUVA) is used in the treatment of psoriasis and represents the only clearly established human photocarcinogen¹. In contrast, there are few examples of nonphotosensitizing drugs or drug products that exacerbate the long-term, harmful effects of UVR on human health. The notable example is organ-transplant patients treated with systemic immunosuppressants such as azathioprine, which is mutagenic and a reported human carcinogen². Indirect effects of drugs that do not absorb light cannot be considered photosensitizers. For example, a drug or drug product could reduce thickness of the stratum corneum, reduce the melanin content of skin, or change the optical properties of the skin in a way that decreases scatter. The common effect of such changes would be an increase in the proportion of UVR that penetrates into the skin and is available for photobiology. The magnitude of such effects can be determined by measuring changes in the minimal erythema dose (MED) in humans. Thus, a noninvasive, well-established photobiologic endpoint in human subjects under actual use conditions can be used to assess long-term human health concerns related to the potential interaction between a nonphotosensitizing drug or drug product and UVR in shorter-term clinical trials.

Discussions with leading experts in photomedicine support the request by the PhRMA Photobiology Working Group to eliminate section IV. B. in the *Draft Guidance* entitled *Decision Tree for Testing NonPhotosensitizing Drugs for Long-Term Photosafety* and serve as the basis for our recommended clinical approach for evaluating nonphotosensitizing drugs.

The Lack of Scientific Justification for Assessment of Human Health Risk using Data Obtained From Multivariate Experiments Evaluating Secondary or Indirect Effects in Rodents

A number of scientific and medical concerns exist regarding the approach for assessing the phototoxicologic risk of nonphotosensitizing drugs as presented in the *Draft Guidance*. It is widely acknowledged that the relevance of results obtained in rodent photoco-carcinogenicity testing overestimates human risk and may have no human relevance at all³. There are multiple reasons for this, including the following:

- ◆ *Absence of Human Photocarcinogens*: Part of the uncertainty surrounding the outcome of rodent photoco-carcinogenicity studies can be attributed to the lack of established human photoco-carcinogens. 8-MOP used in combination with artificial UVR is the only clear example of a human photoco-carcinogen. 8-MOP is weakly mutagenic in the absence of light⁴. After exposure to UVR, 8-MOP is photoactivated and can form DNA photoadducts, crosslinks, or both⁵. This mechanism is believed to account for its phototoxic and photoco-carcinogenic potential. In this regard, the phototoxicologic potency of 8-MOP is quantitatively greater than any other established human phototoxicant. Importantly, the phototoxic potential of 8-MOP was understood before drug approval⁶ and labeling has communicated these risks.

Whereas some studies support a potential human risk of skin cancer with crude coal tar and therapeutic UVR exposure (i.e., Goeckerman therapy) for treatment of psoriasis, use of pharmaceutical grade coal tar without therapeutic UVR has not been found to be a carcinogenic risk factor⁷. Regardless, coal tar, like 8-MOP, is acutely phototoxic. Thus, for either the established (8-MOP) or suspected (coal tar) human photoco-carcinogens, acute photoactivation and phototoxicity are observed after exposure to UVR.

Chronic system immunosuppression in organ transplant patients has also been found to increase the risk of skin tumor formation⁸. The increased risk of skin cancer in these patients is likely the result of severe immunosuppression, although other effects such as phototoxicity cannot be ruled out for drug such as azathioprine⁹. The increased risk of skin cancer accompanying system immunosuppression supports careful handling of compounds with this clinical activity.

Thus, only these few cases support a clinical activity of drug-modified UVR-induced photocarcinogenesis. Interestingly, in all these cases, azathioprine, 8-MOP + UVR, crude coal tar + UVR, the drugs themselves are either genotoxic or carcinogenic without UVR. Regardless, with this limited human data-set, any progression to animal screening approaches, such as rodent photo-co-carcinogenicity testing, should be done with caution, as any demonstration of relevant and reliable clinical predictivity will be limited if not impossible.

- ◆ *Risk assessment of indirect or secondary mechanisms:* Any evaluation of a nonphotosensitizing drug or drug product would, by definition, be the assessment of an indirect or secondary mechanism. In this regard, the mechanism(s) by which a nonphotosensitizing drug may modulate photocarcinogenicity is critically important. For example, tumor promotion has been suggested as a mechanism by which a nonphotosensitizing drug might enhance UV-induced tumorigenesis in rodents¹⁰. Yet, despite over 20 years of study, the human relevance of rodent tumor promotion is unknown, as was noted recently by the Agency¹¹. Importantly, rodent tumor-promotion data are not routinely used for risk assessment¹² for several reasons including strain-to-strain and species-to-species response variability and absence of documentation of skin tumor promotion in humans¹³. Therefore, based on current scientific understanding, rodent photo-co-carcinogenicity outcomes attributed to secondary mechanisms such as tumor promotion have limited or potentially no relevance to human health risk.

In addition, the design of the rodent photo-co-carcinogenicity study is multivariate, further complicating the extrapolation of the study results. The confounding interactions are numerous and include the range of biological responses to different wavelengths of UVR, the impact of various UVR wavebands on the pharmacological effects of the drug, and the cellular and tissue location of any potential drug/UVR interaction.

Biochemical and Structural Differences Between Albino Hairless Mouse and Human Skin:

There are multiple biochemical and structural differences between human and hairless mouse skin which contribute to the expected variance in species response to UVR or drugs or both. Some specific examples are discussed.

- ◆ *Biochemical differences:*
 - ❖ Human and rodent skin differ in their capacity to repair UVR-induced DNA damage. For instance, UVR exposure produces cyclobutane pyrimidine dimers (CPD) and pyrimidine-pyrimidone (6-4) photoproducts. UVR induced photodamage to DNA is repaired by photoreactivation, excision repair or post-replication repair. Photoreactivation is a common phenomenon that is reported to play a role in repairing CPDs in human skin. It has been reported that SKH1 hairless mouse skin has little or no capacity for photoreactivation of CPD¹⁴.

- ❖ The antioxidant capacity of human skin is greater than hairless mouse. In mammalian skin, the antioxidant capacity is comprised of several enzymatic and non enzymatic pathways present in the epidermis and dermis. It has been shown that the antioxidant capacity of human and hairless mouse skin is greatest in the epidermis compared to the dermis and that the *total* antioxidant capacity of human skin is greater than that of hairless mouse skin¹⁵.
- ◆ Structural differences:
 - ❖ The epidermis of the SKH1 (hr/hr) albino hairless mouse, is 1 to 2 cell layers thick and lacks pigmentation. In contrast, the human epidermis is characterized by ridges and pegs comprised on different layers of differentiated cells with a minimum thickness of 5 to 6 cell layers. Further, pigment from melanocytes and hair follicles are present in human but not in SKH1 (hr/hr) hairless mouse skin. Epidermal thickness, which includes the stratum corneum and the uppermost layers of terminally differentiated keratinocytes, and pigmentation are considered the most important protection against acute and chronic effects of UVR¹⁶. Thus, the primary defense mechanisms between human and hairless mice are quantitatively and qualitatively different.
 - ❖ Although the physiochemical properties of the drug determine the extent of its absorption, in general the penetration of a drug is greater through hairless mouse compared to human skin, in some cases by more than one logarithmic unit¹⁷. As was the case with skin thickness and UVR exposure, the enhanced penetration of drug through hairless mouse skin is probably due to the thinner epidermis. Regardless, the greater penetration results in a quantitatively and possibly qualitatively different exposure of both drug and UVR at the critical, basal cell layers.

Given the biochemical and structural differences between hairless mouse and human skin, it should not be surprising that there are functional differences as well. The most significant difference between human and hairless mouse is in response to acute UVR exposure. In human, erythema is arguably one of the best-characterized photobiological responses to acute UVR exposure. In stark contrast, erythema is not a significant event in hairless mouse skin following acute exposure to UVR¹⁸.

Finally, chronic UVR exposure to human skin is believed to play an important role in the etiology of skin cancers. These human skin cancers include primarily melanoma and nonmelanoma skin cancers (NMSC), consisting of squamous and basal cell carcinomas. Within the NMSCs, basal cell carcinomas are the most common malignancy among Caucasian populations¹⁹. The rodent photoco-carcinogenicity study using SKH1 (hr/hr) albino hairless mice is a measure of predominantly squamous cell papilloma and carcinoma formation²⁰. Thus, this model is at best a measure of the least frequent form of human NMSC.

When differences between human and hairless mouse skin are considered, it is our view that the assessment of human health risk from data obtained by rodent photoco-carcinogenicity testing of nonphotosensitizing drugs is not scientifically justifiable. We maintain that the multivariate experiment design evaluating secondary or indirect effects in rodents creates such uncertainty that any decision based on results in this model might be considered inappropriate.

Clinical Approach for Evaluation of Nonphotosensitizing Drugs and Drug Products

We propose that the most meaningful approach for the evaluation of nonphotosensitizing drugs consists of studies performed in humans measuring standard photobiological endpoints. There are several endpoints that might be considered. Ideally, a noninvasive well-characterized measure of skin response to UVR including UVB exposure (290 - 320 nm) would be most promising, because this portion of the UVR spectrum is 1,000 to 10,000 times more potent at producing DNA damage and, in rodents, skin tumors compared to longer, less energetic wavelengths. We believe that the measurement of possible changes in minimal erythema dose (MED) may be a suitable approach for the evaluation of possible secondary or indirect activities of nonphotosensitizing drugs. MED has an action spectrum that resembles that of UVR-induced DNA damage²¹. Because the determination of MED is noninvasive, it can be measured repeatedly. Moreover, the law of UVR-dose reciprocity is followed, making this a practical endpoint for measure.

Other endpoints could be used, but these would require more research before broad application and have disadvantages. For example, determination of the number of sunburn or apoptotic cells or immunocytochemical determination of p53 mutated cells, provide histologic evidence of UVR-induced cell damage likely reflecting the degree of DNA damage. Disadvantages of these measures include their invasive nature and a lack of amenability to repeated testing.

Thus, a hypothetical study might include the determination of MED before, during, and after drug administration. Because steady-state drug delivery and maximal skin response to drug is often achieved only after repeated exposure, both acute and repeated UV/drug exposures could be performed. Information from such a design would provide a determination of possible drug-induced changes in the effective dose of UV or the skin response to UVR such that relevant drug product labeling decisions could be made. Importantly, with this approach the presence or absence of drug product labeling regarding phototoxicologic risk would reflect clinical data that are fully expected to relate to actual use experience.

Guidance for Industry: Guidance on Photosafety Testing

PhRMA comments on specific sections of the Draft Guidance follows:

I. Introduction

- *Page 1, ¶ 1:* “This guidance is intended to help applicants decide whether they should test for photosensitivity and assess potential human risk for **photochemical** carcinogenesis (cancer) . . .”

Comment: Photochemical, by definition, suggests a direct mechanism and rightfully should be the focus of this guidance document, but not nonphotosensitizing drug products.

II. Background

A. Photosensitivity and Photocarcinogenicity

- *Page 2, ¶ 3:* “Although a relatively small percentage of the population may show clinical symptoms of photosensitization, a much larger percentage may have

immediate subclinical effects, with long-term consequences not apparent for many years.”

Comment : This comment is speculative; it postulates that subclinical effects occur in a much larger percentage of exposed persons with a prolonged latent period. Such speculation is difficult to disprove but is equally difficult to prove.

- *Page 2, ¶ 4: Data from animals,....*

Comment: It is worth emphasizing that 8-MOP photochemistry directly damages DNA. Photon absorption provides sufficient energy to support covalent bonds between pyrimidines and either end of this tricyclic compound. Absorption of photons in the 380-400 nm range typically produces cyclobutane photoadducts that are unlikely to produce cross-links. Absorption of photons in the 320-360 nm range produces photoadducts capable of subsequently absorbing a second photon to produce a second cyclobutane photoadduct that cross-links the complementary DNA strands. Such DNA damage is mutagenic and a carcinogenic risk is consequently predictable on mechanistic grounds.

- *Page 3, ¶ 1: “It is believed that other compounds can enhance UV-induced skin carcinogenesis without being photoactivated.”*

Comment: This sentence should be qualified to the extent that “It is believed **but never demonstrated in humans (outside of systemic immunosuppression)** that other compounds . . .”

- *Page 3, ¶ 1. Comment*: The observation that chronic immune suppression is associated with a higher incidence of skin cancer does not establish mechanism. It is not clear what the relationship, if any, is to the effects of prior sun exposure. It is possible to speculate about a variety of possible explanations for the observed association, for example:
 - human papilloma virus strains that have been associated with carcinoma
 - suppression of immune response to tumor-associated antigens
 - response to cytokines elicited by stimulus to the suppressed immune system.

- *Page 3, ¶ 1: “It is believed that other compounds can enhance UV-induced skin carcinogenesis without being photoactivated . . . drug products that thin the protective layers of the epidermis (Pathak and Fitzpatrick, 1983).”*

Comment: There are no data, animal or human, that experimentally support this theoretical concern. In fact, the reference cited (Pathak and Fitzpatrick, 1983 in text, 1974 in references), seemingly to support this view, provides neither data nor discussion regarding enhancement of UV carcinogenesis by such an action. Of course, if the stratum corneum were removed, more UV would penetrate. As well, the barrier function of the skin would be perturbed resulting in water loss or electrolyte imbalance. Such a physiological perturbation would need to be maintained in the absence of adaptative changes and for an extended time period, i.e., several years. Again, theoretical constructs would seem to have limited value in a practical guidance document. At a minimum, such concerns need to be clearly identified as to the nature or origin of the consideration.

- *Page 3, ¶ 1:* “The minimal erythema dose has been used to estimate UVB exposure in humans;”

Comment: The MED is a measure of the threshold of erythema in response to solar simulated radiation. It is weighted at shorter wavelengths of UV with a peak around 300 - 310 nm. **It is not an estimate of UVB.** Minimal erythema dose is more accurately characterized as a measure of sensitivity to photobiologic effect, specifically sunburn, than as an estimate of UVB exposure. As such, experimental protocols have determined MED in individuals as a means to adjust exposure for differences in melanin content and other factors that influence the biologic response to UV. The MED of a skin type I individual may be 20 mJ/cm², whereas a skin type IV individual may have an MED of 50 mJ/cm². The dose of UV used to test for phototoxic reaction could thus be adjusted to the dose producing comparable sunburn reaction (i.e. 1 MED).

- *Page 3, ¶ 1. Comment:* Regarding the measurement of pyrimidine dimer formation and p53 protein induction in human skin as useful markers for enhanced UV exposure and potential damage to the skin (see end of last paragraph) – this is considered to be a highly impractical suggestion because dimer formation and p53 expression cannot be readily measured in the skin.

B. Photobiologic Principles

- *Page 3, ¶ 1:* “Photobiology is the study of the effect of optical radiation . . .”

Comment: It is not clear what the authors mean by “optical radiation.” Photobiology does involve the effects of UVB, UVA and visible radiation. Infra-red photons can transfer heat to the skin, but the energy of such photons is insufficient to produce photochemical reactions and hence do not elicit photobiologic reactions. It is suggested that Photobiology be defined as “The study of the interaction of wavelengths in selected regions of the electromagnetic radiation (EMR) spectrum (i.e., ultraviolet, visible, infrared) with living systems”. The term optical, of or relating to vision, could be misinterpreted.

- “ the first law of photochemistry,”

Comment: We concur with the stated paradigm, “There is no photobiology without photochemistry.” as do other leaders in photomedicine (Williams, 2000).²²

- *Page 3, ¶ 2:* “The nature of a compound’s excited state, the extent of intersystem crossing. . .”

Comment: What is “intersystem crossing”?

- *Page 3, ¶ 4.* ... “the light energy absorbed in the *action spectrum* and to the amount of compound (drug) present in the irradiated tissue.”

Comment: This is not an accurate use of the terminology. The action spectrum is defined as a plot of the reciprocal of the minimal dose required to elicit a defined response at each wavelength (in practice a narrow range of wavelengths is commonly used *in lieu* of monochromatic radiation) over a specific range. The

action spectrum is useful for comparing the relative effectiveness of wavelengths at eliciting the defined response. It would be more accurate to state that the reaction is a function of the amount of drug present and the number of photons absorbed by molecules of the drug.

- *Page 4, ¶ 3:* The term “photodynamic” should be included in the glossary.
- *Page 4, ¶ 4. Comment:* With the notable exception of immunosuppressants, as used to prevent organ rejection in transplant patients, the entire premise of indirect mechanisms of enhancement is without scientifically valid experimental support. Clearly, inhibiting repair mechanisms or altering the protective functions of the epidermis may have an affect on UV-induced skin carcinogenesis. Such theoretical constructs are worthy of consideration but should be appropriately considered and balanced when considering testing. Such considerations need to be carefully constructed to provide the appropriate context of the concern.

An example of the difficulty associated with the application of theoretical concerns to the consideration of UV-induced skin cancers is the topical application of glucocorticoids. The use of topical steroids as anti-inflammatories has been a standard treatment for dermatologic conditions for many years. Because steroids suppress the immune response and cause skin atrophy (i.e., “thinning”) after repeated administration, in theory such events could be risk factors for UV-induced skin cancer. However, studies conducted in albino hairless mice have found that topical application of hydrocortisone reduced UV-induced skin tumor number and onset²³. Such an effect is most likely the result of its anti-inflammatory properties. It would be an oversimplification to suggest that hydrocortisone might be a therapy to prevent UV-induced carcinogenesis, just as is the use of indirect mechanisms to postulate human risk. A more useful approach might be to advise patients and physicians of this theoretical concern. The sponsor might choose to provide experimental evidence to the contrary.

Any treatment that alters the optical properties of the skin would be expected to modify UV-induced skin neoplasms: reduction of scatter or reflectance would have the practical effect of increasing the proportion of UV available for the photobiologic reaction. This, however, sets a very sensitive criterion. For example, hydration of the stratum corneum meets the criterion of reducing scatter and reflectance, and thus by the convention proposed in this guidance would qualify for enhancing UV-carcinogenesis. This may be strictly true, but of limited practical value. The amount of time an individual spends in sunlight is arguably a much more important determinant of the risk of UV-induced skin cancer.

Finally, in the draft guidance, the Jacobs *et al.* 1999 citation regarding the effect of emollients on the latency for UV-induced tumors in hairless albino mice provides no peer-reviewed experimental evidence to support the “optical-clarity” hypothesis. This article is a survey of unpublished observations available exclusively to the Agency. There is little doubt that the results reported accurately portray what was observed in the study reports. The experimental conditions are such that all animals will develop skin cancer. The interpretation of such findings, however, is very much the subject of current debate (Williams 2000,²⁴ Bulera and de la Iglesia, 2000.²⁵ At a minimum, the survey reported in Jacobs *et al.* should be identified as containing information which has not undergone the rigorous peer-review process.

- *Page 5, ¶ 1. Comment:* In the interest of completeness it might be worth mentioning other DNA repair mechanisms that operate in addition to excision repair.

C. Historical Approach to Photosafety Testing

- *Page 5, ¶ 2. Comment:* The authors have previously noted on page 2 that psoralens, tetracyclines, sulfonamides, phenothiazines, fluoroquinolones, dacarbazine, coal tar derivatives, and some nonsteroidal anti-inflammatory agents are photoirritants. Of these, only coal tar derivatives are used by the topical route extensively, whereas psoralens and tetracyclines have very much less topical than systemic use. Moreover, systemically administered drugs are distributed to the entire skin surface, whereas topical treatments are more limited in exposure. When more people are exposed to systemic agents and the extent of total body exposure is greater with systemic agents, what is the basis for greater emphasis on the evaluation of topical agents?
- *Page 5, ¶ 3:* “The regulatory question is whether the drug increases the effect of UV light alone to such an extent that it possesses a significant increase in potential human carcinogenic risk such that the patient and the physician should be informed.”

Comment: This is arguably the most important point of this document from the standpoint of photocarcinogenicity or photoco-carcinogenicity. The key is, “to what extent is there a significant increase in potential human risk”. A most crucial component to address this question is “. . . do the existing or future models provide relevant and meaningful information from which **human risk** can be assessed”. This consideration, although acknowledged, would seem to need a clearer guidance. Specifically, for direct photochemical events, existing animal models such as the SKH1 hr/hr albino hairless mice seem to provide information that may be used to assess human risk (i.e., identification of 8-methoxypsoralen). In contrast, the evaluation of indirect or secondary mechanisms is quite uncertain with respect to the outcome of studies conducted in albino hairless mice. This holds true for other species and strains of animals (i.e., Tg.AC, p53 knockout, etc.). Again, the emphasis should be placed on direct photochemical activation and resultant findings versus response modifiers or indirect effects which are subject to numerous species/strain susceptibilities and have presently no basis for human risk evaluation.

III. TESTING CONSIDERATIONS

A. Considerations for Testing a Drug Product or Drug Substance

- *Page 6, ¶ 1:* “. . . the drug product, not just the active ingredient, should be evaluated”

Comment: The proposal to test the drug product, not just the active ingredient, is considered unwarranted. This does nothing to help resolve the question of what needs to be tested. Whereas excipients may alter optical properties of the skin, resulting in a difference in the effective dose, such differences are small relative to

the total exposure to sunlight. Variability in sun exposure is expected to be more important than changes in skin optics in determining the amount of UV delivered. As proposed, the requirement to test drug product would entail evaluation of each formulation to be marketed to assess differences in the effect of different excipients. Such a requirement clearly is counter-productive and requires a significant amount of effort disproportionate to reasonably expected effect. Unless there is some basis for believing that the excipients do more than alter the effective dose of UV delivered to susceptible cells, their effect is much less important than the amount of exposure to sunlight the individual experiences. It is worth considering how important changes in the extent and depth of penetration are likely to be.

- **Extent.** Changes in extent of penetration are, in effect, changes in dose. Since dose is directly proportional to duration of exposure, differences in time in sunlight are likely to substantially exceed differences attributable to optical characteristics of skin.
 - **Depth.** The action spectrum determined experimentally for UV-carcinogenesis in the mouse shows UVB to be substantially more important than UVA or visible light. Models adapting the action spectrum determined in the mouse to man as well as epidemiologic data similarly implicate UVB as important in man. Thus increasing the penetration potentially increases the dose delivered to epidermal cells, whether keratinocytes or basal cells. However, we are not aware of any evidence, experimental or epidemiologic, that sunlight increases the risk of cancer of cells found in the dermis.
- *Page 6, ¶ 1:* “Vehicles may cause acanthosis, hyperkeratosis, and inflammation in rodent skin (Binder et al., 1997).”

Comment: The work described by Binder *et al.* 1997, found no effect of vehicle on measures of skin response. In fact, the point of this communication was to demonstrate similarities in the dose-response to benzoyl peroxide regardless of the vehicle.

D. Testing for Photosensitivity (Photoirritation and Photoallergy)

1. Testing of Reformulations (Flow Chart A2)

Comment: An important consideration related to phototoxicology testing is the exaggerated exposure conditions inherent in the preclinical and clinical protocols. For example, in the standard phototoxicity (photoirritation) clinical protocol, product is applied under patch occlusion for 24 hours. Such conditions maximize the penetration of the “active” ingredient. Thus, changes in the formula matrix should have little impact on the outcome of phototoxicology testing.

- *Page 7, ¶ 5. Comments:*

What is meant by “nonclinical photoeffects”? Does this mean it would not be necessary to test for surrogate markers (eg p53 mutation or sunburn cells)? Under what circumstances would testing be expected for phototoxic effects of a new formulation?

It is reasonable to rely primarily on the evaluation of the drug for photosensitizing potential. Test methods use a range of doses to evaluate this potential.

The test doses should cover a reasonably expected daily exposure. There is little practical benefit to using higher doses than would be encountered during a full day in sunlight.

Once the photosensitivity has been established, the effect of differences in optical properties of stratum corneum attributable to formulation changes should have little or no effect other than to change the effective dose. Thus evaluating different formulations of the same active are unlikely to provide any information that could be meaningfully added to the label.

2. Tests for Evaluation of Photosensitivity

Comment: Overall, we support the methods and in particular the established nonclinical and clinical safety approaches addressed in this section. Regarding use of the 3T3 test, it should be noted that 3T3 cells lack human metabolism and detoxification mechanisms, thereby questioning the appropriateness of this assay in this case.

IV. Testing for Enhancement of UV-Associated Skin Carcinogenesis (direct Photochemical Carcinogenicity or Indirect Effects in Skin)

A. Considerations and Decision Tree for Testing Photosensitizing Drugs for Long-Term Photosafety

- *Page 8, ¶ 1:* “. . . long-term photosafety testing should be conducted **only** when it can provide useful information.

Comment: We concur with this statement that long-term photosafety testing should be conducted only when it can provide useful, value-added, interpretable information.

However, the remainder of the document is focused on *silent* enhancers of UV-induced carcinogenesis. The theoretical nature of such concerns warrants considerable attention. Most models used for hazard identification have been developed to address a single chemical or drug. The added complexity of multiple interactions where the action of the drug is independent of UV creates substantial uncertainty when considering the results of such investigations. Arguably, the uncertainty diminishes the usefulness of the information.

- *Page 8, ¶ 2:* “Because patients are already cautioned against excessive sunlight exposure during use of photosensitizing drugs, **sponsors could choose to strengthen these warnings with regard to photocarcinogenic potential, rather than conduct testing to determine the photochemical carcinogenicity potential of photosensitizing drugs.**”

Comment: Labeling for photoco-carcinogenicity potential could have the unintended effect of many products carrying such a warning, thereby diminishing

its significance. Regardless, the advice to physicians and patients treated with photosensitizing drugs is the same, namely avoid UV exposure.

- *Page 9, ¶ 2:* “It should be recognized, however, that subclinical photosensitivity responses with prolonged use could also result in increased skin cancer risk.”

Comment: This statement is speculative and should be identified as such. The idea that subclinical photosensitivity might be a risk factor for skin cancer has been addressed earlier in this document.

- *Page 9, ¶ 1, Comments:*
 - 3rd bullet: 8-MOP is an example
 - 4th bullet: coal tar is an example (first reported in 1776 in chimney sweeps and demonstrated experimentally 150 years later in the rabbit)
- *Page 9, ¶ 1 and ¶ 2. Comment:* It may be difficult if not impossible to distinguish acute photosensitizers producing sunburn (¶ 1) or subclinical photosensitivity responses (¶ 9) that result in increased skin cancer risk from UVB, which itself fulfills both of these criteria.
- *Page 9, ¶ 3: Comment:* What are the criteria that define when approvability or utility would be issues? How would scientific validity be established for models or endpoints to be considered relevant?
- *Page 10, ¶ 1:* “Thus, scientifically valid alternative assays....”

Comment: The term “scientifically valid” is subjectively determined. However, there has been no validation, and there are serious technical concerns related to this model (Forbes model), specifically in making human risk assessments.

- *Page 10, ¶ 1.* “Although the most widely performed test for the potential to enhance UV-induced skin cancer is the hairless mouse model with solar simulation, a test that takes approximately 12 months to complete, other tests,....”

Comment: The hairless albino mouse photoco-carcinogenicity model (i.e. Forbes model) may be the most widely performed test for the potential to enhance UV-induced skin cancer, but the absence of data from alternative models is not a substitute for establishing the validity of this mouse model. On the contrary, there are significant reasons to have reservations about the relevance of this model. It is not clear what clinical significance, if any, the positive results demonstrated with some fluoroquinolones have for risk in humans.

B. Decision Tree for Testing Nonphotosensitizing Drugs for Long-Term Photosafety

The approach for Nonphotosensitizing Drugs is described as follows:

- *Page 10, ¶ 1:* “. . . balance the risks associated with these potentially silent enhancers”

Comment: The logic of this opening paragraph is unclear. For instance, the statement that “Patients using a nonphotosensitizing product that enhances UV carcinogenicity may not have an indication, such as sunburn or sun sensitivity, that they have increased their risk of skin cancer” is complete speculation.

1. Reasons to suspect drug may enhance UV-induced skin carcinogenesis (Box 5)

- *Page 11, ¶ 1:* “Some of the mechanisms by which nonphotosensitizing vehicles or drugs may enhance UV-induced skin carcinogenesis include, but are not limited to, immunosuppression, neoplastic promotion, inhibition of apoptosis or DNA repair, irritation, altering the protective layers of the epidermis or changing the optical properties of the skin.”

Comment: With the exception of immunosuppression used to prevent organ rejection and sustain life, these mechanisms are theoretical.

- *Page 11, ¶ 1:* “Such mechanisms are applicable to both rodent and human skin and are biologically plausible mechanisms of enhancement.”

Comment: We do not agree with this general perspective of human risk. For example, the idea of neoplastic promotion has been the subject of debate with respect to human relevance for three decades, without resolution. For internal organs, i.e., liver, and skin the experimental existence of promotion in experimental animal models has not been sufficient to confer human risk. Such phenomena should not be dismissed, but, by the same account, there is no basis for regulatory action.

The “optical clarity” hypothesis has been demonstrated acutely but the translation of this into a chronic event, even ignoring biological adaptation, has only been demonstrated infrequently in experimental rodent models using exaggerated conditions. Studies sponsored by industry demonstrating a statistically significant increase in sensitivity to solar-simulated UV-induced sunburn-cell formation have resulted in the CIR Expert Panel recommending avoiding exposure to the sun. However, the human risk ascribed to the increase in sunburn-cells is arguably quite small and the resulting action (avoid solar UV exposure) is a conservative solution to this concern. Thus, the concerns related to theoretical constructs can be most simply and effectively managed by advising patients and physicians to avoid UV exposure.

There is strong epidemiologic evidence supporting the conclusion that UVB itself is a sufficient basis for explaining most squamous and basal cell skin cancers. Drugs which have been documented to enhance this effect are few.

C. Development of Alternative Assays

- *Page 12, ¶ 2. Comment:* Note: Basal cell carcinomas outnumber squamous cell carcinomas in humans by a ratio of approximately 3:1 but in the hairless albino mouse model only squamous cell carcinomas develop.

- *Page 12, ¶ 2:* “When submitting comments on this draft guidance to the docket, please include any information that would support the evaluation of alternative tests. . . [Such] data would be especially useful during the finalization of this document.”

Comment: Because the comment period is exceedingly short, i.e., 90 days, it is requested that the Agency consider delaying the finalization of this guidance until such time as a panel of photodermatologists and photobiologists can be convened to consider what information would be most helpful and develop a plan to generate such information.

ATTACHMENT

A1. Decision Tree to Identify the need for Short-term Photosensitivity Testing

Comment: Whereas an isolated phenyl ring will not absorb in the 290-700 nm range, addition of a single substituent onto the phenyl ring will bring the point of maximum absorbance up from 254 nm to 260-280 nm. It is likely that tailing of these peaks will result in some absorbance at 290 nm, particularly for the upper range. For chemicals containing two fused aromatic rings, absorbance in the 290-700 range is a given. The bottom line is that MANY compounds will fall under this absorption criterion. It would seem worthwhile to insert another box on the Decision Tree to permit the assessment of basic photoreactivity in *in vitro* systems. It is, after all, stated on Page 3 of the draft that “There is no photobiology without photochemistry.” It would seem reasonable to do an initial chemical photostability study under pertinent UV and visible irradiation conditions. This, done in conjunction with examination of the potential of the compound to produce reactive oxygen species, would provide appropriate guidance as to when photosensitivity testing is needed. An article by Thomas Oppenlander²⁶ entitled “A comprehensive photochemical and photophysical assay exploring the photoreactivity of drugs” presents an *in vitro* approach to evaluating the potential for compounds to behave as photosensitizers. There are in the literature articles describing how the photoreactivity of various known photoactive compounds (including psoralens, tetracyclines, chlorpromazine, amiodarone, the fluoroquinolones) was determined using chemical or *in vitro* systems. Such an approach would minimally require some literature searches, showing that the compounds which are known to be photosensitizers exhibit substantial chemical reactivity under relatively mild photochemistry conditions (i.e., conditions under which non-photosensitizers are inert). This could capture all of the problematic compounds using a limited number of validated, standardizable assays and would obviate the need for some animal testing.

Box # 3. Comment: Compound must be at concentration sufficient to cause response. Also mechanisms such as immunosuppression or thinning of the skin are not considered at this decision point;

Box # 4. Comment: Need to state that negative human data will supplant positive animal data

Box #5. “Indicate in risk communication that no effect observed.”

Comment: If results of phototesting are negative, what is the point of communicating this?

A2. Decision Tree to Identify the Need for Testing After Reformulation of a Topical Preparation

Box #4. “New formulation has significantly different effects on skin that could increase phototoxicity (e.g., allows much greater penetration of UV-absorbing drug substance or excipient into the skin).”

Comment: What constitutes greater penetration of UV absorbing drug substance? Most if not all preclinical and clinical studies are done under **exaggerated exposure conditions** (including dermal occlusion). Thus, what point would reformulation testing accomplish if the drug is already being reevaluated in routine human dermal safety testing?

B. Testing for the Photochemical Carcinogenicity Potential of Photoreactive Photosensitizing Drug Products and Labeling Outcomes

Comment: Box 1. Negative human data should supplant positive animal data.

Comment: Box 4. Can this be qualified as usually a Phase IV commitment?

C. Testing of Nonphotosensitizing Drug Products for Potential to Enhance UV-Induced Skin Carcinogenesis

Comment: Box #4. Systemic exposure by dermal route needs to be considered.

Comment: Box #5. It must be clear that photogenotoxicity studies are not required for all compounds where there is chronic dermal exposure to UV exposed skin. This could erroneously be implied from this chart.

Some editorial comments:

Pg. 1, 2nd paragraph, 4th sentence -- suggest slight rewording: "Sponsors may propose alternative assays that are scientifically sound."

Pg. 2, 2nd paragraph, last sentence -- need period at end of sentence

Pg. 3, 1st complete paragraph, 5th sentence -- spelling of "erythemat" (er.... vs. en....) and delete the "l" at the end of the word

Pg. 4, 2nd paragraph, 2nd sentence --spelling of psoralens (n, not m)

At end of item #4 -- shouldn't there be a blank space between the close parenthesis after "reaction" and the open parenthesis mark before "Kornhauser"

Pg. 7, last sentence in 3rd full paragraph -- remove the word "for" before "photosensitivity"
last paragraph, 3rd sentence -- remove the comma before "drug."

Pg. 8, 1st sentence in first full paragraph -- suggest rewording to read "A number of methods and approaches that test for photosensitivity are currently in use."

Pg. 10, 1st paragraph, 3rd complete sentence ("Tests that are felt.....") -- suggest changing the word "felt" to "considered."

Pg. 11 Section 4 -- to be consistent with the rest of the document, italicize "Warning or test"

Pg. 12, 1st sentence in last paragraph -suggest changing end of sentence to read "...when there is sufficient scientific support".

Pg. 13 (REFERENCES):

Abel listing -- question the "(2 part 1)" given after the Volume # -- maybe this should be checked.

Burren listing -- to be consistent with the approach used throughout the list of REFERENCES, need to add one blank space between Panizzon's and Applegate's initials

Pg. 14, Hessel listing -- need to add one blank space between Mitchell's initials
Johnson, 1997 listing -- spelling of "Tumorignesis"
Kochevar, 1993 listing -- need to add one blank space between Pathak's and Austen's initials

Pg. 15, remove one blank line between the Megaw and the Pathak/Fitzpatrick listing

COMMENTS TO GLOSSARY

- UV – ultraviolet radiation does not include all wavelengths below 400 nm; whereas the lower limit of ultraviolet is arbitrary and varies among different conventions, ionizing wavelengths such as x-rays and gamma rays have wavelengths (e.g. 0.1 - 100 angstroms) that are shorter than 400 nm. The effects of such radiation are traditionally categorized as radiobiologic, not photobiologic.
- UVC – wavelengths less than 290 nm is not an appropriate definition of UVC because it includes ionizing radiation (see above).

REFERENCES

- ¹ Stern et al. (1997) *N Engl J Med* 336: 1041-1045. McKenna et. al. (1996) *Br J Dermatol* 134: 639-642. Stern et al. (1984) *N Engl J Med* 310: 1156-1161.
- ² Clark (1975) *Mutat Res* 28: 87-99. Herbold and Buselmaier (1976) *Mutat Res* 40: 73-84. Sixth Annual Report on Carcinogens (1991) Page 33-35.
- ³ The Summer Toxicology Forum (1996) *Photo Carcinogenesis Testing*, pg 119-189, Washington DC. Kligman (1993) *J Toxicol-Cut & Ocular Toxicol* 12: 205-220. Davies and Forbes (1988) *J Toxicol-Cut & Ocular Toxicol* 7: 241-253.
- ⁴ Bridges and Mottershead (1977) *Mutat Res* 44: 305-312. Quinto et al. (1984) *Mutats Res* 136
- ⁵ Averback et al. (1992) *J Photochem Photobiol. B: Biol* 14: 47-63.
- ⁶ Stern et al. (1988) *J Invest Dermatol* 91: 120-124. Hakim et al. (1960) *Arch Dermatol* 84: 572-576.
- ⁷ Pion et al. (1995) *Dermatol Surg* 21: 227-231. Maughan et al. (1980) *J Am Acad Dermatol* 3: 612-615. Pittelkow et al. (1981) *Arch Dermatol* 117: 465-468.
- ⁸ Bouwes Bavinck et al. (1993) *Br. J. Dermatol.* 129: 242-249. Bouwes Bavinck et al. (1996) *Transplantation* 61: 715-721.
- ⁹ Kelley et al. (1989) *Photochem Photobiol* 49: 59-65.
- ¹⁰ Forbes et al. (1993) *J. Am. Coll. Toxicol.* 12: 417-424.
- ¹¹ Federal Register (1995) 60 (33): 9554-9558.
- ¹² EPA (1987) EPA/600/9-87/013; *The Summer Toxicology Forum* (1992).
- ¹³ Kraus et al (1995) *Regul. Toxicol. Pharmacol.* 21: 87-107; Williams et al. (1983) *Environ. Health Perspect.* 50: 351- 354; Greim et al. (1984) *IARC Sci. Publ.* 56: 487-494; Peto (1984) *IARC Vol* 50.
- ¹⁴ Ley et al. (1977) *Cancer Research* 37: 3243-3248.
- ¹⁵ Shindo et al. (1993) *J Invest Dermatol* 100: 260-265; Shindo et al. (1994) *J Invest Dermatol* 102: 122-124.
- ¹⁶ Lock-Andersen et al. (1997) *Photodermatol. Photoimmunol. Photomed.* 13: 153-158.
- ¹⁷ Simon and Maiback (1998) *Skin Pharmacol. Appl. Skin Physiol.* 11: 80-86.
- ¹⁸ Argenbright and Forbes (1982) *Br. J. Dermatol.* 106: 569-574. Cole et al. (1983) *Photochem. Photobiol.* 37: 623-631.
- ¹⁹ Marks (1995) *Cancer* 75: 607-612. Gallagher et al. (1995) *Arch Dermatol.* 131: 157-163.
- ²⁰ Mark et al. (1990) *J.Toxicol.-Cut & Ocular Toxicol.* 9: 525-537.
- ²¹ Parrish et al (1982) *Photochem Photobiol* 36: 187-191.
- ²² Williams (2000) *Int. J. Toxicol.* 19(1):65-66
- ²³ Bissett et al., *Photodermatol Photoimmunol Photomed*, (1990) 7. 153-158
- ²⁴ Williams (2000) *Int. J. Toxicol.* 19(1):65-66
- ²⁵ Bulera and de la Iglesia (2000) *Int. J. Toxicol.* 19(1):63-64
- ²⁶ Oppenlander *Chimia* (1988), 42 .331