平成 25 年 4 月 28 日

厚生労働科学研究費補助金
医薬品の品質、有効性及び安全性確保のための手法の国際的整合性を目指した調査と妥当性研究（大野班）
光毒試験に関するガイドライン策定のための調査研究班
第 2 回班会議　議事録

日時：平成25年4月22日（月） 13:30～17:30
場所：東京都健康安全研究センター本館6階 会議室6A

出席者：中江大班長（東京都健康安全研究センター）、小野寺博志（PMDA）、笛木修（PMDA）、関澤信一（PMDA）、細井一弘（参天）、岩瀬裕美子（田辺三菱）、中村和市（塩野義）、白菊敏之（大塚、議事録作成）

議題：

4 月 15 日の第 1 回班会議に引き続き、「ICH S10：医薬品の光安全性評価ガイドライン（案）」に寄せられたパブリックコメントへの対応案について議論した。

- ガイドライン（案）の注釈の項には紫外－可視吸収スペクトル測定、モル吸光係数算出について技術的な記載があるが、ガイドラインの Step 4 案の作成時に論文が出版されている必要がある。現在の記載内容は第一選択の溶媒としてメタノールを推奨しているような印象を与え OECD ガイドライン 101 とニュアンスが異なるので、誤解を与えないような修正が必要である。
- JPMA で検討した「光安全性評価の概念図」については、評価の順番を示すような矢印の使用は Step 2 文書の考え方に合致しないため日本案として合意に至らなかった。JPMA で再検討し、5 月 10 日の TF-2 会議の JPMA 最終案を決定する。

協議した対応案を確認するとともに、該当する Step 2 文書の項目、行番号、コメント発出機関・団体、コメント内容と対応を記した EWG 提出用フォームに整理した。

タイムライン：

EWG 提出用フォーム作成を 4 月 23～24 日に完了し、翻訳する（4 月 24 日、翻訳依頼完了）。翻訳完了予定は 5 月 7 日の週で、翻訳の妥当性を班会議メンバー及び JPMA TF-2 メンバーで確認する（5 月 10 日に JPMA TF-2 会議予定）。5 月の第 2 週には、中江班長から各極 EWG メンバーに日本の対応をメール配信する。他極のパブコメ対応が入手できれば、第 3 回班会議（5 月 29 日）で予め検討し，6 月 1～6 日のブリュッセル ICH 会議に臨む。

次回班会議の予定：

2013 年度 第 3 回班会議：2013 年 5 月 29 日（水） 13:30～
東京都健康安全研究センター本館 6 階 会議室 6A

以上

2013年度厚労科研大野ICH支援班光毒性分班第3回分班会議の開催について

みなさま

下記の通り，2013年度厚労科研大野ICH支援班光毒性分班第3回分班会議の開催通知をお送りしますので，よろしくお願い申し上げます．

記

会議名：　2013年度厚労科研大野ICH支援班光毒性分班第3回分班会議
日時：　2013年5月29日（水）13時30分開始，17時30分終了（暫定）
場所：　東京都健康安全研究センター本館6階会議室6A
　　169-0073 東京都新宿区百人町3-24-1
　　電話，03-3363-3231
議題：　ICH S10 step 2 guidelineパブコメへの対応について

以上

中江 大
東京都 専門参事
東京都健康安全研究センター 薬事環境科学部 部長

169-0073 東京都新宿区百人町3-24-1
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平成 25 年 6 月 7 日

厚生労働科学研究費補助金
医薬品の品質、有効性及び安全性確保のための手法の国際的整合性を目指した調査と妥当性研究（大野班）
光毒試験に関するガイドライン策定のための調査研究班
第 3 回班会議 議事録

日時：平成25年5月29日（水） 13:30～17:30
場所：東京都健康安全研究センター本館6階 会議室6A

出席者：中江大班長（東京都健康安全研究センター）、尾上誠良（静岡県立大）、小野寺博志（PMDA）、笛木修（PMDA）、細井一弘（参天）、岩瀬裕美子（田辺三菱）、中村和市（塩野義）、白菊敏之（大塚、議事録作成）

議題：

2013年6月1日からのブリュッセルICH会議を前に、各極のパブリックコメント対応案について議論した。重大なコメントを含んでいるとは思えないが、以下の4つの問題に対処する必要がある。

1. Regional differences
以下の地域間差がみられる記載があるが、可能な限り調和の方向へ努力する。

5.1.2

EU では、動物試験の実施を検討する前に一般的にはバリデートされた in vitro の代替法を選択しなくてはならない。

5.2.1

経皮適用剤の評価について、MECが1000 L mol^{-1} cm^{-1}以上の化合物については、EU及び日本では、光反応性試験（ROSアッセイなど）で陰性結果が得られた場合、更なる光安全性評価を必要としない。米国では一般的に、光反応性試験における陰性結果が得られたとしても、申請予定製剤を用いた更なる臨床光安全性評価が求められる。

5.2.2

適切な条件下において3D皮膚モデルで陰性結果が得られた場合には、その製剤の光毒性ポテンシャルは低いとみなすことができると考えられる。この場合、EU及び日本では、一般に更なる試験実施は必要ない。米国では一般的に、陰性結果が得られたとしても、申請予定製剤を用いた更なる臨床光安全性評価が求められる。

5.2.2

EU及び日本では、適切に実施された*in vivo*動物試験で陰性結果が得られた場合には当該製剤は

光毒性を有さないと判断して差し支えなく、更なる光毒性試験実施は必要ない。米国では一般的に、陰性結果が得られたとしても、申請予定製剤を用いた更なる臨床光安全性評価が求められる。

5.2.2

眼局所適用薬について、米国及び日本においては、眼局所適用薬の光毒性に関し実験的に評価する具体的な推奨はない。EUでは、入手できたデータがハザード特定には十分でないと考えられる場合、*in vitro*評価あるいは別の投与経路を用いた*in vivo*試験法で評価することが推奨される。

Note 5

全身適用薬で血漿中濃度に対する組織中濃度比の高くないものあるいは皮膚に蓄積しないものに関しては、米国では、光毒性の更なる評価は一般的に必要とされない。EU及び日本においても、血漿中濃度に対する組織中濃度比が高いことや組織蓄積も重要と考えられている。

2. Diagram summary

評価のフローチャートあるいは決定樹等の図について挿入を望むコメントが他極においても多数みられた。weight-of-evidence アプローチを採用しているガイドライン(案)の考え方を阻害しないような評価概念図を製薬協の意見として提案する。段階的アプローチを示唆するような図については、FDA が反対した経緯もあり、EFPIA の動向も注視し、議論のタイミングを計る。

3. Validation of assays

ROS assay及び3D skin modelについて正式なバリデーション試験は完了していない。ROS assayについては、JacVAMで第三者評価中であり、2013/4Qのstep 4にはJacVAMホームページに標準プロトコール及びバリデーション試験データが掲載予定である。3D skin modelのバリデーション試験について詳細な情報はない。

4. Ocular pharmaceuticals

眼局所適用薬については、US及び日本は*in vitro*及び*in vivo*ともに現在適切な試験系は存在しないという考えである。一方、EUは現状で適切な試験系は存在しないが、ハザード評価が十分でないと考えられる場合、*in vitro*試験あるいは別の投与経路を用いた*in vivo*試験の実施を推奨するという考えである。現状、眼局所適用薬の具体的な評価系は示されておらず、ガイドラインのスコープから除外することも検討する。

ROS assay のバリデーション試験

ブリュッセル ICH 会議で細井氏からの報告が予定されており、peer reviewer のコメントを踏まえ報告案について議論した。

1　5-FU及びロシグリタゾンを光毒性物質としていることについて、信頼性の高い臨床試験データではないと考えられることから、光毒性物質とは断定できないとした。

2　析出が原因で200 μMで評価不能であった化合物については20 μMのデータを追加する。

3　特異性の低いことへの対応として、評価基準を修正し、singlet oxygen < 25 且つ superoxide anion ≥ 20, < 70 の場合“Weakly photoreactive”とした。

以上

2013 年度厚労科研 ICH 支援班光安全性分班第 4 回分班会議の開催について

みなさま

下記の通り、2013 年度厚労科研大野 ICH 支援班光毒性分班第 1 回分班会議の開催通知をお送りしますので，よろしくお願い申し上げます．

記

会議名：　2013年度厚労科研大野ICH支援班光毒性分班第1回分班会議
日時：　2014年1月23日（木）13時30分開始，18時頃終了予定
場所：　東京都健康安全研究センター本館6階会議室6D
169-0073 東京都新宿区百人町3-24-1
電話，03-3363-3231

議題：　ICH S10 guidelineパブコメへの対応について

備考：　さらなる対面会合の必要性については，本会議の結果により，改めて決定します．

以上

中江 大
東京都 専門参事
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第 4 回分班会議においては，特に議事録を作成しなかった．

[平成 25 年度分担研究報告書添付資料 2]
ICH S10ガイドライン(英文　ICHウェブサイト掲載版)

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

PHOTOSAFETY EVALUATION OF PHARMACEUTICALS

S10

Current Step 4 version

dated 13 November 2013

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

S10
Document History

Code	History	Date
S10	Approval by the Steering Committee under Step 2 and release for public consultation.	15 November 2012

Current Step 4 version

S10	Approval by the Steering Committee under Step 4 and recommendation for adoption to the three ICH regulatory bodies.	13 November 2013

ICH Harmonised Tripartite Guideline

Having reached Step 4 of the ICH Process at the ICH Steering Committee meeting on 13 November 2013 this guideline is recommended for adoption to the three regulatory parties to ICH.

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PHOTOSAFETY EVALUATION OF PHARMACEUTICALS

PHOTOSAFETY EVALUATION OF PHARMACEUTICALS

1. INTRODUCTION

1.1. Objectives of the Guideline

The purpose of this document is to recommend international standards for photosafety assessment, and to harmonise such assessments supporting human clinical trials and marketing authorizations for pharmaceuticals. It includes factors for initiation of and triggers for additional photosafety assessment and should be read in conjunction with ICH M3(R2), Section 14 on Photosafety Testing (Ref. 1). This guideline should reduce the likelihood that substantial differences in recommendations for photosafety assessment will exist among regions.

This guideline is divided into several sections. Section 2 discusses factors to consider in any evaluation of photosafety. Section 3 describes existing nonclinical photosafety tests, but this section does not describe specific testing strategies. Section 4 mentions clinical photosafety assessment. Section 5 provides strategies for determining how to assess photosafety for drugs given by routes intended to produce systemic exposure or by the dermal route using the considerations and tests described in Sections 2, 3 and 4.

Consideration should be given to the use of non-animal methods or clinical data for photosafety assessment which could reduce the use of animals in accordance with the 3R (Replacement/Reduction/Refinement) principles.

1.2. Background

The ICH M3(R2) Guideline provides certain information regarding timing of the photosafety assessment relative to clinical development. It recommends that an initial assessment of phototoxicity potential be conducted, and if appropriate, an experimental evaluation be undertaken before exposure of large numbers of subjects (Phase 3). Similarly, the ICH S9 Guideline (Ref. 2) describes the timing of photosafety testing for oncology products. However, neither ICH M3(R2) nor ICH S9 provides specific information regarding testing strategies. This ICH S10 Guideline outlines further details on when photosafety testing is warranted, and on possible assessment strategies.

1.3. Scope of the Guideline

This guideline generally applies to new Active Pharmaceutical Ingredients (APIs), new excipients clinical formulations for dermal application (including dermal patches), and photodynamic therapy products.

Specific guidance for pharmaceuticals given via ocular routes is not provided because the reliability of in vitro approaches in predicting ocular phototoxicity is unknown and there are no standardised in vivo approaches for assessing phototoxicity for products administered via the ocular routes (see Note 1).

Photodynamic therapy drugs are developed with photochemical reactivity as an inherent aspect of their intended pharmacology and additional assessment of their phototoxicity is not usually warranted. However, an evaluation of the toxicokinetics and tissue distribution of photodynamic therapy drugs is warranted to enable appropriate risk management in patients.

This guideline does not generally apply to peptides, proteins, antibody drug conjugates, or oligonucleotides. Further, this guideline does not apply to components of marketed

products unless there is a new cause for concern for either the API or an excipient (e.g., a reformulation from a tablet to a topical cream).

1.4. General Principles

The photosafety assessment of a pharmaceutical is an integrated process that can involve an evaluation of photochemical characteristics, data from nonclinical studies and human safety information. The photosafety assessment aims to determine whether risk minimization measures are warranted to prevent adverse events in humans.

Four different effects have been discussed in connection with photosafety testing: phototoxicity, photoallergy, photogenotoxicity and photocarcinogenicity. Testing for photogenotoxicity (Note 2) and photocarcinogenicity (Note 6 of ICH M3 (R2)) is not currently considered useful for human pharmaceuticals. This guideline addresses only phototoxicity and photoallergy effects as defined below:

- Phototoxicity (photoirritation): An acute light-induced tissue response to a photoreactive chemical.
- Photoallergy: An immunologically mediated reaction to a chemical, initiated by the formation of photoproducts (e.g., protein adducts) following a photochemical reaction.

Photosensitization is a general term occasionally used to describe all light-induced tissue reactions. However, in order to clearly distinguish between photoallergy and phototoxicity, the term photosensitization is not used in this guideline.

For a chemical to demonstrate phototoxicity and/or photoallergy, the following characteristics are critical:

- Absorbs light within the range of natural sunlight (290-700 nm);
- Generates a reactive species following absorption of UV-visible light;
- Distributes sufficiently to light-exposed tissues (e.g., skin, eye).

If one or more of these conditions is not met, a compound will usually not present a concern for direct phototoxicity. However, increased sensitivity of skin to light can also occur through indirect mechanisms. Such mechanisms are not generally addressed by the testing outlined in this guideline (see also Section 2.4).

2. FACTORS TO CONSIDER IN THE PHOTOSAFETY EVALUATION

2.1. Photochemical Properties

The initial consideration for assessment of photoreactive potential is whether a compound absorbs photons at any wavelength between 290 and 700 nm. A compound that does not have a Molar Extinction Coefficient (MEC) greater than 1000 L mol^{-1} cm^{-1} at any wavelength between 290 and 700 nm (Ref. 3) is not considered to be sufficiently photoreactive to result in direct phototoxicity (see Note 3 for further details).

Excitation of molecules by light can lead to generation of Reactive Oxygen Species (ROS), including superoxide anion and singlet oxygen via energy transfer mechanisms. Although photoreactivity can result in other molecular outcomes (e.g., formation of photoadducts or cytotoxic photoproducts), even in these cases, it appears that ROS are typically generated as well. Thus, ROS generation following irradiation with UV-visible light can be an indicator of phototoxicity potential.

Photostability testing (Ref. 4) can also suggest the potential for photoreactivity. However, not all photoreactive compounds are detected under these conditions, and

photodegradation per se does not imply that a drug will be phototoxic. Therefore, photostability testing alone should not be used to determine whether further photosafety evaluation is warranted.

Assessments of photochemical properties should be conducted using high-quality scientific standards with data collection records readily available, or in compliance with Good Laboratory Practices/Good Manufacturing Practices (GLP/GMP) regulations.

2.2. Tissue Distribution/Pharmacokinetics

The concentration of a photoreactive chemical in tissue at the time of light exposure is a very important pharmacokinetic parameter in determining whether a phototoxic reaction will occur. This concentration depends on a variety of factors, such as plasma concentration, perfusion of the tissue, partitioning from vascular to interstitial and cellular compartments, and binding, retention, and accumulation of the chemical in the tissue. The duration of exposure depends upon clearance rates as reflected by half lives in plasma and tissue. Collectively, these parameters define the mean residence time of the photoreactive chemical in tissue.

Binding, retention, or accumulation of a compound in a tissue is not critical for a phototoxic reaction. If a molecule is sufficiently photoreactive, it might produce a phototoxic reaction at the concentration achieved in plasma or interstitial fluid. However, compounds having longer half-lives in plasma, longer mean residence time in sun-exposed tissues or with higher tissue to plasma concentration ratios are more likely to produce a phototoxic reaction than compounds with shorter half-lives, residence times or lower tissue to plasma ratios. Further, the longer the concentration of a compound is maintained at a level above that critical for a photochemical reaction, the longer a person is at risk for phototoxicity.

Although a tissue concentration threshold below which the risk for phototoxic reactions would be negligible is scientifically plausible, there are currently no data to delineate such generic thresholds for all compounds. Nevertheless, on a case-by-case basis it can be possible to justify that further photosafety assessment is not warranted based upon actual or anticipated tissue drug levels in humans, and taking into consideration the factors discussed above. Examples could include: 1) a drug for which overall systemic exposure levels are very low, or 2) a drug with a very short plasma half-life or tissue residence.

Compound binding to tissue components (e.g., melanin, keratin) is one mechanism by which tissue retention and/or accumulation can occur. Although melanin binding can increase tissue levels, experience with melanin binding drugs suggests such binding alone does not present a photosafety concern.

A single-dose tissue distribution study, with animals assessed at multiple timepoints after dosing, will generally provide an adequate assessment of relative tissue to plasma concentration ratios, tissue residence time and the potential for retention and accumulation. Assessment time points should be appropriately spaced in such a study to account for the drug half-life.

Compounds activated by visible light and exhibiting long elimination half-lives in internal tissues have been demonstrated to cause injury to those tissues if exposed to intense light during medical procedures. Consequently, for those compounds activated by visible light with potent in vivo phototoxicity or known to be phototoxic based on their mechanism of action, such as photodynamic therapy drugs, distribution to internal tissues should be measured and tissue-specific half-lives estimated. Drugs that only absorb UV light or have short tissue elimination half-lives are not likely to present a risk to internal tissues even if they are known to be photoreactive.

2.3. Metabolite Considerations

Metabolites generally do not warrant separate photosafety assessments, as metabolism does not typically result in chromophores that are substantially different from those in the parent molecule.

2.4. Pharmacological Properties

In many cases, drug-induced phototoxicity is due to the chemical structure and not to the pharmacology. However, certain pharmacologic properties (e.g., immunosuppression, perturbation of heme homeostasis) can enhance susceptibility to light-induced effects, such as skin irritation or UV-induced skin tumor formation. The testing strategies outlined in this document are not designed to detect these types of indirect mechanisms. Some of these indirect mechanisms can be identified and evaluated in other nonclinical pharmacology/toxicity testing; however, phototoxicity related to other indirect mechanisms might only become apparent with human experience.

3. NONCLINICAL PHOTOSAFETY TESTS

3.1. General Considerations

Carefully selected conditions that consider both the model system and exposure to a relevant radiation spectrum are critical for nonclinical photosafety testing. Ideally, a nonclinical assay should exhibit both high sensitivity and specificity (i.e., low false negative and low false positive rates). However, to support the assessment strategies described in this document, it is most important that nonclinical photosafety assays show high sensitivity resulting in a low frequency of false negatives (i.e., a high negative predictive value). This is because negative assay results usually do not warrant further photosafety evaluation. The available nonclinical assays, both in vitro and in vivo, are focused primarily on detecting potential phototoxicity, which might or might not translate into clinically relevant phototoxicity.

Selection of irradiation conditions is critical for both in vitro and in vivo assays. Natural sunlight represents the broadest range of light exposure that humans might be exposed to regularly. However, sunlight per se is not well defined and depends on many factors, such as latitude, altitude, season, time of day, and weather. In addition, sensitivity of human skin to natural sunlight depends on a number of individual factors (e.g., skin type, anatomical site and tanning status). Standardized sunlight exposure conditions have been defined by various organizations. Such standards (e.g., Ref. 5) should be considered in order to assess suitability of a sunlight simulator light source, and irradiance and irradiation dose should be normalized based on the UVA part of the applied spectrum. UVA doses ranging from 5 to 20 J/cm^2 are successfully used in current in vitro and in vivo phototoxicity assays. These UVA doses are comparable to those obtained during prolonged outdoor activities on summer days around noon time, in temperate zones, and at sea level. In humans, sunburn reactions caused by UVB normally limit total sunlight exposure. In nonclinical phototoxicity assays, however, the amount of UVB should not limit the overall irradiation and might be attenuated (partially filtered) so that relevant UVA doses can be tested without reducing assay sensitivity. Penetration of UVB light into human skin is mainly limited to the epidermis, while UVA can reach capillary blood. Therefore, clinical relevance of photochemical activation by UVB is considered less important than activation by UVA for systemic drugs. However, UVB irradiation is relevant for topical formulations applied to light-exposed tissues.

The selection and monitoring of appropriate light sources (spectral distribution, irradiance, and dose) and the procedures used should be clearly described in the study methodology (e.g., Ref. 6).

3.2. Photoreactivity Tests Using Chemical Assays

If a drug developer chooses to assess photoreactivity, the assay should be qualified using pharmaceutical agents under appropriate conditions to demonstrate assay sensitivity. One such assay is a ROS assay (e.g., Ref. 7). Data suggest that this assay has high sensitivity for predicting direct in vivo phototoxicants. However, it has a low specificity, generating a high percentage of false positive results. A negative result in this assay, conducted under the appropriate conditions, would indicate a very low probability of phototoxicity, provided a test concentration of 200 μM can be achieved, whereas a positive result (at any concentration) would only be a flag for follow-up assessment.

3.3. Phototoxicity Tests Using in vitro Assays

A number of in vitro assays have been developed for assessing the phototoxicity potential of chemicals. Some of these assays have not been qualified for use with pharmaceuticals. Some assays involve testing compounds that are dissolved in the culture medium, and such methods are often appropriate for the active ingredient or excipients in drug products, depending on their solubility. Other assays involve direct application to the surface of a tissue preparation and can be appropriate for testing entire formulations intended to be administered topically.

The most widely used in vitro assay for phototoxicity is the 3T3 Neutral Red Uptake Phototoxicity Test (3T3 NRU-PT) for which an Organisation for Economic Co-operation and Development (OECD) guideline (Ref. 6) is available. This is currently considered the most appropriate in vitro screen for soluble compounds.

Although the formal European Centre for the Validation of Alternative Methods (ECVAM) validation exercise conducted on this assay indicated a sensitivity of 93% and a specificity of 84%, experience within the pharmaceutical industry suggests a much lower specificity. The original OECD protocol was not validated for pharmaceuticals specifically. Thus, some modifications to the original OECD protocol have been proposed to address the low specificity observed with drug substances (see Note 4). These proposed changes are appropriate for the testing of pharmaceuticals. The sensitivity of the 3T3 NRU-PT is high and if a compound is negative in this assay it would have a very low probability of being phototoxic in humans. However, a positive result in the 3T3 NRU-PT should not be regarded as indicative of a likely clinical phototoxic risk, but rather a flag for follow-up assessment.

The BALB/c 3T3 cell line is sensitive to UVB and the initially recommended irradiation conditions (Ref. 6) involve the use of filters to attenuate wavelengths below 320 nm. However, depending on the light source and filters used, the ratio of UVB to UVA can be adjusted such that it is possible to assess UVB-induced phototoxicity in this test. UVB-induced phototoxicity is rarely a problem for pharmaceuticals with systemic exposure since UVB minimally penetrates beyond the epidermis. However, UVB-induced phototoxicity is more relevant for topical products. For components of topically applied products that absorb predominately in the UVB range, and where in vitro assessment is desired, the use of the 3T3 NRU-PT with modified irradiation conditions (see above) can be considered. Alternatively, in vitro skin models, which better tolerate UVB, could be considered.

Reconstructed human skin models, with the presence of a stratum corneum, permit testing of various types of topically applied materials ranging from neat chemicals to final

clinical formulations. The assays developed with reconstructed human skin to date measure cell viability with and without irradiation. These assays appear to be capable of detecting known human acute dermal phototoxicants. However, the sensitivity of some assays can be less than that of human skin in vivo, wherein the lowest concentration eliciting a positive response can be higher than in human skin in vivo. Consequently, it is important to understand the sensitivity of any assay selected and, if appropriate and feasible, to adjust the assay conditions accordingly (e.g., testing higher strength formulations, increasing exposure time).

There are no in vitro models that specifically assess ocular phototoxicity, regardless of the route of administration. While negative results in the 3T3 NRU-PT or a reconstructed human skin assay might suggest a low risk, the predictive value of these assays for ocular phototoxicity is unknown.

3.4. Photosafety Tests Using in vivo Assays and Systemic Administration

Phototoxicity testing for systemically administered compounds has been conducted in a variety of species, including guinea pig, mouse, and rat. No standardized study design has been established and thus the following factors might be considered as best practices.

For species selection, irradiation sensitivity (i.e., minimal erythema dose), heat tolerance, and performance of reference substances should be considered. Models with both pigmented and non-pigmented animals are available. Although non-pigmented skin tends to be more sensitive than pigmented skin for detecting phototoxicity, pigmented skin should be considered for APIs that bind significantly to melanin (see Section 2.2) if appropriate exposures in target tissues cannot be ensured otherwise.

If an in vivo phototoxicity study is conducted, it is desirable to have some information about the pharmacokinetic profile of the compound before designing the study. This is to ensure that irradiation of the animals is conducted at the approximate T_{max} and to assist in the selection of an appropriate study duration in relation to the intended clinical exposure. Relevant pharmacokinetic data, if not already available, should be collected as part of the in vivo phototoxicity study.

Although phototoxicity is typically an acute reaction, the duration of an in vivo assay should be carefully considered. Accumulation of compound in relevant light-exposed tissues after repeated administration might lead to an increased phototoxic response. Similarly, repeated irradiation after each dose might also lead to an increased phototoxic response due to the accumulation of damage. Generally, studies of a single day or up to a few days' duration of dosing are appropriate, using the clinical route of administration, if feasible. Single or repeated daily irradiations after dosing (around T_{max}) can be used.

Dose selection for in vivo nonclinical phototoxicity testing of systemic drugs should support a meaningful human risk assessment. For such studies a maximum dose level that complies with the recommendations for general toxicity studies in ICH M3(R2) Section 1.5 is considered appropriate. If a negative result is obtained at the maximum dose, testing of lower doses is usually not warranted. However, if a positive result is anticipated, additional dose groups can support a NOAEL-based risk assessment, typically considering C_{max} comparisons. Vehicle and non-irradiated controls can help identify compound-related phototoxicity and distinguish irradiation-induced from non-irradiation-induced adverse reactions. If the maximum systemic exposure achieved in animals is lower than clinical exposure, the reliability of a negative result in predicting human risk is questionable.

The most sensitive early signs of compound-induced phototoxicity are usually erythema followed by edema at a normally sub-erythemogenic irradiation dose. The type of response might vary with the compound. Any identified phototoxicity reaction should be

evaluated regarding dose and time dependency and, if possible, the No Observed Adverse Effect Level (NOAEL) should be established. The hazard identification might be further supported by additional endpoints (e.g., early inflammatory markers in skin or lymph node reactions indicative of acute irritation).

If a phototoxicity study is conducted in animals for a systemic drug that absorbs light above 400 nm, phototoxicity of the retina should be assessed using a detailed histopathological evaluation. For compounds that only absorb light below 400 nm, retinal assessment is usually not warranted because such wavelengths do not reach the retina of the adult human eye due to limited penetration of the cornea, lens and vitreous body.

Adequate performance of in vivo phototoxicity assays, which are not formally validated, should be demonstrated using suitable reference compounds, including pharmaceuticals. Compounds that are phototoxic in humans and that represent different chemical classes and mechanisms of phototoxicity should be included to establish adequacy of the assays. For retinal phototoxicity, a reference compound with a light absorption profile within the visible light range (i.e., above 400 nm) is recommended. The concurrent use of a positive control compound might not be warranted if an in vivo assay has been formally validated or has reached general acceptance and is established in the testing facility.

Testing for photoallergy is not recommended for compounds that are administered systemically. Photoallergy reactions in humans following systemic administration are rare and there are no established nonclinical photoallergy assays for systemically administered compounds.

3.5. Photosafety Tests Using in vivo Assays and Dermal Administration

The main recommendations provided for investigating the systemic route of administration also apply to dermal administration, including those for species selection, study duration, and irradiation conditions. For dermal drug products in general, the clinical formulation should be tested. The intended clinical conditions of administration should be used to the extent possible. Irradiation of the exposed area should take place at a specified time after application, and the interval between application and irradiation should be justified based on the specific properties of the formulation to be tested. Signs of phototoxicity should be assessed based on relevant endpoints (see Section 3.4). The sensitivity of the assay should be demonstrated using appropriate reference compounds. Assessment of systemic drug levels is generally not warranted in dermal phototoxicity studies.

For dermal drug products, contact photoallergy has often been assessed in a nonclinical study along with acute phototoxicity (photoirritation). However, no formal validation of such assays has been performed. While the acute photoirritation observed in these studies is considered relevant to humans, the predictivity of these studies for human photoallergy is unknown. For regulatory purposes, such nonclinical photoallergy testing is generally not recommended.

4. CLINICAL PHOTOSAFETY ASSESSMENT

There are various options for collecting human data, if warranted, ranging from standard reporting of adverse events in clinical studies to a dedicated clinical photosafety trial. The precise strategy is determined on a case-by-case basis.

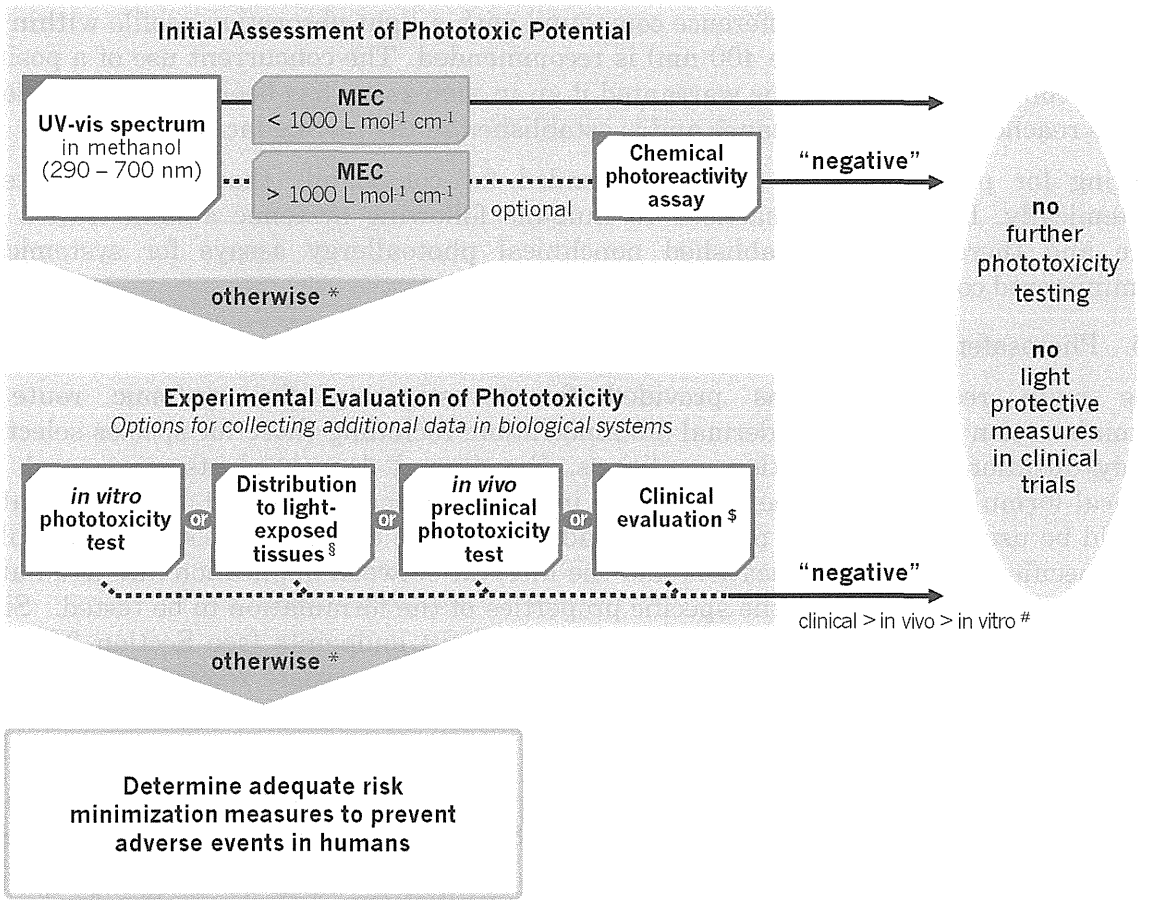
5. ASSESSMENT STRATEGIES

The choice of the photosafety assessment strategy is up to the drug developer. ICH M3(R2) suggests that an initial assessment of the phototoxicity potential based on

photochemical properties and pharmacological/chemical class be undertaken before outpatient studies. Characterization of the UV-visible absorption spectrum is recommended as the initial assessment because it can obviate any further photosafety evaluation. In addition, the distribution to skin and eye can be evaluated to inform further on the human risk and the recommendations for further testing. Then, if appropriate, an experimental evaluation of phototoxicity potential (in vitro or in vivo, or clinical) should be undertaken before exposure of large numbers of subjects (Phase 3).

Figure 1 provides an outline of possible phototoxicity assessment strategies. The figure is based on the strategies outlined in this section of this document. The strategies are flexible. Depending on the particular situation, some portions of the assessment are optional and might not be conducted.

Figure 1. Outline of possible phototoxicity assessment strategies for pharmaceuticals given via systemic and dermal routes



* "otherwise": data do not support a low potential for phototoxicity or have not been generated (assay/test/evaluation not conducted)

\# A "negative" result in an appropriately conducted in vivo phototoxicity study supersedes a positive in vitro result. A robust clinical phototoxicity assessment indicating no concern supersedes any positive nonclinical results. A positive result in an in vitro phototoxicity test could also, on a case-by-case basis, be negated by tissue distribution data (see text). In the United States, for products applied dermally, a dedicated clinical trial for phototoxicity on the to-be-marketed formulation can be warranted in support of product approval.

$ Clinical evaluation could range from standard reporting of adverse events in clinical studies to a dedicated clinical photosafety trial.

§ Tissue distribution is not a consideration for the phototoxicity of dermal products.