ICH S10
PHOTOSAFETY EVALUATION OF PHARMACEUTICALS

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The information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop.
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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 authorization for pharmaceuticals. It includes criteria for initiation of and triggers for additional photosafety testing and should be read in conjunction with ICH M3(R2), Section 14 on Photosafety Testing. This guideline for photosafety assessment should reduce the likelihood that substantial differences in testing requirements and data interpretation will exist among regions.

- Consideration should be given to the use of in vitro alternative 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 photosafety assessment relative to clinical development. It recommends that an initial assessment of phototoxic potential be conducted, and if appropriate, an experimental evaluation be undertaken before exposure of large numbers of subjects (Phase III). Similarly, ICH S9 describes the timing of photosafety testing for oncology products. However, neither ICH M3(R2) nor ICH S9 provide 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) and new excipients for systemic administration, clinical formulations for topical application, dermal patches, ocular products, and photodynamic therapy products.

- 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 marketed products unless there is a new cause for concern.
1.4. General Principles (1):

- 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. This information is used to determine adequate risk minimization measures 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 and photocarcinogenicity (Note 6 of ICH M3 (R2)) is not currently considered useful for human pharmaceuticals. This guideline addresses only phototoxicity and photoallergy.
1.4. General Principles (2):

• Definitions in this guideline
  - 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, this term is not used in this guideline.
1.4. General Principles (3):

• 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; and
  - Distributes sufficiently to light-exposed tissues (e.g., skin, eye).

• If one or more of the above conditions is not met, a compound will not present a photosafety concern.
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 wavelengths between 290 and 700 nm. Absorption with a molar extinction coefficient (MEC) less than 1000 L mol\(^{-1}\) cm\(^{-1}\) is not considered to result in a photosafety concern.

• Reactive oxygen species (ROS) generation following irradiation with UV or visible light can be an indicator of phototoxic potential.

• Photostability testing (see ICH Q1B [3]) alone should not be used to determine whether further photosafety evaluation is warranted.

• Assessments of photochemical properties should be conducted under high-quality scientific standards with data collection records readily available, or in compliance with GLP/GMP regulations.
2.2. Tissue Distribution/Pharmacokinetics (1):

- 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.

- 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 residence times in sun-exposed tissues or with higher tissue to plasma concentration ratios are more likely to produce a phototoxic tissue reaction than compounds with shorter 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.
2.2. Tissue Distribution/Pharmacokinetics (2):

- Compound binding to melanin 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 tissue drug levels and the potential for accumulation.

- 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 a generic threshold for all compounds. Nevertheless, on a case by case basis it may be possible to justify that further photosafety assessment is not warranted based upon actual or anticipated tissue drug levels, and taking into consideration the factors discussed above. One example could be a low-dose inhaled drug for which overall systemic exposure levels are very low.
2.2. Tissue Distribution/Pharmacokinetics (3):

- For those compounds with potent in vivo phototoxicity (or known to be phototoxic based on their mechanism of action such as photodynamic therapy drugs), distribution to internal as well as external tissues and estimates of tissue-specific half-lives should be assessed. Compounds activated by visible light and exhibiting long elimination half-lives in internal tissues have been demonstrated to cause injury to tissues exposed to intense light during medical procedures. 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 evaluations as metabolism does not typically create new chromophores.

2.4. Pharmacological Properties:

• In most cases, drug-induced phototoxicity is due to the chemical structure and not to the pharmacology. However, certain pharmacologic properties can enhance susceptibility to light-induced effects (e.g., immunosuppression, perturbation of heme synthesis). The testing strategies outlined in this document are not designed to detect these types of indirect phototoxicity. Many of these mechanisms can be identified and evaluated in nonclinical pharmacology/toxicity testing (see ICH M3(R2)).
3. Nonclinical Photosafety Testing
3.1. General Considerations (1):

- 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 integrated assessment strategy described in this document, it is most important that nonclinical photosafety assays show high sensitivity (i.e., produce a low frequency of false negatives). This is because negative assay results usually do not warrant further photosafety evaluation. It is not essential that positive assay results always predict a clinically relevant phototoxic response. 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. Therefore, the false positive rate for an assay should still be considered when deciding whether or not to use an assay.
3.1. General Considerations (2):

- 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, 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., CIE-85-1989 [4]) 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 (320 to 400 nm) of the applied spectrum. UVA doses ranging from 5 to 20 J/cm² have successfully been used to establish in vitro and in vivo phototoxicity assays. These UVA doses are comparable to those obtained during longer outdoor activities on summer days at noon time, in temperate zones, and at sea level.
3.1. General Considerations (3):

- In humans, total sunlight exposure is normally limited by sunburn reactions caused by the UVB part of sunlight. 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 UVA for systemic drugs. However, UVB irradiation is relevant for topical formulations.
3.2. Phototoxicity Testing 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 that is subject of a validation exercise is a ROS assay. Preliminary data suggest that this assay has high sensitivity for predicting 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 for the particular assay, would indicate a very low probability of phototoxicity, whereas a positive result would only be a flag for follow-up assessment.

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

- The most widely used in vitro assay for phototoxicity is the “in vitro 3T3 Neutral Red Uptake Phototoxicity Test” (3T3 NRU-PT), and this is currently considered the most appropriate in vitro screen for soluble compounds that are not exclusively UVB absorbers.

- 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 Organisation for Economic Co-operation and Development (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. The sensitivity of the 3T3 NRU-PT remains unquestioned, 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.
3.3. Phototoxicity Testing Using in vitro Assays (3):

- The BALB/c 3T3 cell line is sensitive to UVB and the recommended irradiation conditions involve the use of filters to attenuate wavelengths below 320 nm. UVB attenuation should not present a problem for systemic pharmaceuticals since these wavelengths minimally penetrate beyond the epidermis and hence UVB absorbers in systemic circulation are unlikely to be photoactivated. However, this is not true for topical products that absorb in the UVB range or for systemically administered compounds that distribute to the epidermis. For topical products that absorb predominately in the UVB range, and where in vitro assessment is desired, alternative models (e.g., reconstructed human skin models) which better tolerate UVB might be used.

- 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 models developed to date measure cell viability in the tissue preparation with and without irradiation. While such models appear to be capable of detecting known human dermal phototoxicants, the sensitivity of some models with respect to the dose eliciting a positive response can be lower than in the in vivo human situation. Consequently, it is important to understand the sensitivity of any model selected and, if appropriate, 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. While negative results in the 3T3 NRU-PT or a reconstructed skin model might suggest a low risk, in the absence of data, the predictive value of these assays for ocular phototoxicity is unknown.
3.4. Phototoxicity Testing Using in vivo Assays and Systemic Administration (1):

- To date, no nonclinical in vivo phototoxicity or photoallergy assay has been formally validated. No standardized study design has been established and thus the following criteria might be considered as best practices, if a decision is made by the drug developer to conduct in vivo studies in animals.

- For species selection, irradiation sensitivity, 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, the influence of melanin-binding should be considered when selecting a species/strain to ensure appropriate exposures in target tissues.
3.4. Phototoxicity Testing Using in vivo Assays and Systemic Administration (2):

- Generally, studies of a few days’ duration of dosing are appropriate, but pharmacokinetic properties as well as the intended clinical treatment regimen should be taken into consideration. Whenever feasible, the clinical route of administration should be used. Single or repeated daily irradiations after dosing (around $T_{\text{max}}$) can be used.

- Dose selection for in vivo nonclinical phototoxicity testing of systemic drugs, if conducted, 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.
3.4. Phototoxicity Testing Using in vivo Assays and Systemic Administration (3):

- 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 NOAEL should be established. The hazard assessment might be further supported by additional endpoints.

- In some cases, phototoxicity in the retina should be assessed (usually only warranted for substances absorbing light above 400 nm considering the optical properties of the human eye). If warranted, phototoxicity of the retina should be assessed in established animal models using a careful histopathological analysis.

- Testing for photoallergy is not recommended for compounds that are administered systemically.
3.5. Photosafety Testing Using in vivo Assays and Dermal Administration (1):

- 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 (e.g., occluded, non-occluded, intradermal) 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. 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.
3.5. Photosafety Testing Using in vivo Assays and Dermal Administration (2):

- For dermal drug products, acute phototoxicity (photoirritation) and contact photoallergy have often been investigated in conjunction with nonclinical skin sensitization testing. However, no formal validation of such models has been performed and their predictivity for human photoallergy is unknown. For regulatory purposes, such nonclinical photoallergy testing is generally not recommended.

3.6. Photosafety Testing Using in vivo Assays and Ocular Administration:

- Currently, there are no standardised nonclinical in vivo approaches for assessing phototoxicity following ocular administration.
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 study. 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. For a compound that has characteristics consistent with photoreactivity, nonclinical in vitro and in vivo tests and clinical alternatives are available for photosafety testing. If any one of the tests, having been conducted in an appropriate way, is negative, a compound is unlikely to elicit phototoxicity and further phototoxicity testing is generally not recommended.

• ICH M3(R2) suggests a stepwise approach to photosafety assessment. An initial assessment of phototoxic potential based on photochemical properties and pharmacological/chemical class should be undertaken before outpatient studies. In addition, the distribution to skin and eye can be evaluated to inform further on the human risk and the need for further testing. Then, if appropriate, an experimental evaluation of phototoxic potential (nonclinical, in vitro or in vivo, or clinical) should be undertaken before exposure of large numbers of subjects (Phase III).
5.1. Recommendations for Testing of Pharmaceuticals Given via Systemic Routes (1):

5.1.1. Assessment of Phototoxic Potential

• If the substance has a MEC less than 1000 L mol\(^{-1}\) cm\(^{-1}\) (between 290 and 700 nm), no further photosafety testing is recommended and no phototoxicity is anticipated in humans. Any available data on the phototoxicity of class-related compounds should also be assessed, as this could inform on the decision taken for further assessment. If the drug developer chooses to conduct a test for photoreactivity, the resulting data can support a decision that no further photosafety assessment is warranted. Similarly, if a drug developer chooses to assess drug distribution to light-exposed tissues, the resulting data can support a decision that no further photosafety assessment is warranted. Otherwise, nonclinical and/or clinical photosafety assessment of the substance should be conducted.
5.1. Recommendations for Testing of Pharmaceuticals Given via Systemic Routes (2):

5.1.2. Experimental Evaluation of Phototoxicity (1)

- If the drug developer chooses an in vitro approach, the 3T3 NRU-PT is currently the most widely used assay and in most cases could be considered as an initial test for phototoxicity. The high sensitivity of the 3T3 NRU-PT results in good negative predictivity, and negative results are generally accepted as sufficient evidence that a substance is not phototoxic. In such cases no further testing is recommended and no phototoxicity is anticipated in humans.

- In some situations (e.g., poorly soluble compounds) an initial assessment of phototoxicity in an in vitro assay might not be appropriate. In this case, an assessment in animals or in humans could be considered.
5.1. Recommendations for Testing of Pharmaceuticals Given via Systemic Routes (3):

5.1.2. Experimental Evaluation of Phototoxicity (2)

- If an in vitro phototoxicity assay gives a positive result, a phototoxicity study in animals could be conducted to assess whether the potential phototoxicity identified in vitro correlates with an in vivo response. Alternatively, the photosafety risk could be addressed/managed in the clinical setting. This could include a recommendation for protective measures in clinical trials in lieu of photosafety testing, or until the risk has been assessed (see ICH M3(R2)). A negative result in an appropriately conducted in vivo phototoxicity study (either in animals or humans) supersedes a positive in vitro result. In such cases no further testing is recommended and no phototoxicity is anticipated in humans. In addition, a robust clinical phototoxicity assessment indicating no concern supersedes any positive nonclinical results.
5.2. Recommendations for Testing of Pharmaceuticals Given via Dermal Routes (1):

5.1.1. Assessment of Phototoxic Potential

• If the active substance and excipients have MEC values less than 1000 L mol\(^{-1}\) cm\(^{-1}\) (between 290 and 700 nm), no further photosafety testing is recommended and no phototoxicity is anticipated in humans. Any available data on the phototoxicity of chemical class-related compounds should also be assessed as this could inform on the approach taken for further assessment.

• Tissue distribution is not a consideration for dermal products. Dermal products are administered directly to the skin and hence, unless they are applied to areas not exposed to light, are assumed to be present in light-exposed tissues.
5.1. Recommendations for Testing of Pharmaceuticals Given via Dermal Routes (2):

5.1.2. Experimental Evaluation of Phototoxicity and Photoallergy (1)

- The in vitro 3T3 NRU-PT can be used to assess individually the phototoxicity potential of the API and any new excipient(s), provided that appropriate testing conditions can be achieved (e.g., test concentrations not limited by poor solubility, relevant UVB dose can be applied). In cases where no phototoxic component has been identified in vitro, the overall phototoxicity potential of the clinical formulation can be regarded as low.

- Some properties of the clinical formulation which could influence the potential phototoxic response (e.g., penetration into skin, intracellular uptake) cannot be evaluated using the 3T3 NRU-PT alone. Therefore, confirmation of the overall negative result in an evaluation using the clinical formulation and/or monitoring during clinical trials can still be warranted.
5.1. Recommendations for Testing of Pharmaceuticals Given via Dermal Routes (3):

5.1.2. Experimental Evaluation of Phototoxicity and Photoallergy (2)

- Reconstituted 3D skin models can be used to assess the phototoxicity potential of clinical formulations. It is important to understand the sensitivity of the particular 3D skin model selected and, if appropriate, adjust the assay conditions accordingly (e.g., testing higher strength formulations, increasing exposure time). However, under adequate test conditions, a negative result in a 3D skin model indicates that the phototoxicity potential of the formulation can be regarded as low.

- If an appropriate in vitro model is not available, the initial test could be an in vivo animal phototoxicity test on the clinical formulation. Alternatively, the phototoxic potential in humans can be assessed prior to exposure of large numbers of subjects (ICH M3(R2)).
5.1. Recommendations for Testing of Pharmaceuticals Given via Dermal Routes (4):

5.1.2. Experimental Evaluation of Phototoxicity and Photoallergy (3)

• For dermal products where the API or any new excipient has a MEC value of 1000 L mol⁻¹ cm⁻¹ or higher, a photoallergy assessment is generally warranted in addition to phototoxicity testing. A clinical photoallergy assessment is generally recommended using the to-be-marketed formulation, and a study can be conducted during Phase III, if warranted.
5.3. Recommendations for Testing of Pharmaceuticals Given via Ocular Routes (1):

- For compounds that have a MEC value less than 1000 L mol$^{-1}$ cm$^{-1}$ (between 290 and 700 nm) no phototoxicity is anticipated in humans. Compounds that only absorb light at wavelengths below 400 nm and are to be administered as intraocular injections behind the lens (e.g., in the vitreous) are of low concern, as only light of wavelengths greater than 400 nm reaches the back of the adult eye. However, the lens in children is not completely protective against wavelengths below 400 nm.
5.3. Recommendations for Testing of Pharmaceuticals Given via Ocular Routes (2):

- For compounds that absorb at relevant wavelengths and are given via ocular routes (e.g., ocular eye drops, intraocular injections), an assessment of photosafety is generally recommended. The reliability of in vitro approaches in predicting phototoxicity following ocular administration is unknown and there are no standardised in vivo approaches for assessing phototoxicity for products administered via the ocular route. Nevertheless, the basic principles of phototoxicity assessment still apply and any available data on the phototoxicity of the compound in question or of chemical class-related compounds should be considered in the overall assessment.
Thank You!