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Questions and answers on the 'Note for guidance of photosafety testing'

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The aim of the current Questions & Answers document is to provide clarification to the Note for Guidance on Photosafety Testing (CPMP/SWP/398/01) on revised regulatory positions regarding *specific aspects of photosafety testing*.



Background

Note for Guidance (NfG) on photosafety testing (CPMP/SWP/398/01) was adopted by CPMP in June 2002 and came into operation in December 2002. The key objectives of this document were to define criteria when photosafety testing is needed and to provide guidance on how to evaluate non-clinically the different possible endpoints of adverse photo-reactions. Accumulating data and experiences with regulatory photosafety testing over the past years have revealed some severe shortcomings in the current guideline recommendations. In January 2008 the CHMP released a Concept paper (EMEA/534549/2007) indicating to revise the existing guideline on photosafety testing in order to overcome the identified shortcomings. Meanwhile the International Conference on Harmonisation (ICH) has decided to include photosafety testing as a new topic in the ICH framework and therefore the plans for revising the EU guideline as indicated by the Concept paper will no longer be pursued. This Questioning & Answer document provides an interim solution until an ICH guideline is available and gives clarifications on revised regulatory positions regarding specific aspects of photosafety testing.

Question 1. The Concept Paper on the Need for Revision of the Note for Guidance on Photosafety Testing indicates that the current criteria for deciding whether photosafety testing is needed (i.e., absorption of light in the 290-700 nm range and presence of compound in light exposed tissues) require some refinement to allow a better prediction of possible photobiological properties.

a) Can levels for the Molar Extinction Coefficient (MEC) be used as a threshold below which testing would not be needed?

b) Is there an acceptable concentration threshold for a compound's exposure in either skin or eyes below which photo-adverse reactions are unlikely and therefore no testing needed?

1a. The MEC (also called molar absorptivity, ϵ) is a constant for any given molecule under a specific set of conditions (e.g. solvent, temperature, wavelength) and reflects the efficiency with which a molecule can absorb a photon of light. The existing NfG on Photosafety Testing (CPMP/SWP/398/01) states that "... experiences do not allow for definition of specific levels of ... the molar absorbance ... below which photosafety testing would not be required". Recently published data clearly indicate that compounds with $\text{MEC} < 1000 \text{ L mol}^{-1} \text{ cm}^{-1}$ are of sufficiently low concern with regard to photosafety issues (Henry et al. 2009) and this level can therefore be accepted as an appropriate threshold below which further photosafety testing would not be warranted.

1b. The contention for an exposure concentration threshold of concern below which regulatory testing would not be required because the risk for photo-adverse reactions would be negligible is in principle supported. However, there are no data available at present to delineate such a general threshold applicable to any (new) compound. Consequently, an assessment of relevance of (very low levels of) exposure in either skin or eyes with respect to photosafety issues has to be made on a case-by-case basis.

Question 2. The Concept Paper on the Need for Revision of the Note for Guidance on Photosafety Testing indicates that a tiered testing approach starting with an initial assessment of the phototoxic potential would be more suitable rather than the requirement of several endpoints (phototoxicity, photoallergenicity, photogenotoxicity) in parallel. If a compound is found negative in (a) relevant phototoxicity assay(s) is it necessary to do further tests for photogenotoxicity and/or photoallergenicity?

If study data convincingly demonstrate that a compound is not phototoxic (see also Q&A # 4) further photosafety tests would not be required.

If a compound is shown to be phototoxic testing for photogenotoxicity is not required (see Q&A #3). Testing for photoallergenicity should be considered in this case for pharmaceuticals applied via the cutaneous route but for other routes of application such testing would not be required.

Question 3. The Concept Paper on the Need for Revision of the Note for Guidance on Photosafety Testing indicates that the use of mammalian cell photogenotoxicity tests for regulatory purposes can no longer be justified. What are the current regulatory recommendations for photogenotoxicity testing?

The existing NfG on Photosafety Testing (CPMP/SWP/398/01) recommends that photogenotoxicity testing should preferentially use a photoclastogenicity study (chromosomal aberration or micronucleus test) in mammalian cells in vitro. Experiences with these models in regulatory testing over the last couple of years suggest that these tests are substantially oversensitive and even incidences of pseudo-photoclastogenicity have been reported (Lynch et al. 2006). Therefore, in vitro photoclastogenicity assays are no longer recommended for regulatory photogenotoxicity testing purposes.

According to the existing NfG on Photosafety Testing (CPMP/SWP/398/01) photogenotoxicity testing is considered as a screening approach to predict a possible photocarcinogenic potential. However, the interpretation of photogenotoxicity data regarding its meaning for clinically relevant enhancement of UV-mediated skin cancer is unclear in most cases. The assessment of a potential photocarcinogenic risk is usually based on clinically relevant phototoxicity findings, information on photocarcinogenic potential of chemically related compounds and extent of human exposure (route of administration) and duration of treatment, but irrespective of whether an in vitro photogenotoxicity test is positive or negative. It is therefore recommended to exclude photogenotoxicity testing as routine part of the standard photosafety testing programme.

Question 4. The *in vitro* 3T3 Neutral Red Uptake Phototoxicity Test (3T3 NRU-PT) is recommended by the NfG on Photosafety Testing (CPMP/SWP/398/01) as the preferred initial test for phototoxicity testing. Concern has been raised regarding a perceived high incidence of positives with this assay and its poor predictivity for phototoxic effects *in vivo* (Lynch and Wilcox, 2010). Would it be acceptable to replace the 3T3 NRU-PT for initial phototoxicity assessment by a well-conducted *in vivo* study (animal study or clinical trial)?

It is true that the 3T3 NRU-PT is a very sensitive test and many positive findings are not confirmed in *in vivo* follow-up studies. However, this high sensitivity results in a good negative predictivity (no false negatives) and negative results in the 3T3 NRU-PT are generally accepted as sufficient evidence that a substance is not phototoxic (no further photosafety testing under a tiered approach, see Q&A # 2). Moreover, the 3T3 NRU-PT is the only phototoxicity test model that has successfully undergone a formal validation process and for which an OECD guideline exists (OECD, 2004). In accordance with the directive on the protection of animals used for scientific purposes (2010/63/EU) a replacement of a validated *in vitro* test by an animal study for testing the same endpoints would not be acceptable (see Note 1). An initial assessment of phototoxicity straight in humans could be an acceptable alternative to conducting a 3T3 NRU-PT provided the study design is shown to be appropriate and sufficiently sensitive to detect photoadverse reactions in humans.

If the 3T3 NRU-PT gave a positive result, a phototoxicity study *in vivo* either in animals or man should be conducted to assess whether the potential phototoxicity identified *in vitro* translates into a meaningful *in vivo* response. A negative result in an appropriately conducted *in vivo* phototoxicity study (either in animals or man) would transcend a positive 3T3 NRU-PT result. If a positive animal result is obtained, a negative result in an appropriate conducted clinical phototoxicity study would transcend the non-clinical findings.

Note 1. In cases where an *in vivo* animal phototoxicity study or clinical phototoxicity study had already been conducted it would not be necessary to back-fill with a 3T3 NRU-PT.

Question 5. The Concept Paper on the Need for Revision of the Note for Guidance on Photosafety Testing indicates that recommendations on the timing of photosafety evaluation during drug development should be provided. What are these recommendations?

Recommendations are provided by the recently revised ICH M3 (R2) guideline. According to this document, in cases where there is an identified potential human risk for phototoxicity, an experimental evaluation of phototoxic potential should be undertaken before exposure of large number of subjects (Phase III). For patients with advanced cancer, testing if warranted should be provided prior to marketing (ICH S9).

Question 6. Is there a need for photosafety testing of peptides/proteins?

Peptides/proteins including endogenous proteins can show some UV absorption (usually peak at 280 nm and shoulder at 290) due to the content of aromatic amino acids which can act as chromophores. This is not related to any photosafety concern. In general, there is no need for photosafety testing of peptides/proteins.

References

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