Final Concept Paper
S10: Photosafety Evaluation of Pharmaceuticals
Dated 8 April 2010
Endorsed by the ICH Steering Committee on 9 June 2010

Type of Harmonisation Action Proposed

A harmonised guideline on photosafety evaluation of pharmaceuticals is to be published through the ICH process. A separate ICH guideline on photosafety testing would be a valuable adjunct to the ICH M3(R2) guideline that provides guidance on timing and appropriateness of photosafety assessment, as well as harmonizing disparate regional guidances.

Statement of the Perceived Problem

Absorbance of ultraviolet and visible lights within the range of 290-700 nm and tissue distribution/accumulation in skin or eyes have been set as the basic criteria to initiate phototoxicity testing in the EU and FDA guidance. No definite threshold criteria, however, have been indicated in these guidance documents. Although the OECD guideline suggests that if the molar extinction coefficient (MEC) value is less than 10 liter x mol^{-1} x cm^{-1} the chemical is unlikely to be photoreactive, this value is so low as to be meaningless. Therefore, all test compounds are potentially subject to phototoxicity testing especially in the EU and Japan. More recently, based on the absorptivity of a range of known human phototoxins (Henry, B. *et al*. J Photochem Photobiol B 2009; 96: 56-72), a threshold MEC value of 1000 liter x mol^{-1} x cm^{-1} has been proposed and this was accepted at a recent IWGT Workshop (Basel, 2009).

For phototoxicity testing, the EU guidance document stipulates that a thoroughly validated *in vitro* test is the neutral red uptake assay using 3T3 cells derived from mouse fibroblasts. In contrast the FDA suggests that short-term photoirritation testing in animals or humans should be considered. According to the surveys independently conducted by the EPPIA and JPMA, nearly half of the test compounds show positive results in the *in vitro* testing and about 80% of the positives turn to be negative in *in vivo* testing. The surveys concluded that the *in vitro* testing is too sensitive. Furthermore, an even higher proportion of positive results (about 70%) is seen in the photo-clastogenicity test including some compounds which do not even absorb in the 290-700 nm range (Lynch, A. M. *et al*. Mutagenesis 2008; 23: 111-118). The recent IWGT Workshop (Basel, 2009) concluded that photoclastogenicity testing is no longer justified for regulatory purposes and that photogenotoxicity data of any sort do not add to the overall photosafety assessment of a compound.

Issues to be Resolved

Following major issues have been identified.

- Criteria of light absorbance and skin exposure to initiate phototoxicity testing should be defined;

- Criteria of tissue levels achieved and/or retained in the skin and eye should be defined;
- A consensus on the triggers for photosafety testing should be developed;
- The need for the photosafety testing of drug metabolites should be assessed;
- The values of several *in vitro* and *in vivo* phototoxicity and photo-clastogenicity tests should be described after examining their correlation with clinical data;
- The value or otherwise of photogenotoxicity testing for non-phototoxic agents should be clarified;
- A consensus on the need for photogenotoxicity testing should be developed.

No other ICH guidelines have comprehensively dealt with these issues. Appropriate procedures for photosafety evaluation are expected resolving them for harmonisation. If more data are needed, a data survey might be conducted among the ICH member companies by the EWG.

Background to the Proposal

The EMA and FDA published related guidance documents[1,2]. The EMA has stated intent to revise their guidance for refinement of the criteria and appropriate approches[3]. To address the issues, the EFPIA and JPMA independently conducted surveys on photosafety evaluation[4,5].

1. EMA/CPMP: Note for guidance on photosafety testing, 2002.
2. FDA: Guidance for industry; Photosafety testing, 2003.
3. EMA/CPMP: Concept paper on the need for revision of the note for guidance on photosafety testing, 2008.
4. EFPIA: Review of the performance of the 3T3 NRU *in vitro* phototoxicity assay in the pharmaceutical industry. 2009.
5. JPMA: Survey on the tripartite regulations for photosafety evaluation and data survey for establishment of photosafety evaluation procedures of pharmaceuticals (in Japanese), 2009.

Type of Expert Working Group

The EWG will be comprised of two members (toxicologists) nominated by the six parties of the ICH, and one member nominated by Health Canada, WHO and EFTA as observers. IGPA and WSMI, will also be invited to nominate one representative.

Timeline

A *Step 1* document will be drawn up during the first EWG meeting which is anticipated at the Fukuoka meeting in November 2010. If the EWG determines that a data survey is warranted to set the criteria to initiate the phototoxicity testing and to examine the correlation between nonclinical and clinical data, a questionnaire will be also generated at this meeting. The EWG will prepare a *Step 2* document based on the gathered data in the survey. The *Step 2* document will be published for consultation in June 2012. After collecting and incorporating public comments, a *Step 4* document will be finalised in June 2013. If the EWG decides not to conduct the data survey, the topic will reach *Step 4* six months earlier.