17 March 2011
EMA/CHMP/SWP/170012/2011
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Question and answer on the 'Note for guidance of photosafety testing'

(EMA/CHMP/SWP/336670/2010)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	EFPIA
2	Healthcare Ltd.
3	Medicines Evaluation Board, The Netherlands

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	EFPIA member companies consider the EMA photosafety Q&A document a major step forward, and compliment the CHMP SWP in trying to bring some clarity to this area until the ICH S10 guideline comes into effect. Hopefully this document should help to resolve many of the inconsistent photosafety questions/comments companies have been receiving from various EU regulatory authorities. There is a general concern in the response to Q4 around referring to the 3T3 assay as a rigorously validated in vitro assay. EFPIA would contend that 'in-use' experience has shown this not to be the case, at least within the pharmaceutical arena. This point is discussed in more detail in one of comments to Q4 below. The existing Note for Guidance on Photosafety Testing indicates within the scope (Section 1.2), that the guidance also applies to biotechnology-derived pharmaceuticals. EFPIA member companies are concerned that this statement is being used to apply this guidance to biologicals, including peptides/proteins. These products are expected to absorb light within the range recommended in this guidance (290-700nm), based on the presence of aromatic amino acids. As these products are expected to have no photosafety concerns, similar to endogenous proteins, we would suggest that a Q&A is created to indicate that biologicals are generally out of scope unless they contain chemical 'linker' molecules.	Comment is acknowledged. See response to Q4. Accepted. A new Q&A has been included: 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.
3	It is understood that this document will exist only temporarily. It is set up to declare the existing guideline outdated and to give some guidance until the new ICH Guideline will be in force. This is the main restriction in the present document.	Comments are acknowledged. Regarding the need for more clarity see proposals for revisions below.

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	However, even for a short period there is a need for some more clarity than the document is providing now.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
47-49	1	Suggested wording change to last sentence of response 1b. Proposed change: However, there are no data available at present to delineate such a general threshold applicable to any (new) compound. Consequently, an ~~The~~ assessment of relevance of (very low levels of) exposure in either skin or eyes with respect to photosafety issues ~~remains~~ has to be ~~done~~ made on a case-by-case basis.	Accepted. The answer has been reworded accordingly: 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.
57-59	3	The statement about the assessment of the relevance to be done on a case-by-case basis is too vague. Is the main conclusion that a threshold may exist, but that estimation of this threshold should be done on a weight-of-evidence approach? What type of data would help in establishing such a threshold?	WoE approach is acceptable; details on what type of data would help in establishing such a threshold will be provided in the future ICH S10 guideline.
58-59	1	The word “usually” makes the sentence vague. Other photosafety tests like photoallergy testing might still be requested. Proposed change: Remove the word “usually”. i.e. If study data convincingly demonstrate that a compound is not phototoxic (see also Q&A # 4) further photosafety tests would ~~usually~~ not be required.	Accepted. The answer has been changed: If study data convincingly demonstrate that a compound is not phototoxic (see also Q&A # 4) further photosafety tests would not be required.
58-59/70-71	3	The answer indicates only what should be done in case of a negative (not	Accepted.

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		phototoxic) outcome. What is the outcome is positive? Answer 3 indicates that photogenotoxicity testing is not recommended. Should then photoallergenicity be tested?	Situation of a positive outcome has been added to answer of Q2: 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.
60	2	A concern is if this response means that negative photogenotox data are no longer accepted as (part of) the justification to conclude with “no carcinogenic potential." May data from photogenotox studies other than the chromosomal aberration test and the mononuclear test mentioned still be considered supportive data for such a conclusion re. potential for carcinogenicity?	Note to comment: “mononuclear test” should be “micronucleus test”. Comment is acknowledged. If scientifically justified additional supportive data are in general acceptable. This is not specific to this topic and will therefore not be specificically addressed in the document.
96-98	1	Comment: It is not clear in this sentence if a photogenotoxicity testing to predict photogenotoxic potential is needed when an initial assessment of phototoxicity straight in human is chosen, i.e. when no 3T3 assay has been conducted.	From Q&A #3 it is clear that photogenotoxicity testing is not required.

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88-98	1	Suggest additional wording to response 4 to clarify that a negative result in an in vivo assay would transcend a positive 3T3 result, and that there would be no need to back-fill a 3T3 assay if an in vivo assay has already been conducted: Proposed change: 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 according to rigorous, modern standards and for which an OECD guideline exists (OECD, 2004). In accordance with the animal experiments directive (86/609/EEC) 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 phototoxity straight in humans could be an acceptable alternative to conducting a 3T3 NRU-PT assay provided the study design is shown to be appropriate and sufficiently sensitive to detect photoadverse reactions in humans. However, if the 3T3 NRU-PT assay gave a positive result, an in vivo animal phototoxicity study could 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. Note 1. In cases where an in vivo animal phototoxicity study or clinical	Accepted. Answer has been reworded: 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.

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		phototoxicity study had already been conducted it would not be necessary to back-fill with a 3T3 NRU-PT assay.	
92-96	1	Comment on lines 92-96: ('..*Moreover, the 3T3 NRU-PT is the only phototoxicity test model that has successfully undergone a formal validation process according to rigorous, modern standards and for which an OECD guideline exists (OECD, 2004). In accordance with the animal experiments directive (86/609/EEC) a replacement of a validated in vitro test by an animal study for testing the same endpoints would not be acceptable..'.*). This will be driving the discussion at ICH towards an acceptance of the 3T3. The point which can be made here is that these sentences are not correct as such, i.e. yes the assay has been validated however not so rigorous as suggested since the validation has certainly not focused on testing pharmaceutical products. Subsequently it has been proven by the extensive numbers of false positives that for this particular application (testing pharmaceuticals) the assay has not been properly validated. Thus the message should be there is no real validated assay.	

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		This allows an open discussion on all possible options during ICH. <u>Proposed change:</u> Delete the sentences about validation, i.e. 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 according to rigorous, modern standards and for which an OECD guideline exists (OECD, 2004). In accordance with the animal experiments directive (86/609/EEC) a replacement of a validated in vitro test by an animal study for testing the same endpoints would not be acceptable~~. An initial assessment of phototoxity straight in humans could be an acceptable alternative provided the study design is shown to be appropriate and sufficiently sensitive to detect photoadverse reactions in humans. However, in accordance with the animal experiments directive (86/609/EEC), a replacement of an in vitro test by an animal study for testing the same endpoints would not be acceptable.	Partly accepted. Answer has been slightly changed: Moreover, the 3T3 NRU-PT is the only phototoxicity test model that has undergone a formal validation process and for which an OECD guideline exists (OECD, 2004).
99-102	1	With regards to Q&A No.5, no question is asked here. This should be done in order to help the reader understanding the meaning of the question. <u>Proposed change:</u> Question 5. The Concept Paper on the Need for Revision of the Note for	Accepted. Question 5 has been changed: Question 5. The Concept Paper on the Need for Revision of the Note for Guidance on Photosafety

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		Guidance on Photosafety Testing indicates that recommendations on the timing of photosafety evaluation during drug development should be provided. What are these recommendations?	Testing indicates that recommendations on the timing of photosafety evaluation during drug development should be provided. What are these recommendations?
103-105	1	Suggest response to Q5 should also refer to ICH S9 guideline: Proposed change: Recommendations are provided by the recently revised ICH M3 (R2) and ICH S9 (for oncology) guidelines. According to these documents, 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.	Accepted. Answer has been changed accordingly: 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).
103-105	1	If phototoxicity testing is delayed until prior to Phase III, it would be useful to indicate what, if any, precautions should be taken for Phase I and II clinical trials, and what would be the trigger for applying these precautions. For example, ICH M3 states *"appropriate protective measures should be taken during outpatient clinical studies"*	Not accepted. This issue is addressed in ICH M3 and might be further specified in future ICH S10.
103-105	1	It is very good in this draft document to address timing using ICH M3 guideline. It will be clear by adding extra clarification on the term of "experimental evaluation" by "experimental evaluation (nonclinical, in vitro or in vivo, or clinical)" in case the reader forgets the information in ICH M3 guidance. It would be very helpful if a general scheme of experimental evaluations is provided in this document.	Not accepted. Such a general scheme is already provided in the revised answer to Q2.

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		Proposed change: According to this document an experimental evaluation (nonclinical, in vitro or in vivo, or clinical) of phototoxic potential should be undertaken before exposure of large number of subjects (Phase III). A general scheme is an initiation of an in vitro test (i.e. 3T3 NRU-PT) followed by an in vivo test in animals if the in vitro result is positive. If a positive in vivo result is obtained, a clinical phototoxicity evaluation could be undertaken.	
Question 1	3	In a recent assessment procedure it was indicated that also biologicals (proteins such as monoclonal antibodies) have absorbance of light between 290 and 700 nm. Should it made clear explicitly that for those products phototoxicity testing is not needed?	Accepted. See response to General Comments above (new Q&A #6)