



The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

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DATE: 21 March 2000 **OUR REF:** EMEA/8815/00

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RE: CPMP SWP comments on the FDA Guidance on Photosafety Testing

CC: Prof Jean-Michel Alexandre, Prof Beatriz Silva-Lima, Dr Lutz Müller

Number of Pages (including cover sheet): 4

Original of this fax has been signed by the sender and is available upon request from the signatory.

MESSAGE

Dear Mac,

Please find enclosed the CPMP Safety Working Party comments on the FDA Draft Guidance on Photosafety Testing of 3 January 2000. The SWP Rapporteur for this topic is Dr Lutz Müller from BfArM.

It was good to talk to you in Nîmes and I hope that you
Regards had a safe return home!

See you soon, Rolf

Rolf Bass
Head of Unit
Evaluation of Medicines for Human Use

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The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 20 March 2000
 CPMP/SWP/725/00

**CPMP Safety Working Party Comments on the FDA Draft Guidance on "Photosafety Testing"
 of January 3rd, 2000**

In general the Safety Working (SWP) are in agreement with the considerations for photosafety testing which are described in the guideline draft as of January 3rd, 2000. However, we would like to make the following comments and suggestions for your consideration.

- In general, we feel that the guidance is too detailed. Since a lot of questions regarding suitable test methods and their interpretation are left open or cannot be answered at the moment, it may not be justified to address the issues to that extent as it has been done.
- A clear focus on the hairless mouse model for skin carcinogenesis safety testing may not be justified since this model has not been sufficiently evaluated up to now. Internationally accepted standards for the conduct of such experiments, for the measurement of effects and for the assessment of findings in this model are lacking. Such criteria would be desirable if not needed if a method becomes the method of choice for product safety testing.
- The available information on the concordance between animal data and clinical data on known or suspected human photocarcinogens needs to be described in more detail.
- Section II A, last but one paragraph.
 Comment: It is our feeling that much more is known regarding mechanisms of fluoroquinolone plus UV-induced phototoxicity and photocarcinogenicity than what is stated in this paragraph. There is extensive experimental evidence for an involvement of reactive intermediates and/or reactive oxygen species (e.g. de Mol et al., 1981; Hirose et al., 1990; Robertson et al., 1991; Martinez et al., 1997 and many more).
- Section II A, last paragraph, first sentence.
 Comment: There is sufficient evidence that patients on therapy with immunosuppressive drugs such as cyclosporin are at an enhanced risk for UV-induced skin carcinogenesis.
- Section II C, second paragraph, sixth sentence.
 Comment: A photocarcinogenicity test may also be carried out using non-tumorigenic or only very slightly tumorigenic UV wavelengths and exposure levels (Klecak et al., 1997). Under such conditions, the positive response is not easily measurable as decreased time to skin neoplasm.
 Comment: Either here or elsewhere in the document, it should be pointed out that the hairless mouse model is not suitable for melanoma risk evaluation, an important human health concern, which is related to UV exposure. Hairless mice develop very rapidly basal cell carcinoma as well as squamous cell carcinoma upon UVB irradiation but melanoma formation cannot be studied. Since melanoma formation is considered to be of utmost importance for human risk evaluation, this standard animal model has considerable limitations in its predictivity for humans. Transgenic mouse melanoma models have been generated (Beermann et al., 1999) and DMBA and UVB produced melanoma (Powell et al., 1999) but such animals have not been used for photocarcinogenicity testing to date.
- Section IV A, last paragraph, first three sentences.
 Comment: We would appreciate the inclusion of further considerations for testing for photochemical genotoxicity. From the available data and the parallel experience in standard genotoxicity testing, testing for photochemical genotoxicity should be considered in the phototoxicological assessment of chemicals. Importantly, the main purpose of such testing is to make an assessment of the likelihood of a compound to turn into a photochemical carcinogen

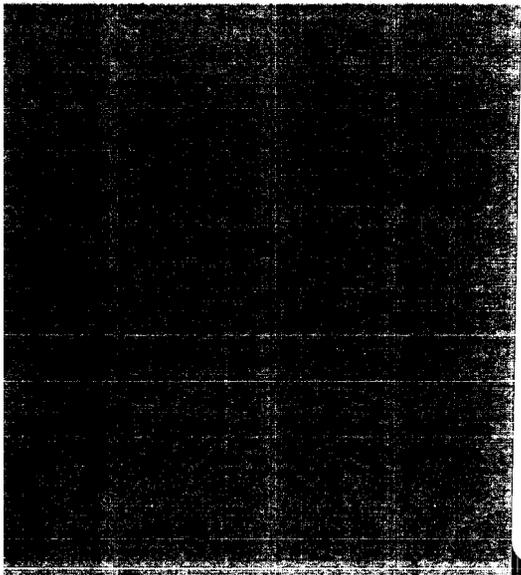
upon activation with UV or visible radiation (Bulera et al., 1999). For such compounds, testing for photochemical genotoxicity preferably in mammalian cells in vitro may be a helpful hazard identification approach before entering animal testing for photochemical carcinogenesis (Loveday, 1996; Müller et al., 1998; Gocke et al., 2000). A publication describing tests methods that are available, detailing test procedure aspects and giving recommendations for testing is in print (Gocke et al. 2000).

- Section IV B, 1, "conditions of use", first two sentences.
Comment: As stated correctly under IV.B.3, skin tumors can appear very rapidly after initiation of treatment with immunosuppressants, i.e. a quite short treatment duration may present a significant risk of enhancing UV-induced skin carcinogenesis. This is of particular importance for those immunosuppressants that may be used to treat various skin diseases such as atopic dermatitis. Hence, please define what is meant with 'chronic use'.
- Flowchart B.
The flowchart should incorporate alternative/surrogate assays such as those mentioned in IV.C before entering BOX 3 (Testing for Photochemical Carcinogenicity). In particular, it would be helpful to mention in vitro phototoxicity testing, testing for photochemical genotoxicity and possibly testing for induction of apoptosis with combined treatment with test compound and UV-light combination.

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