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3 Committee for Medicinal Products for Human Use (CHMP)

4 Question and answers on the 'Note for guidance on
5 photosafety testing'

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7 **Draft**

Draft agreed by Safety Working Party	June 2010
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Comments should be provided using this [template](#). The completed comments form should be sent to SWP-H@ema.europa.eu

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Keywords	Phototoxicity, photoirritation, photoallergy, photogenotoxicity, photocarcinogenicity, non-clinical, UV absorption, <i>in vitro</i> models
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11 The aim of the current question-and-answer document is to provide clarification to the 'Note for
12 guidance on photosafety testing' (CPMP/SWP/398/01) on revised regulatory positions regarding
13 specific aspects of photosafety testing.



14 Background

15 Note for Guidance (NfG) on photosafety testing (CPMP/SWP/398/01) was adopted by CPMP in June
16 2002 and came into operation in December 2002. The key objectives of this document were to define
17 criteria when photosafety testing is needed and to provide guidance on how to evaluate non-clinically
18 the different possible endpoints of adverse photo-reactions. Accumulating data and experiences with
19 regulatory photosafety testing over the past years have revealed some severe shortcomings in the
20 current guideline recommendations. In January 2008 the CHMP released a Concept paper
21 (EMA/534549/2007) indicating to revise the existing guideline on photosafety testing in order to
22 overcome the identified shortcomings. Meanwhile the International Conference on Harmonisation (ICH)
23 has decided to include photosafety testing as a new topic in the ICH framework and therefore the plans
24 for revising the EU guideline as indicated by the Concept paper will no longer be pursued. This
25 Questioning & Answer document provides an interim solution until an ICH guideline is available and gives
26 clarifications on revised regulatory positions regarding specific aspects of photosafety testing.

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

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

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

37 **1a.** The MEC (also called molar absorptivity, ϵ) is a constant for any given molecule under a specific
38 set of conditions (e.g. solvent, temperature, wavelength) and reflects the efficiency with which a
39 molecule can absorb a photon of light. The existing NfG on Photosafety Testing (CPMP/SWP/398/01)
40 states that "... experiences do not allow for definition of specific levels of ... the molar absorbance ...
41 below which photosafety testing would not be required". Recently published data clearly indicate that
42 compounds with $MEC < 1000 \text{ L mol}^{-1} \text{ cm}^{-1}$ are of sufficiently low concern with regard to photosafety
43 issues (Henry et al. 2009) and this level can therefore be accepted as an appropriate threshold below
44 which further photosafety testing would not be warranted.

45 **1b.** The contention for an exposure concentration threshold of concern below which regulatory testing
46 would not be required because the risk for photo-adverse reactions would be negligible is in principle
47 supported. However, there are no data available at present to delineate such a general threshold
48 applicable to any (new) compound. The assessment of relevance of (very low levels of) exposure in
49 either skin or eyes with respect to photosafety issues remains to be done on a case-by-case basis.

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

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

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

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

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

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

88 It is true that the 3T3 NRU-PT is a very sensitive test and many positive findings are not confirmed in
89 *in vivo* follow-up studies. However, this high sensitivity results in a good negative predictivity (no false
90 negatives) and negative results in the 3T3 NRU-PT are generally accepted as sufficient evidence that a
91 substance is not phototoxic (no further photosafety testing under a tiered approach, see Q&A # 2).
92 Moreover, the 3T3 NRU-PT is the only phototoxicity test model that has successfully undergone a
93 formal validation process according to rigorous, modern standards and for which an OECD guideline
94 exists (OECD, 2004). In accordance with the animal experiments directive (86/609/EEC) a
95 replacement of a validated *in vitro* test by an animal study for testing the same endpoints would not be

96 acceptable. An initial assessment of phototoxicity straight in humans could be an acceptable alternative
97 provided the study design is shown to be appropriate and sufficiently sensitive to detect photoadverse
98 reactions in humans.

99 **Question 5. The Concept Paper on the Need for Revision of the Note for**
100 **Guidance on Photosafety Testing indicates that recommendations on the**
101 **timing of photosafety evaluation during drug development should be**
102 **provided.**

103 Recommendations are provided by the recently revised ICH M3 (R2) guideline. According to this
104 document an experimental evaluation of phototoxic potential should be undertaken before exposure of
105 large number of subjects (Phase III).

106 **References**

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