

**Final Concept Paper**  
**S1C(R2): Revision of S1C(R1)**  
**Dose Selection in Carcinogenicity Studies of Pharmaceuticals and Limit Dose**  
*Dated and endorsed by the Steering Committee on 8 June 2006*

**Type of Harmonization Action Proposed**

Revision of the existing guideline S1C: Dose Selection in Carcinogenicity Studies.

**Statement of the Perceived Problem**

In the ICH S1C Guideline the criteria are defined to establish the doses for the life-time carcinogenicity studies. One of the possibilities is to define the maximum dose for this study based on pharmacokinetic endpoints on the basis of exposure (AUC). An endpoint of an AUC in rats being 25-fold the human exposure (at the maximum recommended dose) is defined as a maximum in case of non-genotoxic compounds with a low toxicity profile and the maximum tolerated dose higher than 25-fold ratio. In NOTE 2 it is defined that for these compounds the genotoxicity battery should be negative.

**Issue to be Resolved**

The proposal is to apply the 25-fold ratio for all pharmaceuticals for which there is a need for carcinogenicity studies.

The proposal is to delete the word “non-genotoxic” in the text on page 2. When removing this word the NOTE 2 will become meaningless and this note should be removed too.

**Background to the Proposal**

In the past 10-15 years a lot of experience is gathered with respect to compounds that are tested in the genotoxicity battery as well as in carcinogenicity studies. It appeared that 25% of the compounds positive in mammalian chromosome aberration assays appear to be false positives. In general these compounds are assessed as having no genotoxic risk taking into account all the weight-of-evidence. This can be reflected now also in applying the dose limiting ratio of 25-fold to the maximum dose in case of low-toxic compounds.

**Type of Expert Working Group**

No meeting of a working group is needed. The procedure can be handled in a written e-mail procedure.