Final Concept Paper
M3(R2) Q&As
(Revision of the ICH M3(R2) Guidance on Nonclinical Safety Studies For the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals)
Dated 20 November 2009
Endorsed by the Steering Committee on 8 December 2009

Type of Harmonisation Action Proposed

Maintenance of ICH M3(R2) by Q&As.

Statement of the Perceived Problem

The ICH M3(R2) guidance reached *Step 4* in June of 2009 and is in the process of being implemented. While still in its early phases of the implementation, the complexity of the guidance, its broader scope, and numerous changes in recommendations from the M3(R1) guidance have generated questions that will impact its successful implementation. Several of theses questions and issues can readily be addressed by Q&As. Such an implementation support will forestall the need to develop new guidances or undertake revision of several other existing guidances, such as S5.

Some examples of questions already identified that can be readily answered.

1) The ICH M3(R2) guidance recommends multiple approaches for the top dose of general toxicology studies, including a maximum dose 50-fold the therapeutic target.

a) This approach is not discussed in the ICH S5 guideline for reproductive toxicity. Can the 50-fold margin be used to select the top dose for reproductive toxicity studies?

b) If a 50-fold margin to the therapeutic exposure has been used to select doses for general toxicity studies and dose limiting toxicity has not been observed, can the early clinical dose escalations exceed the therapeutic target? If so what factors should be considered and what margin to the top non-clinical doses studied should be maintained?

Other specific questions received to date are in the areas of PK/TK considerations, exploratory clinical studies, and non-clinical drug combination studies.
It is proposed that the ICH website has a section to which any of the parties or observers can submit questions about ICH M3(R2).

Background to the Proposal

ICH M3(R2) is on the ICH website.

Type of Expert Working Group

The M3(R2) Q&As IWG will comprise one member from each of the six parties, with an alternate. It is proposed that most interactions be by email, with occasional teleconferences. The group could meet briefly once per year, if necessary.