Final Concept Paper
S6(R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
(Revision of the ICH S6 Guideline)
19 June 2008
Endorsed by the Steering Committee on 4 June 2008*

Type of Harmonization Action Proposed

Establish an Expert working group (EWG) to write an addendum to the current guidance of ICH S6.

Statement of the Perceived Problem

A clarification (and sometimes amplification) of this guidance is needed as substantial experience and new information has been gained since *Step 4* (1997). The Nonclinical Safety Experts involved in ICH in S2/S9/M3 agreed that the flexible and case-by-case approach described in the original guidance is still valid and must be preserved.

Disharmony across regulatory regions was identified to be a result of differences in implementation and interpretation of the S6 guidance and in part because of regional specific Points to Consider (PTC) documents. Important PTC documents are Nakazawa et al. (2004) from Japan, and the PTC documents on carcinogenicity and reproductive toxicity of insulin analogues of the EMEA/CHMP.

Regional scientific meetings have been held in 2007 to discuss specific topics that have been identified as issues when applying the S6 Guidance.

In these meetings scientific progress and experience have been discussed. It has been concluded that it is important to evaluate the state of the art of safety testing of biopharmaceuticals (Nakazawa et al 2008, Van der Laan and Spanhaak, 2008, Clarke et al 2008).

Based on the outcome of these discussions the Nonclinical Safety Experts involved in ICH S2/S9/M3 in Portland (June 2008) have agreed that the following topics should be addressed to facilitate the understanding and harmonized application of the guidance provided in S6.

- Species Selection
- Study design
- Reproductive/developmental toxicity
- Carcinogenicity
- Immunogenicity

Details are in the appendix. Harmonization is expected to benefit the 3R's.

* Endorsed by the Steering Committee on 4 June 2008, subject to amendments which have been included in this version dated 19 June 2008.

Type of Expert Working Group

An Expert Working Group includes representatives/experts from the six ICH parties, observers and interested parties, including experts from the biotechnology industry association, WSMI and IGPA.

Timetable

The EWG should be established in the ICH meeting in Brussels in November 2008. Subsequently, the EWG will meet to discuss the issues to be resolved. Based on the list of topics at least two full meetings are needed to have a scientific discussion and to be able to have a process of writing an addendum to the current guidance of ICH S6. A *Step 2* might be reached in November 2009, which after a consultation period might be finalized as a *Step 4* in June 2010

Parties Making the Proposal

The Nonclinical Safety Experts involved in ICH S2/S9/M3 in Portland propose this for ICH consideration.

Proposal for the Rapporteur

It is proposed that EFPIA will be the rapporteur for a *Step 2* document, while the EU might be the regulatory party responsible for the coordination of *Step 4*.

APPENDIX

Topic for clarification 1 Species Selection

- How to justify the choice of a species
- Clarify role of tissue cross-reactivity
- When to use a second species?
- Use of alternative models
  - Use of transgenics
  - Use of homologues

Topic for clarification 2 Study design issues

- Scientific justification of duration
- High dose selection
- Utility and length of recovery

Topic for amplification and clarification 3 Reproductive/developmental toxicity studies

- Justification of species selection
  - Rodents/non-rodents
  - transgenics/homologues

- Considerations when using primates
  - Use of combined study designs. Timing.
  - How to get data on fertility
  - Impact of placental transfer
  - How to get data from the F1 generation?

Topic for clarification 4 Carcinogenic potential

- Justification for the approach to address carcinogenic risk
- Application of in vivo models
  - Length of the studies
  - Use of proliferation indices
  - Use of homologues

Topic for amplification and clarification 5 Immunogenicity

- Extent of characterization
- Impact of neutralizing vs. non-neutralizing.
- Role of PD markers
- Assessment in recovery groups