Concept Paper for the Establishment of a Maintenance Procedure on S5(R3): Detection of Toxicity to Reproduction and Development for Human Pharmaceuticals
Dated 3 March 2019
Endorsed by the Management Committee on 28 March 2019

Type of Harmonisation Action Proposed

The ICH S5(R3) EWG requests that a maintenance procedure is established for the proposed annexes to the guideline. At its teleconference in September 2018, the Management Committee (MC) supported the principle of a Maintenance Procedure for the S5(R3) annexes and that a Concept Paper defining the Maintenance Procedure should be submitted to the MC for support and to the Assembly for endorsement of a new area of work.
Annex 1 addresses the design and conduct of *in vivo* reproductive toxicity studies while Annex 2 outlines points to consider in the development of *in vitro*, *ex vivo,* and non-mammalian *in vivo* assays (alternative assays), their qualification, and potential use to support reproductive safety assessments.

Statement of the Perceived Problem

In the context of the ongoing ICH S5(R3) EWG activities it was recognized that further details complementing both annexes will be needed in the future to achieve the intended goals of the revised guideline in a harmonized fashion.
One key element of the revised ICH S5(R3) is the novel role given to alternative methods and the promotion of novel testing paradigms. Currently, there is limited experience with their use in regulatory risk assessment. As a result, the guideline was written in a general manner.
It is anticipated that, upon implementation of the guideline, regulatory authorities will receive an increasing number of clinical trial and marketing authorisation applications containing results from combined in vivo reproductive toxicity studies and their designs as proposed in Annex 1. As regulatory experience with these in vivo testing approaches advances, it is expected that there will be more clarity on best practices to be included in the Annex 1 and hence the potential for harmonization will increase.

Continuously evolving technologies and regulatory experience are likely to have an impact on the approaches for qualifying alternative assays described in Annex 2 of the guideline. There are also new (e.g. in silico) methods under development, which may not only assist for mechanistic examinations, but also aim to address quantitative components of the risk assessment process. Future regional experience and increasing knowledge about alternative assays will help to get more clarity on their applicability for regulatory submissions.

Readily revised annexes will provide additional explanation, assist in the development and potential regulatory use of qualified alternative assays and help to increase the likelihood of regulatory acceptance of submissions containing qualification exercises of alternative assays.

In view of the above, the maintenance procedure should facilitate proper implementation of novel testing paradigms and regulatory acceptance of alternative assays supporting global 3R (replacement, reduction, refinement) efforts, accelerates its harmonization of its context of use across regions and the communication between applicants and assessors.

Issues to be Resolved

Using this Maintenance procedure, the annexes of ICH S5(R3) will be updated as new reference compounds, qualification approaches or new data become available.

In vivo study designs (Annex 1):

- Recognition and implementation of modifications of *in vivo* studies resulting from advances in our understanding of strengths and weaknesses of these studies in predicting human reproductive risk associated with exposure to pharmaceuticals.

Alternative Assays (Annex 2):

- Reference compound list: integration of new data or compounds
- Qualification of alternative assays: improvement of approaches to qualify an alternative assay using the reference compounds list based on gained experience
- Scenarios of use: inclusion of new scenarios and harmonization of the use of scenarios across regions

Background to the Proposal

It is expected that this maintenance procedure facilitates the full achievement of the provisions of the revised guideline and increase regulatory acceptance of 3Rs (Replacement, Reduction and Refinement) testing approaches when it comes to reproductive and developmental toxicity testing.

Type of Expert Working Group and Resources

Updates to the annexes could be proposed by any ICH Member party, and an assessment of the need for change(s) should preliminarily be conducted by the S5 Maintenance EWG. As a result of this assessment, a recommendation to revise the relevant Annex 1 or 2 from the S5 Maintenance EWG would be made to the ICH MC. If no proposal for updates is received, the S5 Maintenance EWG will stay in dormant state until a proposal is received for assessment.

It is proposed that the S5 Maintenance EWG will be comprised of experts from each of the Founding Regulatory Members and from other ICH Members as per the applicable Rules or Procedures. Additionally, ICH Observers may participate on the S5 Maintenance EWG, pending a favorable decision by the MC. The focus of the S5 Maintenance EWG will encompass safety assessment by toxicologists, and may include specialists with expertise in the design, conduct and interpretation of alternative assays.

Timing

The maintenance procedure will start, at the earliest, one year after *Step 4* adoption / *Step 5* implementation of the ongoing revision. A Founding Regulatory Member will serve for

Rapporteurship for a two-year term, with the Rapporteurship rotating every two years to a new Founding Regulatory Member. The ICH Secretariat will share any proposals received by ICH Member parties with the Rapporteur and ICH Coordinators of all ICH Members. The Rapporteur will facilitate the review of any proposals received by the S5 Maintenance EWG and the S5 Maintenance EWG will make a recommendation on whether the proposal should be supported by the MC.

The Rapporteur will ordinarily rely on correspondence or teleconferencing to avoid unnecessary travel. Based on the discussion, with requests for further information to the proposing group and/or individual as appropriate, the Rapporteur will prepare an assessment report based on the S5 Maintenance EWG's approval with a recommendation to accept, with or without modifications, or reject any proposed revisions.

If a proposal for maintenance is supported by an S5 Maintenance EWG, the S5 Maintenance EWG should submit a revised work plan along with a concept paper to the MC to outline this work. The MC will then provide a recommendation to the Assembly for approval on whether the S5 Maintenance EWG should be tasked with making the revision. The revision will then undergo the usual ICH Step process as outlined in section 2.1 of the SOP of the WGs.

A revision will be considered only on presentation of new data or previously un-recognised data or approaches sufficient to result in a significant change, because of convincing evidence that the existing data used is invalid or insufficient to be useful for regulatory purposes.