

## Maintenance Procedure for S5 Annexes 1 and 2

This Maintenance Procedure applies to revision of Annexes 1 and 2 of the S5 Guideline on Detection of Toxicity to Reproduction and Development for Human Pharmaceuticals.

- Annex 1 addresses the design and conduct of *in vivo* reproductive toxicity studies, and 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. Through the Maintenance Procedure described below, the Annexes of ICH S5 will be updated as new reference compounds, qualification approaches or new data become available. These changes include the following revisions for each of the aforementioned Annexes:
- Annex 1:
  - Recognition and implementation of modifications of *in vivo* studies resulting from advances in understanding of strengths and weaknesses of these studies in predicting human reproductive risk associated with exposure to pharmaceuticals.
- 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.

Updates to the Annexes could be proposed by any ICH Member, 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 Management Committee. If no proposal for updates is received, the S5 Maintenance EWG will stay in dormant state until a proposal is received for assessment.

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 Management Committee (MC).

The S5 Maintenance EWG will primarily 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. At *Step 3* public consultation, to ensure clarity on the matter for public comment, only a document listing any changes should be published, similarly to other maintenance procedures as per Annex 4.

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.