Annex 4: Maintenance Procedure for Q3C, Q3D, and M7

This Maintenance Procedure applies to revision of the Q3C Guideline for Residual Solvents, Q3D Guideline for Elemental Impurities, and M7 Addendum for the Assessment and Control of DNA Reactive (mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk. The procedure explains the process for revising the existing Guidelines as new solvents, metals or impurities are accepted or as new data becomes available. These changes include the following revisions for each Guideline:

- Q3C – Incorporation of Permitted Daily Exposure (PDE) for new solvents and revising the PDE for solvents already listed in Q3C as new toxicological data for solvents becomes available.
- Q3D - Incorporation of Permitted Daily Exposure (PDE) for new elemental impurities/routes of administration and revising the PDE for elemental impurities already listed in Q3D as new toxicological data for elemental impurities becomes available.
- M7 Addendum– Incorporation of acceptable limits (Acceptable Intakes (AIs) or PDEs) for new DNA reactive (mutagenic) impurities and revising acceptable limits for impurities already listed in the Addendum as new data becomes available.

Data and/or proposals pertaining to the revision of the Q3C, Q3D, or M7 Guidelines with supporting information can be submitted directly to the ICH Secretariat from either an ICH Member or Observer or other interested ICH stakeholders.

Information provided within a proposal should be based on significant toxicity data from studies such as repeat-dose studies, reproductive toxicity studies, genotoxicity studies, and carcinogenicity studies and/or other relevant studies. Single-dose toxicity data alone are not sufficient. The toxicity data should be of sufficient quality to calculate a PDE or AI. Genotoxicity and carcinogenicity data are of primary importance for revisions to the M7 Guideline.

An Expert Working Group (EWG) will evaluate any proposals received. The membership of an EWG will generally not change however, the same procedure applies for establishment of an EWG/IWG as outlined in section 1.4.1 – EWG/IWG Membership of this SOP. As appropriate, an ICH Observer may submit a request to the Assembly to nominate an Observer expert to the EWG.

The Rapporteur should be a Founding Regulatory Member and will serve a two-year term. The role of the Rapporteur for each working group will rotate every two years to a new Founding Regulatory Member. The ICH Assembly will be notified following each rotation of the Rapporteur. Proposals will be evaluated once every 2 years following rotation of the Rapporteur. The ICH Secretariat will share any proposals received with the new Rapporteur and ICH Coordinators. The Rapporteur will facilitate the review of any proposals received by the EWG and the EWG will make a recommendation on whether the proposal should be supported by the Management Committee (MC).

If a proposal for maintenance is supported by an EWG, the EWG should submit a revised work plan to the MC to outline this work. The MC will then provide a recommendation to the Assembly for approval on whether the EWG should be tasked with making the revision.

A revision will be considered only on presentation of new data or previously un-recognised toxicity data sufficient to result in a significant change, or because of convincing evidence that the existing data used to calculate a PDE are invalid. Minor changes in a PDE will not be considered. The Regulatory Chair (or in the absence of a Regulatory Chair, the Rapporteur) with the consensus of the EWG members, will assign data reviews to the EWG and request subsequent recommendations.

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 EWG's approval with a recommendation to accept, with or without modifications, or reject any proposed revisions.

After endorsement by the Assembly, either at the next formal meeting or by electronic endorsement, the recommendation of the EWG will be published in each region for public comment (*Step 3* of the ICH process). In addition, the proposal will be provided to each pharmacopoeia for their publication. To ensure clarity on the matter for public comment, only a document listing any changes to the core guideline and/or any new addendums (e.g., with new PDEs) should be published.

After closure of the public comment period, the Regulatory Chair (or in the absence of a Regulatory Chair, the Rapporteur) may convene a meeting of the EWG or will rely on correspondence or teleconferencing to consider the comments and finalise the proposal for the revised Guideline. The final recommendation for the Guideline and implementation is then forwarded to the Assembly for adoption in consultation with the MC. Implementation will follow regional practices. With approval of the ICH Assembly, the change will be provided to the pharmacopoeias at regional/national level for publication.

When a new or revised PDE or AI is recommended by the EWG, approval by the ICH MC is required. Once approval occurs, the information should be disseminated as quickly as possible to all ICH participants and other members of the chemical and pharmaceutical communities. It is recommended that the following actions should be taken by the MC to ensure rapid transmission of the new information:

- Publish relevant information on the ICH website;
- Request publication of revisions by the pharmacopoeias of the ICH regions in their Forums or websites;
- Request that each member publish the new or revised PDE or AI information on its respective websites.