Final Concept Paper

M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk

dated 27 November 2009

Endorsed by the ICH Steering Committee on 9 June 2010

Type of Harmonisation Action Proposed

New Guideline

Statement of the Perceived Problem

There are multiple guidances and positions available addressing approaches to address genotoxic impurities in pharmaceuticals, however, in several important instances the recommendations differ or provide unclear direction. The current ICH guidance on impurity evaluation (Q3A and Q3B) provides guidance on how to identify genotoxic impurities but give no guidance on acceptable levels. The EMA currently has available a final guidance on genotoxic impurities. The FDA has published a draft guidance. PhRMA has published a whitepaper on the topic, while here is no available guidance from Japan. There are some inconsistencies in the guidances between the EMA, FDA, and the recommendations in the ICH general impurities guidance. Importantly, there is a growing consensus that changes to the existing guidances are necessary. For example, analysis of structure activity relationships (SAR) for genotoxicity serve as a trigger for qualification, yet, no guidance is given on the nature of this analysis. Additionally, there is a need to resolve questions such as whether impurities with similar alerts that potentially have similar mechanism of action should not be combined in calculating a Threshold of Toxicological (TTC) and whether the TTC may differ based on differences in the approved duration of use. More recently, an issue has surfaced concerning reevaluation of approved products for genotoxic process impurities when new formulations are approved, such as in development combination drug products.

Issues to be Resolved

- What are acceptable levels of genotoxic impurities during drug development?
- What are acceptable levels of genotoxic impurities for marketing?
- Should those impurities be regulated differently that are likely to have threshold effects?
- Should levels of genotoxic impurities be regulated using a Threshold of Toxicological Concern (TTC) approach?
- Structurally related genotoxic impurities are likely to have similar mechanisms of action. Should these be summed in calculating a TTC?
- What process of qualification testing should be followed for impurities that are metabolites?
- What additional data are needed to support having no special restrictions, or a higher acceptable daily intake than the TTC, for a genotoxic impurity?

Background to the Proposal

- ICH Q3A(R) Impurities in New Drug Substances, 2002
- ICH Q3B(R) Impurities in New Drug Products, 2003
- EMA, Guideline on the Limits of Genotoxic Impurities, 2006
- EMA, Questions and Answers on the CHMP Guideline on the limits of genotoxic impurities, 2008
- US FDA, Guidance for Industry: Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches. Draft, 2008
- A rationale for determining, testing and controlling specific impurities in pharmaceuticals that possess potential for genotoxicity. *Regul Toxicol Pharmacol* 2006;44:198-211

Type of Expert Working Group

The EWG will be comprised of two members (one chemist and one toxicologist) nominated by the six sponsors of the ICH, and one member nominated by Health Canada, WHO and EFTA as Observers. IGPA and WSMI will also be invited to nominate one representative.