Final Concept Paper

ICH M7(R2)：Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk
dated 24 August 2018

Endorsed by the Management Committee on 19 September 2018

Type of Harmonisation Action Proposed

The M7(R2) Expert Working Group (EWG) is developing acceptable limits (Acceptable Intakes (AIs) or Permitted Daily Exposures (PDEs)) for new DNA reactive (mutagenic) impurities and revising acceptable limits for impurities already listed in the Addendum as new data become available. In addition, the M7(R2) EWG is to update the M7 text and develop a Question & Answer document to clarify and address Quality and Safety issues and concerns that have been identified from experience through implementation of M7 since its publication in 2014. This aims to facilitate communication between applicants and assessors. Topics to be discussed are additional clarification on the justification of control strategy for mutagenic impurities in the marketing authorization dossier, organization and depth of information reporting of individual mutagenic impurities, (Q)SAR systems, and other safety-related information.

Statement of the Perceived Problem

The ICH M7 Guideline was finalised in 2014. While preparing the *Step 4* M7 Guideline, interest was expressed by industry representatives in developing AIs or PDEs for new DNA reactive (mutagenic) impurities commonly found or used in drug synthesis. To complement this ICH M7 Guideline, the M7 EWG developed an Addendum to summarize AIs or PDEs for 14 known mutagenic or non-mutagenic impurities. The intent of this Addendum was to provide useful information regarding the acceptable limits of known mutagenic impurities/carcinogenic and supporting monographs. The ICH M7 (R1) Guideline with the Addendum was finalized in 2017. The M7(R2) EWG is currently undertaking a maintenance of the Guideline to expand the Addendum, which will result in the future ICH M7(R2) version. Moreover, based on the experience gained from the application of M7-based control strategies for mutagenic impurities since M7 was finalized, the M7(R2) EWG intends to provide clarity and additional explanation to encourage proper implementation of the concept.

Issues to be Resolved

- Choosing appropriate impurities which should be included in the Addendum
- Developing AIs or PDEs for the selected known mutagenic impurities
- Adapt the classification of anti-HIV therapeutics to medicines for life long treatment
- Seek alignment on the use of new (or is it "alternative?) methodology to calculate AIs or PEDs
- Identifying and drafting Questions and Answers for safety and quality issues based on the experience gained since M7 implementation in 2014

Background to the Proposal

- A recent publication on compound specific limits also containing mutagenic compounds: *Potential impurities in drug substances: Compound-specific toxicology limits for 20 synthetic reagents and by-products, and a class-specific toxicology limit for alkyl bromides. Regul. Toxicol. Pharmacol. 94 (2018), pp. 172–182.*
- M7 suggests that the risk assessment may be based on an estimated (theoretical) purge factor for clearance of mutagenic impurity. It has become an important and desirable approach to show the justification of control strategy for mutagenic impurity. However, M7 does not clarify specific points to consider on using the estimated factor to show the justification. As it turns out, it appears that there are different interpretations, deviated views and expectations among both regulators and industry from the various regions.
- EU proposed the change of treatment duration for HIV medicines in Examples of clinical use scenarios for applying acceptable intakes (Note 7, Table 4). Life expectancy of HIV patients under HRT is close to normal. Treatments have improved, and high treatment compliance has diminished resistance development. Frequent changes of anti-retroviral medicines are not any more done periodically. Therefore, HIV medicines should be classified as medicines for life long treatment.

Type of Expert Working Group

The M7(R2) EWG will be comprised of experts from each of the Founding Regulatory Members and from other ICH Members as appropriate. Additionally, ICH Observers may participate on the M7(R2) EWG pending a favorable decision by the ICH Assembly. The focus of the EWG will encompass safety assessment by toxicologists and quality assessment by chemists.

Timing

The M7(R2) EWG aim for *Step 2* at the F2F meeting in November 2019, and for *Step 4* in 2020.