Final Concept Paper

Addendum to ICH M7 on Risk Assessment and Control of *N*-Nitrosamine Impurities

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Endorsed by the Management Committee on 11 May 2025

1. Type of harmonisation action proposed

Development of an Addendum to the ICH M7 Guideline on *Assessment and Control of DNA Reactive (Mutagenic) Impurities* to address the safety assessment and quality risk management for *N*-nitrosamine impurities (herein also called nitrosamines) leveraging the Formal ICH procedure. The Addendum will include general principles and approaches for establishing acceptable intake limits for nitrosamines, as well as a framework for applying quality principles provided in the ICH M7 Guideline and its Q&A for their assessment and control. The Addendum on *N*-nitrosamines will be included as part of the ICH M7 guideline and upon finalization will be published as ICH M7(R3).

Given that scientific efforts for the past several years have focused on understanding safety and quality hazards and risks related to *N*-nitrosamines, and no other compounds bearing an *N*-nitroso functional group (e.g., *N*-nitroso-guanidines, *N*-nitroso-indoles), the scope of the Addendum will be limited to nitrosamines.

In addition, to demonstrate application of the principles of the ICH M7 Addendum on Risk Assessment and Control of *N*-Nitrosamine Impurities, and to ensure harmonisation of acceptable intake limits across the ICH regions, monographs will be developed, and compound-specific acceptable intake limits will be established for some exemplar nitrosamines. Once the Addendum on *N*-nitrosamine Impurities has reached *Step 4* of the Formal ICH Procedure, new monographs and compound-specific acceptable intake limits will be developed by the ICH M7 EWG Nitrosamine Sub-Group using the ICH M7 Maintenance Procedure. The monographs on *N*-nitrosamines will be included as part of the ICH M7 Addendum on Application of the Principles of the ICH M7 Guideline to Calculations of Compound-Specific Acceptable Intake Limits.

Finally, training materials, including examples, will be developed to elaborate on relevant safety and quality principles and the application of ICH M7 to nitrosamines risk assessment and control.

2. Background to the proposal and statement of the perceived problem

Nitrosamines can be mutagenic and fall under the scope of the ICH M7(R2) guideline. More specifically, nitrosamines belong to the *N*-nitroso class of compounds which is part of the 'cohort of concern' (CoC) as described in the ICH M7(R2) guideline. Very limited guidance is provided on establishing acceptable intake limits for compounds in the CoC. To this end, the ICH M7(R2) guideline recommends a case-by-case approach where carcinogenicity data from closely related structures can be considered when a sufficiently robust carcinogenicity study is not available to establish a compound-specific acceptable intake limits (which is the case for most nitrosamines). No further recommendations are provided.

The pharmaceutical industry and regulatory authorities have been addressing the safety and quality risks posed by nitrosamines in medicines since 2018 when *N*-nitroso-dimethylamine (NDMA) and *N*-nitroso-

diethylamine (NDEA) were identified in some drug products containing angiotensin II receptor blockers. Many other nitrosamines were subsequently identified (and continue to be identified) in marketed drug products at levels that could pose safety and quality risks, including those that originate from the drug substance, drug substance intermediates, related compounds, and drug product components, often during manufacturing and upon storage. The risk of presence of nitrosamines in drug products was considered a public health concern, and due to the limited guidance in the ICH M7(R2) guideline on the assessment and control of impurities in the CoC, some ICH Regulatory Members developed guidance for nitrosamines (e.g. EC, Europe[1-5]; FDA, United States[6-8]; Health Canada, Canada[9]). Notably, to ensure sufficient sensitivity to detect a mutagenic outcome, regulators developed the Enhanced Ames Test (EAT) which includes enhanced testing conditions when assessing the mutagenic hazard of nitrosamines. In addition, the Carcinogenic Potency Categorisation Approach (CPCA) was established in 2023 to assign a nitrosamine to one of five predicted carcinogenic potency categories, each with a corresponding acceptable intake limits that ranges from 18 ng/day up to 1500 ng/day. Significant alignment is observed amongst regulators regarding recommended methodologies. However, the recommended acceptable intake limits in the case where a nitrosamine does not exhibit a mutagenic hazard (for example, EAT and/or *in vivo* mutagenicity study is negative), is not aligned.

Other ICH M7 principles (for example, incorporation of duration of exposure in safety risk assessment, i.e., less-than-lifetime adjustments, and application of control options), have not yet reached consensus and are not currently part of regional regulatory guidelines for nitrosamines. The concerted (and ongoing) efforts of the pharmaceutical industry and regulatory authorities through Health and Environmental Sciences Institute (HESI)[10] and Fraunhofer[11] (as examples), and an extensive body of recent publications provides the scientific basis to support harmonising guidance on both safety and quality aspects of nitrosamine impurity hazard and risk assessment.

3. Issues to be resolved and expected deliverable(s)

The ICH M7 Addendum on *N*-nitrosamines will include recommendations for safety and quality topics to support consistency across the ICH regions. The following topics will be addressed:

- Recommendations for the design and interpretation of the EAT to assess mutagenic hazard.
- Potential to develop a weight of evidence approach based on the outcome of other *in vitro* mutagenicity assays (e.g., *in vitro* assays described in ICH S2(R1)), metabolism/activation data, and *in vivo* studies (e.g., transgenic rodent assay), as warranted for establishing an AI.
- Recommendations for defining acceptable intake limits based on physicochemical and structural features of a nitrosamine. This will include enhancing the CPCA with additional features, as well as a framework for deriving acceptable intake limits based on read-across to a surrogate with compound-specific data.
- Application of less-than-lifetime (LTL) adjustments to acceptable intake limits based on exposure duration and relevant nitrosamine control in clinical development and for marketing authorizations.
- Control of multiple nitrosamines within a drug substance and/or drug product.
- Principles for the design and interpretation of *in vivo* mutation studies, and whether and how the generated data may be used for derivation of acceptable intake limits (including quantitative assessment of *in vivo* data when the results show evidence of mutagenicity).

- Framework for using quality principles recommended in the ICH M7(R2) guideline and its Q&A. The following topic areas will be covered:
  - Recommended principles for conducting robust quality risk assessments for drug products, drug substances, and other drug product components, including high level guidance concerning risk factors for nitrosamines.
  - Recommendations for control strategies for drug substances and extension of control strategies to drug products. This can include options 1-4. High level guidance on documentation in CTDs.
- Monographs and compound-specific acceptable intake limits will be established for some nitrosamines based on the need to support the CPCA framework, and potential establishment of acceptable intake limits based on *in vivo* mutagenicity data. The Methods section of the ICH M7(R2) Addendum on Application of the Principles of the ICH M7 Guideline to Calculations of Compound-Specific Acceptable Intake Limits will be updated if needed.

4. Planning

An ICH M7 Nitrosamine Sub-Group (EWG) was established to develop an Addendum on nitrosamines (i.e., Risk Assessment and Control of *N*-Nitrosamine Impurities), generate monographs that establish compound-specific acceptable intake limits for some nitrosamines, and develop training materials with case examples. The sub-group is composed of safety and quality experts who have been closely involved with the nitrosamine topic including toxicologists and chemists with experience in hazard and risk assessment, drug metabolism, assessment of *in vivo* mutation data and/or (Q)SAR. The ICH M7 Nitrosamine Sub-Group may engage external experts on an ad-hoc basis.

4.1 Timeframe

Following approval of the Concept Paper, it is anticipated that it will take 3 years to reach *Step 1* based on the following considerations:

- Design and interpretation of the EAT – Estimated time to reach consensus on draft recommendations is anticipated to be 18 months. In addition to existing literature, key supporting publications are expected in 2025. While the majority of the recommendations will be drafted within 12 months, the ICH M7 Nitrosamine Sub-Group will incorporate additional guidance when new data become available (for example, positive control strategy).
- Weight of evidence approach based on the outcome of other *in vitro* and *in vivo* mutagenicity assays. Estimated time to reach consensus on draft recommendations is anticipated to be 18 - 30 months.
- Acceptable Intake Limits considering structural features of nitrosamines –
  - ICH M7 Nitrosamine Sub-Group to incorporate updates to the CPCA based on new data and additional assessments of already existing data. Estimated time to reach consensus on draft recommendations is 30 months.
  - Framework for deriving acceptable intake limits based on read-across from a surrogate with compound-specific data. As the read across methodology includes both a structure-activity relationship assessment (for example, comparison of physicochemical characteristics), as well as evaluation of relevant carcinogenicity data, and potentially also mutagenicity data, the estimated time for an agreed draft for this topic is 30-months (to align with the timeframe for drafting the section on the use of *in vivo* mutation studies to derive acceptable intake limits, as well as

recommendations regarding the assessment of structural features and physicochemical characteristics of nitrosamines).

- Application of LTL adjustments – Estimated time to reach consensus on draft recommendations is 18 months, based on existing and anticipated publications of ongoing work.
- Principles for the design and interpretation of *in vivo* mutation studies, and whether and how the generated data may be used for derivation of acceptable intake limits. Recommendations to be drafted over a 30-month period based on existing and forthcoming publications. Publications describing *in vivo* mutation data generated by the pharmaceutical industry are expected by end of 2025. In addition, the ICH M7 Nitrosamine Sub-Group will develop consensus on 1) design of *in vivo* mutagenicity studies to support benchmark dose modelling 2) benchmark dose model methodology and 3) method for calculating an acceptable intake limits based on output of the benchmark dose analysis.
- Framework for quality principles. Estimated time to reach consensus on draft recommendations is 24-30 months (which includes a 12-18 month hold time before initiating development of the draft recommendations). Input from Quality experts will be needed for multidisciplinary topics (CPCA, multiple nitrosamines) from inception of *Step 1* of the ICH process.
- Monographs and compound-specific acceptable intake limits for some exemplar nitrosamines will be drafted in parallel with the nitrosamine addendum. It is anticipated that some monographs will rely on *in vivo* mutation data to establish an acceptable intake limits. Therefore, the timeline for development of these monographs may depend on timing of consensus recommendations reached by the ICH M7 Nitrosamine Sub-Group regarding methods to establish an acceptable intake limits based on *in vivo* mutation data.

4.2 Key Milestones (Estimates)

- *Step 1* (consensus reached on draft Technical Document) – Q2 2028
- *Step 2a/2b* (confirmation of Technical Document by Assembly, Adoption of draft Guideline by Regulatory Members) – Q2 2028
- *Step 3* – (Public consultation and address comments) -Q2 2028 – Q4 2029
- *Step 4* – Finalize Guidance – Q1 2030

5. Impacts of the project and post-hoc evaluation

- May provide recommendations for the design of *in vivo* mutagenicity studies to support dose-response analysis (for example, benchmark dose modelling) for quantitative interpretation of these studies to establish acceptable intake limits. This is beyond the current recommended approaches that rely on carcinogenicity data.
- Supports the safety of existing and new medicines for patients.
- Supports pharmaceutical innovation, leading to the availability on new and improved therapies for patients.
- Supports consistency and transparency of regulatory decisions.
- Promotes alignment of regulatory decisions across the ICH regions.
- Supports 3R principles.
- Following implementation of the *Step 4* guideline, it will be important to assess whether the goal of harmonisation has been achieved.

References

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