

Final Concept Paper
ICH Q3E: Guideline for Extractables and Leachables (E&L)
Dated 30 June 2020
Endorsed by the Management Committee on 10 July 2020

Type of Harmonisation Action Proposed

A new guideline on the assessment and control of extractables and leachables (E&L) is proposed. ICH has developed guidelines covering many aspects of impurities. This includes process and product related substances (Q3A, Q3B), residual solvents (Q3C) and new guidelines covering elemental (Q3D) and mutagenic (M7) impurities. However, E&L impurities are excluded from the scope of the general ICH impurity guidelines. For the purpose of this document, “extractables” are any chemical entities that will extract from components of a manufacturing or packaging system into a solvent under forced conditions. This provides an effective worst case scenario in terms of what can migrate from a component. Knowledge of these extractables is important in identifying potential “leachables” that can migrate via contact with manufacturing systems, container-closure systems, and drug delivery device components.

It is anticipated that the scope of such a guideline would include chemical, biological and biotechnological products, including drug-device combination drug products, however, it will not apply to medical devices as defined by the pertinent ISO guidance. It would also include all associated dosage forms and take into account the extracting/leaching conditions, the route of administration, drug indication and patient exposure.

Statement of the Perceived Problem

No internationally harmonized guidance on E&L assessment and control exists. Specifically, no international guidance that addresses multiple therapeutic modalities and dosage forms; includes identification, qualification, and reporting thresholds; addresses safety assessment; and aligns to the principles of science-based, risk-based and quality-by-design approaches is currently available. This current gap generates uncertainty for industry and regulators due to lack of clarity regarding E&L to meet regulatory expectations. The uncertainty creates potential delays in the approval of regulatory applications, and it can lead to variable interpretation. Ultimately, this may cause delays in the accessibility of medicines to patients. An ICH harmonized guideline addressing the gaps and inconsistencies would remove much uncertainty currently associated with this topic. Such a guideline would assist both applicants and regulators by providing focus on critical aspects, and improving transparency in requirements for medicinal products including drug delivery device components.

Issues to be Resolved

- **Lack of aligned E&L guidance framework:** There is a current lack of alignment, consensus and clarity among existing guidelines, pharmacopoeial and other standards addressing E&L. This lack of alignment leads to variability in both application and interpretation of standards by industry and regulators. These differences with respect to

key areas such as quality and safety assessment impact the global development of new medicines. Development of an ICH guideline provides a clear opportunity to harmonize current expectations covering all medicines, allowing clearer definition of scope and focus on critical quality and safety aspects.

- Lack of guidance alignment regarding: the conduct of E&L studies; the design of an E&L control strategy based on science and risk-based principles; processes to address material and component selection and characterization; risk assessment; and lifecycle management (including post-approval changes) for container-closure systems, manufacturing systems, and drug delivery device components.
- Thresholds: Development of harmonized thresholds for reporting and identifying E&L and qualifying leachables in context of route of administration, drug indication and patient exposure, with an emphasis on science-based and risk-based approaches. The guideline should seek to achieve an appropriate level of detail to ensure it remains relevant and applicable to future innovations in the long term.
- Safety Assessment: Establishment of limits that are relevant to route of administration, drug indication and patient exposure. The guidance will clarify how prior knowledge may be considered to determine the need for further safety studies. Where additional safety data are needed, a common strategy for obtaining these data will be developed.
- Control options: This would include options to mitigate and control process-derived leachables including considerations such as distance along the production stream and processing conditions analogous to ICH M7.
- Alignment with existing ICH guidelines: The guideline would employ principles (e.g., control approaches) consistent with those described within other ICH impurities guidelines (Q3A-D, M7) to create a complementary guideline.
- Pharmacopoeial standards: At present, although there are some pharmacopoeial standards relating to E&L, these are national or regional and generally not aligned across all Pharmacopoeias. Development of a global E&L guidance framework would provide a key opportunity for pharmacopoeias to align.

Background to the Proposal

The variety of documents either directly or indirectly related to E&L issues are limited to specific regions and/or specific drug or manufacturing applications. Some packaging guidelines already exist [e.g., EC, Europe, FDA, United States], and some groups have produced recommendations for specific dosage forms [e.g., Product Quality Research Institute (PQRI)]. In addition, other recommendations exist as pharmacopoeial standards. Furthermore, indirect reference is made to leachables within ICH M7; although application of the guideline to leachables is not intended, safety risk assessment principles outlined therein (e.g., the threshold of toxicological concern [TTC]) may apply. ICH Q3D covers elemental impurities from processing equipment and container closure systems, and ISO 21726 discusses application of a TTC to leachables from devices.

Type of Expert Working Group and Resources

The Expert Working Group should be composed of experts with (bio)pharmaceutical quality, chemistry, manufacturing and control (CMC) and toxicology backgrounds familiar with the assessment and control of extractables and leachables.

Timing

It is expected that this project could be completed within the timeframe outlined in the business plan.