Final Concept Paper

Q6(R1) EWG: Maintenance of the ICH Q6A and Q6B Guidelines

Dated 25 June 2024

Endorsed by the Management Committee on 18 July 2024

1. Type of harmonization action proposed

Revision of the ICH Specification Guidelines Series Q6A and Q6B is recommended to:

a) Update and modernize simultaneously the ICH Q6A and Q6B guidelines by addressing the following:

- Promote consistency between ICH Q6A and Q6B and establish general principles in setting specifications for all product modalities;
- Align with other relevant ICH guidelines and current approaches (e.g. science and risk-based principles described in ICH's Quality Vision and Q8-Q11 guidelines); and
- Revise the scope of the guideline to incorporate contemporary modalities.

b) Develop the complementary training material with relevant examples/case studies.

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

The ICH Q6A and Q6B are foundational guidelines, laying out the guiding principles for establishing specifications for drug substances and drug products that can be adopted globally. Specifications are an essential element of every product's overall control strategy.

Further to a comprehensive assessment of existing Quality guidelines and in consideration of potential future topics, ICH's Quality Discussion Group (QDG) issued the report to the ICH Management Committee entitled "Future Opportunities & Modernization of ICH Quality Guidelines: Implementation of the ICH Quality Vision from the ICH Quality Reflection Paper", which was subsequently published on the ICH website in October 2021. Maintenance of the Q6A and Q6B guideline series was determined as one of the highest priorities based on the evaluation and recommendations from the QDG.

This proposal falls in line with objectives of the ICH Reflection Paper on Advancing Biopharmaceutical Quality Standards to Support Continual Improvement and Innovation in Manufacturing Technologies and Approaches, as well as the ICH Quality Vision to "develop a harmonized pharmaceutical quality system applicable across the lifecycle of the product, emphasizing an integrated approach to quality risk management and science".

ICH Q6A and Q6B Specifications guidelines were adopted in 1999 and their underlying fundamental principles have remained applicable and relevant over time without need for revision. However, the following factors, among others, warrant updating the ICH Q6A and Q6B guidelines:

- Advances in manufacturing process technologies, analytical capabilities and predictive modelling/statistical approaches.
- Adoption of new ICH topics and/or significant updates to existing guideline, e.g., ICH Q2, Q3C-D, Q5A, Q8-Q14, and M7.
- Development of advanced therapeutic modalities.
- Increased propensity for expedited development of new products.

In addition, while ICH Q6A and Q6B guidelines reached *Step 4* more than two decades ago, implementation has been inconsistent, in part due to the absence of clarity on how these guidelines are

intended to be used holistically and with related ICH guidelines. Adding clarity to ICH Q6A and Q6B guidelines' recommendations for establishing specifications would result in a more uniform implementation of the guidelines across ICH regions. Aligning ICH Q6A and Q6B science- and risk-based principles with those articulated in related ICH guidelines ensures that the drug quality controls strategy reflects a holistic approach.

The modern regulatory perspective emphasizes a science and risk-based approach for establishing specifications. Therefore, updating ICH Q6A and Q6B introduces an opportunity to set specification based on holistic approaches that would include e.g.:

- Appropriate use of prior knowledge;
- Appropriate use of pharmaceutical development data;
- Prospective process and product (Critical Quality Attributes, CQA and Critical Process Parameters, CPP) understanding;
- Considerations of the overall control strategy;
- Appropriate use of modelling tools and statistical evaluations;
- Non-clinical and clinical relevance;
- Impact to the safety and efficacy of the drug product.

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

The Expert Working Group will aim to address the following identified issues:

1. Clarify the shared principles between the ICH Q6A and Q6B guidelines, as well as integrate/align their guiding principles with those from other relevant ICH guidelines to ensure consistent terminology and definitions and reflect a holistic approach for setting specifications in ICH Q6A and Q6B as part of an overall product control strategy.

2. Update the scope to also include classes of drug substances and products both chemical entities and biologicals which were not sufficiently covered in ICH Q6A and Q6B (e.g. cell and gene therapies, vaccines, oligonucleotides, antibody-drug conjugates (ADCs), etc.); and drug/biologic-device combination products that meet the definition of a pharmaceutical or biological product.

3. Modernize and align the principles in the ICH Q6A and Q6B guidelines:
   - Align science- and risk-based principles with those articulated in related ICH guidelines to ensure that the control strategy is holistic.
   - Complement traditional reliance on batch data for setting acceptance criteria by emphasizing prior knowledge, science- and risk-based flexible approaches.
   - Emphasize the importance of establishing clinically relevant justification of specifications.
   - Clarify the complementary roles of specifications and process consistency monitoring.
   - Provide clarity on certain quality attributes (e.g. dissolution/drug release, biological activity/potency, etc);
   - Introduce options to accommodate situations where acceptance criteria may be set based on limited batch experience, in accordance with progressive knowledge, science-based and holistic control strategies (ICH Q8 and Q11). In particular, specifications developed for assessment and release of products that address unmet medical need may warrant flexibility in their justifications and are more likely to change with increased experience.
   - Enable harmonized adoption of evolving technologies and associated scientific approaches, e.g., appropriate use of modelling/statistical approaches to set acceptance criteria, and use of advanced process analytical technologies and/or Real Time Release Testing (RTRT), to demonstrate control of specific CQAs.

4. Include considerations on lifecycle management of specifications, in line with concepts agreed in ICH Q12.

Additional Points to Consider, such as:

- Pharmacopoeias:
  - Clarify the role of pharmacopoeias in setting specifications.
  - Include reference to ICH Q4B which covers interchangeability of pharmacopeial methods.
- Development of Specifications:
  - Provide general principles applicable to all modalities within scope.
  - Provide specific considerations for specifications of different pharmaceutical modalities as appropriate.
  - Consider revisions or development of decision trees where appropriate.
  - Clarify the applicability of periodic or skip lot testing expectations and consider alignment with control strategy principles in ICH Q8-11 and ICH M7.
  - Delineate applicability of specifications for release versus shelf-life, complementing considerations included in ICH stability guidelines.
- Reference Standards/Materials: Update expectations and principles for development and lifecycle management of reference standards/materials where appropriate.
- Revise Definitions/Terminology where appropriate.
- Include considerations on the 3Rs (replacement, reduction and refinement of animal tests).

4. Planning

It is proposed that this work is initiated in Q2 calendar year 2024, following finalization of the Concept Paper and establishment of an Expert Working Group. It is anticipated that the development of ICH Q6A/B guideline(s) could reach *Step 1* two years after initiation of an EWG and *Step 4* two years after that.

- Q2 calendar year 2024 - Finalize Concept Paper, Work Plan
- Q2 calendar year 2026 – Complete *Steps 1/2a/b*, Initiate work on training materials
- Q2 calendar year 2028 – Complete *Steps 3/4*

5. Impacts of the project and post-hoc evaluation

Anticipated Benefits of the Proposal

This proposal will update and contemporize ICH Q6A and Q6B guidelines and clarify expectations for technical harmonization in conjunction with other ICH guidelines, integrating science and risk-based pharmaceutical development concepts that will improve implementation and expedite regulatory review of marketing authorization applications and post-approval changes.

For Industry:

- Enable a globally harmonized science and risk-based approach for setting specifications;
- Facilitate global development and regulatory approvals of marketing applications;
- Facilitate expedited product development and patient access;
- Ensure to have an appropriate testing strategy in place to confirm product quality;
- Enable patients' access to high quality, safe and effective medicinal products;
- Foster a holistic and consistent application of relevant ICH guidelines;
- Facilitate the communication between Industry and Regulators.

For Regulators:

- Ensure consistent application of the ICH Q6A/B guideline(s) during the regulatory review of marketing authorization applications;
- Improve efficiency of regulatory review process;
- Facilitate consistency of regulatory decision making;
- Enable patients' access to high quality, safe and effective medicinal products;
- Foster a holistic and consistent application of relevant ICH guidelines;
- Facilitate the communication between Industry and Regulators.