

Final Concept Paper
Q11: Q&As on Selection and Justification of Starting Materials for the Manufacture of Drug Substances

Focus on chemical entity drug substances
dated 22 October 2014

Endorsed by the ICH Steering Committee on 10 November 2014

Type of Harmonisation Action Proposed

An Implementation Working Group (IWG) is proposed to prepare a Questions and Answers (Q&A) document for ICH's *Development and Manufacture of Drug Substances* (Q11) Guideline to provide clarification on what information about the selection and justification of starting materials should be provided in marketing authorisation applications and/or Master Files.

The IWG will provide clarification of the existing principles and will not re-open ICH Q11. As appropriate, references will be made to existing ICH Guidelines, e.g., ICH Q7, ICH Q9, ICH Q10, ICH Q11 and ICH M7, to ensure continuity across all ICH Quality Guidelines. The focus of the Q&A document will be on chemical entity drug substances as that is where most of the differences of opinion have been experienced.

Statement of the Perceived Problem

Evaluation of information related to the manufacturing process and controls for drug substances is an important part of marketing authorisations. Decisions made about the proposed starting material(s) determine what expectations apply to the Quality-related information for both pre-market assessment and for post-market changes. The acceptability of the applicant's proposed starting material also has implications for Good Manufacturing Practices (GMPs), process validation requirements, and inspection-related activities (as outlined in ICH Q7). While it is recognised that ICH Q11 provided good scientific guidance when published in 2012, differences in the interpretation of that guidance are causing problems for industry and regulators.

Issues to be Resolved

Examples of issues that a Q&A document might help resolve include, but are not limited to the following:

- Significant regional differences between regulatory authorities in terms of:
 - Which aspects contribute to the potential unsuitability of starting materials (e.g., number of distinct chemical steps separating starting material(s) from final drug substance, potentially mutagenic impurities, stereochemistry);
 - The amount of regulatory attention given to steps prior to the proposed starting material (e.g., how much of the synthesis of the proposed starting material should be disclosed as part of the justification for the starting material);
 - What information is necessary to support the justification of the starting material.

- Significant resources are frequently used to resolve differences of opinions (regulatory and industry);
- The information provided by industry can be inadequate for regulators to evaluate whether the proposed starting material, manufacturing process, and control strategy provide sufficient assurance of the quality of the drug substance (especially if the proposed starting material occurs late in the manufacturing process);
- Additional burden on industry associated with conservative approaches to defining starting material can include, for example:
 - Validating early steps before the proposed starting material;
 - Evaluating every step of the process for known and potential impurities with the same intensity as the final few steps;
 - Expecting steps prior to proposed starting material to be manufactured under GMP conditions.

Background to the Proposal and Issues

Q11 provided guiding principles to be considered in the selection and justification of starting materials for the manufacture of drug substances. It has become apparent, based on public workshops, symposia, and industry experience with global submissions, that differences of opinion can arise between regulators and industry about how those principles should be applied in specific situations. While it is recognised that each dossier needs to be judged on its own merit, further clarification of the principles of Q11 through a Q&A document (including perhaps, case studies) could help address differences in understanding and interpretation.

The Q&A should provide several benefits for industry, regulators, and patients:

- Improvement in global harmonisation regarding the selection and justification of starting materials used in the manufacture of drug substances for new and generic applications;
- Clarification regarding the relationship between the selection of appropriate starting material and GMP considerations, control strategy, length of synthetic process, and impact of manufacturing steps on DS quality. Clarification: ICHQ7 / GMP is not in scope and not for this IWG;
- Clarification on the type of information that industry should provide in submissions to justify starting material selection;
- Clarify expectations for lifecycle management of starting material .

Type of Expert Working Group and Resources

The proposed Q&A document will provide clarification to complement ICH Quality Guidelines for chemical entity drug substances. In general, biotechnological/biological drug substances will not be within scope; however, the Q&A may clarify special cases. The working group should include representatives from the ICH official members (EU, EFPIA, FDA, PhRMA, MHLW, JPMA, Health Canada and Swissmedic). One member can also be nominated by WHO Observer, EDQM, WSMI, IGPA, and API industry as well as RHIs, DRAs/DoH (if requested).

The primary mechanism for advancing the work of the IWG will be through teleconferences. However, one face-to-face meeting of the IWG may be requested to meet the tight timeline proposed. Given the time zone challenges for scheduling within business hours, the complex nature of this topic, and the anticipated challenges in reaching harmonisation, it will be difficult to complete the Q&A document within the compressed timeline using only teleconferencing and email. A single face-to-face meeting at an ICH meeting would approximately double the amount of time available for discussions between the full IWG. Additionally, face-to-face discussions are more effective than teleconferences especially for members who must participate using a second language.

Timing

Approval of Topic/Rapporteur & IWG Defined

November 10, 2014

First IWG Meeting (teleconference)

November 2014

Step 2a/b document to present to SC

November 2015

Step 4 document sign-off

TBD