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ICH Q11: development and manufacture of drug substances—chemical and biotechnological/biological entities

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The International Conference on Harmonisation (ICH) has endorsed a new guideline concerning the development and manufacture of chemical and biotechnological/biological drug substances. The guideline harmonises the scientific and technical principles relating to the development and description of the drug substance manufacturing process to be included within the Common Technical Document (CTD) and submitted to regulatory authorities in the European Union (EU), Japan and USA. This question and answer is intended to provide the reader with a flavour of the background to the guideline and its relevance for biosimilar and generic drug substances.

Keywords: Biotechnological/biological and chemical substances, drug substance quality, ICH Q11

The need for an International Conference on Harmonisation (ICH) guideline on the development and manufacture of drug substances was endorsed by the ICH Steering Committee in October 2007. This recognised the absence of harmonised guidance for industry and regulatory authorities in this area and the need to consider how principles and concepts described in ICH guidelines Q8 (Pharmaceutical Development), Q9 (Quality Risk Management) and Q10 (Pharmaceutical Quality System) apply to the development of drug substance manufacturing processes.

The ICH Q11 guideline was drafted by an expert working group comprising representatives from regulatory authorities and the pharmaceutical industry in the European Union (EU), Japan and USA. Observers actively contributed to the discussions and included regulators from Canada, China, Singapore and Switzerland, the World Health Organization along with international groups representing biotechnology, generic and self-medication industry sectors.

The ICH Q11 guideline was endorsed by the Steering Committee on 1 May 2012 and was adopted in the EU by the Committee on Human Medicinal Products in May 2012.

This question and answer is intended for those with interest in the development and manufacture of drug substances, those involved in regulatory submissions for marketing authorisations in the EU and quality assessors in competent authorities. It is intended by way of introduction to the guideline. It assumes a general awareness of ICH quality guidelines. Readers should refer to the full text version and other ICH guidelines referred to in this article and available on the ICH website at www.ich.org/products/guidelines/quality/article/quality-guidelines.html

The authors of this article were members of the Q11 expert working group. Direct quotations from the guideline are the

agreed position of the expert working group. Any other views or opinions expressed in this article are those of the authors and should not be attributed to the authors' employers.

What is the purpose of ICH Q11?

The purpose of the guideline is to harmonise the scientific and technical principles relevant to the development and manufacture of drug substances and to provide guidance on the information to be included within the Common Technical Document (CTD) in support of marketing authorisation submissions. The guideline is intended to facilitate the submission of similar information in regulatory submissions within the ICH signatory regions (EU, Japan and USA) and may be helpful to pharmaceutical companies and regulators in other regions.

What is the scope of the guideline?

The guideline is applicable to new chemical drug substances and biotechnological/biological drug substances, as described in ICH Q6A and Q6B, respectively.

It provides guidance on information to be submitted in sections S2.2–S2.6 of the CTD. The guideline will be applicable to biosimilar molecules falling within the scope of Q6B. Although generic chemical substances were not included in the scope of the guideline, the principle of design of robust manufacturing processes through effective development and control, using the approaches described in the guideline, is also relevant for manufacturers of generic chemical substances.

Q11 is not intended as a guide to what to submit in applications during the clinical development of investigational medicinal products but the principles described may be taken into consideration during this time in order to provide information for inclusion in any later marketing authorisation submission.

Q11 does not provide guidance on how to comply with requirements for good manufacturing practice (GMP).

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How does Q11 provide guidance for both biotechnological/biological and chemical drug substances?

The approaches to development of manufacturing processes are similar for both biotechnological/biological and chemical substances in respect of the need to define a robust commercial manufacturing process that consistently provides drug substance of defined quality. Both chemical and biotechnological/biological manufacturing processes are required to consistently produce high purity and potent molecular entities with processes designed to minimise and/or remove impurities. However, the limitations in analytical characterisation for biotechnological/biological substances necessitate a control strategy with greater emphasis on process controls as compared to chemical substances.

Q11 provides common principles for both chemical and biotechnological/biological substances but also provides specific guidance, for example, on drug substance starting materials for new chemical substances and what to submit for process validation studies for biotechnological/biological substances.

Does the guideline introduce additional regulatory expectations?

The guideline does not introduce new regulatory expectations. Different approaches may be taken to the development of a manufacturing process for a new drug substance. The 'traditional' approach continues to be acceptable. More systematic approaches to development along with quality risk management tools can provide greater understanding of sources of variability in the manufacturing process and flexibility in the application of the controls. Both 'traditional' and 'enhanced' approaches to development of the manufacturing process are acceptable and a combination of both approaches can also be used in process development.

Does ICH Q11 replace other ICH guidance on drug substances?

Generally applicable guidance concerning process development is given in ICH Q8, Q9 and Q10. ICH Q11 supplements existing ICH guidance and clarifies the application of concepts described in ICH Q8, Q9 and Q10, as relevant to drug substances. It supports approaches to process development in order to better understand and control sources of variability in the drug substance.

Does the concept of 'design space' as described in ICH Q8 apply to drug substances?

The definition of design space given in ICH Q8 is applicable for both chemical and biotechnological/biological drug substances. Movement within an approved design space would not require prior regulatory approval.

How should movement within a 'design space' be handled for biotech products?

The development and approval of a design space for some biotechnological/biological drug substances can be challenging due to factors including process variability and drug substance complexity, e.g. post-translational modifications. These factors can affect residual risk, e.g. potential for unexpected changes to CQAs (critical quality attributes) based on uncertainties

related to scale sensitivity, which remains after approval of the 'design space'. Depending on the level of residual risk, it may be appropriate for an applicant to provide proposals on how movements within a 'design space' will be managed post approval.

These proposals should indicate how process knowledge, control strategy and characterisation methods can be deployed to assess drug substance quality following movement within the approved 'design space'. This could include proposals for 'design space' verification, as well as a risk-based approach to define stratified actions, e.g. routine testing only, addition of characterisation tests.

What guidance is included in ICH Q11 in respect of selection of the starting material for a chemical drug substance?

Harmonisation was reached on the high level considerations for designation of the starting material for a chemical synthesis manufacturing process and on the information to be submitted in the dossier. It is anticipated that multiple chemical transformation steps from precursor structural fragments will be included in the dossier. Steps that require control due to introduction or removal of impurities in the drug substance should be considered in the designation of the starting material for the drug substance. The design of a suitable control strategy and its execution within GMP provide the basis for consistent quality of the drug substance.

Does the definition of CQA stated in ICH Q8 apply to the drug substance?

The definition of CQA as described in ICH Q8 is relevant for both chemical and biotechnological/biological drug substance. A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

Does Q11 recommend that all drug substance CQA are included in the drug substance specification?

The drug substance specification is only one part of a total control strategy and not all CQAs need to be included in the drug substance specification.

The control strategy should ensure that each drug substance CQA is within the appropriate range, limit, or distribution to assure drug substance quality. Different approaches can be envisaged to the management of specific CQAs, dependent on the knowledge of the relationship between process parameters and the particular CQA. This can include inclusion of a control for that CQA in the drug substance specification with compliance confirmed by testing each batch produced. Alternative approaches may include confirmation of compliance of a CQA using process controls applied upstream from the final drug substance with a control included for the CQA in the drug substance specification that is not tested on every batch. A further situation can be envisaged when a given CQA is controlled by the operating parameters of the process and ensured by process controls without including a control in the drug substance specification.

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Can platform manufacturing data be used for biotechnologically-derived substances?

Significant experience gained through the use of a production strategy similar to those used by the same applicant to manufacture other drugs of the same type, i.e. platform manufacturing, is acknowledged in ICH Q11. Where appropriate, such prior knowledge can be used to leverage some development data and support evaluation/validation studies.

Does Q11 provide guidance on the number of batches required in drug substance process validation studies?

There is no 'magic number'. The number of batches should comply with relevant guidances, e.g. ICH Q7, and can depend on several factors including but not limited to: (1) the complexity of the process being validated; (2) the level of process variability; and (3) the amount of experimental data and/or process knowledge available on the specific process.

To what extent are data generated with small-scale batches relevant to the validation of the commercial process for biotechnologically-derived substances?

The contribution of data from small-scale studies to the overall validation package will depend upon demonstration that the small-scale model is an appropriate representation of the proposed commercial scale. Data should be provided demonstrating that the model is scalable and representative of the proposed commercial process. Successful demonstration of the suitability of the small-scale model can enable manufacturers to propose process validation with reduced dependence on testing of commercial-scale batches.

Does Q11 provide guidance on changing the manufacturing process after approval of a marketing authorisation?

As indicated above, the concept of design space is applicable to drug substances. Following approval, changes within the defined 'design space' do not require regulatory approval.

Q11 also recognises that protocols for managing specific changes to the drug substance manufacturing process and intended to be implemented after approval, may be included for agreement with the regulatory authority during the assessment of the marketing authorisation application.

European legislative requirements for post-approval changes to marketing authorisations are applicable.

Further information on the regulation and detailed classification guidance are available on the European Commission website at ec.europa.eu/health/better-regulation-variations-regulations-developments_en.htm

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