M10 Bioanalytical Method Validation and Study Sample Analysis Questions and Answers

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2024
ICH-Multidisciplinary

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Contains Nonbinding Recommendations

FOREWORD

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has the mission of achieving greater regulatory harmonization worldwide to ensure that safe, effective, and high-quality medicines are developed, registered, and maintained in the most resource-efficient manner. By harmonizing the regulatory expectations in regions around the world, ICH guidelines have substantially reduced duplicative clinical studies, prevented unnecessary animal studies, standardized safety reporting and marketing application submissions, and contributed to many other improvements in the quality of global drug development and manufacturing and the products available to patients.

ICH is a consensus-driven process that involves technical experts from regulatory authorities and industry parties in detailed technical and science-based harmonization work that results in the development of ICH guidelines. The commitment to consistent adoption of these consensus-based guidelines by regulators around the globe is critical to realizing the benefits of safe, effective, and high-quality medicines for patients as well as for industry. As a Founding Regulatory Member of ICH, the Food and Drug Administration (FDA) plays a major role in the development of each of the ICH guidelines, which FDA then adopts and issues as guidance to industry.

Contains Nonbinding Recommendations

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This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

(PREFACE)

In response to questions posted to the International Council for Harmonisation (ICH) draft guidance for industry *Bioanalytical Method Validation* comment period, a number of questions and answers have been devised to provide clarity around some of the bioanalytical issues covered in the guidance.

This question and answer (Q&A) document is intended to provide additional clarification and to promote convergence and improve harmonization of the bioanalytical method validation and study sample analysis.

The scope and organization of this Q&A document follow that of the ICH guidance for industry *M10 Bioanalytical Method Validation and Study Sample Analysis* (November 2022) (ICH M10).[2]

[1] This guidance was developed within the Expert Working Group (*Multidisciplinary*) of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Assembly at *Step 4* of the ICH process, November 2022. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the ICH regions.

[2] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Table 1. Q&As for ICH M10

Guidance Section*	Question	Answer
II (2)	In situations where a matrix is unavailable (e.g., shortage, 3Rs - Reduce, Refine, Replace) can a similar surrogate matrix (e.g., human plasma) be used to dilute samples?	Yes, as long as the use of the surrogate matrix meets the recommendations of the guidance, including accuracy and precision, lack of interferences, etc., and the dilution quality control samples (QCs) are processed in the same way. The rationale should be well justified because the approach might be questioned.
II (2), III (3), IV (4)	When adding a new QC concentration level during study sample analysis without changing the calibration curve range in either chromatographic assays or ligand binding assays, is it necessary to validate the new QC concentration level with a partial validation?	The precision and accuracy of the new QC concentration level should be demonstrated before use in study sample analysis. This can be documented either as a partial validation or as a note to the bioanalytical report.
III (3)	Is it acceptable to demonstrate the absence of analytical interference of the internal standard (IS) itself, any impurities or its isotopic stability based on the analytical results of the zero sample?	Yes, this is applicable for both method validation and study sample analysis.
III (3)	For long-term stability, does a failed time point mean you should not continue with longer time points?	Additional time points can be evaluated. Any failure should be investigated to identify the root cause and the impact on the stability assessment.
III (3)	Can the physicochemical properties of the related substances be used to justify that the related substances do not co-elute or interfere with the analyte measurement during mass spectrometry (MS) analysis?	Yes, but if co-elution of the related substance and the analyte is not excluded, additional investigations should be used to demonstrate chromatographic separation (e.g., for isomers). If the analyte and the related substance co-elute, matrix effect (ion suppression/enhancement) and back-conversion should be evaluated.

continued

Table 1, continued

Guidance Section*	Question	Answer
III (3)	How is the accurate preparation of the stock solution verified?	By comparing two independently prepared stock solutions and demonstrating that the difference of their measured responses is within 5%. $\% \, difference = \frac{\lvert Stock \ solution \ 1 - Stock \ solution \ 2 \rvert}{mean \ value} x \ 100$
IV (4)	Is there a requirement to test specificity in validation with an irrelevant immunoglobulin molecule when the analyte is an immunoglobulin and the assay contains analyte specific reagents (e.g., use of anti-idiotypic antibody or antibodies as capture and/or detection reagents)?	There is no requirement to assess specificity in validation with an irrelevant immunoglobulin as long as the specificity of the reagent(s) has been evaluated during reagent characterization.
V (5)	How should trends of concern or incurred sample reanalysis (ISR) failure be investigated?	The investigation should be driven by a standard operating procedure (SOP) and should take into account the entire process, including sample handling, processing, and analysis. This should also include a scientific assessment of whether there are issues impacting the bioanalytical method, such as interferences and instability.
VI (6)	Given that ICH M10 allows partial validation for matrices within species or same matrix across species, is an N-in-1 approach (multiple species or matrices in one validation) allowed for chromatographic methods for nonclinical studies?	Possibly this approach can be used. However, caution should be taken in using this approach; the rationale should be well justified because the approach might be questioned.

* The numbers in parentheses reflect the organizational breakdown of the document endorsed by the ICH Assembly at Step 4 of the ICH process, November 2022.