M10 Expert Working Group

ICH M10 Guideline:
BIOANALYTICAL METHOD VALIDATION AND STUDY SAMPLE ANALYSIS

Questions and Answers

M10 Q&As

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In order to facilitate the implementation of the ICH M10 Guideline, the ICH M10 Expert Working Group has developed a series of Q&As:

ICH M10 Q&As

Document History

Code	History	Date
M10 Q&As	Adoption by the ICH Assembly under *Step 4.*	16 November 2022

References

ICH M10 Bioanalytical Method Validation and Study Sample Analysis (24 May 2022)

PREFACE

In response to questions posted to ICH M10 comment period, a number of Questions and Answers have been devised to provide clarity around some of the bioanalytical issues covered in the Guideline.

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 ICH M10.

Guideline Section	Questions	Answers
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 guideline, including accuracy and precision, lack of interferences, etc. and the dilution quality control samples (QCs) are processed in the same way. The rationale needs to be well justified because the approach might be questioned.
2, 3, 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.
3	Is it acceptable to demonstrate the absence of analytical interference of the 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.
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.
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 are needed 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.

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%. $\%\ difference = \frac{\lvert Stock\ solution\ 1 - Stock\ solution\ 2 \rvert}{mean\ value} x\ 100$
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(ies) 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 characterisation.
5	How should trends of concern or incurred sample reanalysis (ISR) failure be investigated?	The investigation should be driven by an 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.
6	Given that M10 allows partial validation for matrices within species or same matrix across species, is an N-in-1 approach (multiple species or matrices in 1validation) allowed for chromatographic methods for nonclinical studies?	Possibly this approach may be used. However, caution should be taken in using this approach; the rationale needs to be well justified, because the approach might be questioned.