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ICH M10: Bioanalytical Method Validation and Study Sample Analysis

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Overview

- ICH M10 Guideline
- Changes from the Step 2 Draft Document
- Post Step-4 Updates
- Summary

M10: Purpose

- Recommendations for validation of bioanalytical methods and analysis of study samples
- Ensures the quality and consistency of bioanalytical data (analysis of both chemical and biological drugs in biological samples)
- Harmonises current regional guidelines → facilitate drug development

M10: Background

- Developed October 2016 based on a Concept Paper and Business Plan
- Draft (Step 2 document) published for public consultation on February 26, 2019 → 2500 comments
- Signed off (Step 4 document) on May 24, 2022
  → implemented by the ICH Regulatory Members

ICH M10: BMV and Study Sample Analysis

M10: Content

1.0 Introduction

2.0 General Principles

3.0 Chromatography

4.0 Ligand Binding Assays

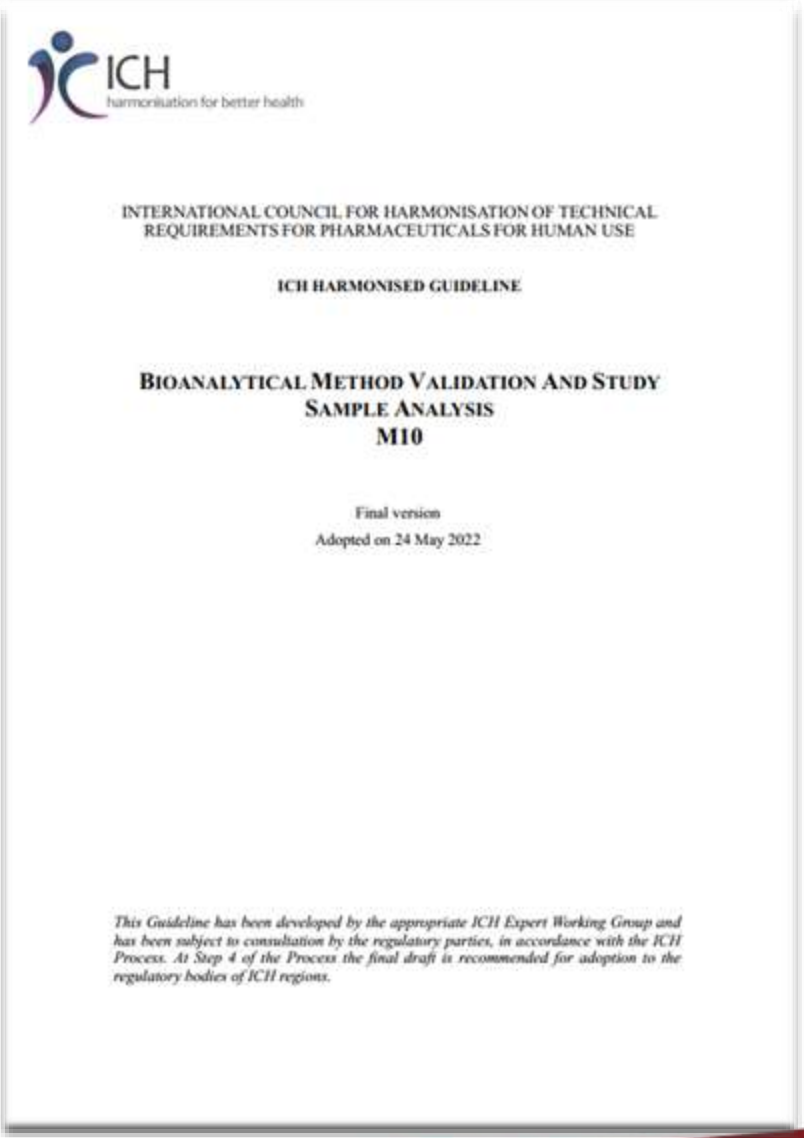
5.0 Incurred Sample Reanalysis

6.0 Partial and Cross Validation

7.0 Additional Considerations

8.0 Documentation

9.0 Glossary



ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

BIOANALYTICAL METHOD VALIDATION AND STUDY SAMPLE ANALYSIS
M10

Final version
Adopted on 24 May 2022

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions.

M10: Scope

- Studies submitted to make decisions on and/or support Approval, Safety, Efficacy and Labelling of a drug product.

- Nonclinical studies
  - Pivotal toxicokinetic and pharmacokinetic studies

- Clinical studies

Chromatography – Changes from the Step 2 Draft Document

- Validation
- Study Sample Analysis

Changes from Step 2 Draft: Chromatography – Section 3.2 Validation

3.2.5 Accuracy and Precision

Recommendation for QCs in non-accuracy and precision validation runs for acceptance of the run:

- Low, medium and high QCs in duplicate
- ≥ 2/3 of the total QCs and ≥ 50% per concentration level within ±15% of nominal values.

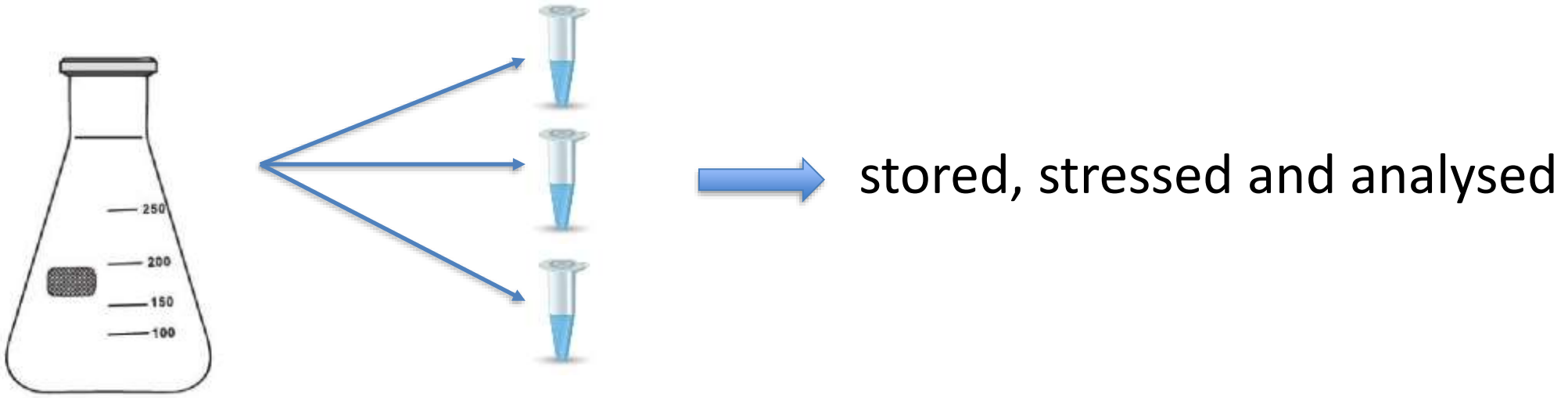
Changes from Step 2 Draft: Chromatography – Section 3.2 Validation

3.2.7 Dilution Integrity

The dilution ~~ratio(s)~~ factors and concentrations applied during study sample analysis should be within the range of the dilution ~~ratios~~ factors and concentrations evaluated during validation.

Changes from Step 2 Draft: Chromatography – Section 3.2 Validation

3.2.8 Stability



One bulk QC should be prepared at each concentration level. For each concentration tested, the bulk sample should be divided into a minimum of 3 aliquots that will be stored, stressed and analysed.

Changes from Step 2 Draft: Chromatography – Section 3.2 Validation

Section 3.2.8 Stability

Multiple Analyte Stability

- Fixed dose combination products and specifically labelled drug regimens
- Freeze-thaw, bench-top and long-term stability tests
- Matrix spiked with all of the dosed compounds

Changes from Step 2 Draft: Chromatography – Section 3.2 Validation

Section 3.2.8 Stability

<u>To be evaluated:</u>

1. Stability of the analyte in matrix
2. Stability of the analyte in processed samples
3. Stability of the analyte and IS in stock and working solutions
4. Stability of the analyte in whole blood

Changes from Step 2 Draft: Chromatography – Section 3.2 Validation

Section 3.2.8 Stability

2. Stability of the analyte in processed samples

- The total time that a processed sample is stored must be concurrent (i.e., autosampler and other storage times cannot be added together).

4. Stability of the analyte in whole blood

  - Conducted when the matrix used is plasma ~~or serum~~

Changes from Step 2 Draft: Chromatography – Section 3.2 Validation

Section 3.2.9 Reinjection Reproducibility

Purpose:

- Establish viability of processed samples & support storage prior to reinjection.

How:

- Reinjecting whole run:
  - calibration standards + ≥ 5 replicates of the low and high QCs after storage
- Precision & accuracy of reinjected QCs

Changes from Step 2 Draft: Chromatography – Section 3.3 Study Sample Analysis

Section 3.3.2 Acceptance Criteria

- Calibration standards in a failed batch cannot be used to support the acceptance of other batches within the analytical run.

- Bracketing of dilution factors for dilution QC (lowest and highest only)

Changes from Step 2 Draft: Chromatography – Section 3.3 Study Sample Analysis

Section 3.3.4 Reanalysis of Study Samples

- Multiple analytes: valid result for one analyte should not be rejected if the other analyte fails

- Comparative BA/BE studies: Separate table reporting values from rejected runs

Ligand Binding Assays (LBA) – Changes from the Step 2 Draft Document

- Validation
- Study Sample Analysis

Changes from Step 2 Draft: LBA – Section 4.2 Validation

Section 4.2.2 Selectivity

- Using blank samples from ≥ 10 sources
  - Use of fewer sources may be acceptable for rare matrices

- Examples of relevant patient populations
  - Renally or hepatically impaired, inflammatory or immuno-oncology, if applicable

Changes from Step 2 Draft: LBA – Section 4.2 Validation

4.2.4 Accuracy and Precision

Recommendation for QCs in non-accuracy and precision validation runs for acceptance of the run:

- Low, medium and high QCs in duplicate
- ≥ 2/3 of the total QCs and ≥ 50% per concentration level within ±20% of nominal values.

Changes from Step 2 Draft: LBA – Section 4.2 Validation

Section 4.2.7 Stability

<u>QC preparation for Stability Evaluation</u>

- One bulk QC at each concentration level

- May need to freeze macromolecules overnight
  - QCs should be frozen for ≥ 12 hours between thawing cycles

- Multiple dosed compounds stability
  - On a case-by-case basis

Changes from Step 2 Draft: LBA – Section 4.3 Study Sample Analysis

Section 4.3.2 Acceptance Criteria

- Calibration standards in a failed batch cannot be used to support the acceptance of other batches within the analytical run.

Section 4.3.4 Reanalysis of Study Samples

- Separate table reporting values for rejected runs (BA/BE studies)

Changes from the Step 2 Draft Document

- Incurred Sample Reanalysis
- Partial and Cross Validation
- Additional Considerations
- Documentation

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Section 5 Incurred Sample Reanalysis

- Acceptance criteria within ±20% (chromatography) and within ±30% (LBA)

Section 6.1 Partial Validation

- Added change in anticoagulant in biological fluids for LBA methods.

Section 6.2 Cross Validation

Demonstrates how the reported data are related when:

- Multiple bioanalytical methods
- Multiple bioanalytical laboratories

Note:

- Data from different fully validated methods
- Data are not to be combined across studies

Cross Validation Not Required

Section 7 Additional Considerations

- Methods for Analytes that are also Endogenous Molecules

- Parallelism
  - Study specific
  - Conducted during study sample analysis

Section 8.1- Summary Information

- Minor modifications to terminology

- List of regulatory site inspections for BA/BE studies
  - Three years prior to study
  - One year post study

Section 8.2- Documentation

- Specific requirements for BA/BE studies separated out
- For non- BA/BE studies, randomly selected chromatograms from 5% of ~~studies~~ samples submitted in dossier
- Separate table reporting values for rejected runs (BA/BE studies)

Post Step-4 Updates

Frequently Asked Questions (FAQs) published May 25, 2022

Split into 2 documents
November 2022

New Q&A document

- Majority of the content from original M10 FAQ

New FAQ document

- 3 remaining FAQs → training slides
- To be removed from the ICH website

Post Step-4 Updates

- FDA: Posted to website November 2022
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m10-bioanalytical-method-validation-and-study-sample-analysis

- HC: Posted to website January 2023
  - https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-council-harmonisation/guidelines.html#multidisciplinary_guidelines

- Training Slides being finalised by the Expert Working Group (EWG).
  - Examples to illustrate certain aspects of the guideline
  - Questions requiring complex answers

Summary

Finalised M10 Guideline:

- same scientific regulatory requirements being applied in different regions ✓
- avoids unnecessary duplicative testing ✓
- supports streamlined global drug development ✓

Thank you to the members of the ICH M10 EWG

Comments can be submitted to ich@hc-sc.gc.ca