14th JBF Symposium
ICH M10 の実装に向けて
– 国内外のバイオアナリストによる最新の議論 –
March 1, 2023 Tower Hall Funabori, Tokyo, Japan

Overview of ICH M10 guideline

ICH M10ガイドラインの概要

Akiko Ishii-Watabe, Yoshiro Saito

National Institute of Health Sciences, MHLW, Japan

Contents

ICH M10:
Bioanalytical Method Validation and Study Sample Analysis

1. **History and EWG activity of M10**
2. **Finalised M10 guideline, Q&A, and FAQ**
3. **Future perspectives of regulated bioanalysis**

Regional Bioanalytical Method Validation guidelines/guidances (Before M10)

FDA Guidance for Industry: Bioanalytical Methods Validation (**2001**)
→ revision (**2018**)

EMA Guideline on Bioanalytical Method Validation (**2011**)

MHLW Guideline on Bioanalytical Method Validation for Chromatography (**2013**), for Ligand Binding Assay (**2014**)

Health Canada (**2012**)

ANVISA (**2012**)

MFDS (**2013**)

CFDA (**2015**)

Global Bioanalysis Consortium

Establishment of M10 guideline will result in the harmonisation of current regional guidelines/guidances and support streamlined global drug development.

Dr. Noriko Katori (2013)

Future Science Ltd
Bioanalysis
Volume 5, Issue 11, June 2013, Pages 1321-1323
https://doi.org/10.4155/bio.13.71

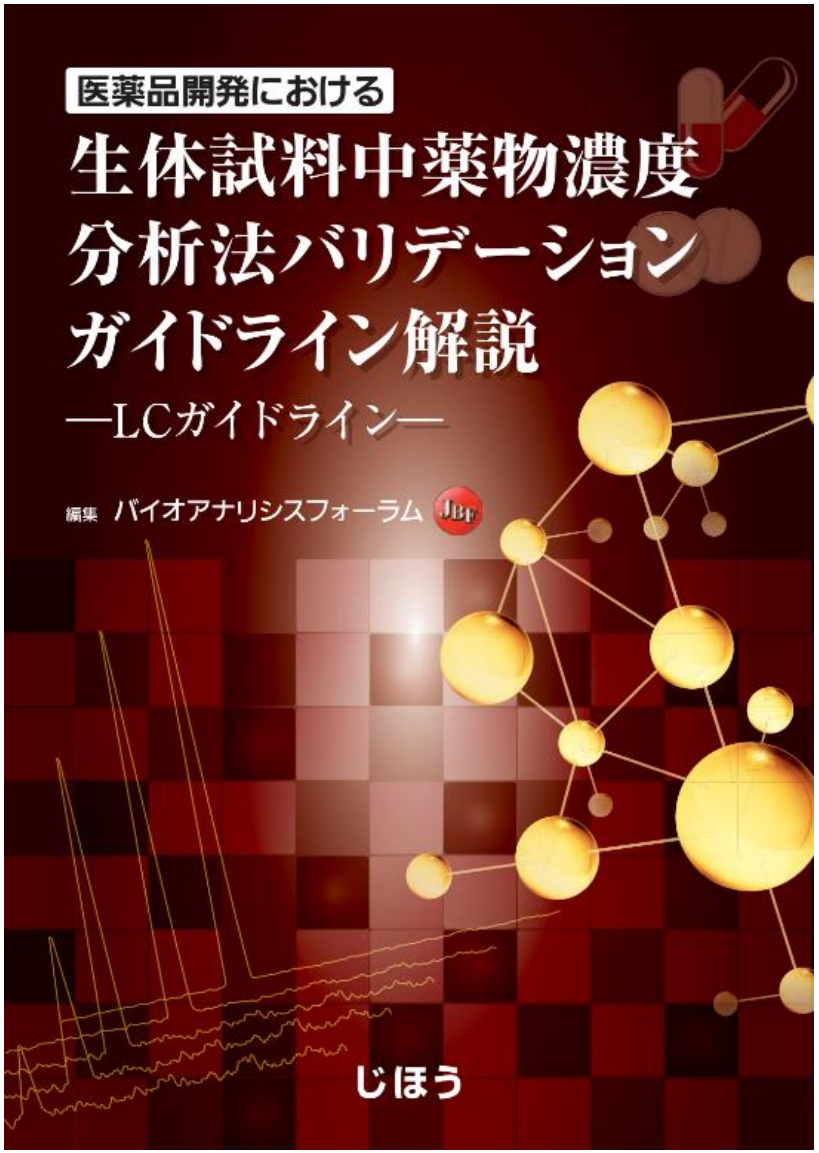
Bioanalysis

Editorial

Regulated bioanalysis in Japan: where do we come from and where are we going?

Noriko Katori
Project Team for Pharmacogenetics, National Institute of Health Sciences,1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158-8501, Japan. katori@nihs.go.jp

Published online: 6 June 2013.



目 次

https://www.jiho.co.jp/Portals/0/ec/product/ebooks/book/46922/46922.pdf

LBA team (2015)

Future Science Ltd
Bioanalysis
Volume 7, Issue 9, May 2015, Pages 1151-1156
https://doi.org/10.4155/bio.15.43

Bioanalysis

Regulatory

Japanese bioanalytical method validation guideline: the world's first regulatory guideline dedicated to ligand-binding assays

Mami Imazato-Hirano[1], Yoshitaka Taniguchi[2], Masaaki Kakehi[3], Yoji Kuze[3], Takahiro Nakamura[4], Yoshiyuki Minamide[5], Kazuhiro Miya[6], Jun Hosogi[7], Masataka Katashima[8,9], Kotaro Maekawa[9,10], Haruhiro Okuda[11], Shingo Niimi[11], Nana Kawasaki[11], Akiko Ishii-Watabe[11] & Noriko Katori[11]

ICH M10 Bioanalytical Method Validation

ICH
harmonisation for better health

Multidisciplinary Guidelines

Those are the cross-cutting topics which do not fit uniquely into one of the Quality, Safety and Efficacy categories. It includes the ICH medical terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI).

- M1 MedDRA Terminology
- M2 Electronic Standards
- M3 Nonclinical Safety Studies
- M4 Common Technical Document
- M5 Data Elements and Standards for Drug Dictionaries
- M6 Gene Therapy
- M7 Genotoxic Impurities
- M8 Electronic Common Technical Document (eCTD)
- M9 Biopharmaceutics Classification System-based Biowaivers
- **M10 Bioanalytical Method Validation**

M10 was one of the new topics firstly adopted in renovated ICH framework at the Lisbon meeting in June 2016, via topic suggestion by MHLW/PMDA.

(2015 ICH Renovation)

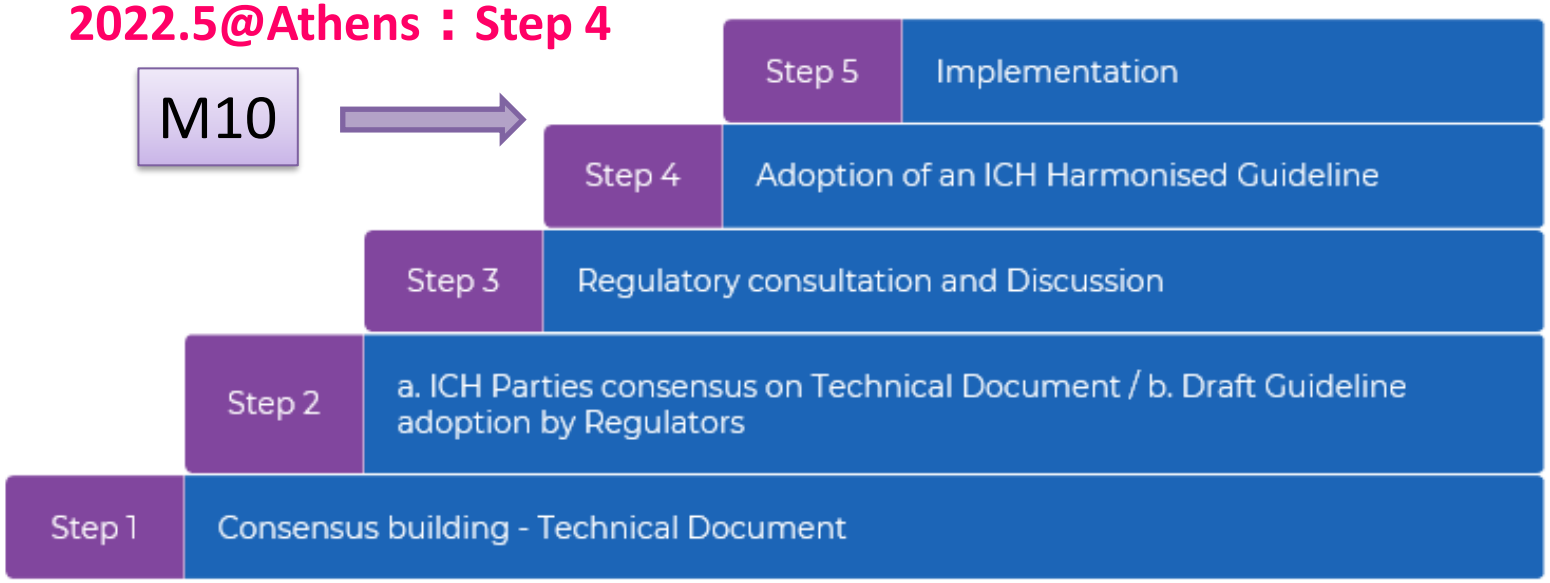
Harmonization steps of ICH guideline

Formal ICH Procedure

The Formal ICH Procedure is a step-wise procedure consisting of 5 steps (see below, click to have information on a particular step). This procedure is followed for the harmonisation of all new ICH topics.

2022.5@Athens：Step 4

M10



MHLW Notification

2019 Public consultation

2019.1 after Charlotte meeting

2016.11
1st F2F EWG meeting in Osaka

https://www.ich.org/page/formal-ich-procedure

M10 EWG members (Feb. 2023)

	Organisation	Name
Founding Regulatory Members	EC, Europe	Alfredo García-Arieta, Jan Welink
	FDA, US	Brian Booth (Regulatory Chair), Tsai-Lien Lin, Renmeet Grewal
	MHLW/PMDA, Japan	**Akiko Ishii-Watabe, Yoshiro Saito, Daisuke Iwata**
Standing Regulatory Members	Health Canada, Canada	Anna Edmison, Richard Siggers
	Swissmedic, Switzerland	Katharina Walter
Regulatory Members	ANVISA, Brazil	Dulcyane Neiva Mendes, Thais Correa Rocha
	MFDS, Republic of Korea	Choongyul Ahn
	NMPA, China	Chunmin Wei, Yuzhu Wang
	TFDA, Chinese Taipei	Chang Ya-Wen, Jia-Chuan Hsu
Founding Industry Members	EFPIA	Joanne Goodman, Philip Timmerman
	PhRMA	Enaksha Wickremsinhe
	JPMA	**Masayo Hashimoto, Masanari Mabuchi**
Industry Members	IGBA	Mohammed Bouhajib
	BIO	Faye Vazvaei
Observers	WHO	Luther Gwaza
	IFPMA	Marcio Silva
	PIC/S	Stephen Vinter

M10 Guideline, FAQs and Q&A

M10 EWG Bioanalytical Method Validation and Study Sample Analysis

This Guideline is intended to provide recommendations for the validation of bioanalytical methods for chemical and biological drug quantification and their application in the analysis of study samples. Adherence to the principles presented in this Guideline will ensure the quality and consistency of the bioanalytical data in support of the development and market approval of both chemical and biological drugs.

The objective of the validation of a bioanalytical method is to demonstrate that it is suitable for its intended purpose. Changes from the recommendations in this Guideline may be acceptable if appropriate scientific justification is provided. Applicants are encouraged to consult the regulatory authority(ies) regarding significant changes in method validation approaches when an alternate approach is proposed or taken.

Rapporteur: Dr. Akiko Ishii-Watabe (MHLW/PMDA, Japan)

Regulatory Chair: Dr. Brian Booth (FDA, United States)

Date of *Step 4*: 24 May 2022

Status: *Step 5*

Guideline
- M10 Guideline

Endorsed Documents
- M10 Concept Paper
- M10 Business Plan
- M10 Work Plan

WG Presentations / Trainings
- M10 Step 4 Presentation

Other documents
- M10 FAQs

WG list

Guideline

FAQ

A part of training materials

M10 Q&As Questions and Answers: Bioanalytical Method Validation and Study Sample Analysis

ICH M10 Q&As have been devised to provide clarity around some of the bioanalytical issues covered in the ICH M10 Guideline. The ICH M10 Q&As are intended to provide additional clarification and to promote convergence and improve harmonisation of the bioanalytical method validation and study sample analysis. The scope and organisation of this Q&A document follow that of ICH M10 Guideline.

Date of *Step 4*: 16 November 2022

Status: *Step 5*

Questions and Answers
- M10 Q&As

Q&A

https://www.ich.org/page/multidisciplinary-guidelines

Title of M10 guideline

(Step2: Public consultation)

Bioanalytical Method Validation

(Step4:Harmonised)

Bioanalytical Method Validation and Study Sample Analysis

To align with the contents of the guideline

Section 3	**Section 4**
Chromatography	Ligand binding assay
3.1 Reference standard	4.1 Key reagents
3.2 Validation	4.2 Validation
3.3 Study Sample Analysis	4.3 Study Sample Analysis

Table of contents of M10 guideline

Section 1: Scope

Category	Contents
Analyte	・Chemical and biological drugs (incl. Drugs that are also endogenous molecules) ・Metabolites
Matrix	・Biological samples (e.g., blood, plasma, serum, other body fluids or tissues)
Method	・LC or GC typically used combination with MS ・Ligand binding assay
Study	・ Nonclinical TK studies conducted according to the principles of GLP, and nonclinical PK studies conducted as surrogates for clinical studies ・ All phases of clinical trials including comparative BA/BE studies

Out of scope：Biomarker assay
Anti-drug antibody assay

M10 FAQ

Question

The guideline states that it is applicable to "nonclinical pharmacokinetic (PK) studies conducted as surrogates for clinical studies…" Please provide an example for such studies.

Answer

One example which includes nonclinical PK data to support human dosing is rescue agents for acute radiation syndromes or anthrax etc., under the Animal Rule (FDA, United States).

Section 3&4 Performance characteristics to be validated

Section	Chromatography	LBA
2.2.1 Full validation	Selectivity Specificity Matrix effect Calibration curve and Range Accuracy and Precision Carry over Dilution Integrity Stability Reinjection reproducibility	Specificity Selectivity - Calibration curve and Range Accuracy and Precision Carry over Dilution linearity and Hook effect Stability -
7. Additional considerations		7.2 Parallelism

Selectivity

Ability of an analytical method to differentiate and measure the analyte in the presence of interfering substances in the biological matrix (non-specific interference).

Chromatography	Ligand Binding Assay
➢ at least 6 individual sources/lots (non-haemolysed and non-lipaemic) ➢ Criteria： blank sample：not be more than 20% of the analyte response at the LLOQ, not more than 5% of the IS response in the LLOQ sample ➢ Lipaemic matrices ✓ at least 1 source ✓ matrix can be spiked with triglyceride ➢ Haemolysed matrices ✓ at least 1 source ✓ spiking matrix with haemolysed whole blood (at least 2% V/V)	➢ at least 10 individual sources/lots ➢ spiking the individual blank matrices at the LLOQ and at the high QC level ➢ Criteria： blank sample：below the LLOQ in at least 80% of the individual sources accuracy of spiked samples： within ±25% at the LLOQ within ±20% at the high QC level in at least 80% of the individual sources ➢ Lipaemic matricx ✓1 source ➢ Haemolysed matrix ✓1 source ➢ Patient matrices ✓at least 5 individual patients

Specificity

Ability of an analytical method to detect and differentiate the analyte from other substances, including its related substances (e.g., substances that are structurally similar to the analyte, metabolites, isomers, impurities or concomitant medications).

Chromatography	Ligand Binding Assay
➢ If the presence of related substances is anticipated ➢ Criteria： response of interfering compound： not more than 20% of analyte response at LLOQ, not more than 5% of IS response in the LLOQ sample ➢ Back-conversion of a metabolite to the parent analyte should be evaluated, when relevant.	➢ Spiking highest concentration of related molecules in blank sample, LLOQ and ULOQ ➢ Criteria： blank sample response：below LLOQ accuracy of LLOQ and ULOQ：within ±25%

M10 Q&A (Chromatography)

Question

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?

Answer

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.

M10 Q&A (LBA)

Question

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)?

Answer

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.

Matrix effect

The direct or indirect alteration or interference in response due to the presence of unintended analytes or other interfering substances in the sample.

Chromatography	LBA
➢At least 6 different sources/lots of matrix , analyse at least 3 replicates of LQC and HQC ➢Criteria：accuracy：within ±15%, precision：< 15% ➢Relevant patient population or special population (e.g. , hepatically impaired or renally impaired), when available ➢Haemolysed or lipaemic samples, on a case-by-case basis	—

Calibration Curve and Range

Calibration Curve: The relationship between the instrument response and the concentration of analyte in the sample within a given range.

Calibration Range: the interval between the upper and lower concentration of analyte in the sample

Chromatography	Ligand Binding Assay
➢ Calibration Curve： ・blank sample, zero sample , at least 6 concentration levels of calibration standard including LLOQ and ULOQ ・a minimum of 3 runs over several days ➢Criteria：back-calculations：within ±15% of nominal conc. (LLOQ, ULOQ：within ±20%) at least 75% of calibration standards with a minimum of 6 calibration standards	➢ Calibration Curve： ・blank sample, at least 6 concentration levels of calibration standard including LLOQ and ULOQ ・anchor point samples may be used to improve curve fitting ・a minimum of 6 runs over several days ➢ Criteria：back-calculations：within 20% of nominal value（LLOQ, ULOQ：±25%） at least 75% of calibration standards with a minimum of 6 calibration standards including LLOQ and ULOQ

Accuracy and Precision

Accuracy: The degree of closeness of the measured value to the nominal or known true value under prescribed conditions. Accuracy (%) = ((Measured Value-Nominal Value)/Nominal Value) × 100

Precision: The closeness of agreement among a series of measurements.
Precision (%) = (Standard Deviation / Mean) x 100

Chromatography	Ligand Binding Assay
➢ QC: LQC: within 3 times of LLOQ MQC: around 30-50% of CC range HQC: at least 75% of ULOQ	➢ QCs: LQC: within 3 times of LLOQ MQC: around geometric mean of CC range HQC: at least 75% of ULOQ
➢Within-run accuracy and precision：at least 5 replicates at each QC conc in each run	➢Within-run accuracy and precision：at least 3 replicates at each conc level (5 level)
➢Between-run accuracy and precision：at least 3 analytical runs over at least 2 days	➢Between-run accuracy and precision：at least 6 analytical runs over at least 2 days
➢ Criteria accuracy：within ±15% （LLOQ：within ±20%） precision (%CV)：not exceed 15% （LLOQ：not exceed 20%）	➢ Criteria： accuracy：within ±20% （LLOQ, ULOQ：±25%） precision：not exceed 20% （LLOQ, ULOQ：not exceed 25%） total error：not exceed 30% （LLOQ, ULOQ：40%）

Carry-over

The appearance of an analyte signal in a sample from a preceding sample.

Chromatography	Ligand Binding Assay
➢Analyse blank samples after the calibration standard at ULOQ ➢Criteria：blank sample following the ULOQ : not greater than 20% of the analyte at the LLOQ, 5% of the response of IS ➢Specific measures should be considered, tested during the validation and applied during the analysis of the study samples, so that carry-over does not affect accuracy and precision.	✓ Generally not required. ✓ Evaluate if the assay platform is prone to carry-over ➢Analyse blank samples after the calibration standard at ULOQ ➢ Criteria：blank sample: below the LLOQ

Dilution Integrity (Chromatography)
Dilution Linearity and Hook Effect (LBA)

Dilution Integrity: Assessment of the sample dilution procedure to confirm that the procedure does not impact the measured concentration of the analyte.

Dilution Linearity: A parameter demonstrating that the method can appropriately analyse samples at a concentration exceeding the ULOQ of the calibration curve without influence of hook effect or prozone effect and that the measured concentrations are not affected by dilution within the calibration range in LBAs.

Chromatography	Ligand Binding Assay
➢Dilution QC: greater than the ULOQ ➢At least 5 replicates per dilution factor ➢Criteria： accuracy ：within ±15% precision：not exceed 15%	➢Dilution QC: above the ULOQ Undiluted dilution QC (for Hook effect) and at least 3 levels of diluted dilution QC ➢At least 3 independently prepared dilution series, with number of replicate used in sample analysis ➢Criteria：accuracy ：within ±20% precision：not exceed 20% ➢If Hook effect is observed: Steps should be taken to mitigate this effect during the analysis of study samples.

Stability

Chromatography	Ligand Binding Assay
1) Stability of the Analyte in Matrix Freeze-thaw matrix stability Bench top (short-term) matrix stability Long-term matrix stability 2) Processed sample stability 3) Stock and working solutions stability (analyte and IS) 4) Whole blood stability (if applicable) ➢Criteria：within ±15% of nominal value ➢ For fixed dose combination products and specifically labelled drug regimens, stability tests of an analyte in matrix should be conducted with the matrix spiked with all of the dosed compounds.	1) Stability of the Analyte in Matrix Freeze-thaw matrix stability Bench top (short-term) matrix stability Long-term matrix stability ➢Criteria：within ±20% of nominal value ✓ Chemical drugs：extrapolate the stability to lower temperature ✓ Biological drugs：bracketing approach ➢ For fixed dose combination products and specifically labelled drug regimens, stability tests of an analyte in matrix should be conducted with the matrix spiked with all of the dosed compounds, on a case-by-case basis.

➢ The bulk sample should be divided into a minimum of 3 aliquots that will be stored, stressed and analysed.

Reinjection Reproducibility

Chromatography	Ligand Binding Assay
In the case of equipment failure ➢ Reinjecting a run that is comprised of calibration standards and a minimum of 5 replicates of the low, middle and high QCs after storage. ➢ precision and accuracy	—

Section 3&4 Study Sample Analysis

Chromatography	Ligand Binding Assay
➢Analytical run Blank sample, zero sample, at least 6 level of calibration standard, at least 3 levels of QCs (in duplicate or at least 5% of the study sample), study sample ➢Criteria <u>Calibration standard:</u> At least 75% of standard including 6 conc. level, within ±15% of nominal value (LLOQ within ±20%) <u>QCs:</u> At least 2/3 of the total QCs and at least 50% at each concentration level, within ±15% of the nominal values	➢Analytical run Blank sample, at least 6 level of calibration standard, at least 3 levels of QCs (2 sets or at least 5% of the study sample), study sample ➢Criteria <u>Calibration standard:</u> At least 75% of standard including 6 conc. level, within ±20% of nominal value (LLOQ, ULOQ within ±25%) <u>QCs:</u> At least 2/3 of the total QCs and at least 50% at each concentration level, within ±20% of the nominal values

- At least 2 QC levels should fall within the range of concentrations measured in study samples.
- In case of a narrow range of analyte concentrations of the study samples:
  - ✓ narrow the calibration curve range (partial validation)
  - ✓ adapt the concentrations of the QCs
  - ✓ add new QCs

M10 Q&A (Study sample analysis)

Question

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?

Answer

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.

Section 6 Partial validation

Examples for chromatography

- Analytical site change using same method (i.e., bioanalytical method transfers between laboratories)
- A change in analytical method (e.g., change in detection systems, platform)
- A change in sample processing procedures
- A change in sample volume (e.g., the smaller volume of paediatric samples)
- Changes to the calibration concentration range
- A change in anticoagulant (but not changes in the counter-ion) in biological fluids (e.g., heparin to ethylenediaminetetraacetic acid (EDTA))
- Change from one matrix within a species to another (e.g., switching from human plasma to serum or cerebrospinal fluid) or changes to the species within the matrix (e.g., switching from rat plasma to mouse plasma)
- A change in storage conditions

Cross Validation

Examples

- Data are obtained from different fully validated methods within a study.
- Data are obtained within a study from different laboratories with the same bioanalytical method.
- Data are obtained from different fully validated methods across studies that are going to be combined or compared to support special dosing regimens, or regulatory decisions regarding safety, efficacy and labelling.

➢ Cross validation should be assessed by measuring
✓the same set of QCs (low, medium and high) at least in triplicate **and**
✓study samples (if available) that span the study sample concentration range (n≥30)

➢ Bias can be assessed by Bland-Altman plots or Deming regression. Other methods appropriate for assessing agreement between two methods (e.g., concordance correlation coefficient) may be used too. Alternatively, the concentration *vs.* time curves for study samples could be plotted for samples analysed by each method to assess bias.

Section 7.1 Methods for Analytes that are also Endogenous Molecules

Approaches where matrices without interference are not available:

	Chromatography	LBA
Surrogate matrix approach	✓	✓
Surrogate analyte approach	✓ (stable isotope-labelled analyte is used as surrogate standard)	not applicable
Background subtraction approach	✓	✓
Standard addition approach	✓ (only applicable for linear response)	△

＊Example of each approach will be provided in M10 training slides

$$Accuracy\ (\%) = 100 \times \frac{(\text{Measured concentration of spiked sample} - \text{endogenous concentration})}{\text{Spiked concentration}}$$

$$= 100 \times \frac{\text{Measured concentation of spikec sample}}{(\text{Endogenous concentration} + \text{Spiked concentration})}$$

Section 7.6 New or Alternative Technologies

- When a new or alternative technology is used as the **sole** bioanalytical technology from the onset of drug development, cross validation with an existing technology is **not** required.

Section 7.6.1 Dried Matrix Methods (DMM)

Benefits of DMM

- ✓ Collection of reduced blood sample volumes as a microsampling
- ✓ Ease of collection, storage and transportation

Further validation required for DMM:

- Haematocrit (especially for spotting of whole blood into cards)
- Sample homogeneity (especially for sub-punch of the sample on the card/device)
- Extraction of the sample from the dried matrix

- DMM sample collection for ISR is required. (multiple punches)

Conclusion

- Basic principles of regulated bioanalysis were harmonised by M10.
- The implementation in details should be done by science- and risk-based considerations.

Future deliverables of M10 in FY2023

EWG
- ◆ Training slides

In Japan
- ◆ Step 5 document of guideline text (MHLW Notification in Japanese)
- ◆ Q&A (MHLW Office memorandum in Japanese)
- ◆ Answers to comments collected during public consultation in 2019

Future perspectives on regulated bioanalysis

- Critical issues for regulated bioanalysis beyond M10 for other new modalities analysed by new methodology would be:

  Well understanding of
  - ✓ Characteristics of the drug product
  - ✓ Pharmacokinetic profiles of the drugs in related to efficacy and safety
  - ✓ Bioanalytical methods

  ⇨ Reliable data satisfying the intended purpose

- Same principles may be applied for other analytes outside M10 (e.g., biomarker, anti-drug antibody).

Further contribution of bioanalytical community is required for new drug development.

謝辞

ICH M10 EWG

MHLW/PMDA副トピックリーダー	岩田大祐
JPMAトピックリーダー	橋本雅世
JPMA副トピックリーダー	間渕雅成

（敬称略）

ご清聴ありがとうございました