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Perspective on international harmonisation of bioanalytical method validation by the establishment of ICH M10

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Contents

1. Adoption of BMV topic M10 in ICH
    - Concept paper
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2. Outline of discussion in M10 EWG

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Current reginal Bioanalytical Method Validation guidelines/guidances

FDA Guidance for Industry: Bioanalytical Methods Validation (**2001**)
→ revision DRAFT (**2013**)
→ revision DRAFT2 (under internal consultation)

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**)

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

ICH M10 Bioanalytical Method Validation

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 is one of the new topics firstly adopted in renovated ICH framework at the Lisbon meeting in June 2016

Members of M10 Informal WG and EWG

	Informal WG	EWG@Osaka 2016	EWG@Montreal 2017	EWG@Geneva 2017
Regulatory Members	MHLW/PMDA (3) FDA (2) EC (1) Health Canada (2) Swiss Medic (2)	MHLW/PMDA (3) FDA (2) EC (1) Health Canada (2) Swiss Medic (2)	MHLW/PMDA (3) FDA (2) EC (1) Health Canada (2) Swiss Medic (2) ANVISA (2) MFDS (2)	MHLW/PMDA (3) FDA (2) EC (1) Health Canada (2) Swiss Medic (2) ANVISA (2) MFDS (2) CFDA (2)
Industry Members	JPMA (2) PhRMA (1) EFPIA (2)	JPMA (2) PhRMA (2) EFPIA (2) IGBA (2)	JPMA (2) PhRMA (2) EFPIA (2) IGBA (2) BIO (1)	JPMA (2) PhRMA (2) EFPIA (2) IGBA (2) BIO (1)
Observers	—	WHO (1)	WHO (1) TFDA (2)	WHO (1) TFDA (2) IFPMA (1)
Total	**8 Members (15 Experts)**	**10 Members (19 Experts)**	**14 Members (26 Experts)**	**16 Members (29 Experts)**

M10 EWG members

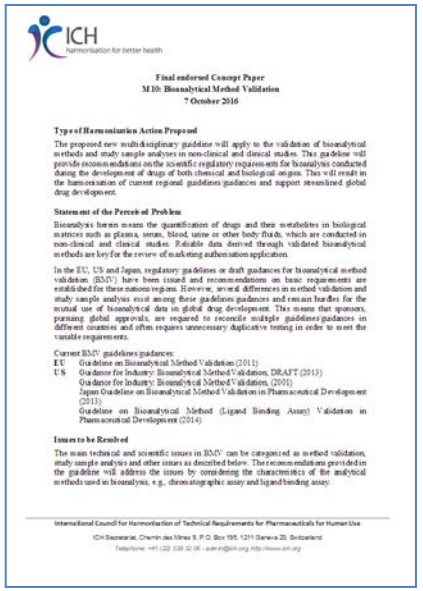
	Member	Name
Regulatory Members (8)	EMA	Alfredo García-Arieta
	FDA	Brian Booth, Tsai-Lien Lin, Renmeet Grewal
	MHLW/PMDA	Akiko Ishii-Watabe, Yoshiro Saito, Daisuke Iwata
	Health Canada	Anna Edmison, Richard Siggers
	Swissmedic	Katharina Walter, Hans Kemmler
	ANVISA	Dulcyane Neiva Mendes, Thais Correa Rocha
	MSDF	Kyungshin Lee, Seung Eun Choi
	CFDA	Chunmin Wei, Yuzhu Wang
Industry Members (6)	EFPIA	Joanne Goodman, Philip Timmerman
	PhRMA	Timothy Heath, Marianne Scheel Fjording
	JPMA	Seiji Tanaka, Masataka Katashima
	IGBA	Laura Coppola, Charles Donnelly
	BIO	Faye Vazvaei
	IFPMA	Ning Zhang
Observers (2)	WHO	Luther Gwaza, Stephanie Croft
	TFDA	Chang Ya-Wen, Wen-Yi Hung

http://www.ich.org/products/guidelines/multidisciplinary/article/multidisciplinary-guidelines.html

M10 timeline

2016. 6	Adoption of M10 as a new topic
2016. 7	Establishment of M10 Informal WG
2016. 10	Concept Paper, Business Plan : Endorsement by MC
2016. 10	Establishment of M10 Expert WG (EWG)
2016. 11	**1st face-to-face EWG meeting in Osaka, Japan**
	Draft technical document ver.0
2017. 3	1st Teleconference
2017. 4	2nd Teleconference
2017. 5	3rd Teleconference
2017. 5	**2nd face-to-face EWG meeting in Montreal, Canada**
	Draft technical document ver.1→2
2017.10	1st Teleconference
2017.10	2nd Teleconference
2017.11	**3rd face-to-face EWG meeting in Geneva, Switzerland**
	Draft technical document ver.2→3

ICH M10 Concept paper



ICH
harmonisation for better health

Final endorsed Concept Paper
M10: Bioanalytical Method Validation
7 October 2016

Type of Harmonisation Action Proposed

The proposed new multidisciplinary guideline will apply to the validation of bioanalytical methods and study sample analyses in non-clinical and clinical studies. This guideline will provide recommendations on the scientific regulatory requirements for bioanalysis conducted during the development of drugs of both chemical and biological origins. This will result in the harmonisation of current regional guidelines/guidances and support streamlined global drug development.

Statement of the Perceived Problem

Bioanalysis herein means the quantification of drugs and their metabolites in biological matrices such as plasma, serum, blood, urine or other body fluids, which are conducted in non-clinical and clinical studies. Reliable data derived through validated bioanalytical methods are key for the review of marketing authorisation applications.

In the EU, US and Japan, regulatory guidelines or draft guidances for bioanalytical method validation (BMV) have been issued and recommendations on basic requirements are established for these nations/regions. However, several differences in method validation and study sample analysis exist among these guidelines/guidances and remain hurdles for the mutual use of bioanalytical data in global drug development. This means that sponsors, pursuing global approvals, are required to reconcile multiple guidelines/guidances in different countries and often requires unnecessary duplicative testing in order to meet the variable requirements.

Current BMV guidelines/guidances:
EU Guideline on Bioanalytical Method Validation (2011)
US Guidance for Industry: Bioanalytical Method Validation, DRAFT (2013)
Guidance for Industry: Bioanalytical Method Validation, (2001)
Japan Guideline on Bioanalytical Method Validation in Pharmaceutical Development (2013)
Guideline on Bioanalytical Method (Ligand Binding Assay) Validation in Pharmaceutical Development (2014)

Issues to be Resolved

The main technical and scientific issues in BMV can be categorized as method validation, study sample analysis and other issues as described below. The recommendations provided in the guideline will address the issues by considering the characteristics of the analytical methods used in bioanalysis, e.g., chromatographic assay and ligand binding assay.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

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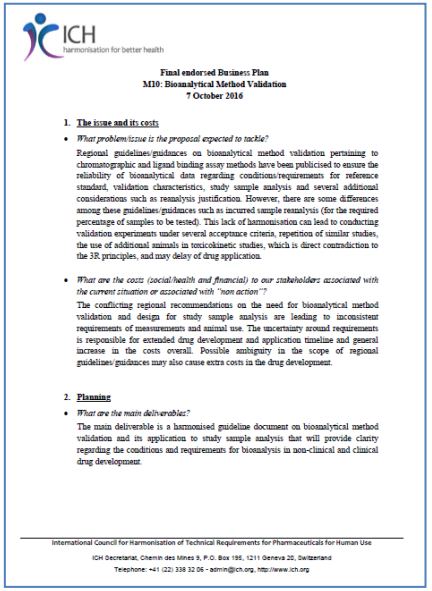
ICH M10 Business Plan



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1. **The issue and its costs**

- *What problem/issue is the proposal expected to tackle?*

Regional guidelines/guidances on bioanalytical method validation pertaining to chromatographic and ligand binding assay methods have been publicised to ensure the reliability of bioanalytical data regarding conditions/requirements for reference standard, validation characteristics, study sample analysis and several additional considerations such as reanalysis justification. However, there are some differences among these guidelines/guidances such as incurred sample reanalysis (for the required percentage of samples to be tested). This lack of harmonisation can lead to conducting validation experiments under several acceptance criteria, repetition of similar studies, the use of additional animals in toxicokinetic studies, which is direct contradiction to the 3R principles, and may delay of drug application.

- *What are the costs (social/health and financial) to our stakeholders associated with the current situation or associated with "non action"?*

The conflicting regional recommendations on the need for bioanalytical method validation and design for study sample analysis are leading to inconsistent requirements of measurements and animal use. The uncertainty around requirements is responsible for extended drug development and application timeline and general increase in the costs overall. Possible ambiguity in the scope of regional guidelines/guidances may also cause extra costs in the drug development.

2. **Planning**

- *What are the main deliverables?*

The main deliverable is a harmonised guideline document on bioanalytical method validation and its application to study sample analysis that will provide clarity regarding the conditions and requirements for bioanalysis in non-clinical and clinical drug development.

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The issue and its costs

There are some differences among regional guidelines/guidances such as incurred sample reanalysis (for the required percentage of samples to be tested).

This "lack of harmonisation" can lead to conducting validation experiments under several acceptance criteria, repetition of similar studies, the use of additional animals in toxicokinetic studies, which is direct contradiction to the 3R principles, and may delay of drug application.

The uncertainty around requirements is responsible for extended drug development and application timeline and general increase in the costs overall. Possible ambiguity in the scope of regional guidelines/ guidances may also cause extra costs in the drug development.

Discussion in Osaka (Nov. 2016)

Purpose

Gap Analysis on controversial issues in current regional guidelines/guidances and Scientific Discussion towards Harmonisation

Goal

Establish the outline of 1st draft of M10 guideline

M10's mission

To provide recommendations on Bioanalytical Method Validation and Study sample Analyses to obtain the reliable drug/metabolite concentration data in biological matrices, which will be used for regulatory submission.

MHLW/EMA/FDA BMV guidelines (Scope)

MHLW 2013&2014	EMA 2011	FDA draft 2013
Methods LC or GC with or without MS spectrometry, ligand-binding assay	Chromatographic methods, ligand-binding assay	LC or GC with or without MS spectrometry, ligand-binding assay, and immunological and microbiological procedures
Phases Clinical studies (Inc. BE studies) Non-clinical TK studies	Clinical studies (Inc. BE studies) Non-clinical TK studies	Clinical studies (Inc. BE studies) Non-clinical TK studies Non-clinical PK studies
Analytes Drugs, Metabolites (Inc. biologics with same amino acid sequence by LBA) (Exc. endogenous compounds)	Drugs, Metabolites	Drugs, Metabolites Endogenous compounds (Conceptual) Biomarkers (Conceptual)
Biological matrices Not specified (e.g., serum, plasma, urine)	Not specified (e.g., blood, serum, plasma, urine and saliva)	Not specified (e.g., blood, serum, plasma, urine, tissue, skin)

Diagnostic kit included

MHLW/EMA/FDA BMV guidelines (Chromatogr. section)

MHLW (Chromatogr.) 2013	EMA 2011	FDA draft 2013
4. Analytical Method Validation 4.1. Full validation 4.1.1. Selectivity 4.1.2. Lower limit of quantification 4.1.3. Calibration curve 4.1.4. Accuracy and precision 4.1.5. Matrix effect 4.1.6. Carry-over 4.1.7. Dilutional integrity 4.1.8. Stability 4.2. Partial validation 4.3. Cross validation **5. Analysis of Study Samples** 5.1. Calibration curve **5.2. QC samples** 5.3. ISR **5.4. Carry-over** **6. Points to Note** 6.1. Calibration range 6.2. Reanalysis 6.3. Chromatographic integration **6.4. System suitability** **6.5. Recovery**	**4. Analytical Method Validation** 4.1. **Full validation of an analytical methods** 4.1.1. Selectivity 4.1.2. Carry-over 4.1.3. Lower limit of quantification 4.1.4. Calibration curve 4.1.5. Accuracy 4.1.6. Precision 4.1.7. Dilutional integrity 4.1.8. Matrix effect 4.1.9. Stability 4.2. Partial validation 4.3. Cross validation **5. Analysis of Study Samples** 5.1. Analytical run 5.2. Acceptance criteria of an analytical run 5.3. Calibration range 5.4. Reanalysis of study samples 5.5. Integration **6. ISR**	**A. Reference standards** **B. Bioanalytical Method Development and Validation** 1. Selectivity 2. Accuracy, precision and recovery 3. Calibration curve 4. Sensitivity 5. Reproducibility 6. Stability **C. Validation Method: Use, Data Analysis, and Reporting**

MHLW/EMA/FDA BMV guidelines (LBA section)

MHLW (LBA) 2014	EMA 2011	FDA draft 2013
3. Reference Standard **4. Analytical Method Validation** 4.1. Full validation 4.1.1. **Specificity** 4.1.2. Selectivity 4.1.3. Calibration curve 4.1.4. Accuracy and precision 4.1.5. **Dilutional linearity** 4.1.6. Stability 4.2. Partial validation 4.3. Cross validation **5. Analysis of Study Samples** **5.1. Calibration curve** **5.2. QC samples** 5.3. ISR **6. Points to Note** 6.1. Calibration range 6.2. Reanalysis 6.3. **Carry-over** 6.4. **Cross-talk** 6.5. Critical reagents 6.6. **Interfering substances**	**7.1 Method Validation** 7.1.1 Full validation 7.1.1.1 Reference standards 7.1.1.2 **Specificity** 7.1.1.3 Selectivity 7.1.1.4 Carry-over effect 7.1.1.5 Matrix selection 7.1.1.6 **Minimum required dilution** 7.1.1.7 Calibration curve 7.1.1.8 Precision and accuracy 7.1.1.9 **Dilution linearity** 7.1.1.10 **Parallelism** 7.1.1.11 Stability of the sample 7.1.1.12 Reagents 7.1.1.13 Commercial kits **7.2 Partial Validation and Cross-validation** **7.3 Analysis of Study Samples** 7.3.1 Analytical run 7.3.2 Acceptance criteria 7.3.3 ISR	**A. Key reagents** **B. Bioanalytical Method Development and Validation** 1. **Selectivity** 2. Accuracy, precision and recovery 3. Calibration curve 4. Sensitivity 5. Reproducibility 6. Stability **C. Validation Method: Use, Data Analysis, and Reporting**

Future plan

✓ Discussion on the current technical document ver.3

2018. 6（Kobe） 4th face-to face meeting
↓ Internal consultation
↓ Revision of the technical document

2018.11（US） 5th face-to face meeting
↓ Step 1 Sign-off

Acknowledgements

M10 EWG

M10 AMED research group

MHLW

Thank you for your attention!