# Regulatory Reflections on the BMV Guideline/Guidance Harmonization

EBF - Focus Workshop: Industry input into ICH M10
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# Current regional Bioanalytical Method Validation guidelines/guidances

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

**Health Canada** 2012

**FDA**
Guidance for Industry Bioanalytical Methods Validation (2001)
→ revised DRAFT (2013)

**MFDS** 2013

**MHLW**
Guideline on Bioanalytical Method Validation
Chromatography(2013)
LBA (2014)

**ANVISA** (2003)
→ revised (2012)

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

# ICH M10 Bioanalytical Method Validation

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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 is the new topic adopted at ICH Lisbon meeting in June 2016**

# ICH M10 timeline

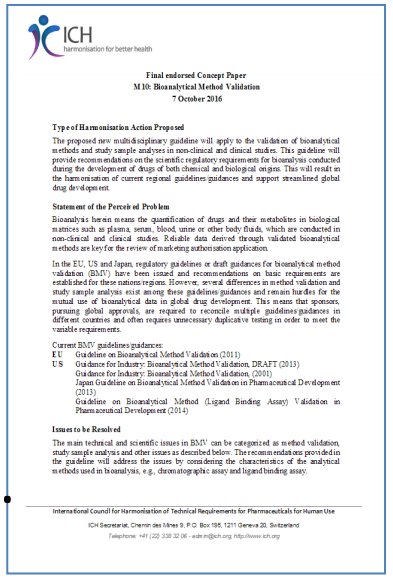
| | |
|---|---|
| 2016. 7 | Establishment of M10 Informal WG |
| 2016. 7~8 | Concept Paper, Business Plan : Discussion via e-mail in IWG |
| 2016. 8 | Concept Paper, Business Plan : Submission to MC |
| 2016. 10 | Concept Paper, Business Plan : Endorsement by MC |
| 2016. 10 | Establishment of M10 Expert WG (EWG) |

**2016. 11. 7～11. 10　1st face-to-face EWG meeting in Osaka, Japan**

| | |
|---|---|
| ～2017. 2 | Technical Document DRAFT preparation |
| 2017. 3~5 | 1st -3rd Teleconference |
| 2017. 5 | 1st Draft of the Technical Document |

**2017. 5. 29～6. 2　2nd face-to-face EWG meeting in Montreal, Canada**

# ICH M10 Concept paper



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**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 application.

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.

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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.

# ICH M10 Business Plan

## 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.

# GAP ANALYSIS ON DESCRIPTION AMONG

**MHLW GUIDELINES (2013, 2014)**
**EMA GUIDELINE (2011)**
**FDA DRAFT GUIDANCE (2013)**

# ICH Members (from Jun 2017)

- Reguratory (8)
  - ✓Japan (MHLW/PMDA), USA (FDA), EU (EC/EMA)
  - ✓Canada (Heaith Canada), Swiss (Swiss Medic)
  - ✓Brazil (ANVISA), Korea (MFDS), China (CFDA)
- Industry (6)
  - ✓Japan (JPMA), USA (PhRMA), Europe (EFPIA)
  - ✓Biologics (BIO ), Generic (IGBA), OTC (WSMI)

*orange: new members from 2017

# Comparison Items

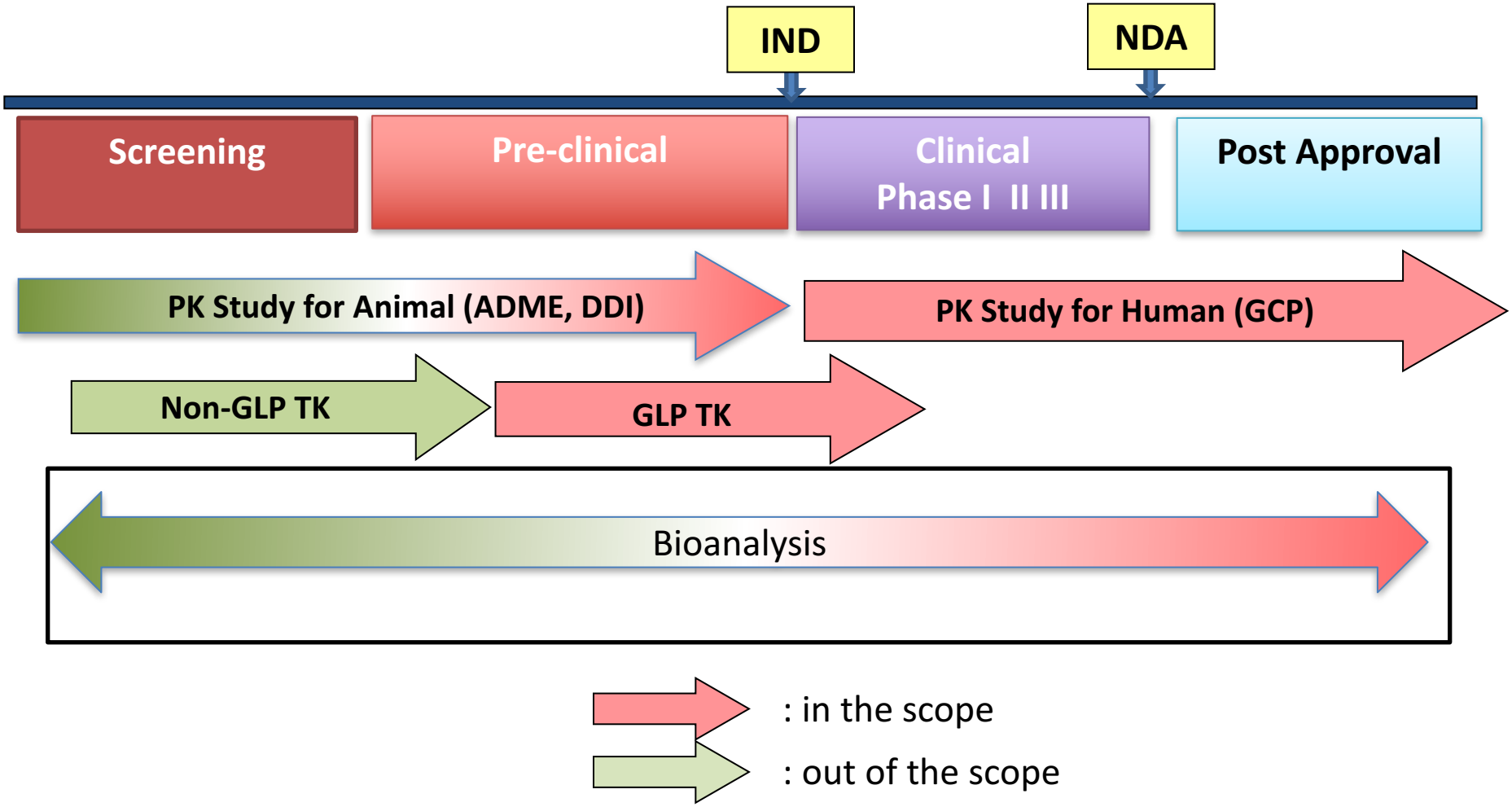
- Scope
- Full/Partial  Validation
- Cross Validation
- Stability
- Incurred sample reanalysis
- Selectivity
- Matrix Effect
- Specificity (LBA)
- Calibration curve, accuracy and precision (Chromatogr.))
- Calibration curve, accuracy and precision (LBA)
- Study sample analysis: Calibration curve (Chromatogr.)
- Study sample analysis: Calibration curve (LBA)
- Study sample analysis: QC sample (Chromatgr.)
- Study sample analysis:QC sample (LBA)
- Critical reagent (LBA)

# Scope

| | MHLW 2013&2014 | EMA 2011 | FDA draft 2013 |
|---|---|---|---|
| **Method** | LC or GC with or without MS<br>Ligand-binding assay | Chromatographic methods<br>Ligand-binding assay | LC or GC with or without MS<br>Ligand-binding assay,<br>**Immunological and microbiological procedures** |
| **Phase** | Clinical studies (Inc. BE studies)<br>Non-clinical TK studies | Clinical studies (Inc. BE studies)<br>Non-clinical TK studies | Clinical studies (Inc. BE studies)<br>Non-clinical TK studies<br>**Non-clinical PK studies** |
| **Analyte** | Drugs, Metabolites<br>(**Inc. biologics with same amino acid sequence by LBA**)<br>(Exc. endogenous compounds) | Drugs, Metabolites | Drugs, Metabolites<br>**Endogenous compounds (Conceptual)**<br>**Biomarkers (Conceptual)** |
| **Biological matrix** | 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**) |

# Regulatory Bioanalysis

## Development Stage and Bioanalysis



# Full and partial validation

| | MHLW 2013, 2014 | EMA 2011 | FDA draft 2013 |
|---|---|---|---|
| **Full** | Per facility<br>**Per species**<br>**Per matrix** | Per facility<br>**Per species**<br>**Per matrix** | Per facility |
| **Partial (Example, changes of)** | • Analytical method transfer<br>• Analytical instruments<br>• Calibration range<br>• Anticoagulant<br>• Analytical conditions<br>• Sample volume (Chromatogr.)<br>• Rare matrices<br>• Storage conditions<br>• **Concomitant drugs**<br>• **MRD (LBA)**<br>• **Critical reagent lot (LBA)** | • Analytical method transfer<br>• Equipment<br>• Calibration range<br>• Anticoagulant<br>• Sample processing procedure<br>• Limited sample volume<br>• Storage conditions<br>• **Another matrix or species** | • Analytical method transfer<br>• Instruments/software<br>• Analytical methodology<br>• Relevant concentration range<br>• Anticoagulant<br>• Sample processing procedure<br>• Limited sample volume<br>• Rare matrices<br>• **Selectivity in concomitant medication**<br>• **Species within matrix**<br>• **Matrix within species** |

# Cross validation

| | MHLW 2013, 2014 | EMA 2011 | FDA draft 2013 |
|---|---|---|---|
| **Do when** | 1) Data are generated in multiple laboratories within a study,<br>2) when comparing analytical methods used in different studies, after a full or partial validation. | 1) Data are obtained within a study from different laboratories, applying the same method.<br>2) Data are obtained from different methods within and across studies. | **change labo**<br>Two or more bioanalytical methods are used to generate data within the same study or across different studies. |
| **Assess-ment** | QC (low, midium, high)<br>: Mean accuracy within<br>±20% (chromatogr.)<br>±30% (LBA)<br>of nominal (≥3 repeats)<br><br>Study sample:<br>variability should be<br>±20% (chromatogr.)<br>±30% (LBA), 2/3 samples | QC :<br>within ±15% of nominal or may be wider<br><br>Study sample:<br>variability should be<br>±20% for at least 67% of the samples | Described in SOP (using QC and study samples) |

# Stability

| | MHLW 2013, 2014 | EMA 2011 | FDA draft 2013 |
|---|---|---|---|
| **Do by** | Similar conditions (e.g., for **solvent** or matrix type, container materials, storage condition) | Similar conditions (e.g., for sample matrix, **anticoagulant**, container materials, storage, **analytical condition**) | Similar conditions (e.g., for matrix, container system) |
| **Asess-ment** | ✓ stock and working solution (max. and min. conc.)<br><br>✓ In matrix (low and high QCs) by ≥ 3 replicates<br>• Freeze-thaw<br>• Short term<br>• Long term<br>• Processed samples (Chromatogr.)<br>within<br>±15% (Chromatogr.)<br>±20% (LBA)<br>of nominal | ✓ stock and working solution & IS (can be taken bracketing approach for conc. and temp.)<br><br>✓ In matrix (low and high QCs)<br>• Freeze-thaw<br>• Short term<br>• Long term<br>• Processed samples (Chromatogr.)<br>within<br>±15% (Chromatogr.)<br>±20% (LBA)<br>of nominal | ✓ stock solution<br><br>✓ In matrix (low and high QCs/calibrators (≥ 3 replicates)<br>• Freeze-thaw (≥ 3 cycles)<br>• Bench-top (Short term)<br>• Long term<br>• Processed samples (in autosampler)<br>within ±15% of nominal |

# Incurred sample reanalysis

| | MHLW 2013, 2014 | EMA 2011 | FDA draft 2013 |
|---|---|---|---|
| **Do for** | Representative studies with PK as primary end-point (TK, Phase I, etc.) for each matrix/species and BE studies. | Representative studies with PK as primary end-point (TK, BE, Phase I, etc.) for each matrix/species | All BE and pivotal PK or **PD**, studies and TK studies for each species and method |
| **Sample** | Approximately **10%** of the samples (total samples ≦ 1000)<br><br>Approximately **5%** of the samples (samples > 1000) | 10% of the samples (samples ≦ 1000)<br><br>5% of the samples (samples > 1000) | **7%** of the samples |
| **Criteria** | Assay variability should be within<br>±20% (chromatogr.)<br>±30% (LBA)<br>for at least 2/3 of the samples analyzed in ISR | Assay variability should be within<br>±20% (chromatogr.)<br>±30% (LBA)<br>for at least 67% of the samples analyzed in ISR | Assay variability should be within<br>±20% (small molecules)<br>±30% (large molecules)<br>for at least two-thirds (67%) of the samples analyzed in ISR |

# Selectivity

| | MHLW 2013, 2014 | EMA 2011 | FDA draft 2013 |
|---|---|---|---|
| Chro-matogr. | Evaluate using blank samples from ≥6 individuals.<br>No response or <20% of the response (in LLOQ for analyte) and <5% (of IS). | Evaluated using blank samples from ≥6 individuals.<br><20% of the response (in LLOQ for analyte) and <5% (of IS). | Evaluate using blank samples from ≥6 individuals.<br>Be ensured at LLOQ. |
| LBA | Evaluate using blank samples from 10 individual sources and near-LLOQ QC samples.<br>May consider to include lipemic, haemolysed or disease samples, if necessary.<br><br>Blank samples<br>≥80%: blow LLOQ.<br>Near LLOQ QC samples<br>Accuracy: ≥80% of samples<br>≤±20% of nominal.<br>(≤±25% at LLOQ) | Evaluate using spiked blank samples from 10 individuals (at or near-LLOQ). Include lipemic and haemolysed samples, and strongly recommend to include disease samples.<br><br>At or near LLOQ samples<br>Accuracy: ≥80% of samples<br>≤±20% of nominal.<br>(≤±25% at LLOQ) | Cross-reactivity of metabolites, concomitant medications, and their significant metabolites, or endogenous compounds should be evaluated.<br><br>Matrix effects should be evaluated, in cases for e.g.,<br>• Comparing calibration curve in biological fluids with calibrators in buffer using at least 10 sources of blank matrix.<br>• Evaluating parallelism using diluted study samples with diluted standards.<br>• Determining nonspecific binding. |

# Matrix effects

| | MHLW 2013, 2014 | EMA 2011 | FDA draft 2013 |
|---|---|---|---|
| **Chroma-togr.** | Investigated for mass spectrometry methods, using at least 6 lots of blank matrix from different sources.<br>Matrix factor (MF) should be calculated for each lot.<br>The precision of MF calculated from the 6 lots : ≤15 %.<br>Or can be evaluate QC samples. | Investigate for mass spectrometry methods, using at least 6 lots of blank matrix from individuals.<br>Matrix factor (MF) should be calculated for each lot.<br>The CV of the IS-normalised MF calculated from the 6 lots : ≤15 % by using a low and a high level of analyte.<br>Recommend to include other samples (e.g., haemolysed, hyperlipidaemic, special populations). | Appropriate steps should be taken to ensure the lack of matrix effects throughout the application of the method. Matrix effects on ion suppression or enhancement or on extraction efficiency should be addressed. |
| **LBA** | Not described. | Not described.<br>(Assess by parallelism) | Not described. |

# Specificity (LBA)

| | MHLW 2013, 2014 | EMA 2011 | FDA draft 2013 |
|---|---|---|---|
| **Assess-ment** | Evaluate using blank samples and blank samples spiked with the related substance.<br>QC samples with the analyte conc. near LLOQ and ULOQ should be evaluated after the spiking.<br><br>Blank or spiked blank samples:<br>blow LLOQ.<br>Spiked QC samples:<br>Accuracy:<br>≤±20% of nominal.<br>(≤±25% at LLOQ, ULOQ) | Evaluate using QC samples by spiking increased conc. of related molecules or drugs for concomitant use.<br><br>At both LLOQ and ULOQ.<br>Accuracy:<br>≤±25% of nominal. | Not described |

# Critical reagent (LBA)

| | MHLW 2014 | EMA 2011 | FDA draft 2013 |
|---|---|---|---|
| **Assess-ment** | Usually include binding reagents.<br><br>Partial validation is in principle required when their lot is changed.<br><br>*In Q&A*<br>Expiration date is not necessarily required, as long as the quality is ensured by evaluation of data from calibration standards and QC samples. | Include binding reagents and enzymatic moieties.<br><br>When changing their batches during validation or sample analysis, the analytical performance of the method must be verified.<br><br>Conditions guaranteeing the maintenance of the stability of both non critical reagents and critical reagents should be documented. | Include reference standards, antibodies, tracers, and matrices.<br><br>Assay reoptimization or validation may be important when changing key reagent(s).<br>e.g.<br>Labeled analytes (tracers)<br>• Reoptimize binding.<br>• Verify performance with standard curve and QCs.<br>Antibodies<br>• Check key cross-reactivities.<br>• Repeat tracer experiments.<br>Matrices<br>• Repeat tracer experiments. |

# Calibration curve, accuracy and precision (Chromatogr.)

| | MHLW 2013 | EMA 2011 | FDA draft 2013 |
|---|---|---|---|
| **Calibration curve** | **Back-calculated concentrations** : within **±15%** of nominal conc. (±20% at LLOQ)<br><br>At least **75%** of calibration standards and a minimum of **6** concentrations including LLOQ and max. conc. meet the criteria. | **Back-calculated concentrations** : within **±15%** of nominal conc. (±20% at LLOQ)<br><br>At least **75%** of calibration standards and a minimum of **6** concentrations meet the criteria. | **Back-calculated concentrations** : within **±15%** of nominal conc. (±20% at LLOQ )<br><br>At least **75%** of calibration standards and a minimum of **6** concentrations including LLOQ meet the criteria. Min. of 6 runs. |
| **Accuracy and precision**<br><br>**(QC samples)** | **At least 4 conc. of QCs, 5 replicates and 3 analytical run.**<br><br>**Accuracy** : within **±15%** (±20% at LLOQ )<br>**Precision** : not exceed **15%** (20% at LLOQ) | **At least 4 conc. of QCs, 5 replicates and 3 analytical run.**<br><br>**Accuracy** : within **±15%** (±20% at LLOQ )<br>**Precision** : not exceed **15%** (20% at LLOQ) | **At least 3 conc. of QCs, min. 5 determinations per conc. and different analytical run.**<br><br>**Accuracy** : within **±15%** (±20% at LLOQ )<br>**Precision** : not exceed **15%** (20% at LLOQ) |

# Calibration curve, accuracy and precision (LBA)

| | MHLW 2014 | EMA 2011 | FDA draft 2013 |
|---|---|---|---|
| **Calibration curve** | **Back-calculated concentrations** : within **±20%** of nominal conc. (±25% at LLOQ and ULOQ)<br><br>At least **75%** of calibration standards and a minimum of **6** concentrations including LLOQ and ULOQ meet the criteria. | **Back-calculated concentrations** : within **±20%** of nominal conc. (±25% at LLOQ and ULOQ)<br><br>At least **75%** of calibration standards and a minimum of **6** concentrations (evenly distributed) meet the criteria. | **Back-calculated concentrations** : within **±20%** of nominal conc. (±25% at LLOQ )<br><br>At least **75%** of calibration standards and a minimum of **6** concentrations including LLOQ meet the criteria. Min. of 6 runs. |
| **Accuracy and precision (QC samples)** | **At least 5 conc. of QCs, at least 6 analytical runs**<br><br>**Accuracy** : within **±20%** (±25% at LLOQ and ULOQ)<br><br>**Precision** : not exceed **20%** (25% at LLOQ and ULOQ) | **At least 5 conc. of QCs, at least 6 independent runs**<br><br>**Accuracy** : within **±20%** (±25% at LLOQ and ULOQ)<br><br>**Precision** : not exceed **20%** (25% at LLOQ and ULOQ) | **At least 3 conc. of QCs, Min. 5 determinations per conc. and different analytical run.**<br>**Accuracy** : within **±20%** (±25% at LLOQ )<br><br>**Precision** : not exceed **20%** (25% at LLOQ) |

# Study sample analysis: Calibration curve (Chromatogr.)

| | MHLW 2013, 2014 | EMA 2011 | FDA draft 2013 |
|---|---|---|---|
| **Accuracy of back calculation** | • Within **±15%** of nominal conc. **(±20% at LLOQ** ) | • Within **±15%** of nominal conc. (**±20% at LLOQ** ) | • Within **±15%** of nominal conc. **(±20% at LLOQ** ). |
| **Calibration curve** | • At least 75% of the calibration standards and a minimum of 6 con. meet criteria<br>• In case the calibration standard at LLOQ or the highest level did not meet the criteria in study sample analysis, the next lowest/highest-level calibration standard may be used as the LLOQ or the upper limit of the calibration curve. In this case, all QC samples (low, medium and high) meet the criteria. | • At least 75% of calibration standards and a minimum of 6 conc. meet the criteria.<br>• In case the calibration standard at LLOQ or the highest level did not meet the criteria in study sample analysis, the next lowest/highest-level calibration standard is acceptable as the LLOQ or the upper limit of the calibration curve. In this case, all QC samples (low, medium and high) meet the criteria. | • at least 75% of calibration standards and a minimum of 6 conc. including LLOQ meet the criteria. (In the section B: Bioanalytical Method Development and Validation.)<br>• Runs should be rejected if the calibration standards or QCs fall outside the acceptance criteria stated above (III.B.2). |

# Study sample analysis: Calibration curve (LBA)

| | MHLW 2013, 2014 | EMA 2011 | FDA draft 2013 |
|---|---|---|---|
| **Accuracy of back calculation** | • within ±20% of nominal conc. (±25% at LLOQ and ULOQ) | • within ±20% of nominal conc. (±25% at LLOQ and ULOQ) | • within ±20% of nominal conc. (±25% at LLOQ ) . |
| **Calibration curve** | • At least 75% of the calibration standards and a minimum of 6 con. meet criteria<br>• In case the calibration standard at LLOQ or ULOQ did not meet the criteria in study sample analysis, the next lowest/highest-level calibration standard may be used as the LLOQ or the upper limit of the calibration curve. If modified, all QC samples (low, medium and high) meet the criteria. | • At least 75% of calibration standards and a minimum of 6 conc. meet the criteria. | • Runs should be rejected if the calibration standards or QCs fall outside the acceptance criteria stated above.<br>• at least 75% of calibration standards and a minimum of 6 conc. meet the criteria. |

# Study sample analysis: QC sample (Chromatgr.)

| | MHLW 2013, 2014 | EMA 2011 | FDA draft 2013 |
|---|---|---|---|
| **Number and location** | • At least 3 **conc. of QCs** (low-, mid-, and high) within the calibration range **in duplicate** (or **at least 5 % of the number of study samples, whichever is higher**).<br>• QC samples should be placed before and after study sample analysis. | • At least 3 **conc. of QCs** (low-, mid-, and high) within the calibration range **in duplicate** (or **at least 5 % of the number of study samples, whichever is higher**). | • **Minimum number of QCs** to ensure proper control of the assay should be **at least 5% of the number of unknown samples or a total of six QCs, whichever is greater.**<br>• QCs should be interspersed with study samples during processing and analysis. |
| **Conc.** | • **The low-level is within 3 times the LLOQ, the mid-level is in the midrange of the calibration curve, and the high-level needs to be at least 75% of the upper limit of the calibration curve.** | • Not described. | • Not described. |

# Study sample analysis: QC sample (Chromatgr.)

| | MHLW 2013, 2014 | EMA 2011 | FDA draft 2013 |
|---|---|---|---|
| **Criteria** | • At least **2/3 of QC samples** and **50% at each concentration level** should be **within 15%** of the nominal value. | • At least **67% QC samples** and **50% at each concentration level** should be **within 15%** of the nominal value.<br>• The overall accuracy and precision of QCs of all accepted runs should be calculated. In case the overall accuracy and precision exceed 15%, should be justified. In the case of BE trials it may result in the rejection of the data. | • At least **67% QC samples** and **50% at each concentration level** should be **within 15%** of the nominal value (Described as "Runs should be rejected if the calibration standards or QCs fall outside the acceptance criteria stated above. ")<br>• Accuracy and precision should be provided for both inter- and intra-run and tabulated for all runs (passed and failed) |

# Study sample analysis:QC sample (LBA)

| | MHLW 2013, 2014 | EMA 2011 | FDA draft 2013 |
|---|---|---|---|
| **Number and location** | • At least 3 conc. **of QCs** (low-, mid-, and high) within the calibration range **in duplicate** (or **at least 5 % of the number of study samples, whichever is higher**). | • At least 3 conc. of QCs (low-, mid-, and high) within the calibration range **in duplicate**. | • QCs should be interspersed with study samples during processing and analysis.<br>• The **minimum number of QCs** to ensure proper control of the assay should be **at least 5% of the number of unknown samples or a total of six QCs, whichever is greater.** |
| **Conc.** | • **The** low-level is within 3 times the LLOQ, the mid-level is in the midrange of the calibration curve, and the high-level needs to be at least one-third of the ULOQ of the calibration curve. | • Not described. | • Not described. |

# Study sample analysis:QC sample (LBA)

| | MHLW 2013, 2014 | EMA 2011 | FDA draft 2013 |
|---|---|---|---|
| **Criteria** | • At least **2/3QC samples** and **50% at each concentration level** should be **within 20%** of the nominal value. | • At least **67% QC samples** and **50% at each concentration level** should be **within 20%** of the nominal value**.** Exceptions to this criterion should be justified. | • At least **67% QC samples** and **50% at each concentration level** should be **within 20%** of the nominal value (Described as "Runs should be rejected if the calibration standards or QCs fall outside the acceptance criteria stated above.")<br><br>• Accuracy and precision should be provided for both the inter-run and intra-run experiments and tabulated for all runs (passed and failed). |

# M10 potential future plan

| | | |
|---|---|---|
| 2017. 11 | 3rd EWG meeting in Geneva | |
| 2018. 6 | 4th EWG meeting in Kobe | |
| | **Step 1** Consensus within EWG members | |
| | **Step 2a/b** Endorsement of Technical Document by Assembly | |
| 2018. 7~ | **Step 3** Public consultation in each country/region | |
| 2018. 11 | 5th EWG meeting | Revision of draft guideline |
| 2019. 6 | 6th EWG meeting | |
| | **Step 4** Adoption as an ICH harmonised guideline | |
| 2019.7~ | **Step 5** Implementation at each region | |

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- Biomarker TF members
- Large Molecule MS TF members

# QUESTION?