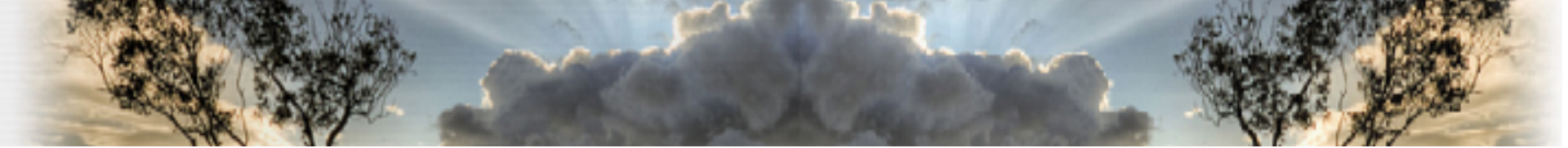
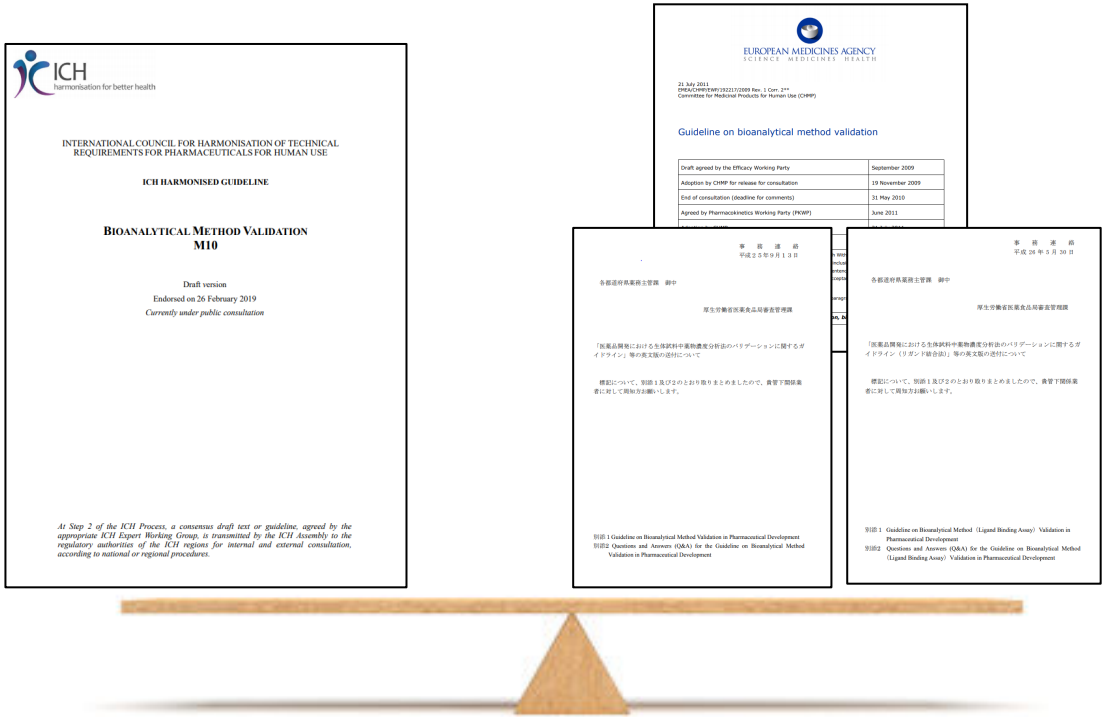


ICH M10 Draft Guideline: comparison with EMA and MHLW Guidelines

Joanne Goodman, on behalf of the EBF

Does the new draft guideline create alignment?



Does the new draft guideline create alignment?

ICH's mission is to achieve greater harmonisation worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner

(source: www.ich.org)

To prevent overload ……

- Focus on the major topics for comparison of these guidelines
  - Topics will be spoken about in depth throughout the meeting
  - Some positive changes and clarifications
  - However, there are those that will bring challenges in our everyday activities for reasons of:
    - Resource
    - Cost
    - Time
- Further comparisons are included in the back up slides for future reference (but not exhaustive)

Introduction and Scope

EMA	MHLW	ICH M10 Differences
Drug concentrations in biological matrices (such as serum, plasma, blood, urine, and saliva) Support regulatory applications Animal TK studies clinical trials Bioequivalence studies Well characterised, fully validated and documented Acceptance criteria wider than those defined in this guideline may be used in special situations, based on the intended use of the method	Concentrations of drugs and their metabolites in biological samples Clinical and animal TK studies Drug concentrations used for the assessment of characteristics such as in vivo pharmacokinetics, bioavailability, bioequivalence, DDI Well characterised Study results supporting applications for drug marketing authorization Flexible adjustment can be applied in case of using the specific type analytical method or depending on the intended use	**Pivotal** nonclinical TK/PK studies and all phases of clinical trials Full method validation is expected for the primary matrix**(ces)** intended to support regulatory submissions. Additional matrices should be partially validated as necessary. Analytes that should be measured in nonclinical and clinical studies and the types of studies necessary to support a regulatory submission are described in other ICH and regional regulatory documents Studies that are subject to GLP or GCP, the bioanalysis of study samples should also conform to their requirements

Method Development

EMA	MHLW	ICH M10 Differences
No specific section but small references throughout	In an LBA full validation, the minimum required dilution (MRD) should be defined *a priori* (i.e., in the course of method development) to dilute samples with buffer solution LBA: If presence of related substances is anticipated in biological samples of interest, the extent of the impact of such substances should be evaluated. Specificity may be evaluated in the course of method development Q&A: Q7. & A7. In an LBA, specificity is dependent on the reactivity of the binding reagent. Therefore, if the characteristics of the binding reagent are well known from its development phase, it may not be necessary to repeat the specificity test in validation	Dedicated section for method development States examples of method development activities Does not require extensive record keeping or notation. However, the applicant should record the changes to procedures as well as any issues and their resolutions to provide a rationale for any changes made to validated methods immediately prior to or in the course of analysing study samples for pivotal studies.

Full Validation

EMA	MHLW	ICH M10 Differences
Any analytical method (new/literature) in matrices such as blood, serum, plasma, urine, saliva Same anticoagulant as study samples Each species and matrix concerned but an alternative matrix may be used if justified Validation parameters listed One analyte/drug and multiple analyte methods; two different drugs, parent drug with its metabolites, or the enantiomers or isomers of a drug. In these cases the principles of validation and analysis apply to all analytes of interest.	New/literature methods for one or more analytes usually in plasma, serum, whole blood or urine Close as possible to sample matrix including anticoagulants although justification of surrogate matrices, if justified Validation parameters listed For LBA: the minimum required dilution (MRD) should be defined a priori (i.e., in the course of method development) to dilute samples with buffer solution Plate-based LBA 2 wells per sample	Should be performed when establishing a bioanalytical method for the quantification of an analyte in clinical and in **pivotal** nonclinical studies When a commercial kit is repurposed for bioanalytical use in drug development For LBA: parallelism (if necessary and if so conducted during sample analysis) and singlet analysis if sample testing is conducted in singlet Must be the same matrix

Cross Validation

EMA	MHLW	ICH M10 Differences
Within and across studies Data within a study from different laboratories, applying the same method Differences in sample preparation or the use of another analytical method may result in different outcomes Performed in advance of study samples being analysed if possible Same set of QC samples or study samples should be analysed by both analytical methods. For QC samples, obtained mean accuracy by the different methods within 15% (may be wider, if justified). For study samples, the difference within 20% of mean for at least 67% of the repeats.	Within and across studies Same set of QC samples or same set of study samples analysed at both labs or by both methods, mean accuracy at each concentration or the assay variability Two or more labs within a study: mean accuracy of QC samples, at least 3 replicates at each level, within ±20% (Chrom), ±30% (LBA) theoretical concentration, considering intra- and inter-laboratories precision. Study samples: assay variability within ±20% (Chrom), ±30% (LBA) for at least two-thirds of the samples Cross validation between different methods (different assay principles), both validation procedure and criteria should be separately defined based on scientific judgment according to the type of the analytical methods	Across studies "for regulatory decisions regarding safety, efficacy and labelling" Not generally required to compare data obtained across studies from different laboratories using the same validated method at each site Both QCs **and** study samples that span the study sample concentration range (if available n≥30) **Bland-Altman plots or Deming regression (bias). Or concentration vs. time curves for incurred samples plotted for samples analysed by each method. If disproportionate bias is observed between methods, the impact on the clinical data interpretation should be assessed. The use of multiple bioanalytical methods in the conduct of one comparative BA/BE study is strongly discouraged.**

Matrix Effect/Matrix Factor: Chromatography

EMA	MHLW	ICH M10 Differences
At least 6 lots of blank matrix (individual donors), less may be justified. Includes formulation components (unless excipients are not metabolised) Haemolysed, lipaemic, special populations Matrix factor (MF) - ratio of peak area with matrix to the peak area minus matrix. IS normalised MF calculated by dividing the MF of the analyte by the MF of the IS. The CV of the IS-normalised MF calculated from the 6 lots of matrix should not be greater than 15%. Low and high (max 3x LLOQ and close to the ULOQ). Or, variability of the response from lot to lot using at least 6 lots of matrix, spiked at a low and high concentrations. Data included in validation report. Overall CV for the concentration = not greater than 15%.	Matrix effect is evaluated by calculating the matrix factor (MF) by comparing the analyte response in the presence of matrix with that in the absence of matrix. MF should be calculated using matrix from at least 6 different sources. The MF may be normalized by its internal standard. The precision of the MF calculated should not exceed 15%. Matrix effect can also be evaluated by analysing QC samples, each prepared using matrix from at least 6 different sources. The precision of determined concentrations should not be greater than 15%. It may be acceptable to use matrix obtained from less than 6 sources in the case that matrix is limited.	Removal of Matrix Factor At least 3 replicates of low and high QCs, each prepared using matrix from at least 6 different sources/lots. Fewer may be acceptable in rare cases. Accuracy within ±15% of the nominal concentration Haemolysed or lipaemic matrix samples during method validation on a case by case basis

Selectivity: Chromatography and LBA

EMA	MHLW	ICH M10 Differences
At least 6 individual sources (Chrom), 10 for LBA. Use of fewer sources is acceptable in case of rare matrices. Chrom: Response is <20% of the LLOQ for the analyte and 5% for the internal standard LBA: Within 20% (25% at the LLOQ) of the nominal spiked concentration in at least 80% of the matrices evaluated Interference caused by metabolites of the drug(s), from degradation products formed during sample preparation, and from possible co-administered medications Possibility of back-conversion of a metabolite into parent be evaluated, when relevant. The and the impact on the study results discussed.	At least 6 individual sources (chrom), 10 (LBA) and may be acceptable to use less in cases of limited matrix Chrom: The absence of interference with each analyte and its internal standard should be confirmed Chrom: No response attributable to interfering components in the blank samples or that a response attributable to interfering components is not higher than 20% of the response in the LLOQ for the analyte and also not higher than 5% of the internal standard. LBA: Within 20% (25% at the LLOQ) of the nominal spiked concentration in at least 80% of the matrices evaluated	Blank samples obtained from at least **10** individual sources (chrom) and by spiking the individual blank matrices at the LLOQ **and at the high QC level** (chrom and LBA) Response of the blank samples should be below the LLOQ in at least 80% of the individual sources. Accuracy should be within ±25% at the LLOQ and within ±20% at the high QC level of the nominal concentration in at least 80% of the individual sources evaluated. Selectivity in lipaemic samples and haemolysed samples evaluated once using a single source of matrix. Selectivity should be assessed in samples from relevant patient populations (five individual patients).

Specificity: Chromatography

EMA	MHLW	ICH M10 Differences
No section for chromatography	No section for chromatography	In the case of LC-MS based methods, the evaluation may include comparing the molecular weight of a potential interfering related substance with the analyte and chromatographic separation of the related substance from the analyte Should not be more than 20% of the analyte response at the LLOQ and not more than 5% of the IS response in the LLOQ sample The possibility of back-conversion is defined in this section using similar language to selectivity text from EMA

Specificity: LBA

EMA	MHLW	ICH M10 Differences
May be conducted after the original validation is completed as more data on the behaviour of the analyte become available QC samples adding increasing concentrations of available “related molecules” or drugs expected to be concomitantly administered, into drug-naive sample matrix (matrix obtained from animals or subjects never exposed to the analyte) and measuring the accuracy of the macromolecule of interest at both LLOQ and ULOQ Acceptance criteria of the QC samples should be within 25% of the nominal values	May be evaluated in the course of method development. Additional specificity testing may have to be conducted after a method validation is completed. Blank samples and blank samples spiked with the related substance at concentration(s) anticipated in study samples; in addition, QC samples with the analyte concentrations near the lower limit of quantification (LLOQ) and near the upper limit of the quantification (ULOQ) of calibration curve should be evaluated after spiking with the related substance at anticipated concentration(s). Blank sample +/- related substance should be below the LLOQ; accuracy of QC samples +/- related substance within ±20% of the theoretical concentration (or ±25% of the at the LLOQ and ULOQ)	In the event of non-specificity, impact on the method should be evaluated by spiking increasing concentrations of interfering molecules in blank matrix and measuring the accuracy of the target analyte at the LLOQ and ULOQ Essential to determine the minimum concentration of the related molecule where interference occurs. Appropriate mitigation during sample analysis should be employed, e.g., it may be necessary to adjust the LLOQ/ULOQ accordingly or consider a new method.

Accuracy and Precision: Chrom & LBA

EMA	MHLW	ICH M10 Differences
Within-run: single run, 5 samples/level (min 4 levels covering curve range: LLOQ, within 3x LLOQ (low QC), around 30 - 50% of the calibration curve range (MQC), and at least at 75% of the upper calibration curve range (high QC)). Within 15% for the QC samples (LLOQ within 20%). Between-run: LLOQ, low, medium and high QC samples from at least three runs analysed on at least two different days should be evaluated. Within 15% for the QC samples, (LLOQ) 20%. LBA: 6 runs, multiple days, 5 QC samples (anticipated LLOQ, less than 3 times the LLOQ, mid, high and anticipated ULOQ) should be used to assess accuracy, precision (20%, 25% LLOQ and ULOQ and the total error of the method (30%, 40% at LLOQ and ULOQ). **Frozen QCs.**	Chrom: Minimum of 4 levels (LLOQ and low, mid, and high levels) within the calibration range. The low-level should be within 3 times the LLOQ, **the mid level is around the midpoint on the calibration curve,** and the high-level should be at least 75% of the upper limit of the calibration curve. Within-run: at least 5 replicates at each concentration in a single analytical run Between-run: 3 analytical runs. Within 15% except at the LLOQ, where it should be within 20%. LBA: 6 runs, 5 QC samples (LLOQ, 3x the LLOQ, mid point of curve, high and anticipated ULOQ) should be used to assess accuracy, precision (20%, 25% LLOQ and ULOQ and the total error of the method (30%, 40% at LLOQ and ULOQ).	**Geomean for MQC placement is allowed for LBA but not chromatography** Chrom: within-run is at least 5 replicates at each QC concentration level **in each analytical run**. Between-run accuracy and precision using each QC concentration level in at least 3 analytical runs over at least two days. **Fresh calibrators in at least 1 run**. LBA: The analyte should be spiked at the LLOQ, within 3x LLOQ (low QC), around the geometric mean of the calibration curve range (medium QC), and at least at 75% of the ULOQ (high QC) and at the ULOQ. 3 replicates per run at each QC concentration (LLOQ, low, medium, high, ULOQ) in at least 6 runs over 2 or more days.

Calibration Curve and Range: LBA

EMA	MHLW	ICH M10 Differences
Range not mentioned in LBA section (specifically in the chromatography section) Surrogate matrices are allowed for the calibration curve	In case the calibration range is changed, partial validation should be performed. However, it is not necessary to reanalyse the study samples that have been quantified prior to the change in the calibration range. The use of a surrogate matrix should be justified as much as possible in the course of establishing the analytical method	**Matrix must be identical** **This language for curve range is new for LBA:** Unanticipated clustering at one end of the calibration curve, analysis stopped and either the calibration range narrowed (i.e., partial validation), existing QC concentrations revised, or QCs at additional concentrations added to the original curve before continuing with study sample analysis. 2 QC samples must fall in the range of samples.

Dilution Linearity and Hook Effect: LBA

EMA	MHLW	ICH M10 Differences
The back-calculated concentration for each dilution should be within 20% of the nominal concentration after correction for dilution and the precision of the final concentrations across all the dilutions should not exceed 20%. No mention of multiple assessments	QC sample exceeding the ULOQ of a calibration curve and its serial dilutions at multiple concentrations. The absence or presence of response reduction (hook effect or prozone) is checked in the analysed samples, and if discovered, measures should be taken to eliminate response reduction in study sample analysis. Accuracy and precision in the measurements corrected for the dilution factor should be within ±20% deviation of the theoretical concentration and not more than 20%, respectively. No mention of multiple assessments	Dilution linearity should be demonstrated by generating a dilution QC analysed undiluted (for hook effect) and diluting this sample (to at least 3 different dilution factors) with blank matrix to a concentration within the calibration range. **For each dilution factor tested, at least 3 runs should be performed using the number of replicates that will be used in sample analysis.**

Stability: Chromatography and LBA

EMA	MHLW	ICH M10 Differences
Low and high QC samples (blank matrix spiked with analyte at a concentration of a maximum of 3 times the LLOQ and close to the ULOQ) which are analysed immediately after preparation and after the applied storage conditions that are to be evaluated For small molecules it is considered acceptable to apply a bracketing approach, i.e. in case stability has been proved for instance at -70°C and -20°C, it is not necessary to investigate the stability at temperatures in between. For large molecules (such as peptides and proteins) stability should be studied at each temperature at which study samples will be stored.	Chromatography: Stability is evaluated by at least 3 replicates per concentration level (high and low) with QC samples before and after storage. Mean accuracy in the measurements at each level should be within ±15%. LBA: Low and high QC samples prepared using a matrix that is as close as possible to the actual study samples. At least 3 replicates per QC concentration level before and after stability storage. Mean accuracy in the measurements at each level should be within ±20%. Other criteria could be used if they are deemed scientifically more appropriate for the evaluation of a specific analyte.	Minimum of **3** stability QCs should be prepared and analysed **per concentration level/storage condition/timepoint** Includes EMA language for temperature ranges (difference from MHLW) Multiple analytes with a fixed combination, or due to a specific drug regimen If samples are consistently above the curve range, the concentration of the stability QCs should be adjusted (considering the applied sample dilution for LBA), to represent the actual sample concentration range. Stock and working solutions can only be prepared from reference standards that are within the stability period as documented in the CoA (either expiration date or the retest date in early development phase).

ISR

EMA	MHLW	ICH M10 Differences
10% where number of samples is less than 1000 and 5% of the number of samples exceeding 1000 samples. Cmax and in the elimination phase. 20% (Chrom) or 30% (LBA) difference in results for at least 67% of the repeats. Tox once per species, all pivotal bioequivalence trials, first clinical trial in subjects, first patient trial, first trial in patients with impaired hepatic and/or renal function Animal studies: may be done only in early Phase studies, if these are representative for pivotal studies in terms of dose administered and concentrations obtained.	Approx 10% of the samples reanalysed in cases where the total number of study samples is less than 1000 and approximately 5% of the number of samples exceeding 1000. Cmax and elimination phase. Within 20% (Chrom) or 30% (LBA) for 2/3 of samples. Tox studies for each different species, representative clinical pharmacokinetic studies in healthy volunteers and patients with renal/hepatic impairment, as well as bioequivalence studies For non-clinical studies, ISR may be performed with samples obtained in a independent non-GLP study, if the study design is similar to the relevant toxicokinetic study in terms of sampling condition	For preclinical studies, ISR should, in general, be performed for the main nonclinical TK studies once per species. However, ISR in a PK study instead of a TK study might also be acceptable, as long as the respective study has been conducted as a pivotal study, **used to make regulatory decisions**. All pivotal comparative BA/BE studies, first clinical trial in subjects, **pivotal early patient trial(s)**, once per patient population, first or pivotal trial in patients with impaired hepatic and/or renal function Examples of when ISR fails and investigation

Conclusions

- In some cases, the draft ICH M10 draft guideline allows for added flexibility and some areas have been clarified
- However, ICH M10 brings with it increased requirements compared to existing EMA and MHLW guidance documents
  - More than just harmonisation
  - Will result in increased time, resources and cost and potentially not aligned with the mission of ICH
  - Preclinical requirements should be less
- Further clarification of some aspects of the guideline are needed to allow the correct interpretation across industry and regulatory agencies within the ICH regions
- Some elements may be handled through additional training as part of the ICH process

Acknowledgements

- EBF community
- EBF steering committee


thank you
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rahmat

BACK UP SLIDES

Partial Validation

EMA	MHLW	ICH M10 Differences
Minor changes to a fully validated method Transfer of the bioanalytical method to another laboratory, change in equipment, calibration concentration range, limited sample volume, another matrix or species, change in anticoagulant, sample processing procedure, storage conditions etc. All modifications should be reported and the scope of revalidation or partial validation justified Can range from as little as the determination of the within-run precision and accuracy, to an almost full validation	Minor changes to a fully validated method The items in a partial validation are determined according to the extent and nature of the changes made to the method Analytical method transfers between laboratories, changes in analytical instruments, calibration range, sample volume used for analysis, anticoagulant, critical reagents (LBA), MRD (LBA), sample-processing procedures or analytical conditions, sample storage conditions, confirmation of impact by concomitant drugs, and use of rare matrices Acceptance criteria should be the same as those employed in full validation	**Document divided up for Chromatography and LBA**

Critical Reagents (LBA)

EMA	MHLW	ICH M10 Differences
Binding reagents (e.g. binding proteins, aptamers, antibodies or conjugated antibodies) and those containing enzymatic moieties	Direct impact on the results of an LBA-based bioanalytical method and usually includes, but is not limited to, binding reagents (e.g., unlabelled or labelled antibodies)	Identified and defined in the assay method and considered early in method development bearing in mind reliable procurement/production
When changing reagent batches, performance of the method must be verified to ensure that it is not altered compared with the original or previous batch	Should be selected by considering the specificity for the analyte and should be stored under conditions that ensure consistent quality	Data sheet: identity, source, batch/lot number, purity (if applicable), concentration (if applicable) and stability/storage conditions
Stability of both non critical reagents (e.g. buffers, diluents or acidification reagents) and critical reagents should be documented in order to ensure that the performance of the method is not affected over time	Quality of critical reagent should be appropriately maintained throughout the period of use in analytical method validation and study sample analysis	Reagent performance evaluated using the bioanalytical assay new vs. old
	Partial validation is in principle required when the critical reagent lot is changed	Minor and major changes defined
		Minor change: a single comparative accuracy and precision assessment is sufficient. Major change: additional validation experiments.
		Retest dates allowing the extension

Reference standards: Chromatography

EMA	MHLW	ICH M10 Differences
Suitable internal standard(s) (IS) and quality is ensured Obtained from an authentic and traceable source Suitable sources of reference standard listed CofA required purity, storage conditions, expiration date and batch number. Not required for IS if suitability demonstrated. MS detection: a stable isotope-labelled IS is recommended to be used. Highest isotope purity (no isotope exchange reaction occurs). The presence of any unlabelled analyte should be checked and if relative amounts of unlabelled analyte are detected the potential influence has to be evaluated during method validation.	Certificate of analysis or an alternative statement that provides information on lot number, content (purity), and storage conditions should accompany the standard As a reference standard, it is advisable to obtain a material of known chemical structure from an authenticated source and clarify the expiration date A certificate of analysis is not necessarily required for an internal standard, but the lack of analytical interference with the analyte should be demonstrated before use as the internal standard	Cals and QCs may be prepared from the same stock solution provided accuracy and stability of the stock solution have been verified Technically justify absence of an IS It is important that the reference standard is well characterised and the quality (purity, strength, identity) The reference standard should be identical to the analyte. If this is not possible, an established form (e.g., salt or hydrate) of known quality may be used. Stock and working solutions can only be prepared from reference standards that are within the stability period as documented in the CoA (either expiration date or the retest date in early development phase).

Reference Standards: LBA

EMA	MHLW	ICH M10 Differences
Heterogeneous and potency and immunoreactivity may vary Well characterised and documented (e.g. certificate of analysis and origin) and purest reference standard available at the time should be procured Same batch as used for dosing in the non clinical and clinical studies is strongly recommended In case of change of batch, an analytical characterisation and bioanalytical evaluation should be carried out prior to use to ensure that the performance characteristics of the method are not altered	Certificate of analysis or an alternative statement that provides information on lot number, content (amount, purity, or potency) and storage conditions should accompany the standard Expiration date or its equivalent is preferably clarified Material is procured from an authenticated source and is of well-controlled quality	Highly complex structure and its reactivity with binding reagents for bioanalysis may be influenced by a change in the manufacturing process of the drug substance Manufacturing batch of the reference standard used for the preparation of calibrators and QCs is derived from the same batch of drug substance as that used for dosing in the nonclinical and clinical studies whenever possible Emphasis on bioanalytical evaluation should be performed when batch is changed

Selectivity: LBA

EMA	MHLW	ICH M10 Differences
At least 10 sources of sample matrix at or near the LLOQ, including lipaemic and haemolysed samples plus relevant disease population Low end of an assay but may be prudent also to evaluate selectivity at higher analyte concentrations. If concentration dependent, determine the minimum concentration and adjust the lower level of quantification accordingly, before assay validation. Within 20% (25% at the LLOQ) of the nominal spiked concentration in at least 80% of the matrices evaluated	At least 10 individual sources and near-LLOQ QC samples (i.e., QC samples at or near the LLOQ). It may be acceptable to use matrix samples obtained from less than 10 sources. Assay results for at least 80% of the blank samples should be below the LLOQ; at least 80% of the near-LLOQ QC samples should demonstrate an accuracy of within ±20% of the theoretical concentration (or within ±25% at the LLOQ)	At least 10 individual sources and by spiking the individual blank matrices at the LLOQ **and at the high QC level** For lipaemic and haemolysed samples, tests can be evaluated once using a single source of matrix In the case of relevant patient populations there should be at least five individual patients

Thank you