Workshop on ICH M10

G1 - Scope interpretation – splits into 3 round tables

Philip Timmerman – EBF
G1A: Enric Bertran/Delphine Maux**: Primary/secondary matrix**
G1B: Steve White/Salvatore Calogero**: rare matrix/tissues**
G1C: Katja Zeiser/Michaela Golob**: Pivotal studies)**

14 November 2023 – Barcelona, Spain

Introduction to Round table G1

The scope of G1 = Scope of ICH M10

Before we start

1.1. Objective

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.

Introduction to Round table G1

Before we start

1.2. Background

Concentration measurements of chemical and biological drug(s) and their metabolite(s) in biological matrices are an important aspect of drug development. The results of studies employing such methods contribute to regulatory decisions regarding the safety and efficacy of drug products. It is therefore critical that the bioanalytical methods used are well characterised, appropriately validated and documented in order to ensure reliable data to support regulatory decisions.

This guideline intends to facilitate development of drugs in accordance with the principles of 3Rs (Reduce, Refine, Replace) for animal studies, where valid.

Introduction to Round table G1

1.3. Scope

This guideline describes the validation of bioanalytical methods and study sample analysis that are expected to support regulatory decisions. The guideline is applicable to the bioanalytical methods used to measure concentrations of chemical and biological drug(s) and their metabolite(s) in biological samples (e.g., blood, plasma, serum, other body fluids or tissues) obtained in nonclinical toxicokinetic (TK) studies conducted according to the principles of GLP, nonclinical pharmacokinetic (PK) studies conducted as surrogates for clinical studies, and all phases of clinical trials, including comparative bioavailability/bioequivalence (BA/BE) studies, in regulatory submissions. Full method validation is expected for the primary matrix intended to support regulatory submissions. Additional matrices should be validated as necessary.

For studies that are not submitted for regulatory approval or not considered for regulatory decisions regarding safety, efficacy or labelling (e.g., exploratory investigations), applicants may decide on the level of qualification that supports their own internal decision making.

The information in this guideline applies to the quantitative analysis by ligand binding assays (LBAs) and chromatographic methods such as liquid chromatography (LC) or gas chromatography (GC), which are typically used in combination with mass spectrometry (MS) detection.

For studies that are subject to Good Laboratory Practice (GLP) or Good Clinical Practice (GCP) the bioanalysis of study samples should also conform to their requirements.

The bioanalysis of biomarkers and bioanalytical methods used for the assessment of immunogenicity are not within the scope of this guideline.

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Pre-meeting survey (56 responses)

	the question	Yes	No
Q1	Do you think the scope of ICH M10 is too wide?	6	46
Q2	if so, what should be excluded?		
Q3	Do you understand the difference between primary and other matrix and the opportunities given by the guideline?	27	6
Q4	Do you understand the difference between rare matrix and tissues in general and the opportunities given by the guideline?	29	5
Q5	Do you understand "pivotal study"?	25	9
Q6	Do you interpret that the guideline requires Method validation to be under GLP?	7	36
Q7	Are you applying the ICH M10 guideline for Biomarkers?	5	40
Q8	if yes, why?		
Q9	Are you applying the ICH M10 guideline for other types of studies beyond the intended PK/TK scope of M10?	5	36
Q10	If so, for which?		

Yes	No
6	46
27	6
29	5
25	9
7	36
5	40
5	36

13-25%

13-25 % of the responders in unclear…that's a lot for a guidance

As in, do I stop at a red light? Not sure…

Yes	No
6	46
27	6
29	5
25	9
7	36
5	40
5	36

13-25%

Moreover…

More variation of opinion in the comments, where a

- Yes is not necessarily a Yes
- The explanation given by one differs from the one give by others (pivotal, secondary matrix)

It begs some questions and discussions

Do we really see eye to eye on

- Primary vs secondary matrix
- Urine and tissues
- Defining ‘pivotal’
- GLP

Are we:

- Complacent
- Afraid from regulator or sponsor
- Scientists
- still a little hesitant to proceed with the new opportunities

Let's kill a few birds before we start

	the question	Yes	No
Q6	Do you interpret that the guideline requires Method validation to be under GLP?	7	36

EBF Recommendation: **NO**

- For studies that are subject to Good Laboratory Practice (GLP) or Good Clinical Practice (GCP) the **bioanalysis of study samples** should also conform to their requirements.
- We follow the line of Q&A for EMA where this M10 sentence was copied from:

  see → https://www.oecd.org/chemicalsafety/testing/glp-frequently-asked-questions.htm

6. What standard should be applied to the validation of methods which are used in GLP studies and how should it be applied?

Unless stipulated in national regulations, there is **no requirement to perform method validation in compliance with GLP**. Since parameters of the validated method are used in the GLP study (for example threshold, linearity, accuracy, precision, stabilities, equipment settings, etc.), data should be accurately recorded and stored in a manner that protects its integrity. Validation data may be required for study reconstruction and, consequently, it should be retained for an appropriate period of time. (posted on 21 January 2016)

Let’s kill a few birds before we start

	the question	Yes	No
Q7	Are you applying the ICH M10 guideline for Biomarkers?	5	40

EBF Recommendation: **ICH M10 is not for Biomarkers** (or ADA for that matter)

- *The bioanalysis of biomarkers and bioanalytical methods used for the assessment of immunogenicity are not within the scope of this guideline*

It’s Context of Use….the context of use of data generated by BMV = PK (we added TK in 2001…)

The context of use of BM is not, so, after understanding the context of use of the appropriate and likely different scientific or analytical criteria should be considered

Too big for 1 round table → 3 round tables

1. Primary matrix definition - (Moderators: Enric Bertran/Delphine Maux)

- *Full method validation is expected for the primary matrix intended to support regulatory submissions. Additional matrices should be validated as necessary*
- **The challenge**: if we don't agree on '*primary*' vs. '*additional matrices*', all matrices will be in scope

2. Rare matrix vs. tissues - (Moderators: Steve White/Salvatore Calogero)

- **The challenge is twofold**: (1) unless exceptions, tissues are never 'primary matrix' in the vast majority of studies anyway and are out of scope and (2) rare matrix are a subcategory. Nevertheless, we see industry moving into including tissues in full/partial validation.

3. Defining Pivotal studies definition - (Moderators: Katja Zeiser/Michaela Golob)

- 'Pivotal' is only mentioned in the ISR section, but we include it reading between the lines of the Scope section: *'This guideline describes the validation of bioanalytical methods and study sample analysis that are expected to support regulatory decisions.'*
- From the comments, there are a variety of opinions on what is 'pivotal'
- **The challenge**: if we cannot identify '*expected to support regulatory decisions*', or how broad can you interpret '*support*', virtually all studies will become in scope

Outcome of round tables in separate slide decks

- G01FB-A. Enric-Delphine - Primary matrix.pptx
- G01FB-B. Steve - Salvatore - rare matrix.pptx
- G01FB-C. Katja - Michaela - pivotal studies.pptx

Raw data from the pre-meeting survey comments

- In the next slides we provide the unredacted details from 56 survey files reaching us prior to the deadline.
- Surveys that have arrived after the deadline could not be included anymore, for logistic reasons. Please speak up if your comment wasn't already captured in the other 56 files

On Q1: Do you think the scope of ICH M10 is too wide?

- Not sure qPCR is covered (may be out of scope but used for quantification)
- The standard is likely to raise

On Q2: if so, what should be excluded?

- Whole blood stability
- Tissue 'validation'
- "bioanalytical methods and study sample analysis that are expected to support regulatory decisions".
- What is NOT expected to support regulatory decisions. Provide guidance.
- Endogenous molecules paragraph
- other body fluids or tissues should be removed
- early phase pre-clinical studies and single and multiple ascending dosing phase I, certain aspects should be limited to BE studies

On Q3: Do you understand the difference between primary and other matrix and the opportunities given by the guideline?

- Y (the primary matrix should be fully validated whereas the level of val./qualification is more open for additional matrices
- Y - However, "other matrix" should probably be more clearly defined.
- Not clear - and does not align with clinical study objectives so can cause confusion between RegBA and ClinOps
- Most clients will asked still for full validation package for other matrices. How can this be solved?
- Harmonisation is the main advantage,
- I rather make sure we are compliant and not thinking too much
- Considering rare matrix
- Y - Probably, we use it as the first matrix, where additional matrix are the new indications
- Y, but the guideline should be clarified for supportive studies other than primary matrix.
- Y, I think it is quite clear that usually plasma/serum is the primary matrix and all others such as urine, CSF, tissues are in most cases secondary matrix
- Y (at least, I hope so)
- NOT SURE
- Could be clearer
- Y, but the guideline should be clarified for supportive studies other than primary matrix.

Although we say ‘yes’, reading the comments, it’s actually not really a ‘yes’ and continued discussion and sharing is likely critical to come to common understanding

On Q4: Do you understand the difference between rare matrix and tissues in general and the opportunities given by the guideline?

- Y (rare matrix = every thing else than human)
- No definition of 'rare' in guideline (EBF terminology)
- Yes - Cost have no impact to defined "Rare" from my view
- "Rare matrix: i.e. rare disease patient matrix
- Tissues: i.e. serum versus brain, muscles…"
- Yes, but disappointing that matrix substitution is not allowed to a larger extent (3R).
- Y - However, in the scope of ICH M10 it should probably more defined especially the differences (not all tissues are rare). See 2.2.1.
- yes we can interpret the guideline but could be differences of opinion - e.g. Is mouse plasma considered a rare matrix?
- N - definition rare matrix unclear
- I think we self regulate too much.
- Difficult to draw the line for what is rare and what is not
- Y, but not clear for sponsor
- Y, however we are still a little hesitant to proceed with the new opportunities
- Y (at least, I hope so)
- Needs better guidance on definition of a rare matrix
- Y, but not clear for sponsor

Although we say ‘yes’, reading the comments, it’s actually not really a ‘yes’ and continued discussion and sharing is likely critical to come to common understanding

On Q5: Do you understand "pivotal study"?

- Y, But I am not sure, which study is pivotal Yes - Phase IIb and Phase III
- "Definition: Usually a phase III study which presents the data that the FDA uses to decide whether or not to approve a drug."
- N - Not in the context as it is used in ICH M10
- Y/N - we know what it is but it is not clear in the guideline
- We interpret Pivotal as label claims & filing studies but pivotal definition is not clear per ICHM10
- Large Phase III normally contracted out?

We could maybe do a small exercise and ask the 25 'Y' responders to define 'pivotal'.
Likely to predict a variety of definitions and everybody has their own truth.

On Q6: Do you interpret that the guideline requires Method validation to be under GLP?

- N, But sample analysis must be under GLP - thus the lab is GLP - thus often the validation
- N (only sample analysis is conduction to either OECD GLP or GCP)
- Yes - not really required by guideline, but we want to run the validation in a regulated environment with involvement of QA
- For method validation supporting Tox GLP studies ICHM10 is supportive but not fully required
- Y, While not explicit the guideline is required when subsequent phases are conducted to GLP therefore a risk averse strategy is to carry out validations to GLP.
- No, but we do it anyway do to expectations from some authorities
- GCP is closer to the patients, and uses the GLP spirit Hence the GCLP concept
- Y, since analysis, documentation thereof and reporting are quite explicitly described and there are criteria for almost every parameter assessed given
- not sure - there is no OECD GLP on validation studies
- No, not claiming GLP compliance

Surprisingly we are trying to shoot in our own foot again; Let's kill this one fast before it happens to usagain **Mval is clearly NOT under GLP**:

<< For studies that are subject to Good Laboratory Practice (GLP) or Good Clinical Practice (GCP) ***the bioanalysis of study samples*** *should also conform to their requirements >>*

On Q7: Are you applying the ICH M10 guideline for Biomarkers?

- Y some of the sections
- NO - We refer to whitepapers and FDA (2018)
- biomarkers are normally exploratory end points
- N - Biomarkers are out of scope of ICH M10
- No, but I may in the future
- No - M10 is not for Biomarker method validation

On Q8: if yes, why?

- For inspiration- lack of a proper guideline for biomarker
- easy to explain; same process
- Specifically not in scope of M10 (although there is a clash with endogenous analytes)
- apply principles to PD
- As general guidance but adapted to fit of purpose, Depends on client's requests. Some request validated methods.
- Only the applicable experiments with respect to experimental design and acceptance criteria

Let's kill this one fast before it happens to us:
The **bioanalysis of biomarkers is not within the scope of this guideline**

On Q9: Are you applying the ICH M10 guideline for other types of studies beyond the intended PK/TK scope of M10?

- we use them as guidance for our non regulated preclinical studies
- Yes as guidance build up Validation according " Content of use"
- Partly
- mRNA, several analytes not dosed. Like the LNP, the protein itself,…
- N (but in the of spirit of the guidance)
- N (but in the of spirit of the guidance)
- general principle applied for qualifications or other activities
- No - but M10 is in most cases in drug development only applicable for TK not PK. (See Q&A on ICH.org)

Not sure if the responses pick up the scope creep we see trending – let's make sure we surface what is fermenting slowly to become our next headache

On Q10: If so, for which?

- Mouse PK, DRF studies - to in-use-qualify our assay before transfer to CRO for GLP
- pharmaceuticals for veterinary use
- Metabolites,
- qPCR
- In support to all GLP Tox studies
- We use the framework and themes of ICH M10 but not applying it as is to this space.
- Depending on sponsor requirements
- Lipid form the nanoparticle, therapeutic protein that the body produces,…
- For residue studies in plasma
- PK/TK
- Urine assays are following the guideline as these aren't at this time out of scope of standard, overall policies