Workshop on ICH M10

C3 - Focus on urine

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Introduction to Round table C03

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.

Pre-meeting survey

	the question	Yes	No
Q1	Are you clear on the difference primary and additional matrices in the guideline?	16	7
Q2	If urine is being analysed (and they are not the primary matrix), do you apply the ICH M10?	14	6
Q3	if yes, why?		
Q4	if no, what are the criteria / process you apply		
free text			

Key message from the pre-meeting survey comments :

- **Is it really clear** for urine **when** a **full validation versus "as necessary validated"** ?
  - As per ICH M10, full validation of urine is not required, unless it is a primary matrix, yet many validate urine as if it was the primary matrix → Is it due to a lack of knowledge or fear or other?
  - 'at sponsor request' seems the most important driver
  - For discussion: Can a decision tree be helpful to decide on when to use ICH M10?

- Many interpretations on what means "**validated as necessary**"
  - Scientific discussion needs to happen, i.e. What are key parameter to validated regarding the context? Add non-specific binding? Dilute with plasma and use method plasma? 3 R ?
  - …..

⇨ **When and How ?**

Key message from the round tables

Theme/question: Is urine a primary matrix ?

Comments:

- Urine is almost never a primary matrix , very rare cases where urine is primary (safety)
- Mostly as additional matrix
- One case where urine is primary route of excretion

Theme/question: In case of urine is a not a primary matrix, why following the full ICH M10 for urine method validation ?

Comments

- Distinction between full and scientific validation may be “thin” , Reflect that it is often similar effort and cost for full validation vs scientific validation
- Avoids risk in the future
- Stability required therefore close to a full validation
- CROs clients often asking for full validation
- Won’t recommend scientific validation to clients in case of risk of not being accepted by agencies
- Sponsor may not know what is needed

Theme/question: Key driver to define parameter for urine method development/validation

Comments:

- Use a scientific validation approach (→ *EBF paper: Bioanalysis. 2015 Sep;7(18):2387-2398.*)
- Context of use
- How data are use is key
- fit for purpose validation

Theme/question: Key parameter for urine method development ?

Comments:

- Non-specific binding testing to recommend appropriate collection (add agent)
  - Test container, process , time
  - May also test pH effect
  - Test darkness
  - Min max concentration
  - Various sources of matrix for selectivity
- Recommendation of collection to avoid solubility issue

When :

- 50 % perform testing during development and repeat again during “validation”
- 50% have data in the development part

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: Are you clear on the difference primary and additional matrices in the guideline?

Yes	No
16	7

- Check what is defined in the clinical protocol; If not a primary endpoint then do not validate
- N (primary is for regulatory submission: what does it mean?)
- no, we assume primary matrix is plasma or serum (for PK)
- NOT SURE
- no, we assume primary matrix is plasma or serum (for PK)
- Y, but this should be assessed more by primary, secondary and exploratory objectives of clinical protocol and submissions purposes

On Q2: If urine is being analysed (and they are not the primary matrix), do you apply the ICH M10?

Yes	No
14	6

- Sometimes
- sometimes
- Depending on sponsors requirements
- Unless the target is in the urinary track, urine is not done or done to fit for purpose
- Urine can be collected and only analysed if needed.
- It depends on the scope of the analysis (exploratory or validated after a abundance of a metabolite > 10% of unchanged compound)
- depends on the case and objectives, but usually yes

On Q3: if yes, why?

- As per sponsor x4
- chapter 6.1 bullet no. 7
- as fit for purpose method
- fit for purpose allowed by M10, extended acceptance criteria, reduced number of experiment
- Application of M10 means a result is 'valid' and can be used for subsequent processing and interpretation of the study result. There is no other means of determining categorically what is appropriate for scientific validity of the sample data and what won't be thrown out by an educated/ill educated inspector.
- Generally supporting urine human samples analysis
- driven by the client and as CRO its not always known if being used for submission
- established workflow, easy to explain
- considering worst case scenario, plus endpoint in a clinical study can be secondary
- on Sponsor request only we apply the ICH M10
- to simplify our SOP

On Q3: if yes, why?

- guides FFP validation
- If related to endpoint
- good quality level of the method
- To be homogenous
- Used in pivotal studies and calibration curve and is different than primary matrix
- experimental design and criteria are same(except few changes with respect to blood/plasma/serum e.g. heamolized/ lipemic matrix etc.
- ICH M10 is the regarded as the general acceptable industry standard
- TO HAVE A DEFINED APPROACH/PROCESS (i.E. Partial validation for urine matrix and criteria to be applied to assure accuracy/reproducibility and robustness of the data)
- as it is an additional matrix
- if secondary objective or data needed to support submissions

On Q4: if no, what are the criteria / process you apply

- Exploratory criteria
- EBF SV
- Fit for purpose - SOP driven approach and criteria
- No for preclinical urine samplessame as for primary matrices
- our SOP fit for purpose validation
- Not specified
- only a small non specific binding experiment is needed.
- Dilute with plasma and use plasma method.
- If urine is important concentrations will be high.
- guides FFP validation
- Exploratory with only an A&P items
- If stable labelled Internal standard is available we would use basically the same criteria. We would do stability testing, matrix effect testing and many of the other tests required for plasma. In many cases in the past a urine assay would not require extraction but dilution only.
- if exploratory objective could be considered a fit for purpose assay