Workshop

Towards harmonised implementation of the ICH M10 Guideline

Charters 1 & 2 – Introduction and General

Matt Barfield,
on behalf of the EBF

15 November 2022, Barcelona

Flow of the session

- Scope
- The Positives – what's new – gone and what is liked
- Topics that require discussion
  - 6 topics identified from the EBF survey
  - Examples of questions asked
  - Potential solutions for discussion
- Panel discussion based on the above selection
- Panel discussion on any other topics raised by the audience
- Follow-up action items

Introduction – The scope

- Scope of the guideline was one of industry's major concerns
  - Which studies and analytes are in scope?
  - From which phase of development is the guideline applicable?
  - Areas where leaner approaches can be applied?
- ICH M10 does give additional clarity on the above questions – but is it enough?
- Are industry and regulators available to interpret the guideline requirements and read them the same?
  - Pre and post ICH M10 survey in EBF illustrates more experience and discussion is required – there is still room for different interpretations
  - No change in industry's interpretation on other matrices or metabolites as pre-ICH, even though the guideline is providing help

What's new – gone and what is liked

Introduction

- Biomarkers and immunoginicity are out of scope. This differentiation makes a clear definition that pK validation doesn't equal Biomarker/immunoginicity validation
- Appreciate that 3 R's is called out

General Principles

- Matrix differences e.g. Ethnicity and gender are not considered to be different
- Formal validation plans/protocol for each indiviulal assay is not needed as long as covered in a SOP
- Lots of positive comments around "*Bioanalytical method development does not require extensive record keeping or notation. Once the method has been developed, bioanalytical method validation proves that the method is suited to the analysis of the study samples. If a problem is encountered with the method during the analysis of nonclinical or clinical study samples that requires that the analysis be stopped, any changes to the method and the rationale should be documented*" The feeling is less is now required, but not by all…

Topics for discusion

- Metabolites in scope
- Non Clinical PK Studies
- Full validation for all non Clinic GLP studies
- Method development - What is minimally needed for record keeping?
- Parallelism
- Primary *vs* secondary matrices – what is primary? What is secondary?

Looks like a relatively easy catch

Which metabolites are in scope,

A good starting point is the updated EBF recommendation on metabolite quantification

Best practices for metabolite quantification in drug development: updated recommendation from the European Bioanalysis Forum

Philip Timmerman[1], Stefan Blech[2], Stephen White[3], Martha Green[4], Claude Delatour[5], Stuart McDougall[6], Geert Mannens[1], John Smeraglia[5], Stephen Williams[4] & Graeme Young[3]

Bioanalysis, Volume 8, Issue 12, June 2016, Pages 1297-1305

Future Science Ltd
Bioanalysis
Volume 3, Issue 24, December 2011, Pages 2729-2730
https://doi.org/10.4155/bio.11.250

Bioanalysis

Regulatory Focus

When do you need a validated assay?

Brian Booth
Division of Clinical Pharmacology V, Office of Clinical Pharmacology, Center for Drug Research & Evaluation Research, US FDA, Silver Spring, MD 20993-002, USA. brian.booth@fda.hhs.gov

The European Bioanalytical Forum has developed a paradigm for addressing this issue **[1]**. Essentially, the scheme describes the development and use of an analytical method with varying degrees of validation. In cases where the metabolite is known or expected to be toxicologically active, the notion is to use a validated method for the metabolite beginning with preclinical studies and continuing with clinical development. In the case where the activity of the metabolite is unknown, less validated screening and qualified methods may be more appropriate until a determination is made regarding the toxicology of the metabolite. The European Bioanalytical Forum scheme makes very reasonable sense and may be a very valuable tool for industry.

When using AMS or ^{14}C, use scientific criteria relevant to the technology. Be cautious not to mix up profiling and quantification purposes

discovery | pre phase 1 | phase 1 | 2a/2b | 3 | 4

- Focus on *in vitro*
- Limit *in vivo* metabolite quantification
- Screening

Preclinical and clinical studies

- Plasma, serum or blood.
- Use **screening** (preferred for earlier phases) and **scientifically validated** methods (preferred @ SAD/MAD) to document the ICH M3(R2) coverage of metabolites.
- Consider **relative exposure** ratios in absence of reference standards
- Metabolite quantification in other matrices for profiling purposes

Clinical studies only

- Plasma, serum or blood.
- use **regulatory validated** methods to quantify only those metabolites contributing to >25% activity (not only AUC) relative to unchanged drug.
- No other metabolites require quantification
- consider selection of studies and/or selection of samples/subjects instead of all samples from all subjects in all studies

Milestone: around Multiple Ascending Dose (MAD) in human

- Document ICH(M3) coverage of metabolites (MIST perspective
- Ensure coverage of human disproportionate metabolites in animal studies (may require separate Tox study)
- Document PD activity (collaborate with clinical/pharmacology partners)

- Consider quantification in special studies (e.g. DDI) of other metabolites using **scientifically validated** methods

Up for discussion and from the legacy EBF catalogue

- Good to check most recent guidelines on metabolism/DDI/… from different Has to see if things changed since 2016
- If not, likely the only metabolites requiring validated methods are metabolites contributing to activity (25% on AUC compared to UD (free fraction based) or 10% on total drug exposure…need to check) from **Phase 3 onwards**
- Metabolites contributing to toxicology should be able to be mitigated as part of metabolite profiling in earlier phases of development – at max, they should be validated when dosed.

But there are new kids on the block

- Peptides, oligos…proteins…
- Experience building, so monitoring is required

- Does NCE strategy fit new scaffolds and the ICH M10

Maybe a cyber FW in the near future

- is easy to organise
- Allows us to stay ahead of the curve

Non Clinical PK Studies

Very straightforward only need 1 example

Full validation for all non Clinic GLP studies Whole blood stability and Lipemic

- States non clinical TK studies
- 3.2.1 - This evaluation is not necessary for nonclinical studies unless the drug impacts lipid metabolism or is administered in a particular animal strain that is hyperlipidaemic.
- Whole blood stability??

Method development –
What is minimally needed for record keeping?

The message has been consistent

- Considering the ICH paragraph finds its origin in the FDA 2018 Guidance, refer to FDA EBF podium presentation 2018 - Sriram Subramaniam

- 2 aspects- Life cycle of the assay – having the information to tell the story as the assay evolves

  - Initial method development, very high level
  - Re-development after validation – records of what was changed and reason why
  - Focus is on changes to the assay during the lifecycle of the asset

Parallelism

ICH M10 Guideline on bioanalytical method validation and study sample analysis

- It's a guideline, you can do more if it makes scientific sense
- On the other hand don't do more just because……..

14

Primary vs secondary matrices

- Important to understand what will the data be used for?
- Need to really understand this from the stakeholder and ensure they are clear what context the data will be used for

- What happens when the stakeholder changes their mind or they are unsure?

15

Acknowledgements

- The panel
- All of you

Contact Information

Questions: info@e-b-f.eu

European Bioanalysis Forum vzw
www.e-b-f.eu