Taking tiered approach beyond MIST

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on behalf of the EBF

Spotlight Workshop
6th EBF Open Symposium
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Crystal City III

"Characterization of UMMs should proceed using a flexible," tiered " approach to bioanalytical methods validation. ……in early drug development using bioanalytical methods with limited validation, ……. As a minimum, the specifics of this tiered validation process should be driven by scientifically appropriate criteria, established a priori"

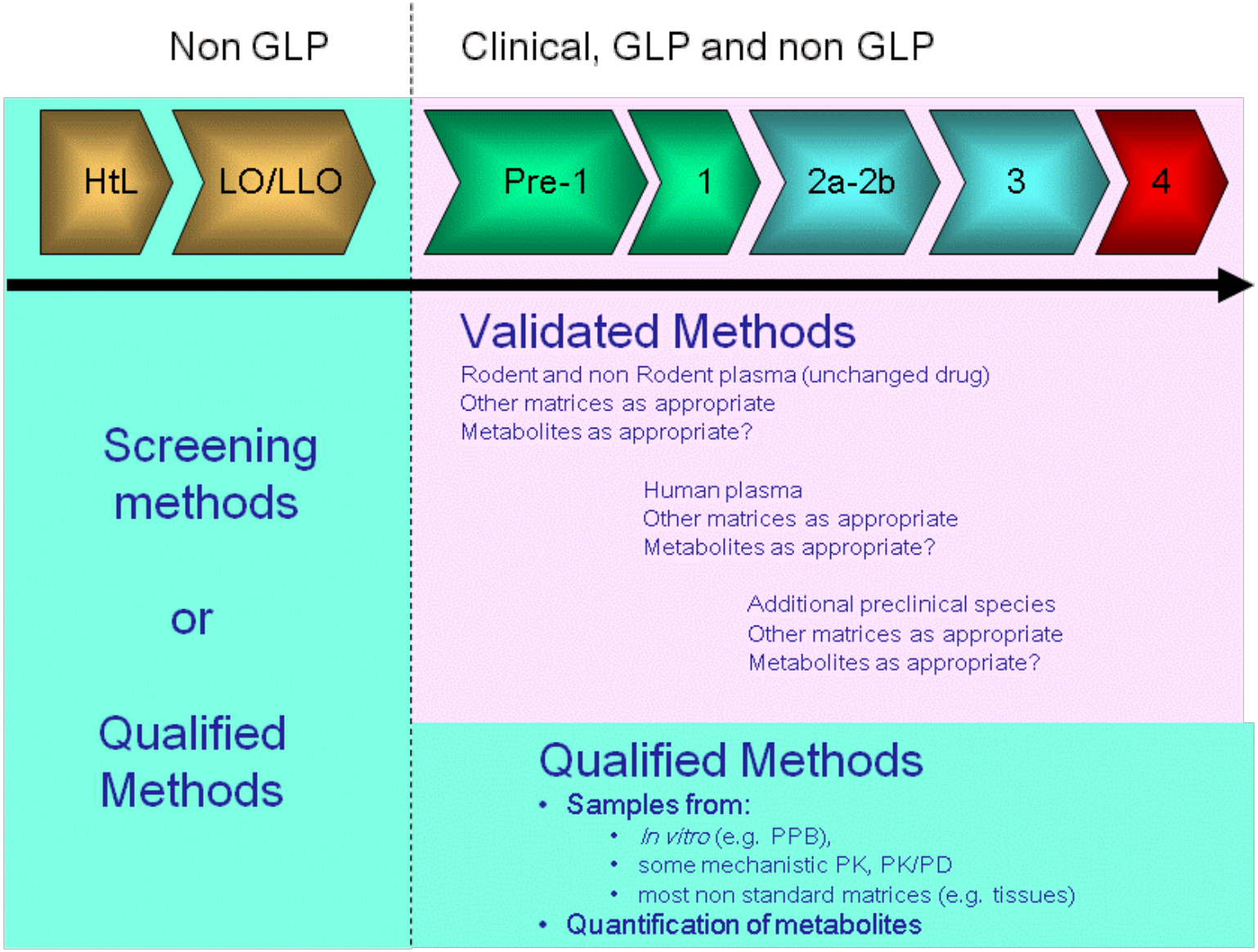
More details

Workshop/conference report - Quantitative bioanalytical methods validation and implementation: Best practices for chromatographic and ligand binding assays

C. T. Viswanathan, et al. AAPS J. 2007 March; 9(1): E30–E42

2008: EBF topic team

- EBF identified opportunity to broaden tiered approach discussion beyond UMMs or Metabolites in Safety testing


Non GLP
Clinical, GLP and non GLP
HtL
LO/LLO
Pre-1
1
2a-2b
3
4
Validated Methods
Rodent and non Rodent plasma (unchanged drug)
Other matrices as appropriate
Metabolites as appropriate?
Human plasma
Other matrices as appropriate
Metabolites as appropriate?
Additional preclinical species
Other matrices as appropriate
Metabolites as appropriate?
Screening methods
or
Qualified Methods
Qualified Methods
• Samples from:
• In vitro (e.g. PPB),
• some mechanistic PK, PK/PD
• most non standard matrices (e.g. tissues)
• Quantification of metabolites

But….

- With ICH3 (M2) Guidance coming in effect in 2008/2009, the EBF team choose to **first focus their efforts** on translating tiered approach principles into practice for MIST

MIST

Recommendation:

1. Define 3 levels of quality for Tiered approach
2. Provide content to semantics of Tiered approach focusing on Qualified methods
3. Provide practical guidance on which quality standards to apply for MIST

More details on next slides or:

Best practices in a tiered approach to metabolite quantification: views and recommendations of the European Bioanalysis Forum
Philip Timmerman, Morten Anders Kall, Sirpa Laakso et al
Bioanalysis, July 2010, Vol. 2, No. 7, Pages 1185-1194

1. Define limited levels of quality

Screening methods

- Usually not generated in BA dpts
- No acceptance criteria
- Standards without CoA
- Qualitative and/or response data, for early decision making

Qualified methods

- Method with appropriate level of scientific validation (accuracy, precision, stability,…) generating concentration data to allow documented and reproducible decision making

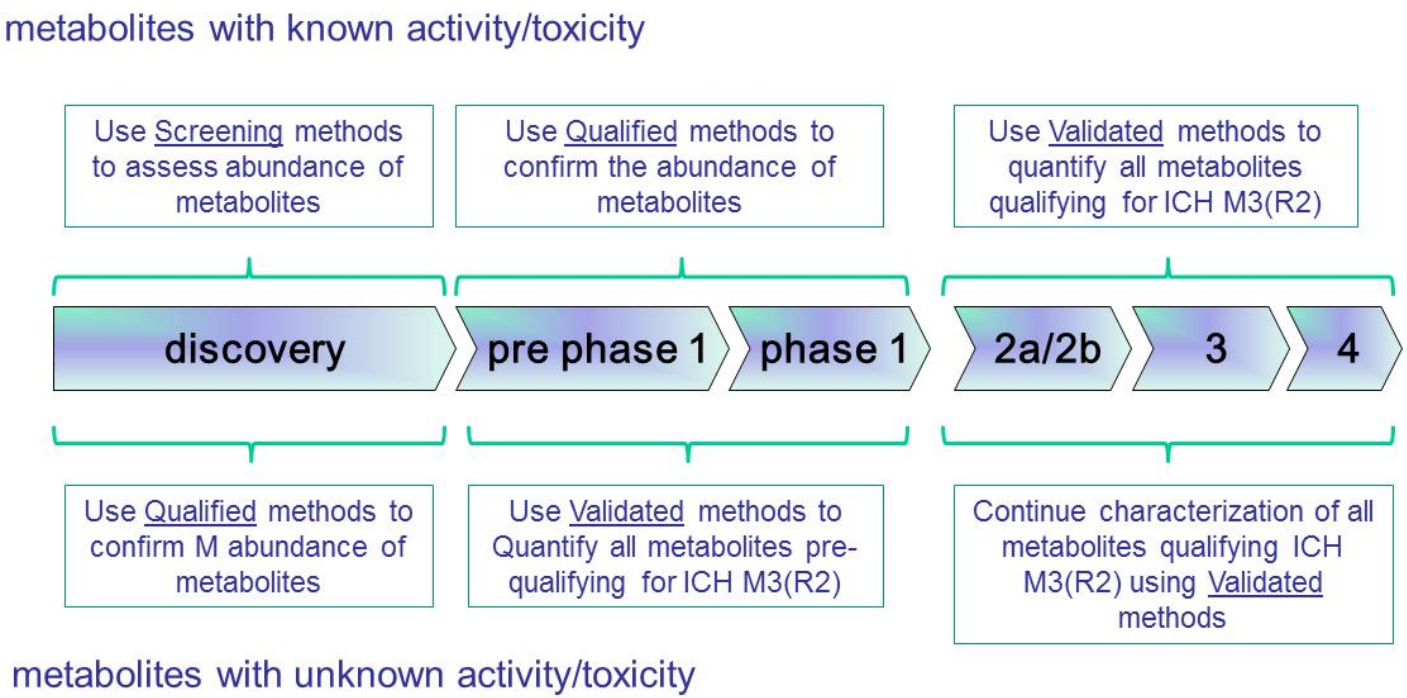
Validated methods

- Method validated in accordance with the Regulated BA Guidance.

2. Tiered method performance parameters excerpt

Parameters	Screening	Qualified	Validated
Concentration results obtained?	No	Yes	Yes
Reference standard	Yes or No	Yes, with COA	Yes, with COA
Method development	Yes, but limited	Yes, but limited	Yes
Pre-study method performance assessment	No; rely on method development) & in-study data	Preferred	Yes, as per regulatory guidance and SOP
Calibration curve for pre-study and in-study runs	Not applicable	Yes, but fewer calibration standards allowed (> 3)	Yes, as per regulatory guidance and SOP
Etc…			

3. Practical guidance on quality standards for MIST excerpt



Acknowledged:

When do you need a validated assay? –

Brian Booth, December 2011, Vol. 3, No. 24, Pages 2729-2730

"The European Bioanalysis Forum has developed a paradigm for addressing issue of metabolites in safety. …… The EBF scheme makes very reasonable sense and may be a very valuable tool for industry."

From our MIST publication onwards

- During multiple discussions in other EBF teams, we often included a reflection if it makes sense to comment on including a reflection on the level on qualification / validation required in discussed areas of (regulated) Bioanalysis
- Reflections were captured in our slide decks or publication
- A few examples on the following slides

Some examples

- Biomarkers
- Tissue analysis
- Blood stability testing
- Plasma protein binding
- Peptides and proteins
- Accelerator Mass Spectrometry
- Contribution to meetings/workshops

Biomarkers (BM)

Recommendation:

- Analysis of BMs using a novel assay.
- Analysis of BMs using an existing assay.

In both cases, the approaches reflect on qualification versus validation and acceptance criteria

More details:

EBF Recommendation on method establishment and bioanalysis of Biomarkers in support of drug development.

Bioanalysis, Aug 2012, Vol. 4, No. 15, Pages 1883-1894

Tissue analysis

Document exposure of dosed drug (or metabolites) in tissue homogenates:	Recommended level of Bioanalytical rigour
Unique endpoint of PK/safety in topical dosing (e.g. skin, lung,..)	**Consider validated assay**
a priori identified safety assessment in a GLP study	**Prior to considering a validated assay, consider assessing exposure in nonGLP study using a qualified assay**
PK study, mechanistic/GLP tox./PD study	**Use a qualified assay**
Understanding relative tissue distribution in any study type	**Use alternative simplified bioanalytical processes (evaluate need of absolute conc).**

More details

EBF Recommendation on method establishment for tissue homogenates, Bioanalysis, *Bioanalysis, in press*

Blood stability testing

Recommendation:

Follow a step-wise or parallel approach to assess the blood stability analyzing whole blood, and not the plasma fraction with qualified assay

More details

Blood stability testing: EBF view on current challenges for regulated bioanalysis *A. Freisleben, M. Brudny-Kloeppel, H. Mulder, et. al, Bioanalysis, Jun 2011, Vol. 3, No. 12, Pages 1333-1336*

Peptides and proteins

Discussion:

- ….
- it is the EBF's current thinking not to copy regulated requirements for small molecule bioanalysis for peptides and proteins when analysing them using LC-MS(/MS) with the exception for small intact peptides.

More details:

LC-MS/MS of large molecules in a regulated BA environment – which acceptance criteria to apply? Perspective from the EBF

M. Knutsson, R. Schmidt, P. Timmerman. Bioanalysis, Sep 2013, Vol. 5, No. 18, Pages 2211-2214

Plasma protein binding

Recommendation:

Drug Discovery phase

- ..
- Use generic analytical method (based on principles of screening or qualified assay)

Drug Development phase

- ….
- Use qualified assay with pre-study or in-study method qualification: to document calibration, acc&prec., specificity, carry-over and stability.

More details :

Bioanalysis for plasma protein binding studies in drug discovery and drug development: views and recommendations of the EBF

B. Buscher, S. Laakso, H. Mascher, et. al. in press, Bioanalysis

EBF

Accelerator Mass Spectrometry

Recommendation

- We recommend:
  - alternative criteria for MVAL, particularly the therapeutic dose/concomitant iv tracer microdose study design with high probability for included in submissions.
  - on parameters for the qualification of methods to ensure that data are obtained of sufficient quality for decision making.

More details:

European Bioanalysis Forum Recommendation: Scientific Validation for quantification by Accelerator Mass Spectrometry

David Higton, Graeme Young, Philip Timmerman et. al. Bioanalysis, Nov 2012, Vol. 4, No. 22, Pages 2669-2679

Contribution to meetings/workshops

- External to EBF
  - AAPS Annual meeting 2009 (MIST
  - BSAT 2009/2010 (MIST)
  - CPSA Shanghai 2012/2013 (Biomarkers, Tissues)
  - Reid Forum 2013 (Tissues)
- Contribution to GBC A2 and A10
- EBF
  - Focus Meeting Hatching

    More details

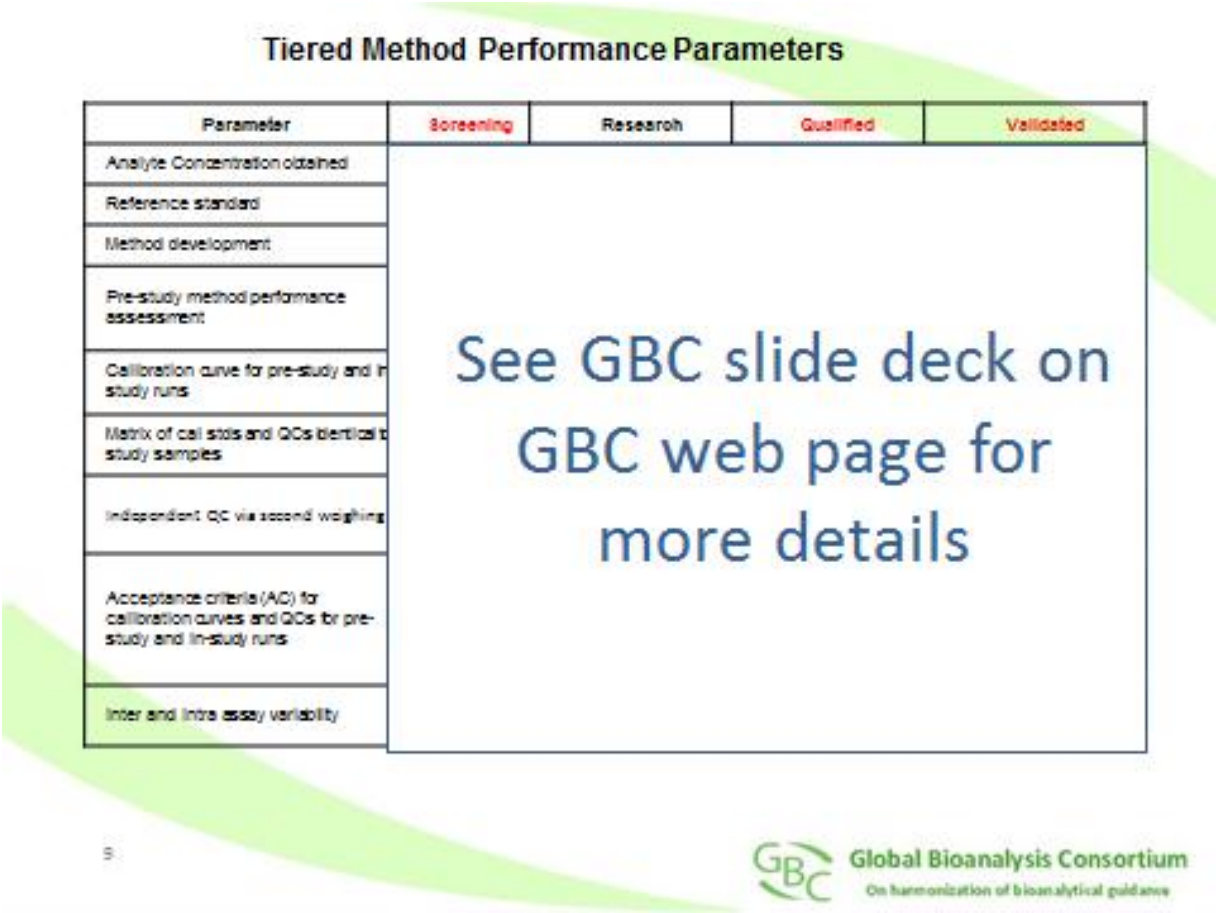
    Managing scientific, technical and regulatory innovation in regulated bioanalysis: a discussion paper from the European Bioanalysis Forum

    Philip Timmerman, Neil Henderson, John Smeraglia, et al Bioanalysis, Jan 2013, Vol. 5, No. 2, Pages 139-145
  - Focus Meeting Large Meets small
  - Focus Workshop e-data and Spotlight Workshop

    More details: ***previous workshop slides (Defining raw data in regulated bioanalysis***

    …..soon on conference website

GBC A2 – Tiered approach



GBC – A10: new technologies

AMS: builds on EBF Recommendation

Regulated framework?

MHLW, Japan

Annex Application of a tiered approach

……. In such cases, the so-called tiered approach may be applied for analytical method validation for efficient pharmaceutical development. The tiered approach is a strategy to initially limit the characterization of analytical method and to gradually expand parameters to be characterized and the extent toward a full validation as the development process proceeds. ……...

The 2013 draft FDA Guidance

……. For pivotal studies that require regulatory action for approval or labeling, such as BE or PK studies, the bioanalytical methods should be fully validated. For exploratory methods used for the sponsor's internal decision making, less validation may be sufficient.

EMA Guidance

No reference to tiered approach…….should we knock on the door to get more understanding

In summary…

EBF & Tiered approach – a continued commitment...

Publications:

- 2008: TA and MIST introducing 3 tiers; Blood Stability
- 2010: Biomarkers; AMS; Discussion paper new technologies
- 2012: In vitro PPB; Tissue analysis; LC-MS Peptides

Teams touching on TA:

- 2008: Tiered Approach Initial team
- 2009: TA 'MIST'; Blood stability
- 2010: AMS; Biomarkers
- 2011: Tissues
- 2012: LC-MS of peptides

Meetings:

- 2010: LC-MS peptide/proteins
- 2011: Workshop – hatching, new technologies
- 2012: Managing e- and raw data

Interactions / Contribution:

- 2009: AAPS
- 2010: GBC-A2

Acknowledgment

- The full EBF community for their continued input
- AAPS, GBC, APA, CPSA, Reid, and others for their openness to invite us.
- All of you for embracing and stimulating tiered approach as an acceptable strategy in regulated bioanalysis


Thank You