2016 ASMS Regulated Bioanalysis Interest Group Workshop

Current Status of Strategy and Practice of a Tiered Approach

Room 220, level 2

Wednesday 5:45-7:00 pm

Jian Wang (BMS) presiding

Panelists: Moucun Yuan (PPD), Jack (John) Kellie (GSK), Qin Ji (BMS)

There are about 50 scientists form pharmaceutical companies, CROs and national institutes attended the workshop. The workshop had introduction presentations covering overview, perspectives from pharmaceutical companies and CROs in 15 minutes followed by 60 minutes open discussion. The workshop provided an opportunity for attendees to exchange opinions, experiences, and practices with the ultimate goal of having a better understanding of how to apply a tiered approach as part of the bioanalytical strategy.

The workshop reviewed the recent development and current status of strategy and practice of tiered approach in bioanalysis. The recommendations from various bioanalytical societies and organizations such as Global Bioanalytical Consortium (GBC) and European Bioanalytical Forum (EBF) were discussed. The current position and opinions, such as the concept of scientific verses regulatory validations, stage-appropriate and assay-appropriate validations, from EBF were discussed in details.

The audience expressed the concern in executing tiered bioanalytical approach in routine work in both pharmaceutical companies and CROs. The workshop discussion in general agreed with the concerns as outlined in the recent EBF publication [1] about "if there is real added value to propose a variation on an established theme". Since "a bioanalytical laboratory may need to setup a fully assay validation after all" the relevance of saving a few days of time in early phases of development and value of the creation of a second set of standards were questioned. The workshop suggests further discussion of the topic in conferences and workshops. Selected slides and some references are attached.

Fit-for-purpose (FFP) bioanalytical assays

- 2006 Crystal City Conference Report and FDA (2008) Guidance for Industry Safety Testing of Drug Metabolites recommended PK characterization of unique and/or major human metabolite as early as feasible.

- Characterization should proceed using a flexible, "tiered" approach to bioanalytical methods validations. The specifics of the tiered validation approach is driven by scientifically appropriate criteria. Validation effort increases as a product moves from early to late development.

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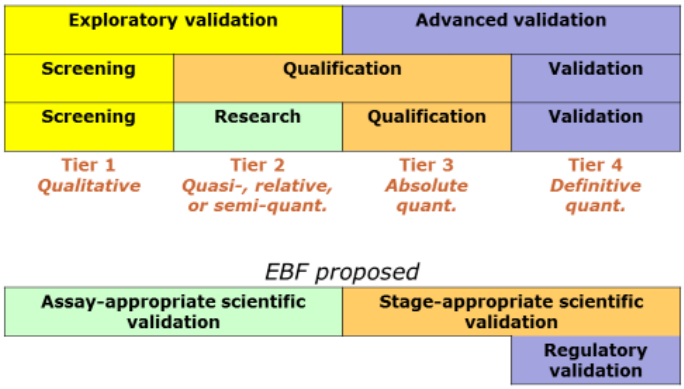
PPD

CRO Concerns Around the Tiered Approach

Moucun Yuan

ASMS RBIG Workshop, San Antonio TX, 8 Jun 2016

Tiered Approach Concepts



Terminology confusion

- *Validated* means only "fully" validated (to guidance)?
- *Qualification* is or isn't a form of validation?
- *Qualified*: how or for what?
- What's wrong with "partial or limited" validation?
- Validation criteria vs. parameters (and/or experiments)
- *Criteria*: assay criteria or acceptance criteria?
- 'Earlier tier' means 'lower tier data' = lower quality?
- *Qualified data* is uncertain (or even invalid) data?
- *Scientific* vs. regulatory validation?

Most BA CROs

- Labs set up to support regulated studies
  - GLP systems/practices
  - SOPs
  - Training
- Don't do many screening or research tier assays
- Mainly two tiers in practice

Feature	Method Qualification	Method Validation
Study intent	Non-regulated	Regulated
Reference standard	Authenticated, often COA	COA
Parameters	Subset	All (per guidance)
Experiments	Standard (or abbreviated?)	Standard (per guidance)
Criteria	Standard (or relaxed?)	Standard (per guidance)
QA involvement	No	Yes
Cost	Lower	Much higher?
Time	Shorter	Much longer?

CRO concerns in applying a tiered approach

- Don't want to be caught between sponsor and regulators
- Quality perception stigma (qualified data < quality data)
- Need to protect reputation (avoid getting 483s or worse)
- Guidelines do not provide a framework; details left to individual lab or scientist
- Don't want to recommend an approach later deemed to be wrong (in a critical decision or regulatory situation)
- Often have minimal access to prior knowledge of drug properties and other key supporting information
- Not part of sponsor project team discussions (between BA, data users, and decision makers) to assess needs and risks

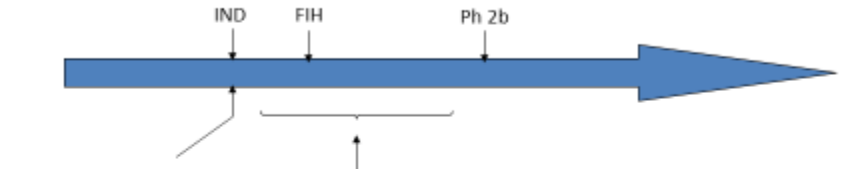
Fit-for-Purpose (FFP) Bioanalytical Method Validation in Support of Clinical and Safety Studies: Pharma's perspectives

Regulated Bioanalysis Interest Group Workshop (RBIG)

2016 ASMS

San Antonio, TX, June 8, 2016

Metabolite monitoring in early drug development



Discovery package:

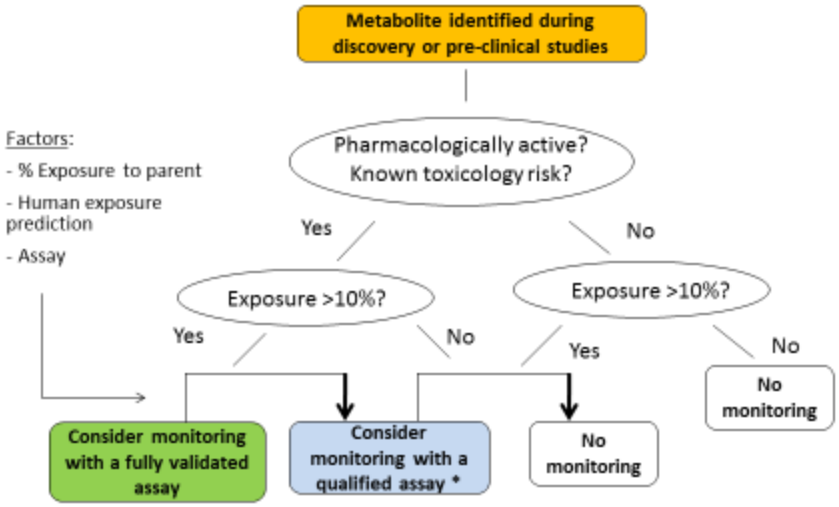
- Preliminary in vitro metabolism across species
- Preliminary plasma metabolite profiles and PK in animals

Factors:

- Pharmacological activity
- Toxicology risk
- Exposure
- Human exposure prediction

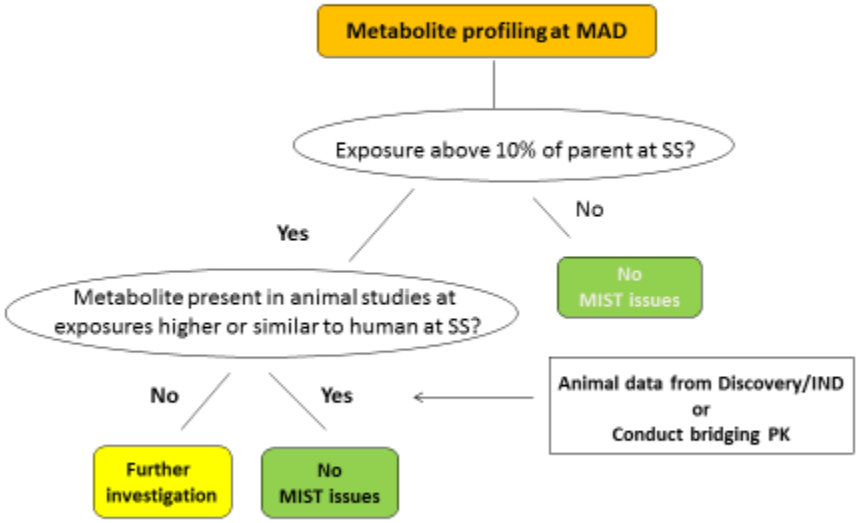
IND Tox studies and **Phase I** clinical generally supported by FFP qualified LC-MS/MS assays

Initial metabolite monitoring based on animal data (IND Tox-FIH)



*consider whether monitoring in IND Tox is necessary or whether Information from discovery is sufficient

Metabolite monitoring based on human data



References

1. Timmerman P, *et al.* Tiered approach into practice: scientific validation for chromatography based assays in early development –a recommendation from the European Bioanalysis Forum. *Bioanalysis* (2015) 7(18), 2387–2398

2. Timmerman P, *et al.* Best practices in a tiered approach to metabolite quantification: views and recommendations of the European Bioanalysis Forum. *Bioanalysis* 2(7), 1185–1194 (2010).

3 Lowes S, *et al.* Tiered approaches to chromatographic bioanalytical method performance evaluation: recommendation for best practices and harmonization from the Global Bioanalysis Consortium Harmonization Team. *AAPS J.* 17(1), 17–23 (2015).

4. Timmerman P. Tiered approach revisited: introducing stage-appropriate or assay-appropriate scientific validation. *Bioanalysis* 6(5), 599–604 (2014).

5. Timmerman P, *et al.* Feedback from the European Bioanalysis Forum Workshop: taking tiered approach to the next level. *Bioanalysis* 6(19), 2593–2598 (2014).

6. Hougton R, *et al.* Recommendations on biomarker bioanalytical method validation by GCC. *Bioanalysis* (2012) 4(20), 2439–2446

7. Timmerman P, *et al.* Scientific or regulated validation: a tiered approach? Meeting report from a joint EBF/DVDMDG workshop. *Bioanalysis* (2015) 7(14), 1703–1710.