Bioanalytical Methods Considerations and New Horizons

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Non-prescriptive/conceptual (Issues)

- Describes the issues that need to be satisfied for a validated method and the minimum standards
  - Allows for scientific judgment
  - Prescriptive may be too restrictive
  - Cannot conceive & capture all situations

- Not intended to be an extensive treatise on method validation or analytical platforms
Documents areas of consensus
Useful guide as we edit the Guidance
We have just finished collating the public comments
Active editing/writing this March
Crystal City V Workshop Report

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Non-Consensus areas *(more interesting!)*

• Not enough science/experience yet
• Basic philosophical differences
Non-Consensus areas

• **LC/MS:**
  - Analyte stability in presence of co-medications
  - Industry-not needed (rare events)
  - Agency: co-formulations and fixed regimens

• Multi-batch runs-QCs
  - Agency-QCs on all plates
  - Industry-not necessary
Non-Consensus areas

• LBA:
  • ULOQ acceptance criteria
    • Industry-25%
  • Agency: 20% (based on experience)
  • Would probably dilute in any case
  • Adding QCs if samples are bunched
    • Industry-not necessary-narrow range
Non-Consensus areas

- ISR-
  - Agency-flat 7%
  - Industry-at least 5%
  - Other agencies: 10%/5%

- Reference Stock Expiration
  - Industry-solutions of stock no longer subject to expiration date
  - Agency-need to extend stability
Non-Consensus areas

- ADCs
  - Industry-proposed specific acceptance criteria
  - Agency: insufficient experience
  - Both: should be based on performance
Non-Consensus areas

- LC/MS-proteins
  - Industry-proposed specific acceptance criteria
  - Agency: insufficient experience
  - Both: should be based on performance
New areas

- Biomarkers
Biomarkers

“Do you really want to include that in the Guidance?”

“Do we really need to do biomarker validation?”

Yes….

• Using biomarkers for safety, efficacy and patient selection and treatment

• As important, if not more important than characterizing PK of a new drug
Biomarker Example: Phase 3 Efficacy

Phase 3 Study-Endocrine drug
PK/PD Comparability Study

PD: Diagnostic kit—
• met design parameters

Reactivity with drug varied 3 Fold

Study data is uninterpretable

Need: High Reliability—(fully validated)
**Biomarker Example: Phase 1 Exploration**

- **Discovery**
- **Pre-Phase 1**
- **Phase 1**
- **Phase 2a/2b**
- **Phase 3**

Phase 1 Dose-escalation, safety, PK,
**Exploratory biomarker**

Reactivity with drug

Maybe the variability doesn’t matter
So much here……
Biomarkers: FFP Method Validation

What does FFP mean?...and when?

How much Validation Do I need here?

VS.

How much Validation Do I need here?

It depends on the level of risk......
The Questions We Need Answers to….

Am I measuring what I think I am measuring?
• Is the assay selective/specific for the analyte?
• Does anything interfere with the measurement?

What are the limits to these measurements?
• How high and low can I measure?
• What happens if you beyond these limits?

How much variability/error is in the measurement?
• How accurate/precise is the measurement?
• How much accuracy/precision do I need?

How do handling conditions affect the measurement?
• What affects the sample (even before I measure it?) Sample collection?
2. How much variability/error is in the measurement?
• What is needed? Are we looking for small(ish) continuous changes, or large discrete changes?
Some Takeaways…

Biomarkers & FFP

• Need **high reliability** (validation) when biomarkers are used for decision making
  • Study outcomes (approval)
  • Patient instructions

Biomarkers & FFP

• If the biomarker assay is for exploration, we can use less reliability (“less validation”)
Some Takeaways (cont’d)…

How much is less?

• No single universal paradigm of FFP
• Can’t predict all possible scenarios
• Development of cardiovascular drug may differ significantly from that of an oncology drug
  • Phase 1 biomarker data may require greater reliability in one setting compared to another

Get FDA feedback early
• Submitting data in the NDA or BLA limits everyone’s options for addressing issues
Harmonization

“We should harmonize guidances.”
Perception:
Regulatory agencies are sailing in different directions
Harmonization

New Drugs Filings

Bioanalysis worldwide-
Same Science

Harmonizing would seem to make sense....
Harmonization—may be not so easy…..

- Small molecules—might be manageable
- But many new topics that are not developed…..
Harmonization—may be not so easy…..

How would we manage this?
• ICH?
• OECD?
• Other?

• Not all countries are covered by these treaties…..
• Extremely long processes…..
  • Would it be worth it? Science will have moved on
Harmonization—is it really Evolution?

..and the scientists came together to discuss, debate, agree…
Self-alignment....governments & industry
Summary

There has been considerable alignment across the industry

- More agreement than disagreement
- Based on science, debate discussion
- A single document that accounts for bioanalytical scenarios?—never
  - Science should direct our conclusions, actions
Thank You

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