Reflections on Biomarker Assay Validation

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on behalf of EBF Biomarker team

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Introduction

- Biomarker Assay validation
  - A ”hot” topic
  - No clear guidance
  - Do we agree in the Bioanalytical Society?
  - Do regulators agree?

- Spring 2011: Established topic team 14 within EBF

Content

- Definitions on biomarker
- Diversity among biomarker assays
- Diversity among biomarker use
- Current understandings – within member companies
- EBF topic team 14

- Reflections from EBF

Official definition

- **<u>Biological marker (biomarker)</u>**: A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.
- *(Clinical Pharmacology & Therapeutics (2001) **69**, 89–95)*

Biomarker types

- Diagnostic Biomarker
- Safety Biomarker
- PD Biomarker
- Efficacy Biomarker
- Surrogate Biomarker
- Prognostic Biomarker
- Predictive Biomarker

- Decision/No decision

Which entities to measure

- Small molecule type, eg steroid hormone
- Peptide
- Proteins
- Antibodies
- RNA

- Quantitative, Quasi quantitative and Qualitative

Many assays used for biomarkers

- Immunoassays (ELISA, ECL etc)
- Automated clinical immunoassay platforms (eg Immulite, Elecsys)
- LC-MS
- Clotting activity
- Chromogenic activity assays
- RNA readouts: microarray/real-time PCR/RNA-Seq etc
- DNA readouts: SNPs, somatic mutations, circulating DNA etc
- Cell readouts: flow cytometry, circulating cells etc

Use (company definitions) of Biomarkers

- Early drug development phases
- Exploratory biomarker
  - Used for first time in a clinical trial/Study
  - Unlikely to be used for decision making
  - Decision risk for the project not the patient
  - Assay developed or
  - use commercial assay
  - Only limited or no validation

- *Moving forward the Biomarker may become more important for the clinical studies*

Use (company definitions) of Biomarkers

- Late drug development phases
- Decision making biomarker
- Primary and/or Secondary endpoint
  - Previously used in a clinical trial
  - Concluded to be a relevant marker
  - Responsive or predictive biomarker
  - Used for decision
  - Potential impact on project viability
- Assays validated

Biomarker assay Validation requirements

- Primary endpoint – Validated
- Secondary endpoint – Qualified/Validated
- Exploratory – Developed/Qualified

- What Validation parameters have to be tested in each stage?
- Would this be applicable for all biomarkers?
- If not- why not and for which biomarkers?

Validation parameters could be

Validation Parameter	Early stage (Exploratory)	Late stage (Decision making)
Normal range	No	Yes
Precision	Yes	Yes
Accuracy	Yes	Yes
Selectivity	No	Yes
Dilution linearity	No	Yes
Parallellism	No	Yes
Hook effect	No	Yes
Stability		
Bench top	Yes	Yes
Short term	No	Yes
Long term	No	Yes
Freeze thaw	No	Yes

Yes – only if applicable, strongly depending on assay

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Some gaps between practice and guidelines

More guidance perhaps required on:

- Dealing with endogenous biomarker background in QC prep
- Compensating for use of different (recombinant) protein standards for calibration curve and QC samples (if using commercial kits)
- Use of incurred vs. spiked samples for stability measurement – which is best?
- Where variation outside of limits is acceptable e.g. Accuracy but not precision

Conclusive remarks

- Discussions in EBF in early stage
- We hope to agree and influence the level of validation of biomarker assays – although it is very complex and many companies have quite different approaches
- TT will continue to discuss and bring topic to EBF Strategy meeting in Q1-2012
- Your continued input is appreciated
- Synergize with other initiatives on Biomarkers (e.g. GBC)

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Thank you for your attention