Reflections on Biomarker Assay Validation

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*on behalf of EBF Biomarker team*

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http://www.europeanbioanalysisforum.eu
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

- **Biological marker (biomarker):** 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

<table>
<thead>
<tr>
<th>Validation Parameter</th>
<th>Early stage (Exploratory)</th>
<th>Late stage (Decision making)</th>
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<tbody>
<tr>
<td>Normal range</td>
<td>No</td>
<td>Yes</td>
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<td>Precision</td>
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<td>Accuracy</td>
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<tr>
<td>Freeze thaw</td>
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</table>

Yes – only if applicable, strongly depending on assay
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)
Acknowledgement

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Thank you for your attention