Biomarkers, Companion Diagnostics and Enabling Technologies and Services for Personalized Medicine

Gary J. Kelloff, MD
National Cancer Institute
Special Advisor, Division of Cancer Treatment
Chair, Cancer Steering Committee of the
Foundation for the National Institutes of Health
Biomarkers Consortium

March 7, 2012

Analytical & Clinical Validation

Biomarker validation is the process of assessing the assay and its measurement performance characteristics, and determining the range of conditions (including clinical settings) under which the assay will give reproducible and accurate data

Qualification

Biomarker qualification is the evidentiary process of linking a biomarker with biological processes and clinical endpoints.

Qualification is verification that the biomarker is “fit-for-purpose.”

Wagner *et al.*, Clin Pharm Therap 2007; 81: 104–107

Biomarker Validation and Qualification

- "Qualification" of biomarkers as tools for efficient drug development described in the *Critical Path Initiative*.
- Features of this process:
  - Biomarkers measured using specific devices (*e.g.*, assays or instruments); if marketed, assays reviewed by FDA CDRH for ability to measure the biomarker analytically; CDRH clearance does not imply qualification.
  - Biomarkers considered for qualification are independent of specific device performing the measurement; any device measuring biomarker is expected to yield equivalent results.
  - Biomarker qualification not achieved without analytical and clinical validation of at least one device to measure the biomarker.

Kelloff GJ, Sigman CC. Nat Rev Drug Discov 2012; 11: 201–14

Biomarker Validation and Qualification

- Qualification data include consensus methods and evidence correlating biomarker measurements with sufficient clinical outcomes; standardization is limiting factor in acquiring these data.
- Qualification intended to provide generalizability across multiple clinical disorders, drugs, or drug classes, and to benefit patients.
- Qualified biomarker used for qualified "context of use" in IND and NDA/BLA submissions without need for further CDER review.
- FDA term "context of use" describes setting(s) in which the biomarker is qualified, and boundaries within which the available data justify its use. Context of use may expand as new data are obtained.

- Qualification also enables collaboration among stakeholders, reducing costs for individual stakeholders and providing biomarkers useful to multiple parties.

Kelloff GJ, Sigman CC. Nat Rev Drug Discov 2012; 11: 201–14

Challenges and Recommendations For Biomarker Based Drug Development

Challenge	Recommendation
• High Content Screening Assays, NextGen Sequencing, $1,000 Genome Sequence	• Match Data to Outcomes, Manage High Volume Data
• Increasing Importance of Cytogenetic, Epigenetic, and Proteomic Data	• Require Further Standards Development
• Co-development of Diagnostics and Therapeutics	• More Efficient Sequencing of Research and Development
• Clarification of Regulatory Pathway	• Molecular *versus* Target-organ Based Disease Approvals
• International Harmonization and Standardization	• Address Economic and Cultural Differences
• Multi-sector Cooperation	• Address Precompetitive and Intellectual Property Issues
• Increasing Interest and Clarity in Clinical Utility	• Provide Access to Complete Datasets with Outcomes
• Increasing Efficiency and Sophistication of Clinical Trial Designs	• Mitigate Risk of False Positives and False Negatives
• Increasing Numbers of Molecular Targets and Analytically Validated Assays	• Clarify FDA Clearance *vs* CLIA –Facilitated Access, Insurance Coverage Policy

Kelloff GJ, Sigman CC. Nat Rev Drug Discov 2012; 11: 201–14