Session 3:

Evidentiary Considerations for Biomarker-Based Enrichment of Clinical Study Populations to Increase Efficacy or Safety of Drugs

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August 21, 2015

Session 3 Agenda

2:00-2:15	Biomarker-based enrichment of clinical study populations	**Scott Patterson, PhD** Gilead Sciences, Inc
2:15-2:30	Neuroimaging enrichment biomarkers for CNS diseases	**Adam Schwarz, PhD** Eli Lilly and Co.
2.30-2.45	Case study: Polycystic Kidney Disease: From Bench to Bedside	**Arlene Chapman, MD** University of Chicago
2.45-3.00	Statistical considerations for BQ for biomarker-based enrichment in clinical studies	**Suzanne Hendrix, PhD** Pentara Corporation
3.00-3.40	Panel Discussion	

Biomarker-Based Enrichment of Clinical Study Populations

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Aims of Presentation

Address the following questions:-

- What is the relationship between Biomarker Qualification and how the biomarker is tested?
- How are patient selection and enrichment biomarkers used in drug development?
- What drives the need for biomarker qualification?
- Where do the biomarkers come from?
- How much evidence is required to consider qualifying a biomarker?
- What are the considerations should a qualified biomarker be used in clinical practice?

Biomarker & Test Qualification Background

Biomarker

- Biomarkers being considered for qualification are conceptually independent of the test method
- *But,* the biomarker must be reliably measured, *so,* the performance characteristics of the test method must be defined

Test Device

- FDA clearance or approval of a test device does not imply its qualification for drug development or evaluation
- *Nor* does biomarker qualification imply a test device has been FDA cleared or approved for use in patient care

Biomarkers and Clinical Trial Enrollment

- **A variety of characteristics are employed to define the patient population in clinical trials**
  - Patient characteristics (ECOG, DAS, etc)
  - Biomarkers used in the “Practice of medicine”
  - *Biomarkers for specific patient selection (IDE)*
- **Biomarkers used to monitor and predict outcome**
  - Safety assessments
  - Efficacy measurement or prediction (accepted surrogates)
  - *Biomarkers being evaluated for broader utility (Qualification)*

Patient Selection vs. Enrichment Biomarkers

Patient Selection

- Biomarker measured at screening, result defines trial eligibility
- Ultimate patient population will require testing using an FDA approved device to measure biomarker according to **Intended Use**
- Only used for multiple therapeutics if they are directed against the same target/pathway – evaluated separately each time

Enrichment

- Biomarker measured at screening, result defines trial eligibility
- Biomarker measured during trial (one or more times) and result may alter course of therapy in trial (removal, dose withheld, etc.)
- Once qualified, biomarker used for development and evaluation across multiple therapeutics according to the **Context of Use**
- Biomarker may not become part of ultimate patient population diagnostic test regimen*, or*
- Biomarker may be used in the practice of medicine for patient care

When Does the Need Become Apparent?

- **Existing clinical trial challenges:-**
  - Endpoint(s) imprecise
  - Timeframe to endpoint too long for expeditious trial
  - Endpoint reflects serious disease progression
- **Known biomarker/mechanism**
  - Evolution of the biomarker measurement
    - Improvement in accuracy or accessibility
  - Biomarker measured for different purpose
- **Unknown/poorly characterized biomarker/mechanism**
  - Growing body of evidence may reveal unanticipated utility
  - New biomarker developed from improved understanding of disease mechanism

NB: Duration of prospective biomarker qualification can’t occur faster than the timeframe for the emergence of the clinical endpoint

Revelation of Biomarkers for Qualification

- **Evidence for a biomarker may emerge over time from multiple clinical trials**
  - *NB: For molecular biomarkers, if appropriate samples have been banked (& analyte stable), carefully planned retrospective analyses may speed qualification*
- **In what form does the evidence emerge?**
  - Positive correlations between biomarker and disease process/outcome
  - Ability to measure the pathological/physiological process (biomarker) advances
  - Increased understanding of importance of pathological/physiological patient subgroup (prognostic)
- **Key is understanding the relationship between the biomarker and the disease and its longitudinal progression**

Qualification Selection Considerations

- **Careful definition of the Context Of Use for the specific biomarker is critical**
  - Foundation of Biomarker Qualification
  - Is trial design of completed studies appropriate (let alone banked samples, stability, etc)
- **What level of predictive accuracy indicates potential utility?**
  - Context dependent
- **What is the availability of tools to measure the biomarker?**
  - Harmonization throughout process important
  - Consider whether this will be required for the practice of medicine once drugs evaluated using this biomarker are marketed

Qualified Biomarkers, IVDs, Clinical Trials

- **Ideally, results of the biomarker of interest are already in a patients medical record**
  - Enhance enrollment potential
  - Eliminate need for separate biomarker assay development and IVD filing
- **‘Context of Use’ and ‘Intended Use’**
  - May overlap in some situations and not others
  - For marketed regulated products, may require additional claims to be sought
- **All-comers trials with stratification vs. selection**
  - If biomarker results not available IDE maybe required for selection
- **Harmonization or measurement across sites**
  - Accuracy of biomarker measurement

Biomarker Qualification and Timeframe

Prospective Trials	Previously Conducted Trials	
	Biomarker measured	**Samples banked**
Timeframe:		
Duration matches timeframe to emergence of clinical endpoint	Trial timeframe eliminated Expeditious	Trial timeframe eliminated Expeditious
Biomarker measurement:		
Single assay can be specified/harmonization possible	Likely more than one assay employed/bridging study to harmonize?	Single assay can be specified/harmonization possible
Considerations:		
Greatest control over entire process – longest timeframe	Success dependent upon trial conduct and biomarker measurement	Success dependent upon trial conduct and quality/ascertainment of samples

Biomarker Measurement Considerations

- **Previously measured**
  - How well were assay performance characteristics defined?
  - If biomarker measured in different labs was cross-site reproducibility determined?
  - Any samples banked to confirm assay reproducibility?
  - Analyte stability established?

- **Banked Samples**
  - Analyte stability established?
  - Opportunity to ensure testing conducted with consistent assay whose performance characteristics have ben established (locked down)

Labeling and Drug Development Tools

- **For qualified biomarkers that will be used in the clinic beyond drug development and evaluation:-**
  - If, the biomarker defines a patient population and whether they may benefit from the drug based upon ongoing biomarker measurement, then,
  - How should this information be conveyed in the drug label?
- **Considerations on the consequence of such a result:-**
  - Testing should not become a barrier to patients being able to receive therapy
  - How many centers will offer such testing?
  - Will maintaining consistency of measurement be an issue?
- **Success most likely if biomarker already utilized in clinical practice (likely a different purpose)**

Closing Thoughts

- **Therapeutic area and knowledge of disease process will influence likelihood that the necessary coordinated efforts for biomarker qualification will occur**
- **Banked samples for qualification of molecular biomarkers more likely in diseases with rapid progression (i.e., consider oncology)**
- **Long term efforts with prospective (and retrospective) evaluation appear more likely in non-oncology settings?**
- **Need to keep a long-term view of the measurement of the biomarker in mind – is it only for drug development and evaluation or may it be adopted in clinical practice?**

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Panel Session Questions?

- **Methods for biomarker measurement**
  - How early can they be harmonized?
- **Biomarkers used in the Practice of Medicine**
  - Can existing data be used to support biomarker qualification?
- **Ultimate use of biomarker?**
  - Important to consider whether qualified biomarker only used drug development and evaluation or may it be adopted in clinical practice?

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