Session 3:
Evidentiary Considerations for Biomarker-Based Enrichment of Clinical Study Populations to Increase Efficacy or Safety of Drugs

Scott D. Patterson, PhD
Vice President, Biomarker Sciences

August 21, 2015
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Biomarker-Based Enrichment of Clinical Study Populations

Scott D. Patterson, PhD
Vice President, Biomarker Sciences

August 21, 2015
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 patient's 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

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<tr>
<th>Prospective Trials</th>
<th>Previously Conducted Trials</th>
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<tr>
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<td>Biomarker measured</td>
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<tr>
<td><strong>Timeframe:</strong></td>
<td>Trial timeframe eliminated</td>
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<tr>
<td>Duration matches timeframe to emergence of clinical endpoint</td>
<td>Expeditious</td>
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**Biomarker measurement:**

<table>
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<tr>
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<th>Likely more than one assay employed/bridging study to harmonize?</th>
<th>Single assay can be specified/harmonization possible</th>
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**Considerations:**

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<th>Success dependent upon trial conduct and biomarker measurement</th>
<th>Success dependent upon trial conduct and quality/ascertainment of samples</th>
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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 been 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?