A Regulatory Perspective on Strategies for Implementation of Biomarkers in Clinical Trials

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Key Questions

• Is there really a business case for biomarkers in drug development?

• What are scientific and strategic considerations in clinical biomarker Qualification?

• What challenges currently exist and how can they be circumvented?
The Case for Biomarkers in Drug Development and Evaluation

Assessing the translatability of drug projects: what needs to be scored to predict success?

Martin Wehling

Translatability scoring in drug development: eight case studies

Alexandra Wendler and Martin Wehling

Lessons learned from the fate of AstraZeneca’s drug pipeline: a five-dimensional framework

David Cook, Dearg Brown, Robert Alexander, Ruth March, Paul Morgan, Gemma Satterthwaite and Menelas N. Pangalos
Key Contributors to Drug Development Project Success

Right target
- Strong link between target and disease
- Differentiated efficacy
- Available and predictive biomarkers

Right tissue
- Adequate bioavailability and tissue exposure
- Definition of PD biomarkers
- Clear understanding of preclinical and clinical PK/PD
- Understanding of drug–drug interactions

Right safety
- Differentiated and clear safety margins
- Understanding of secondary pharmacology risk
- Understanding of reactive metabolites, genotoxicity, drug–drug interactions
- Understanding of target liability

Right patients
- Identification of the most responsive patient population
- Definition of risk–benefit for given population

Right commercial potential
- Differentiated value proposition versus future standard of care
- Focus on market access, payer and provider
- Personalized health-care strategy, including diagnostic and biomarkers

Cook 2014 [PMID 24833294]
Biomarker-related Determinants of Success

• Availability of safety/efficacy prediction biomarkers
  – Grading: No biomarker/distal vs. well accepted surrogate
  – Development: None vs. started with high likelihood for leverage throughout development

• Strategy
  – Does not reach beyond current stage of development vs.
  – Covers all major aspects of even distal clinical development

• Targeted aspects
  – Disease sub-classification (prognostic enrichment)
  – Responder subsets identifiable (matching pathobiology to pharmacology)

Adapted from Wehling 2009 [PMID 19543224]
Key Questions

• Is there really a business case for biomarkers in drug development?

• **What are scientific and strategic considerations in clinical biomarker Qualification?**

• What challenges currently exist and how can they be circumvented?
Scientific and Strategic Considerations

- High
- Low

"Risk"

- Exploratory (agnostic)
- Decisional

Intended Developmental/Regulatory Use

- Regulatory Scrutiny
- Low

Graph showing the relationship between "Risk" and Regulatory Scrutiny.
Consideration #1: Starting with the End in Sight

• What **SPECIFIC** decisions are we trying to influence?
  – Go/No Go (internal)

  – Go/No Go (regulatory)
    • Enable/enhance early phase clinical trial monitoring (e.g., animal toxicity seen, animal toxicity of unknown clinical relevance seen, or some other regulatory discomfort exists)
    • Approval (accelerated, traditional)
Consideration #1: Starting with the End in Sight

• What **SPECIFIC** decisions are we trying to influence?
  – Trial design planning and analysis
    • Dose selection (prospective, post-hoc)
    • Patient selection (prognostic, predictive)
    • Endpoint selection
    • Adaptation

  – “Supportive”
    • Provide interpretive context (assurance, insight, understanding) for what is seen clinically*

*Not a decision, but what may start out as supportive may become pivotal*
Consideration #1: Starting with the End in Sight

• What **SPECIFIC** biomarker utility are we trying to achieve?
  – Measure function, damage, or adaptive response (pharmacological, pathological)
  – Predict efficacy/toxicity
  – Detect bona fide activity (e.g., response, damage) in a “better” way (e.g., easier, earlier, more sensitively/specifically)
  – Add incremental benefit over standard markers
Consideration #1:
Starting with the End in Sight

- Answering these two questions with clarity should help:
  - Develop clear contexts of use (COU)
  - Determine best pathway for “vetting”
  - Anticipate evidentiary requirements
  - Assess feasibility
  - Workstream and resource planning

- Action item: Map the universe of clinical COUs in AD, PD (there are probably not as many as we think)
Consideration #2:
Deciding What Approach To Take

• What are the possibilities?
  – CDER BQP
  – Product-specific negotiation (under IND)
  – Community-based scientific development and vetting

• What could drive choice of one over another?
  1. What is the goal: scientific input, collaboration, regulatory endorsement?
  2. Are we trying to “replace” a standard endpoint or approach?
  3. How comfortable do we want regulators to be?
  4. What “mass” of regulators do we want to be comfortable?
  5. What do we want regulatory “acceptance” to look like (e.g., guidance or a series of ok’s [e.g., within the context of a single development program])?
  6. How predictable do we want future dialogues to be (e.g., guidance as a shared starting point)?
  7. What is the time horizon?
Consideration #3: Preparing for Early Dialogue

- **COU/Decisions**
  - What actions can specifically be based on biomarker results
  - Which biomarkers, which tissues, what times
  - Rationale for selection of biomarkers
  - Multi-analyte considerations
  - Use in conjunction with standard biomarkers, entry criteria

- **Current Knowledge**
  - Support for biomarker use in a given context (and not supportive)
  - Knowledge gaps and need to address
  - Sources of variability and relative importance
  - Data available
  - Methodological approaches (including analysis of existing data)
  - New studies needed

- **Test Method**
  - Method description
  - Analytical performance
  - Plans for cross-validation if different platforms
Miscellaneous Thoughts on Translational* Strategy

• Plan to establish utility in a narrow context of use ("added value" or "outperformance")
• Plan to generate sufficient information on biomarkers with an eye toward myriad major uses in drug development
• "Learn and confirm" (devil is in the details [e.g., if detection or prediction; individual vs. population])
  – Clear goal, phenotype definition, plan for discovery and validation
  – Prospective studies can be small (extensive phenotyping) or have occurred in the past (data quality, curation, phenotype definition)
  – Confidence that the biomarker is measuring what we think it’s measuring may not always be sufficient to construct a COU
  – COU will drive risk tolerance (what are the risks of “qualifying” if we are uncertain about given aspects of the biomarker)
• Action item: 1) a COU opportunities list; 2) strawman evidentiary work ups; 3) a reassessment of academic involvement

* Here I mean portability (e.g., from non-clinical to human; across disease phenotypes; across phases of development, etc).
Key Questions

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Challenges (That Will Likely Always Exist)

- Extensive workup linking biomarker to meaningful phenotype
- Translation (e.g., across species)
- Lack of access to relevant human tissue
- Variability (the known and the unknown)
- Multiplicity (statistical and scientific)
- Rarity of endpoints
- Difficulty of scientific consensus building (e.g., “fit-for-purpose” evidentiary standards)
- ROI: qualification can be logistically hard, expensive, and take a long time
A Holistic Approach to Enable Biomarker Development and Acceptance

1. **Mindset**: Qualification efforts operationally and methodologically embedded in the organization

2. **Open innovation**: Consider different models to generate collaboration and “competition” among internal and external partners

3. **Purpose**: Teams created/exist to drive outcomes

4. **Execution**: Design processes and practices (beyond strategy and structure)

5. **Knowledge management**: Ideas, technology, projects, experiences are stored, recycled, reused (nothing thrown away)

6. **Metrics**: Use metrics to assess quality/performance/outcomes

7. **Leadership**: Helps define expected outcomes and conditions for success

Adapted from FL Sax (Quintiles 2012) in summary of Hay Group (2009)
Take Home Messages

• There is significant need for useful biomarkers to aid in making a spectrum of decisions
• Clarity on the desired outcome is critical (start at the end)
• Several approaches to gaining biomarker acceptance exist each with its strengths and limitations
• Early engagement with FDA on biomarker qualification predictably centers on COU/decision-making intention, current knowledge and available data, test methodology
• Translation will likely be driven by a series of (hopefully structured) learn and confirm exercises
• Challenges will exist but are not insurmountable
• Design principles (including open innovation and metric development), data standardization, and data sharing are critical and should be considered prior to embarking on a qualification initiative
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