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

OPINION

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

Martin Wehling

Translatability scoring in drug development: eight case studies

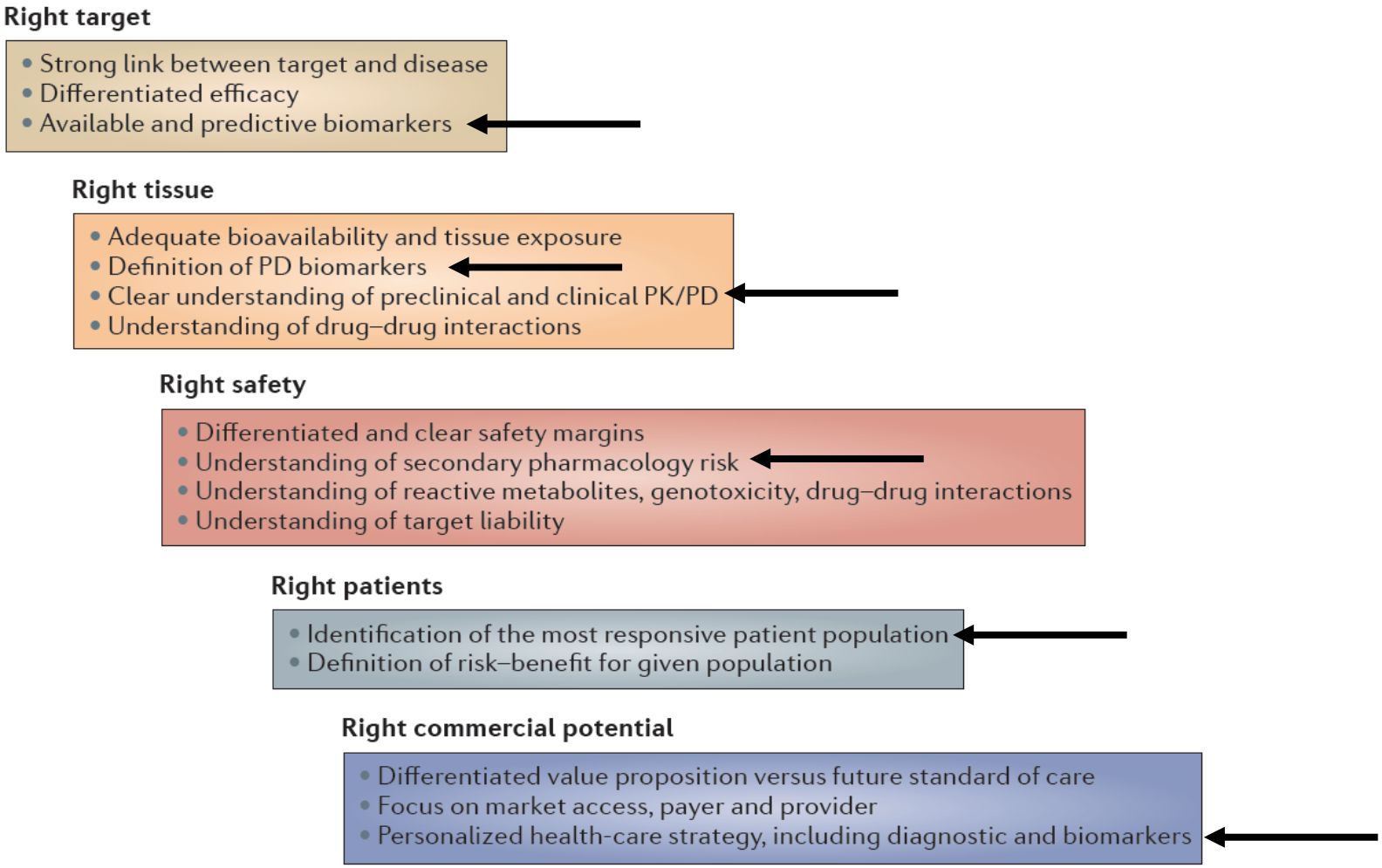
Alexandra Wendler and Martin Wehling*

OUTLOOK

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



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]

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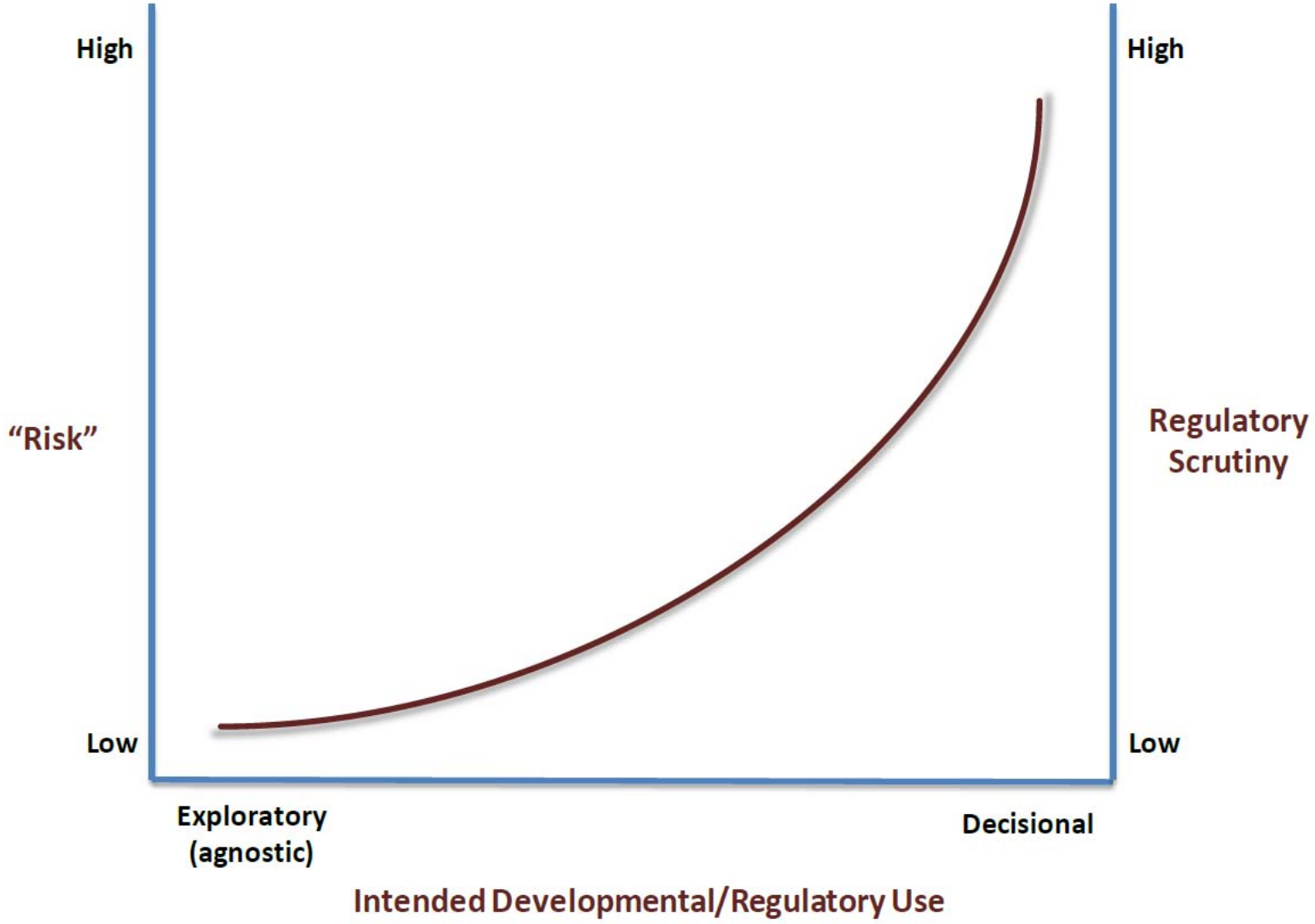
Scientific and Strategic Considerations



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).

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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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