A United States Regulator’s Perspective on Risk-Benefit Considerations

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Benefit/Risk Assessments

- Assessment of B/R is a qualitative approach that is grounded in quantification of various data elements
  - Benefits – Efficacy endpoints from controlled clinical trials
  - Risks – Harms reported in clinical trials and other sources (e.g., spontaneous adverse event reports)

- Evaluation of B/R is dynamic
  - Knowledge of benefits and risks evolves over product life-cycle

- Decisions on B/R require judgment on the part of the regulator and are influenced by:
  - Statutory/regulatory standards
  - Societal expectations
  - Personal values and perspectives
Risk-Benefit Considerations in Drug Regulatory Decision-Making

What’s On The Regulator’s Mind?

- Adverse Event Incidence
- Communication
- Trial Design and Conduct
- Risk of Products In Same Class
- Clinical Relevance Of Endpoint
- Expected Patient Compliance
- Availability of Other Therapies
- Treatment Effect
- Nature of Disease
- Trial Drop-outs
- Serious Adverse Event Incidence
- Off-Label Potential
- Risk in Chronic Use
- Restricted Distribution
- Risk Management
- Study Population
- Statistical Significance
- Relative Efficacy
- Medication Guides
- Education
- Labeling
- Patient Preference
- Efficacy in Subgroups

Uncertainty
What Might Help a Regulator?

...a framework that moves them from here:
What Might Help a Regulator?

...to here:
Desirable Properties

- Simple and user-friendly
- Address critical issues
- Capture expert views faithfully
- Represent transparently
- Compatible with quantitative analysis of clinical benefit and safety information
- Facilitate communications (internal and external)
- Broadly applicable
### Potential Qualitative Framework

<table>
<thead>
<tr>
<th>Consideration</th>
<th>Favorable Benefit-Risk</th>
<th>Non-Contributory</th>
<th>Unfavorable Benefit-Risk</th>
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</thead>
<tbody>
<tr>
<td>Severity of Condition</td>
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<td>Unmet Medical Need</td>
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<td>Clinical Benefit</td>
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<td>Risk</td>
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<td>Risk Management</td>
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Framework Attributes

- Simple, not simplistic, design based on mental model approach
- Supports sound expert judgment, not a replacement for it
- Identifies and respects areas of expert disagreement
- It tells the story:
  - What is the problem?
  - What other potential solutions exist?
  - What is the benefit of proposed solution?
  - What am I worried about?
  - What can I do to mitigate/monitor those concerns?
Value of Framework

• Provides a high-level snapshot – the “big picture” – of the issues relevant to the regulatory decision
• Provides concise bottom-line description of the evidence on each topic and the B-R implications
• Supports more structured discussions of the range of issues involved in B-R assessments
• Could improve predictability and consistency through a standardized structure
• Could function as a living document, able to be updated based on new information
Judgment and B/R

- Science provides data to inform our analyses of B/R, it does not provide the answers – judgment is required
- Regulators make judgments on B/R at the population level
- Doctors and patients must translate the population B/R information to make judgments on an individual patient level
Choice and B/R

• What is the value of having additional choices for treatment of a specific condition?
  – U.S. statutory standard does not require that a new therapeutic be superior to available choices, only that it be safe and effective for the intended use
  – This standard implicitly values choices and frames regulatory decision-making
Choice and B/R

- Who should be making the choices on what products are available to doctors and patients
  - Our system requires that regulators decide on what products are approved
  - Our system also assumes that prescribers and patients have a role in decision-making
  - Where to set that balance is influenced by many factors and significantly impact judgments made by regulators both pre-approval and postmarketing
Summary

• Regulatory R/B decision-making is a qualitative science grounded in quantitative data.

• Judgment is required in making regulatory R/B decisions and those judgments are influenced by many factors, both extrinsic and intrinsic.

• Clearly outlining the available data and how decisions (judgments) were made can improve transparency of the decision-making process.
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