Benefit-Risk Considerations in CDER: Development of a Qualitative Framework

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What problem are we trying to address?

- CDER identified the need for a more structured benefit-risk assessment in the review process
  - Better communicate the reasoning behind CDER's decisions
    - Which benefits/risks or other factors were considered?
    - How was evidence interpreted?
    - How were risks and benefits weighed?
  - Ensure the "big picture" is kept in mind during a complex, detailed review
- This effort was initiated in 2009 and has continued with the support of internal and external decision science and drug regulatory experts

A Balancing Act: Judgment vs. Quantitative Analysis

- **We examined formal quantitative methods, but had some concerns**
  - Reducing complex considerations into a single scale cannot capture the nuanced assessments in FDA's decisions
  - Quantitative analysis risks obscuring subjective expert judgment
- **We determined that a structured qualitative approach best fit our needs**
  - Approach best reflects the reality that B-R assessment is a qualitative exercise grounded in quantification of various data
  - Flexible to accommodate more complex supporting quantitative analyses that can aid, rather than replace, expert judgment
  - Rigorously communicates the basis for decisions in words

Key Goals and Design Principles of a Benefit-Risk Framework

- **Support review staff**
  - Facilitate identification of critical issues regarding benefits and risk
  - Faithfully capture the review team's careful deliberations and represent expert views transparently
  - Ensure that the benefit-risk balance is kept in mind throughout review
  - Recognize dynamic nature of B-R assessment over the lifecycle
  - Efficiently align with a review team's existing processes
- **Support signatory authorities**
  - Provide an internal communication vehicle between the review team and the signatory authority
  - Assist in communication about the decision (e.g., preparation of the decision memo)

Framework Development

- **Developed and tested a conceptual framework**
  - Explored 6 case studies of past regulatory decisions to "tease out" the range of benefits and risks considered
  - One-on-one interviews of key review disciplines painted the picture of the relevant issues for each decision
- **Road-tested in more recent regulatory decisions**
  - Explored 2 additional case studies using a focus group process
  - Framework revised as a result
- **Overall process and development guided by senior management**
  - Office of New Drugs, Office of Surveillance and Epidemiology, Office of Biostatistics
  - Recognized that effective decision support must begin with an understanding of how the decision-makers think, i.e., you must bring them along for the "ride"

Benefit-Risk Assessment Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Summary of evidence:	Conclusions (implications for decision):
Unmet Medical Need	Summary of evidence:	Conclusions (implications for decision):
Benefit	Summary of evidence:	Conclusions (implications for decision):
Risk	Summary of evidence:	Conclusions (implications for decision):
Risk Management	Summary of evidence:	Conclusions (implications for decision):
Benefit-Risk Summary and Assessment		

The Rows: Key Benefit-Risk Considerations

Information on the Therapeutic Area

- Analysis of Condition
- Unmet Medical Need

→ Provide clinical context for weighing benefits and risks

Product-Specific Information

- Benefit
- Risk

→ Use all information available to make judgments on the benefits and risks to the population

- Risk Management

→ Describe risk management plan (if required) and its expected impact to reduce or further characterize safety concerns

The Columns: Evidence and Conclusions

Evidence and Uncertainties

- What you know (facts)
- What you don't know (uncertainties and underlying assumptions)
- How good are the data?

Conclusions and Reasons

- What do you make of the data and uncertainties?
- Analysis of the information and its clinical relevance
- Drawing conclusions within each key consideration

Benefit Risk Summary & Assessment – A balanced written analysis of the factors and their tradeoffs that summarizes the resulting regulatory recommendation or action

Sample Framework Questions: Therapeutic Area

Analysis of Condition

- Describe the condition that is treated or prevented by the drug.
- What are the clinical manifestations of the condition, what is known about its natural history, and how does severity vary across sub-populations?

Unmet Medical Need

- Describe the other therapies used to treat the condition, including approved and off-label pharmacological therapies and non-pharmacological therapies.
- How effective and how well-tolerated are these alternatives, and what evidence is available to support these conclusions?

Sample Framework Questions: Product-Specific

Benefit

- Describe the trials (including strengths and weaknesses) that were conducted to establish efficacy.
- What endpoints were evaluated and how are they clinically meaningful? How did the benefits vary across sub-populations of responders?

Risk

- Characterize the safety concerns identified in the clinical trials. What was the incidence of the risk in the study population, and does the incidence vary by sub-population? Is there a range in the severity of the risk, does it change with continued exposure, and is it reversible when treatment is stopped?
- How might the incidence change in the post-market setting? Is additional work needed to further characterize the risk?

Risk Management

- Which risks (if any) require mitigation or further characterization? What tools are recommended to address the risks, and what is the expected contribution of each tool to the overall risk management plan.
- What would constitute a successful risk management plan, how that might be measured, and if the desired impact is not achieved, at what point should the risk management plan be re-evaluated?

B-R Framework designed to "tell the story" of the regulatory decision

- **What is the problem?**
  - *Analysis of the Condition*
- **What other potential interventions exist?**
  - *Unmet Medical Need*
- **What is the benefit of the proposed intervention?**
  - *Benefit*
- **What am I worried about?**
  - *Risk*
- **What can I do to mitigate/monitor those concerns?**
  - *Risk Management*

Where are we now?

Road-testing in "live" reviews

- **6 ongoing reviews in CDER's Office of New Drugs**
- **Evaluate and further refine framework**
  - How is the framework helpful to reviewers and signatory authorities?
  - How could it be improved?
- **Support implementation into CDER review process**
  - How can use of the framework align with current processes?
  - When should the framework be populated?
  - Who should do it?

Benefit-Risk in PDUFA V: FDA's Commitments

- Publish a 5-year plan that describes FDA's approach to implement a structured benefit-risk framework by December 31, 2012 and begin execution by September 30, 2013
- Conduct two public workshops on benefit-risk from the regulator's perspective that will begin by December 31, 2013
- Develop an evaluation plan to ascertain the impact of the benefit-risk framework
- Revise review templates, decision memo templates and MaPPs as appropriate to incorporate FDA's approach

Parting Thoughts

- **Virtue of the Approach**
  - Integrating the decision-makers in this effort has had the effect of improving organizational "buy-in"
- **Value of the Framework**
  - Provides a high-level snapshot—the "big picture"—and the concise bottom-line descriptions of the issues relevant to the regulatory decision
  - Sufficiently flexible to accommodate a wide range of considerations through a question-based approach within a standard structure
  - Facilitates greater explicitness of the issues identified in a review and discussion of what will really matter in the regulatory decision
  - Clearly articulates the clinical reasoning and judgment behind regulatory decisions which can improve transparency in the decision-making process