

Advancing Structured Benefit-Risk Assessment in FDA Review

The Duke-Margolis Center for Health Policy • Washington, DC

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For human drug review, structured benefit-risk assessment may be defined as the suite of systematic processes and tools to assess and communicate: a) the public health benefits and risks of medical products; and b) the relative weighing of those benefits and risks in support of FDA's regulatory decisions. FDA's qualitative Benefit-Risk Framework serves as the foundational element of CDER's (FDA Center for Drug Evaluation and Research) and CBER's (FDA Center for Biologics Evaluation and Research) structured benefit-risk assessment. With implementation of the Benefit-Risk Framework underway, there remains interest in exploring more technical approaches to benefit-risk assessment that might support decision-making in targeted cases. Today's meeting will provide stakeholders the opportunity to explore and discuss how to strengthen the value of the Benefit-Risk Framework through the application of technical and decision-analytic approaches to structured benefit-risk assessment in both the pre-market and post-market review of drugs and biologics. Input from this meeting will support the Agency in its continued efforts to advance and integrate structured benefit-risk assessment in FDA's human drug review.

The specific objectives for the meeting are to discuss: 1) when and how application of structured benefit-risk assessment approaches and tools can contribute the greatest value to support regulatory decision-making, 2) key considerations for ensuring that benefit-risk assessment approaches and tools are fit-for-purpose in FDA's drug regulatory context, and 3) strategies for incorporating patient input (derived through both qualitative and quantitative methods) into structured benefit-risk assessment.

9:00 a.m. Welcome and Introduction

Gregory Daniel, Duke-Margolis Center for Health Policy

9:15 a.m. Overview of Benefit-Risk Assessment in Human Drug Review

Presentation: *Sara Eggers, Center for Drug Evaluation and Research, U.S. Food and Drug Administration (15 min)*

Objective: Introduce the Benefit-Risk Framework and discuss how today's workshop fits into FDA's broader efforts to advance structured benefit-risk assessment.

Presentation: *Richard Forshee, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration (15 min)*

Objective: Review the current landscape of decision-analytic approaches that have been explored or contemplated for benefit-risk assessment in human drug review.

Q&A (10-15 min)

10:00 a.m. Session I: Defining the Potential for Decision-Analytic Approaches to Inform the Benefit-Risk Framework

Objective: Discuss the value of the Benefit-Risk Framework as a structured qualitative approach and explore opportunities for strengthening and clarifying the role and value of the framework. Discussion will elicit perspectives on, broadly, how targeted application of more technical approaches within the framework may add value to regulatory benefit-risk assessment. Discussion will also identify important regulatory constraints and parameters that impact the feasibility and applicability of these approaches.

Structure:

- **Opening commentary:** *Baruch Fischhoff, Carnegie Mellon University (10 min)*
- **Regulatory response:** *Steven Anderson, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration (5 min)*
- **Moderated Discussion**

Questions to address:

- What are possible opportunities for strengthening the value of the Benefit-Risk Framework? (e.g., making the Benefit-Risk Framework a standard communication tool, integrating it into Advisory Committee Meetings, etc.)
- What additional value could more formal decision-analytic approaches bring to FDA's benefit-risk assessment process, and in what situations?
- What are the important questions that need to be addressed in order to successfully apply such approaches in the context of drug regulatory evaluation (i.e., to ensure they are fit-for-purpose)?

11:00 a.m. Break

11:15 a.m. Session II: Framing Decision Problems and Characterizing Uncertainties about Benefits and Risks

Objective: Explore more structured methods (beyond the current framework) to frame complex regulatory decision problems and characterize uncertainty about the benefits and risks of a drug. Types of approaches (qualitative, semi-quantitative, and quantitative) that may be relevant to this topic include decision trees, value trees, visualization tools, subjective probability elicitation, and probabilistic modeling.

Structure:

- **Opening commentary:** *Lawrence Phillips, London School of Economics (10 min)*
- **Regulatory response:** *Theresa Mullin, Center for Drug Evaluation and Research, U.S. Food and Drug Administration (5 min)*
- **Moderated Discussion**

Questions to address:

- In what situations (e.g. types of regulatory decisions) could the approaches described above add value to the benefit-risk assessment and communication, and how?
- How could such approaches be integrated into drug review and the Benefit-Risk Framework, from a process point of view?
 - What would be required from FDA review staff?
 - Are there processes to engage external experts?
 - What information would be needed from the Applicant?
- What are the key considerations for ensuring these approaches are fit-for-purpose within those contexts? (i.e., sufficiently transparent to all stakeholders, adequately supports clear judgment, etc.)
- What might be realistic measures of success in applying these approaches?

12:15 p.m. Lunch

1:15 p.m.

Session III: Weighing Benefits and Risks in Human Drug Review

Objective: Examine qualitative and quantitative decision-analysis methods that can be used to support FDA efforts to make tradeoffs about the benefits and the risks (including uncertainties) of a given product. Types of methods that may be relevant to this topic include weighting processes and sensitivity analyses of various kinds.

Structure:

- **Opening commentary:** *Bennett Levitan, Janssen Research & Development (10 min)*
- **Regulatory response:** *Peter Stein, Center for Drug Evaluation and Research, U.S. Food and Drug Administration (5 min)*
- **Moderated Discussion**

Questions to address:

- Understanding that these types of approaches may require significant effort, in what situations should FDA consider applying more formal processes to assessing benefits *versus* risks approaches to support their decision-making?
 - Are there specific approaches that may be most tractable in certain circumstances?
- How could such approaches be integrated into both drug review and the Benefit-Risk Framework, from a process point of view?
 - What would be required from FDA review staff?
 - Are there processes to engage external experts?
 - What information would be needed from the Applicant?
- What are the key considerations for ensuring these approaches are fit-for-purpose within those contexts? (i.e., sufficiently transparent to all stakeholders, adequately supports clear judgment, etc.) What might be realistic measures of success in applying these approaches?

2:15 p.m.

Session IV: Incorporating Patient Input into Benefit-Risk Assessment

Objective: Explore outstanding questions regarding formally applying and using systematic approaches to assessing patients' priorities, preferences, and information needs to inform FDA's benefit-risk assessments. Approaches may include formal methods such as discrete choice analysis or best-worst scaling, but it must be recognized that patient input can come from many other sources. A goal of this session is to outline concrete steps that can be undertaken in order to address methodological and practical challenges with applying such methods in the drug regulatory context.

Structure:

- **Opening commentary:** *Brett Hauber, RTI Health Solutions (10 min)*
- **Regulatory response:** *Laura Lee Johnson, Center for Drug Evaluation and Research, U.S. Food and Drug Administration (3-5 min)*
- **Regulatory response:** *Telba Irony, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration (3-5 min)*
- **Moderated Discussion**

Questions to address:

- In what situations could dedicated patient preference studies add the most value to CDER's and CBER's benefit-risk assessments, and how?

- What are the key regulatory considerations for ensuring that these approaches can support CDER's and CBER's benefit-risk assessments?
- In lieu of patient preference studies, are there other approaches that FDA could consider to more systematically incorporate patient input into benefit-risk assessment?

3:15 p.m. Break

3:30 p.m. Session V: Identifying Key Themes and Potential Paths Forward

Objective: Reflect on the day's discussion, specifically revisiting any key concerns or issues that were identified in Session I, as well as any themes that emerged throughout the day.

Structure:

- **Moderated Discussion**

Questions to address:

- What are the key considerations for FDA as it continues its efforts to incorporate more decision-analytic approaches into drug review?
- What is a research agenda that would help advance the use of these methods to support FDA decision-making?

4:15 p.m. Closing Remarks

Gregory Daniel, Duke-Margolis Center for Health Policy

4:30 p.m. Adjournment

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