Decision Analysis at FDA's Center for Drug Evaluation and Research

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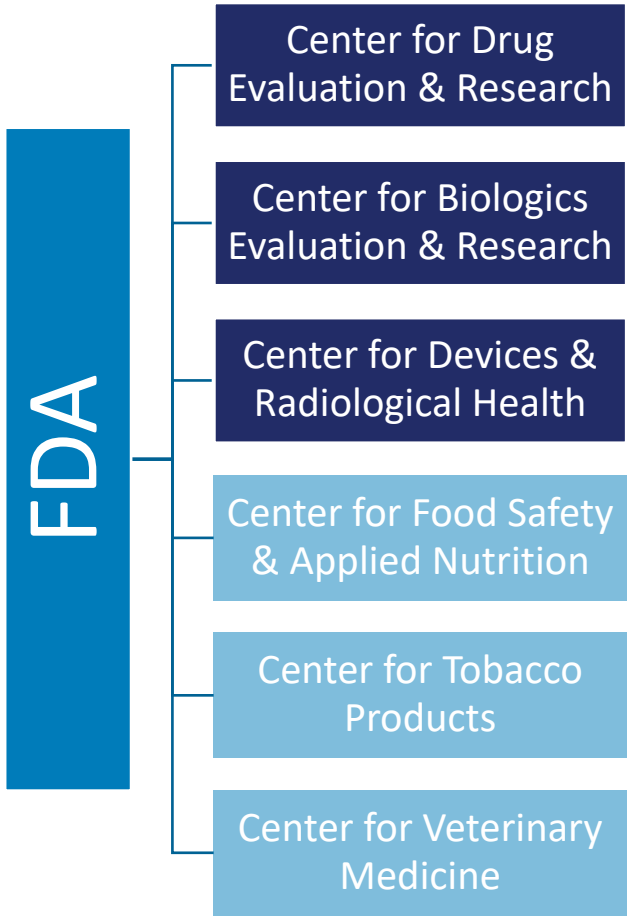
Session Objectives



1. Provide a window into medical product approval decisions at FDA
2. Discuss some of the techniques used by decision-makers
3. Identify connections between Agency decisions and stakeholder actions

Session Outline

- Dr. Lackey (CDER):
  - Context for Agency benefit-risk assessments for human drugs & biologics
  - Qualitative, descriptive example of benefit-risk assessment
- Dr. Yang (CBER):
  - Case study of the Agency assessment of the COVID Vaccine
  - Quantitative techniques to estimate outcomes
- Dr. Gebben (CDRH):
  - *Presented by Dr. Eggers (CDER)*
  - Application of patient preferences for device decision-making

Drug Regulatory Context

“To be approved for marketing, a drug must be safe and effective for its intended use.”

Effective is codified in statute:

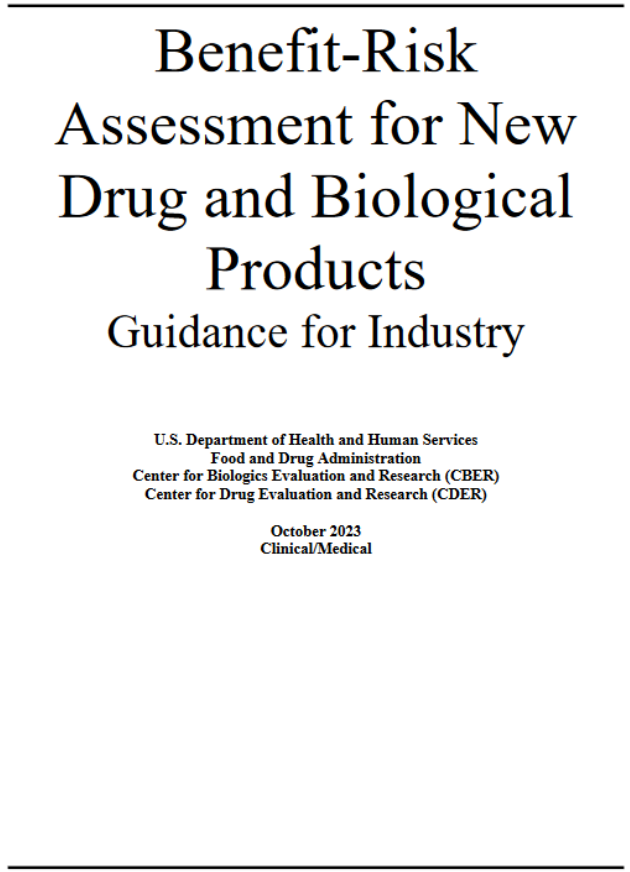
- Demonstrates “substantial evidence that the **drug will have the effect** it purports or is represented to have under proposed labeled conditions of use” (21CFR314.125, 21CFR314.126)

“Safe” is not explicitly define in statute or regulations

- Interpreted as the determination that a **drug’s benefits outweigh its risks**

CDER & CBER Guidance for industry

- FDA's approach to, and considerations for, **benefit-risk assessment for regulatory decision-making**
  - Straightforward vs challenging assessments
  - How patient experience data informs benefit-risk assessment
  - Lifecycle of benefit-risk assessment (including postmarket)
- Concepts to guide **sponsors' benefit-risk activities**
  - Benefit-risk planning to establish a favorable benefit-risk profile
  - Sponsor-FDA interactions to inform planning
  - **Patient preference information and additional benefit-risk analyses**
  - Effectively presenting benefit-risk information in submissions


Benefit-Risk Assessment for New Drug and Biological Products

Guidance for Industry

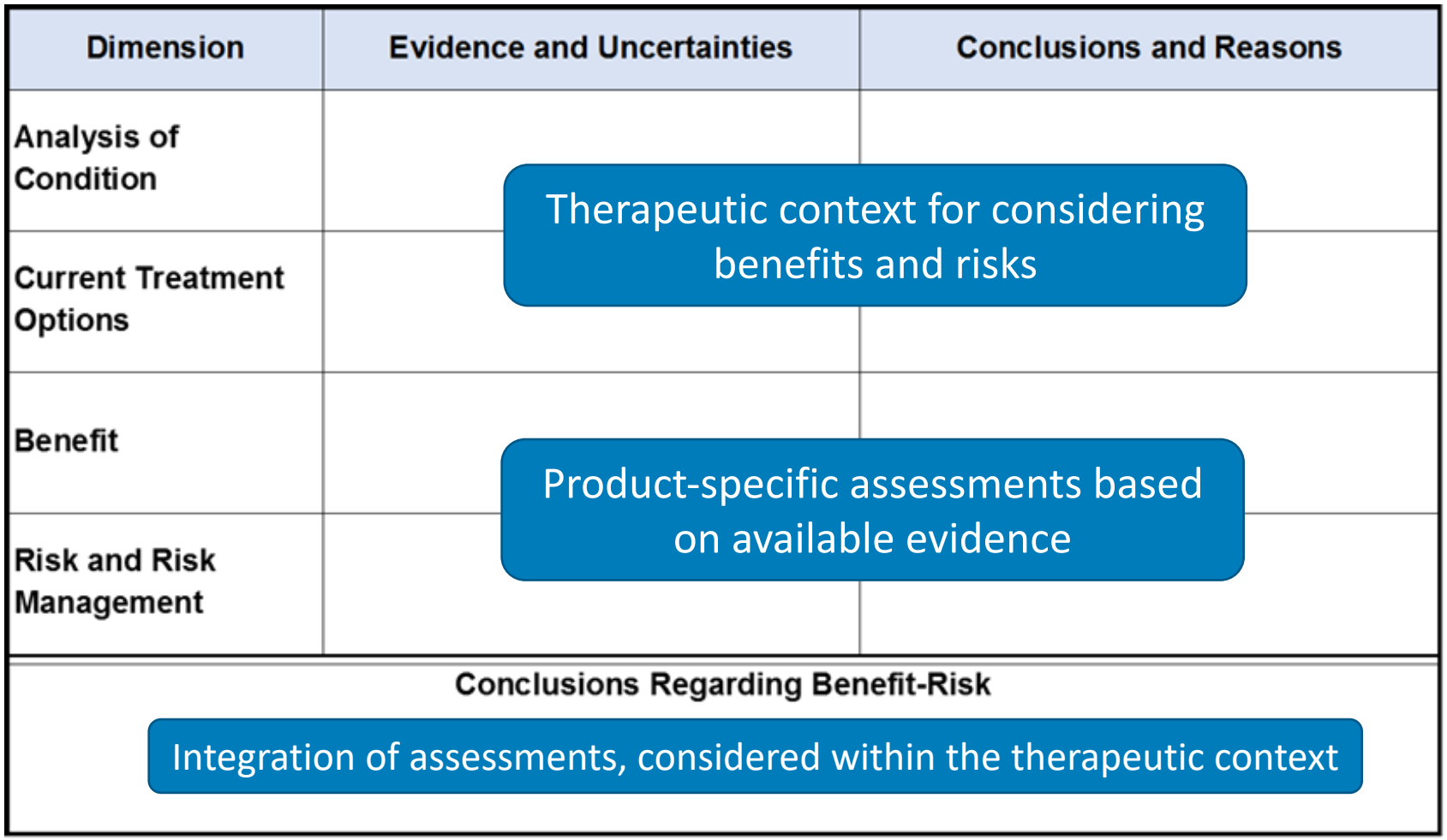
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)

October 2023
Clinical/Medical

Final Guidance: https://www.fda.gov/media/152544/download

The Benefit-Risk Framework is the vehicle for conducting FDA's benefit-risk assessment

It provides a structured, descriptive approach for **identifying, assessing, and communicating important considerations** that factor into a drug's benefit-risk assessment.



Key considerations

Abbreviated — see Final Guidance for full list

Therapeutic Context:

- Intended use and unmet need
- Patient population and relevant subpopulations
- Most relevant aspects of the condition
- Current therapies and their use in this population

Benefit:

- Strengths and limitations of the evidence
- Endpoints vs outcomes
- Generalizability of demonstrated benefits
- Characteristics of the drug (e.g., route of administration)

Risk & Risk Management:

- Strengths and limitations of the evidence
- Level of certainty for a causal association
- Differences between clinical trials and postmarketing
- Likely effectiveness of proposed approaches to mitigate risk

Conclusions Regarding Benefit-Risk:

- Strength of evidence
- How therapeutic context affects assessment
- Relative importance of the benefits and risks
- Whether certain labeling, REMS or a PMR is necessary

Patient Input: potentially informative for all aspects

Uncertainty: anticipated and potentially avoidable vs unanticipated

See p. 9-11 in Draft B-R Guidance for additional detail.

Some BR assessments are more challenging, particularly when serious risks are identified

- In such cases, FDA must determine that the benefits and risks are sufficiently characterized and that the benefits to the indicated population will outweigh the serious safety risks if the product is approved.
- This determination requires a thorough assessment of the available evidence and uncertainties, and careful consideration of a complex set of factors.
- Examples of ways FDA may determine a drug has a favorable benefit-risk profile:
  - By clearly demonstrating direct and meaningful benefit on the most important clinical outcomes
  - Representing a specific important advantage over available therapies
  - Identifying and targeting the indication to a subpopulation for whom the benefits outweigh the risks even if they do not in a broader population

See p. 4 in Final Guidance for additional detail.

Structured benefit-risk planning

- **Definition:** a purposeful activity carried out by the sponsor to incorporate consideration of the product's benefit-risk assessment throughout the drug development lifecycle
- **Objective:** direct drug development towards reducing important uncertainties and establishing a favorable benefit-risk profile
  - Targeted population
  - Reducing risks
  - Demonstrate benefits outweigh risks
- End of Phase 2 (EOP2) meeting is typically a **critical timepoint for FDA-Sponsor interactions**
  - Information is available from early development, other products in the class, etc.
  - Discussions can influence the design of phase 3 studies

See p. 14-17 in Final Guidance for additional detail.

Additional benefit-risk analysis

- Builds upon the integrated review of the evidence and the structured benefit-risk assessment tools discussed earlier

Estimation of clinically important benefit or risk outcomes not directly measured

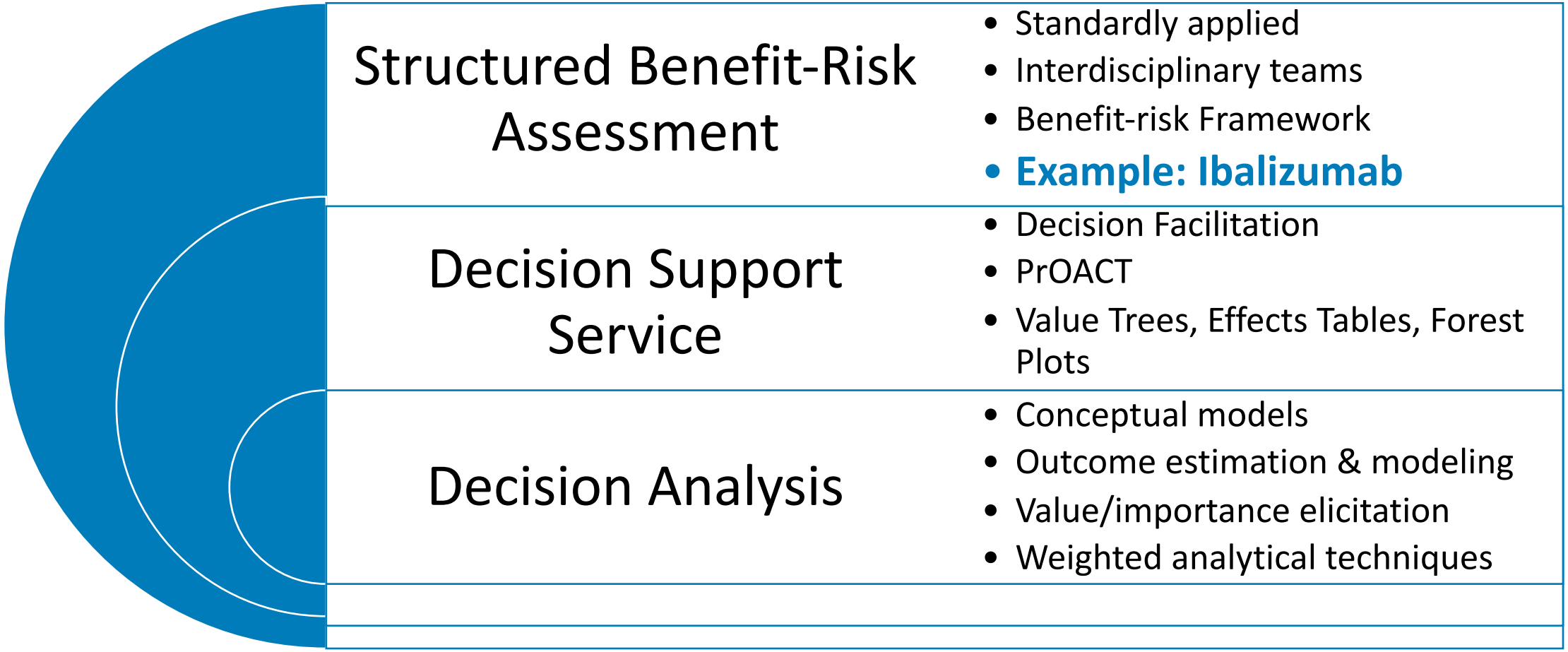
Modeling of benefit and risk outcomes in the real-world setting

Integrating benefits and risks in a combined analysis

See p. 19-20 in Final Guidance for additional detail.

CDER's Approach & Example

Decision support and analysis at FDA/CDER



A little structure goes a long way

- Help decision makers step through the process in a systematic manner
  - Increase consistency in decision making approach
  - Ensure all critical factors are considered
  - Focus attention on the most relevant aspects of the decision
- BRFs are completed for every new drug approval decision and are increasingly used at other stages in the lifecycle
  - Available in posted reviews at Drugs@FDA

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk and Risk Management		
Conclusions Regarding Benefit-Risk		

Decision facilitation can help

- Service launched within FDA/CDER in 2018, building off the experience of the Benefit-Risk Framework
- Small dedicated team supporting regulatory and policy decisions, especially those that involve benefit-risk assessment
- Available by-request, tailored to the needs and constraints of those seeking support
- Methods grounded in PrOACT but team uses additional tools as the need arises, given available time and data

PrOACT

Problem, Objective, Alternative, Consequences, Tradeoffs

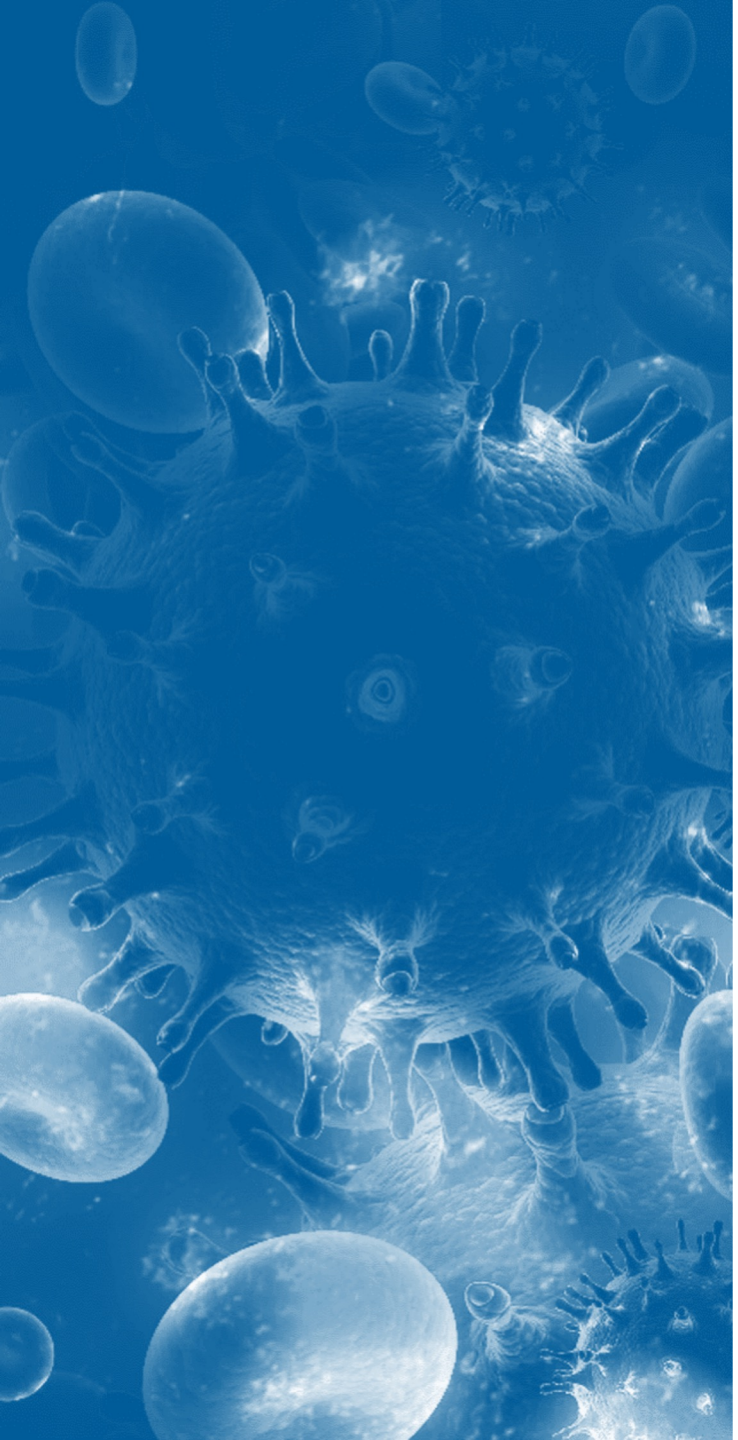
Hammond, Keeny, & Raiffa. 2015. *Smart Choices: A Practical Guide to Making Better Decisions.*

Decision analytical techniques can further inform decision-making

- MCDA and other techniques add to the benefit-risk assessments FDA review teams routinely perform
  - Forces **externalization of judgements** and allowing sensitivity testing
  - Other techniques can also be appropriate
- Availability of **information about event severity** and patient experience supports specification of tradeoffs – opportunity for data collection
- **Prior experience with the compound** factors into regulatory decision-making

See Lackey et al. Circulation. 2021;144:655-658 for an application of MCDA for drug decision-making (https://doi.org/10.1161/CIRCULATIONAHA.120.053294)

Example of Decision Structuring: Ibalizumab



Ibalizumab Benefit-Risk Framework

Introduction

- In March 2018, FDA approved Trogarzo [ibalizumab] for the treatment of adults with multi-drug resistant HIV-1 infection

- Following slides summarize the structured benefit-risk assessment performed **at the time of approval**
  - BRF by primary clinical reviewer completed 2 months before action
  - A condensed BRF included in signatory review at time of approval
  - Signatory BRF considered the official BRF; primary reviewer's BRF is also instructive
  - Both reviews are publicly available at Drugs@FDA
    - Signatory: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761065Orig1s000SumR.pdf
    - Primary reviewer, p 12 - 16 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761065Orig1s000MedR.pdf

Ibalizumab Benefit-Risk Framework

Therapeutic Context – *Condensed & Summarized*

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Over 1M people living with HIV in the U.S. • Most patients can adequately manage virologic suppression with current anti-retroviral treatments (ART) • There is a rare subset of heavily treatment-experienced patients whose infection is multi-drug resistant (MDR) • Patients with MDR HIV are at higher risk of AIDS events and death • For these patients, providers must tailor regimens, often resulting in more burdensome, less well-tolerated, and less effective treatment • **Heavily treatment-experienced patients with MDR HIV infection need new and effective antiretroviral products that lack cross-resistance with commercially available products**	
Current Treatment Options		
Benefit		
Risk and Risk Management		
Conclusions Regarding Benefit-Risk		

Ibalizumab Benefit-Risk Framework

Benefit – *Condensed & Summarized*

Dimension	Evidence and Uncertainties	Conclusions and Reasons

Analysis of Condition	• Given this rare, serious disease, regulatory flexibility allowed for a single, single-arm pivotal clinical trial of shorter duration
	• In the pivotal trial, 83% of participants achieved reductions in HIV RNA ≥ 0.5 log_{10} after seven days of ibalizumab monotherapy
	  • Compared to 3% of participants in the seven-day pre-treatment control period
	  • Reduction in HIV RNA ≥ 0.5 log_{10} is highly predictive of meaningful clinical benefit
	  • This evidence clearly demonstrates ibalizumab's shorter-term virologic activity
	• Trial limitations limited ability to quantify contribution of ibalizumab to long-term virologic suppression
	  • 24 and 25 week data of ibalizumab used as part of individualized combinations offer supportive evidence	

Current Treatment Options		
Benefit		
Risk and Risk Management		
Conclusions Regarding Benefit-Risk		

Ibalizumab Benefit-Risk Framework

Risk and Risk Management – *Condensed & Summarized*

Dimension	Evidence and Uncertainties	Conclusions and Reasons

Analysis of Condition	• The safety database is small and lacked placebo-control data
	  • Limits ability to assess drug causality and ability to identify rare events
	  • However, sufficient to assess frequent adverse events and acceptable for this serious disease with unmet need
	• The adverse events were generally consistent with events expected in patients with advanced HIV/AIDS
	  • Adverse events occurring in ≥ 5% of patients: dizziness, diarrhea, rash, nausea
	  • One serious reaction in pivotal trial: immune reconstitution inflammatory syndrome	

Current Treatment Options		
Benefit		
Risk and Risk Management	• Post-marketing pharmacovigilance will be important to further assess safety profile, especially for rare adverse events	
Conclusions Regarding Benefit-Risk		

Ibalizumab Benefit-Risk Framework

Conclusions – *Condensed & Summarized*

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk and Risk Management		

Conclusions Regarding Benefit-Risk

- There is a need for new and effective therapies for patients with MDR-HIV who cannot achieve complete virologic suppressions with currently available ART
- Ibalizumab clearly demonstrated clinically-meaningful benefit in reducing virologic activity
- Based on the submitted data, ibalizumab has a favorable safety profile
- Uncertainties about long-term benefit and potential for rare safety issues remain, but these uncertainties are acceptable in light of the unmet need for this rare disease population
- **Overall benefit of ibalizumab is favorable for the treatment of HIV-1 infection in heavily treatment-experienced patients with MDR HIV-1 and failing their current ART**

Conclusions

Final Thoughts

- Benefit-risk planning by sponsors can be used to strengthen the evidence generated by a development program — **reducing uncertainty and informing the final benefit-risk assessment**
- Additional tools, such as value trees, effects tables, PPI, and additional analysis, **can inform aspects of the overall benefit-risk assessment**
  - Process is as important (if not more important) than results
  - Should be pre-specified to the extent possible
  - None replace the integrated, qualitative assessment
  - All can be reflected in the Benefit-Risk Framework

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  - Virginia Sheikh
  - Adam Sherwat
  - Jeffrey Murray

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