Benefit-Risk Assessment of Human Drugs and Biologics at FDA

Dr. Leila Lackey
Decision Support and Analysis Team
Office of Program and Strategic Analysis (OPSA)
Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration (FDA)

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What is benefit-risk assessment in human drug review?

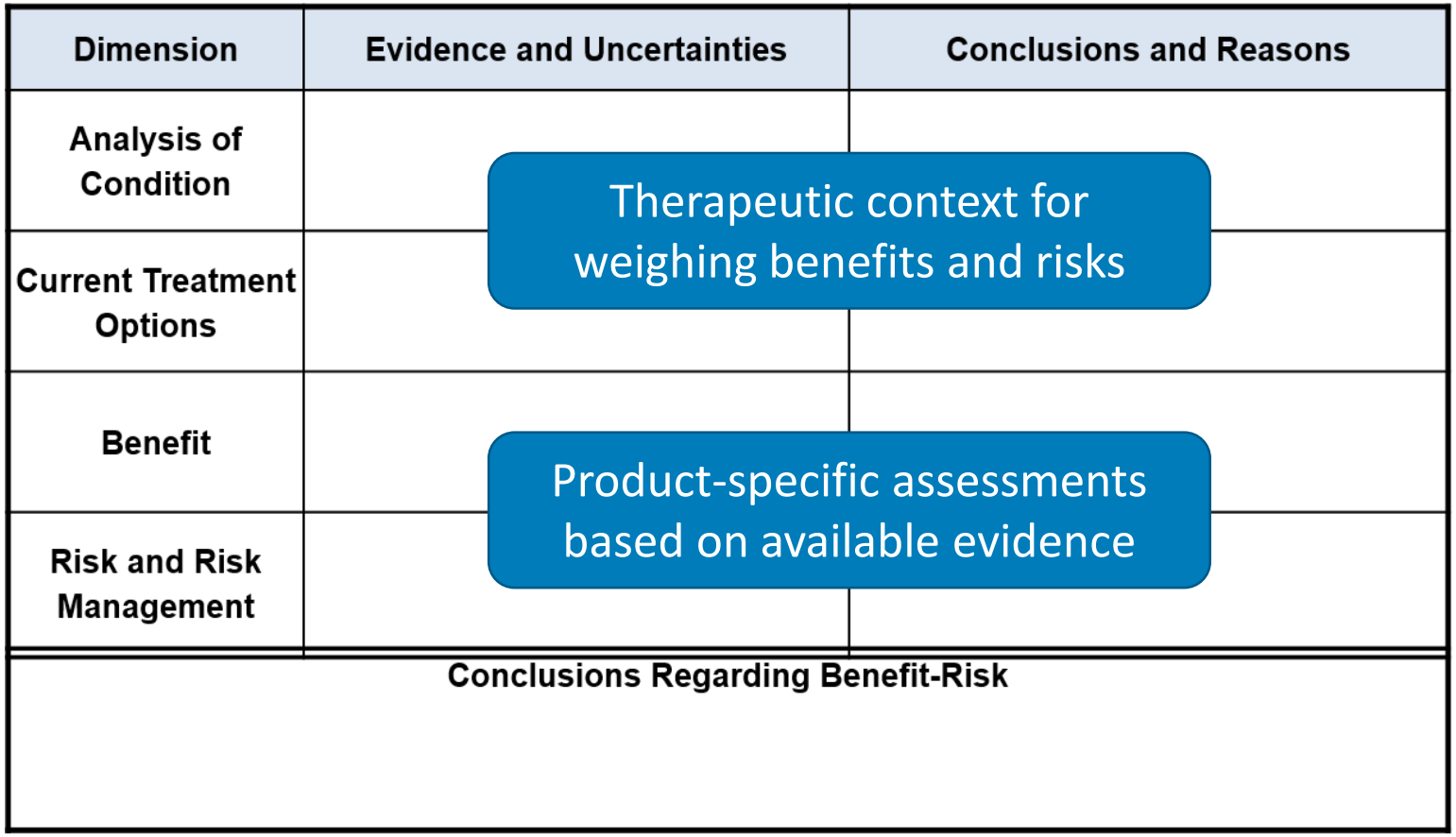
Evaluation of the demonstrated benefits and risks of a medical product, and

Making a **judgment** as to whether the expected benefits outweigh the potential risks associated with its expected use

From FDA's Patient-Focused Drug Development Glossary, available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm610317.htm

FDA's Benefit-Risk Framework:
Structured approach for human drug review

- Structured approach for B-R assessment and communication
- Implemented into new drug review
  Satisfying 2012 PDUFA* commitment and FDASIA** requirement
- Reflects reality: B-R assessment is fundamentally a qualitative exercise
- Flexible to include supporting quantitative analyses



*Prescription Drug User Fee Act; **Section 905 of the Food and Drug Administration Safety and Innovation Act of 2012

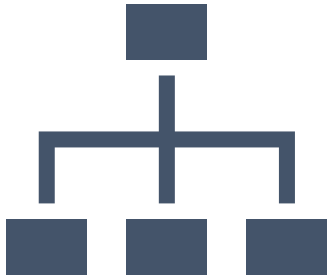
FDA's Benefit-Risk Framework:
Desired outcomes

Clear and concise snapshot

- Sharpen focus on the most relevant issues
- Articulate the applied clinical reasoning and judgment
- Faithfully capture deliberations

Consistent and accessible

- Improve transparency in the decision-making process
- Provide standard structure for communication
- Provide an accessible record of the decision for reference



Aligned with review process

- Fit naturally within existing review processes
- Apply broadly to the range and lifecycle of regulatory decisions

FDA's Benefit-Risk Framework:

Key considerations for assessments

BRF Section	Key Considerations *Patient input and uncertainty considered throughout*
Analysis of Condition	• Proposed indication: severity, target population, relevant clinical aspects • Patient-focused disease burden
Current Treatment Options	• Available therapies: efficacy, safety, and utilization • Unmet need: unaddressed aspects of patient's disease burden
Benefit	• Strengths/limitations of clinical trials and development program • Clinical trail results: significance and generalizability to expected use by target population • Relationship between study endpoints and clinical outcomes important to patients
Risk & Risk Management	• Strengths/limitations of clinical trials and development program • Serious adverse events, tolerability concerns, product quality • Expectations about real-world use and risk mitigation strategies
Conclusions Regarding Benefit-Risk	• How the therapeutic context affects threshold for benefit and tolerance for risk & uncertainty • If approved, need for labeling, REMS, or additional postmarket data collection • Additional information needed to inform uncertainties in benefit-risk assessment

2019 FDA Discussion Document: https://healthpolicy.duke.edu/sites/default/files/atoms/files/discussion_guide_b-r_assessment_may16.pdf

FDA's Benefit-Risk Framework:

We have received positive feedback …

External organization completed evaluation in Sept 2017

Reviewed documentation for 43 applications

Interviewed >300 stakeholders:

- FDA review staff and signatories
- Drug Applicants
- Patients and healthcare providers

Most FDA staff believed the BRF has value in organizing thinking and documenting concise view of review

External stakeholders largely felt that BRFs are

- Effective at communicating reasoning behind FDA's regulatory decision
- Clear and understandable to motivated readers who have some background
- Useful to inform their own decision making (e.g., developing, prescribing, using therapies)

FDA's Benefit-Risk Framework:

… and suggestions for improvement

External organization completed evaluation in Sept 2017

Reviewed documentation for 43 applications

Interviewed >300 stakeholders:

- FDA review staff and signatories
- Drug Applicants
- Patients and healthcare providers

Stakeholders offered insightful suggestions:

- Improve presentation of content and consistency among BRFs
- Expand use of BRFs to more applications
- Enhance incorporation of patient perspectives, clinical considerations, and quantitative B-R assessments
- Make it easier for stakeholders to find and access BRFs

PDUFA VI commitments on benefit-risk:

FDA committed to continuing the effort

2018

March 30, 2018 - Published updated plan for continued implementation of structured benefit-risk assessment

2019

May 16, 2019 - Conducted a public meeting to gain stakeholder input

2020

Publish draft guidance on FDA's approach to B-R assessment

2021

Conduct a 2nd evaluation of the Benefit-Risk Framework implementation

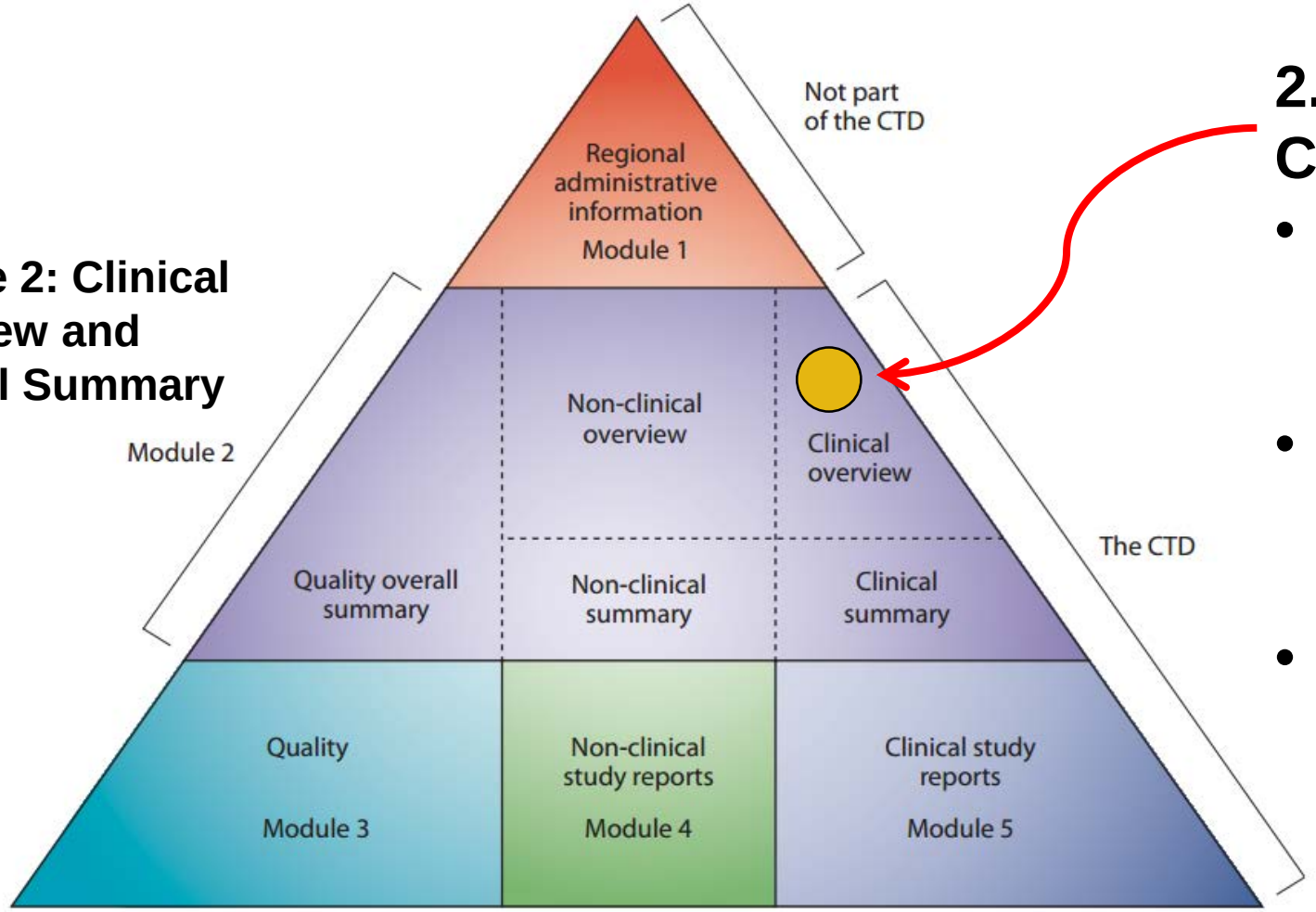
2018 FDA Benefit-Risk Implementation Plan: https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM602885.pdf

FDA Benefit-Risk Guidance:
Topics outlined in statute

- From PDUFA VI:
  - Articulate FDA's decision-making context and framework for benefit-risk assessment **throughout the human drug lifecycle**
  - Discuss appropriate **interactions between sponsors and FDA** during drug development to understand the therapeutic context for regulatory decisions
  - Discuss appropriate approaches to **communicate to the public FDA's thinking** on a product's benefit-risk assessment, such as through using the B-R framework at AC meetings
- From 21 CC: discuss how **patient experience data** can be used to inform benefit-risk assessment

FDA Benefit-Risk Guidance:
Alignment with ICH guidelines

Module 2: Clinical Overview and Clinical Summary



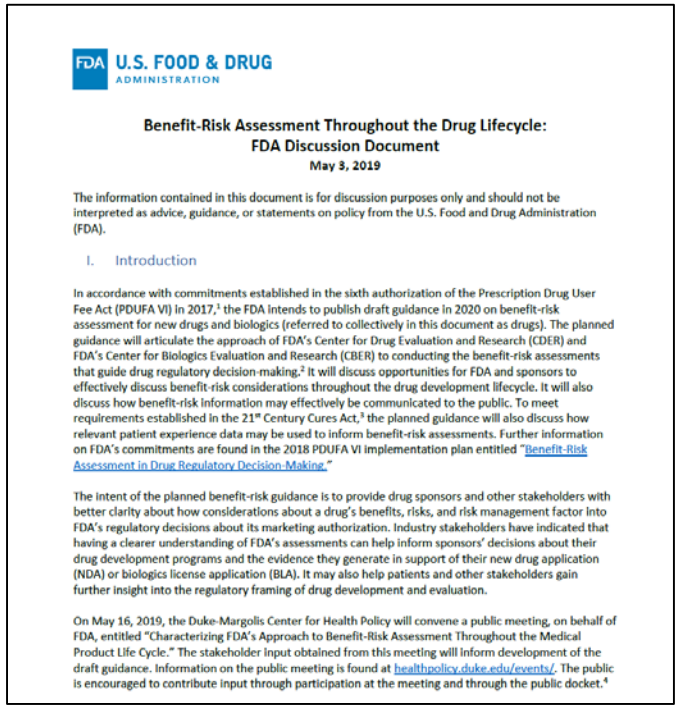
2.5.6 Benefits and Risks Conclusions

- ICH guidelines (M4E(R2)) updated in 2016[1]
- FDA Revised our CTD-Efficacy Guidance to Industry in 2017[2]
- Sections of 2.5.6 align with the Benefit-Risk Framework

1. ICH m4E(R2): https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4E_R2_Efficacy/M4E_R2__Step_4.pdf
2. ICH M4E(R2) – Efficacy Guidance for Industry: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM465221.pdf

FDA Benefit-Risk Guidance:

FDA 2019 discussion document



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Benefit-Risk Assessment Throughout the Drug Lifecycle:
FDA Discussion Document
May 3, 2019

The information contained in this document is for discussion purposes only and should not be interpreted as advice, guidance, or statements on policy from the U.S. Food and Drug Administration (FDA).

I. Introduction

In accordance with commitments established in the sixth authorization of the Prescription Drug User Fee Act (PDUFA VI) in 2017,[1] the FDA intends to publish draft guidance in 2020 on benefit-risk assessment for new drugs and biologics (referred to collectively in this document as drugs). The planned guidance will articulate the approach of FDA's Center for Drug Evaluation and Research (CDER) and FDA's Center for Biologics Evaluation and Research (CBER) to conducting the benefit-risk assessments that guide drug regulatory decision-making.[2] It will discuss opportunities for FDA and sponsors to effectively discuss benefit-risk considerations throughout the drug development lifecycle. It will also discuss how benefit-risk information may effectively be communicated to the public. To meet requirements established in the 21st Century Cures Act,[3] the planned guidance will also discuss how relevant patient experience data may be used to inform benefit-risk assessments. Further information on FDA's commitments are found in the 2018 PDUFA VI implementation plan entitled "Benefit-Risk Assessment in Drug Regulatory Decision-Making."

The intent of the planned benefit-risk guidance is to provide drug sponsors and other stakeholders with better clarity about how considerations about a drug's benefits, risks, and risk management factor into FDA's regulatory decisions about its marketing authorization. Industry stakeholders have indicated that having a clearer understanding of FDA's assessments can help inform sponsors' decisions about their drug development programs and the evidence they generate in support of their new drug application (NDA) or biologics license application (BLA). It may also help patients and other stakeholders gain further insight into the regulatory framing of drug development and evaluation.

On May 16, 2019, the Duke-Margolis Center for Health Policy will convene a public meeting, on behalf of FDA, entitled "Characterizing FDA's Approach to Benefit-Risk Assessment Throughout the Medical Product Life Cycle." The stakeholder input obtained from this meeting will inform development of the draft guidance. Information on the public meeting is found at healthpolicy.duke.edu/events/. The public is encouraged to contribute input through participation at the meeting and through the public docket.[4]

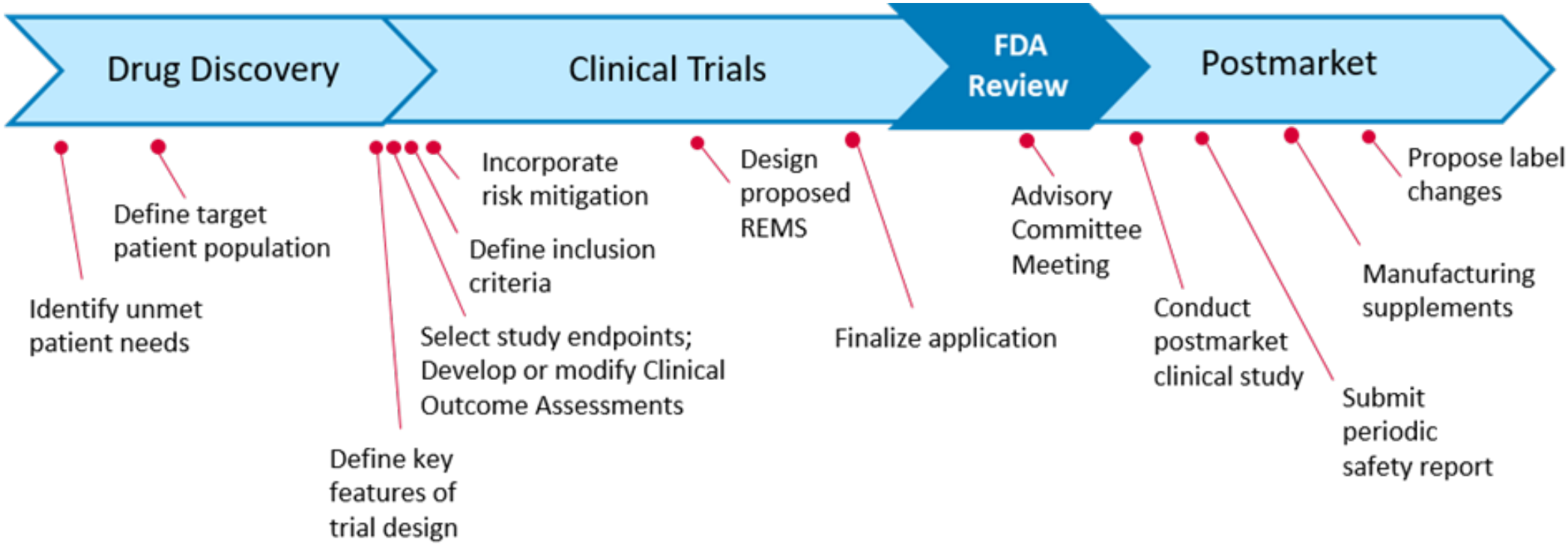
- Provides background on FDA's approach to benefit-risk assessment for regulatory decisions regarding marketing authorization.
- Identifies topics that FDA may address in draft guidance
- The intent is to provide a clearer understanding of how considerations on a drug's benefits, risks, and uncertainties factor into FDA's regulatory decisions about marketing authorization.
- This understanding can help inform sponsors' decisions about their drug development programs.

2019 FDA Discussion Document: https://healthpolicy.duke.edu/sites/default/files/atoms/files/discussion_guide_b-r_assessment_may16.pdf

FDA Benefit-Risk Guidance:

Development activities along drug lifecycle

Sample milestones along the drug lifecycle that may have a particular bearing on benefit-risk assessment of a marketing authorization. Milestones may not apply to all drug development programs.



2019 FDA Discussion Document: https://healthpolicy.duke.edu/sites/default/files/atoms/files/discussion_guide_b-r_assessment_may16.pdf

FDA Benefit-Risk Guidance:

Public comments on discussion document

- Strong support for incorporating the patient voice throughout the lifecycle to support benefit-risk assessment
- Explore the use of more structured tools and quantitative methods – value trees, effects tables, explicit weighting, MCDA
- Early communication between FDA and sponsors on benefit-risk assessment and related issues – End of Phase 2 meeting critical
- Align guidance with other efforts, such as ICH
- Increase use at Advisory Committee and make final frameworks more accessible

Final Thoughts:

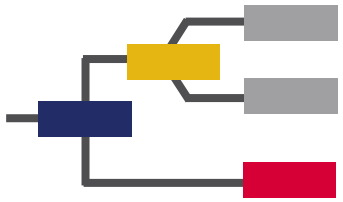
Benefit-risk assessment must be fit-for-purpose

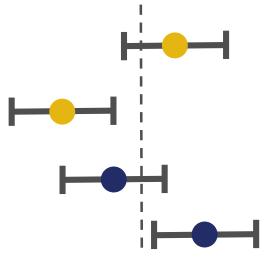
- It must fit within FDA's regulatory context
  - Our mission is to protect and promote public health
  - We are bound to our laws
  - Our decisions set precedent

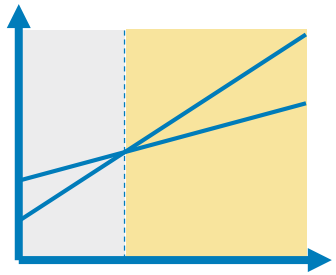
- It must fit within FDA's processes
  - There are hundreds of regulatory decisions every year, most are time-sensitive
  - Decision making involves large multi-disciplinary teams of experts
  - Reviews are conducted within a highly structured set of policies, procedures, and templates

Final Thoughts:

How might more advanced analyses add value?







The Benefit-Risk Framework can accommodate use of decision-analytic tools to help **address uncertainty** and **assess tradeoffs**.

Critical questions:

- When would their application add the greatest value?
- How can we adapt the methods to fit the regulatory and operational constraints?
- How do we build the necessary capacity?
- What should be the measures of success?

FDA Resources on Benefit-Risk Assessment

"Benefit-Risk Assessment Throughout the Drug Lifecycle"

2019 FDA Discussion Document

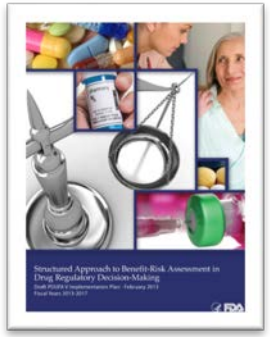
https://healthpolicy.duke.edu/sites/default/files/atoms/files/discussion_guide_b-r_assessment_may16.pdf

"Benefit-Risk Assessment in Drug Regulatory Decision-Making"

PDUFA VI Implementation Plan

March 2018

https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM602885.pdf



"Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making"

PDUFA V Implementation Plan

February 2013

Relevant reading: Sections 1 and 2

https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf