Using Benefit Risk in Making Post Market Decisions

Adam E Saltman MD PhD
Medical Officer, FDA CDRH Office of Compliance
AFDO 2018

Objectives

- Understand why FDA is interested in the benefit-risk approach to medical device availability and compliance decisions
- Learn about CDRH's postmarket benefit-risk guidance document
- Understand when a formal postmarket benefit-risk evaluation could help decision-making
- Explore some example applications of benefit-risk thinking

Why is FDA Interested?

BENEFIT-RISK IN THE POSTMARKET WORLD

Why Benefit-Risk?

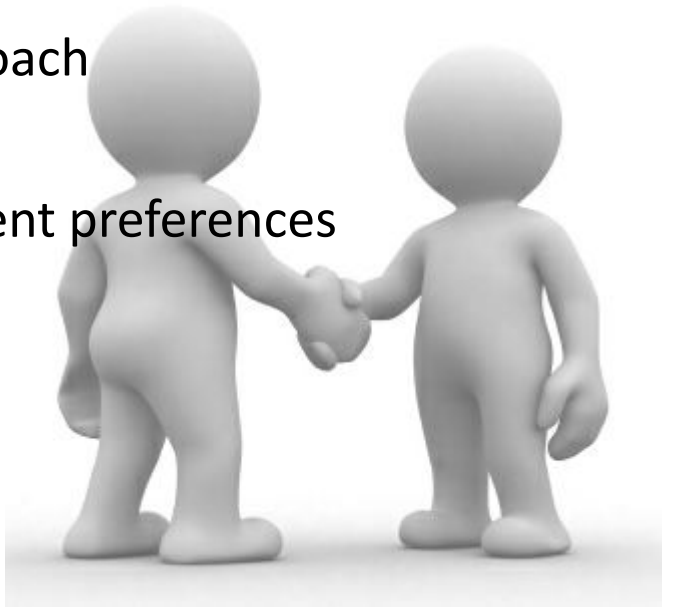
- CDRH's mission
  - Protect and promote the public health
  - Assure that patients and providers have timely and continued access to **safe, effective, and high-quality** medical devices and safe radiation-emitting products
  - Facilitate medical device innovation by advancing regulatory science, providing industry with **predictable, consistent, transparent, and efficient regulatory pathways, and assuring consumer confidence** in devices marketed in the U.S.

Why Benefit-Risk?

- Focus on patients
  - Make compliance and enforcement decisions that **put the patient first**
- Promote consistency
  - A framework to consistently and systematically apply B-R principles
  - Internally and externally

Why Benefit-Risk?

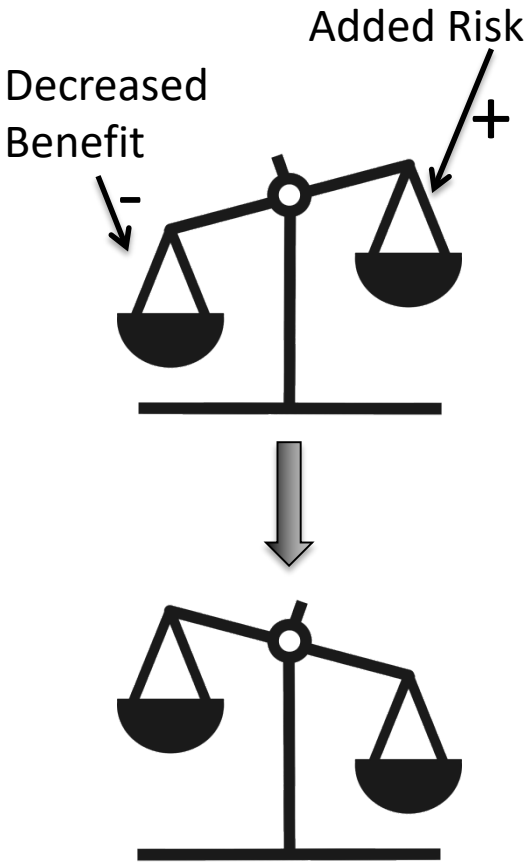
- Encourage new thinking
  - Customize approaches
  - Use creative problem solving
  - Develop new tools
- Interface with Industry
  - Engage using a balanced and situational approach
  - Facilitate conversation
  - “Compliance” → quality, patient benefit, patient preferences
  - Align stakeholders (CDRH, ORA, Industry)
  - Share tools and techniques



The Balance May Have Changed

- Benefit may be reduced
- Risk may be increased
- Situations
  - Product recalls
  - Inspectional observations
  - Complaints and allegations

- **Does the benefit still outweigh the risk?**
  - Sometimes yes,
    even with decreased benefit and increased risk



CDRH'S POSTMARKET BENEFIT-RISK GUIDANCE DOCUMENT

Contains Nonbinding Recommendations

Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions

Guidance for Industry and Food and Drug Administration Staff

Document issued on December 27, 2016.

The draft of this document was issued on June 16, 2016

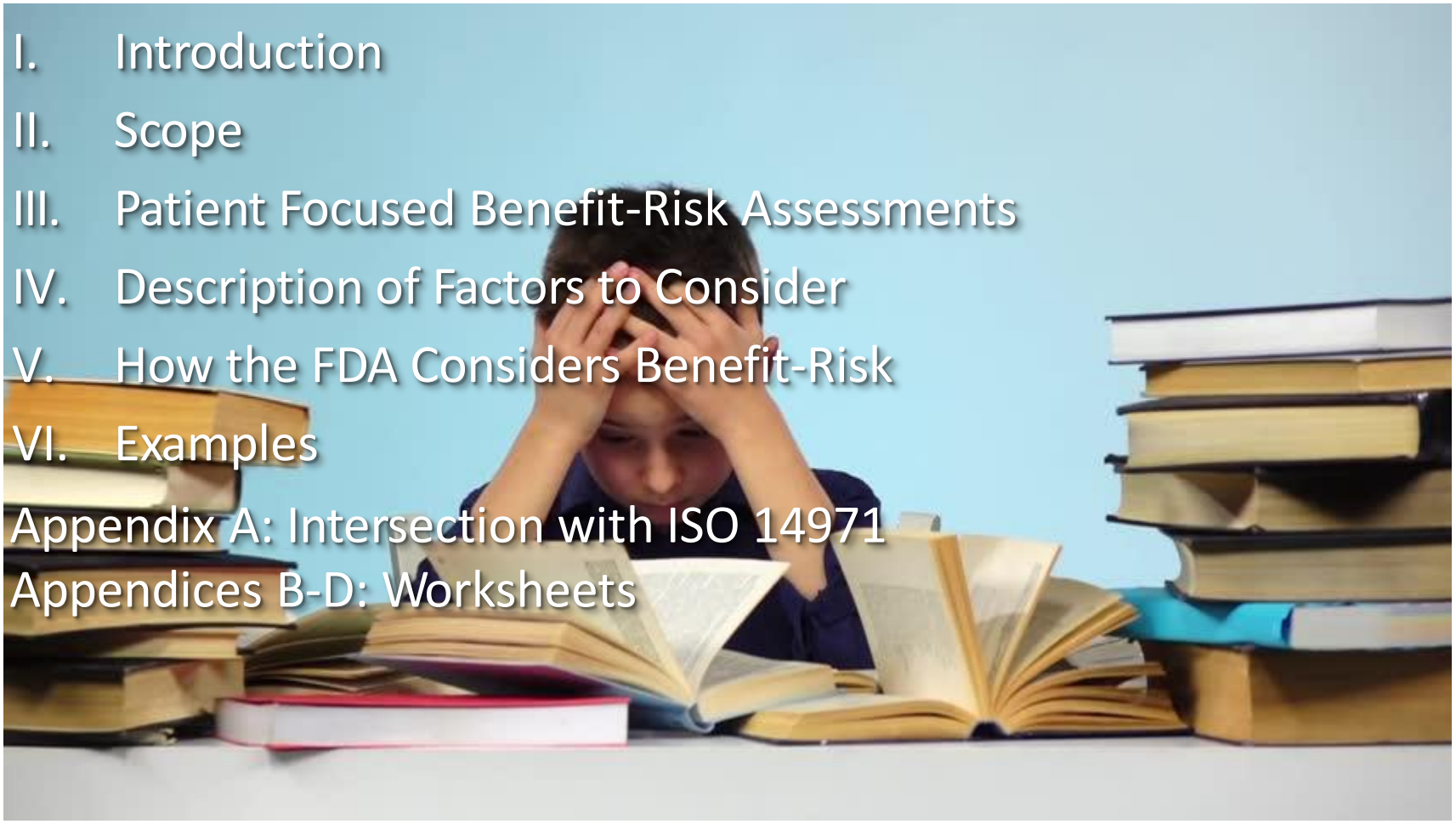
For questions about this document regarding CDRH-regulated devices, contact the Office of Compliance at 301-796-5900.

https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM506679

FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DEVICES & RADIOLOGICAL HEALTH

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

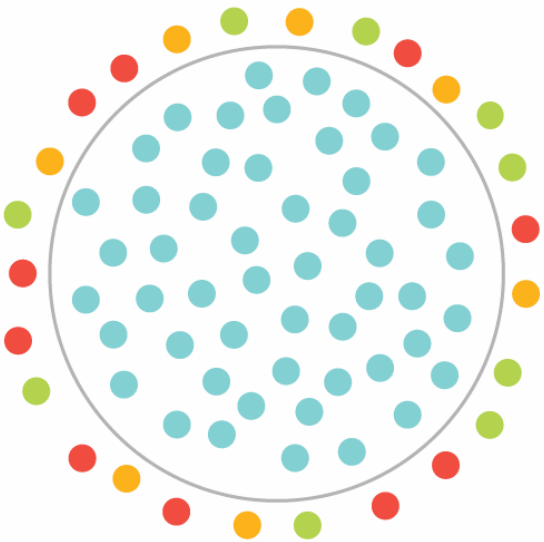
Contents



I. Introduction

- Provide rationale
  - A general framework: Optimize B-R balance
  - Improve consistency and transparency
  - Align FDA and Industry
  - Harmonize with premarket benefit-risk assessment
  - Include patient focus and Real World Evidence
- Outline methodology
  - Evaluation techniques, e.g., pilots

II. Scope



- Devices included
  - Diagnostic and therapeutic devices, except
- Devices excluded
  - CBER devices
  - Combination products where CDRH is not the lead
  - Electronic Product Radiation Control products
- Situations included
  - Evaluation of device shortage situations
  - Selection of the appropriate regulatory engagement mechanism
  - Evaluation of recalls
  - Petitions for variance from the Quality Systems regulation (21 CFR 820) for which there were inspectional observations during a Premarket Approval (PMA) inspection

III. Patient Focused Benefit-Risk Assessments

- "The FDA has the authority to limit the availability of violative medical devices…"
- "Considering the [B-R] profile of the device may prevent regulatory actions with unintended adverse impact for patients…"
- "Decisions regarding these actions should be made while focusing on the impact for patients"

IV-A. Factors to Consider: Benefit

- Type
- Magnitude
- Likelihood
- Duration
- Patient perspective
- Healthcare professionals & caregivers
- Medical necessity

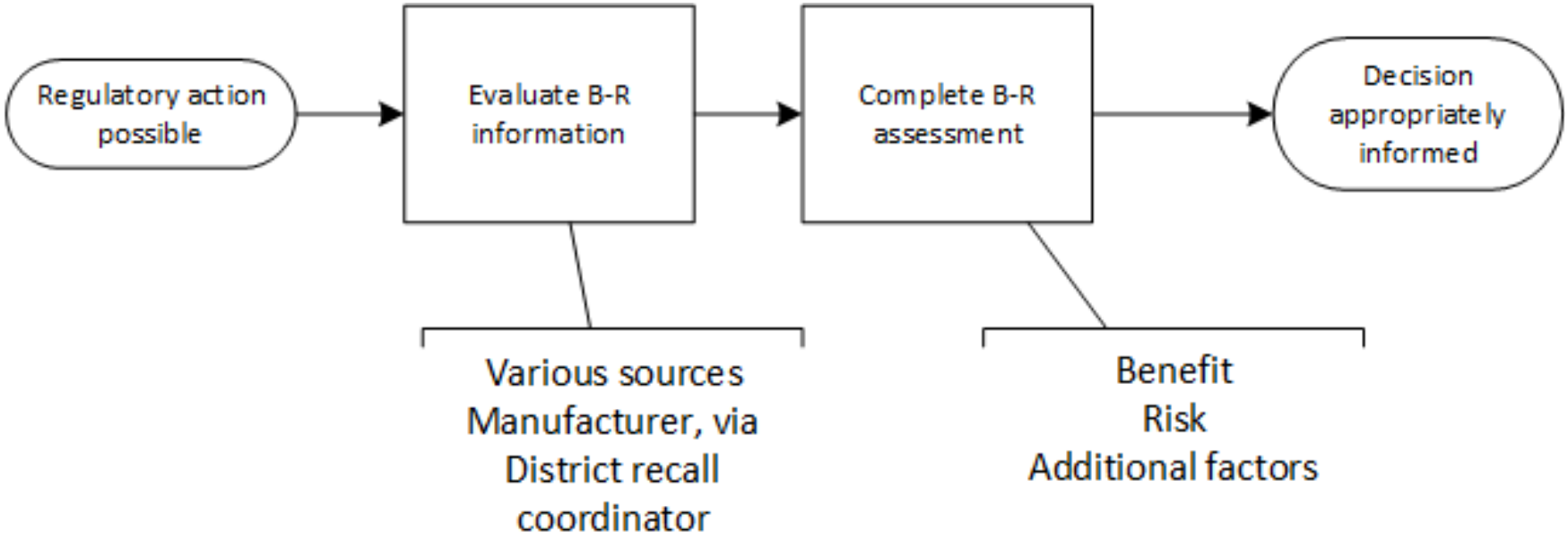
IV-B. Factors to Consider: Risk

- Severity
- Likelihood
- Distribution of nonconforming devices
- Duration of exposure
- False(+) or false(-) results
- Patient tolerance
- Healthcare professionals & caregivers

IV-C. Factors to Consider: Additional

- Data uncertainty
- Risk mitigation
  - Hazard detectability
  - Failure mode
- Scope of the issue
- Patient impact
- Preference for availability
- Nature of violations or nonconforming product
- Firm compliance history

V. How FDA Considers Benefit-Risk



V. How FDA Considers Benefit-Risk

	High Benefit Low Risk	Low Benefit High Risk
Product Availability	Ensure patients have access	Limit patient access
Compliance / Enforcement	Work with firm; address underlying issues	Take formal action

VI. Additional Examples

Product Availability

- Recall of a high benefit, implantable, coated device with low additional risk →
  Could there be a shortage?
- Variance petition related to a high benefit drug delivery system →
  Are the risks posed by QS issues sufficiently mitigated?
- Nonconforming biological indicator with high benefit and mitigated additional risk →
  Should continued access be allowed?
- Malfunction of a pregnancy test with low benefit and moderate additional risk →
  Should continued access be allowed?
- Recall of a radiation therapy device with high benefit and increased risk for some patients →
  Should continued access be allowed?

Compliance and Enforcement

- Low benefit, low additional risk aesthetic device →
  Warning Letter, or an alternative approach?
- Inspection with observed QS deficiencies for high benefit spinal fixation system →
  Warning Letter, or an alternative approach?

Appendix A: Intersection with ISO 14971

- "The concepts within, and **output from**, a firm's quality management system that incorporates ISO 14971 may be used as **inputs to** benefit-risk assessments."

Appendix A: Intersection with ISO 14971

- Sec 6.2: “If … the required risk reduction is not practicable, the manufacturer shall conduct a risk/benefit analysis of the residual risk…”
- Sec 6.5 (B-R assessment): “If this evidence does not support the conclusion that the medical benefits outweigh the residual risk, then the risk remains unacceptable. If the medical benefits outweigh the residual risk, then proceed to 6.6. For risks that are demonstrated to be outweighed by the benefits, the manufacturer shall decide which information for safety is necessary to disclose the residual risk. (Annex D.6.)”

Appendices B-D: Worksheets

Benefit

- How does the device benefit the patient?
- What is the patient's perspective on benefit?
- Is the device medically necessary?

Risk

- What is the severity of the risk?
- What is the likelihood of harm?
- Were nonconforming devices distributed?
- Will patients tolerate the risks?

Other factors

- What is the impact to the patient?
- What was the nature of the violation or nonconformity?
- What is the firm compliance history?

Is this New?

- *You've been doing benefit-risk all along!*
- Now we're going to
  - Have a structured way to do it
    - Develop tools
  - Always get the right information
    - Every time
    - Every situation
  - Write it down
    - Institutional memory
  - Share it
    - Inside FDA, between FDA and industry

The Triggers

WHEN IS A BENEFIT-RISK ASSESSMENT USEFUL?

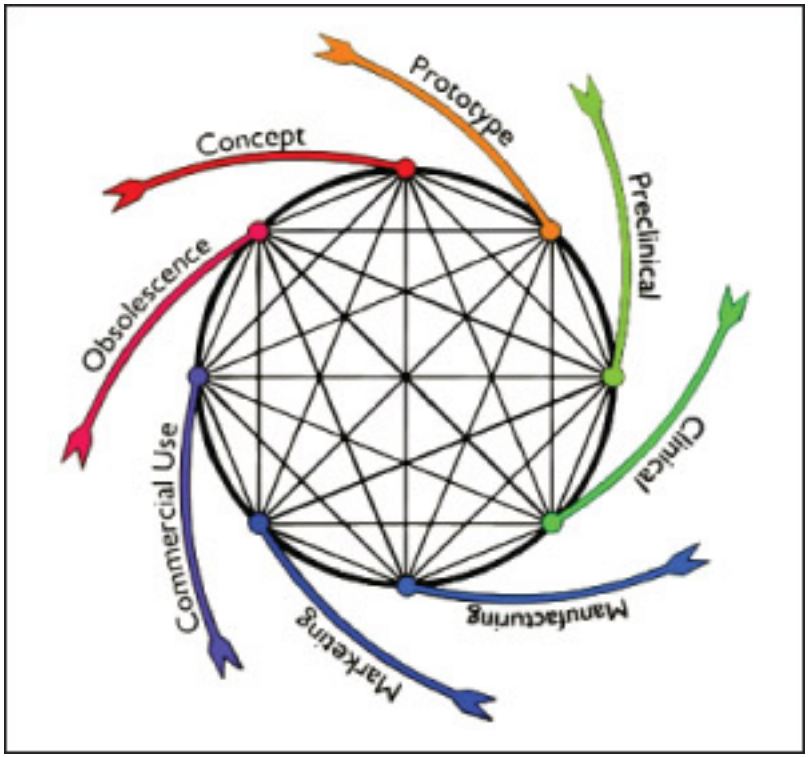
Benefit-Risk and TPLC

- Not every step
- Finding candidates
  - Product availability?
- Potential targets
  - Concept
  - (Preclinical?)
  - Clinical

Premarket

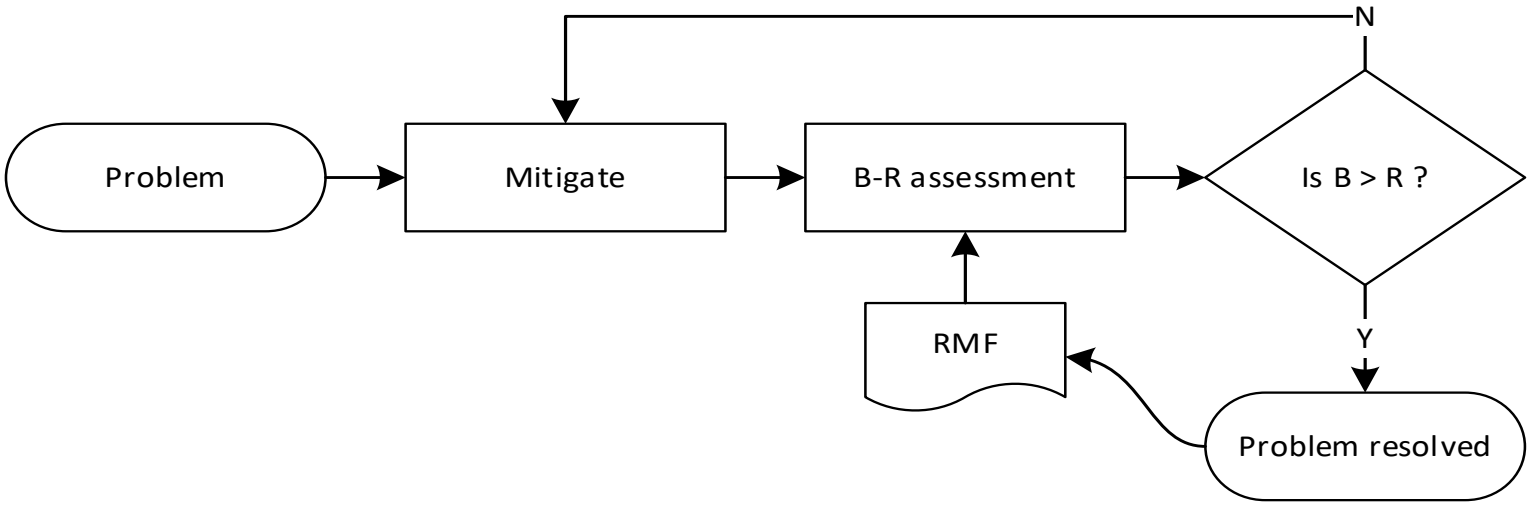
  - Commercial use
  - Obsolescence

Postmarket



Beware: Risk Creep Trap

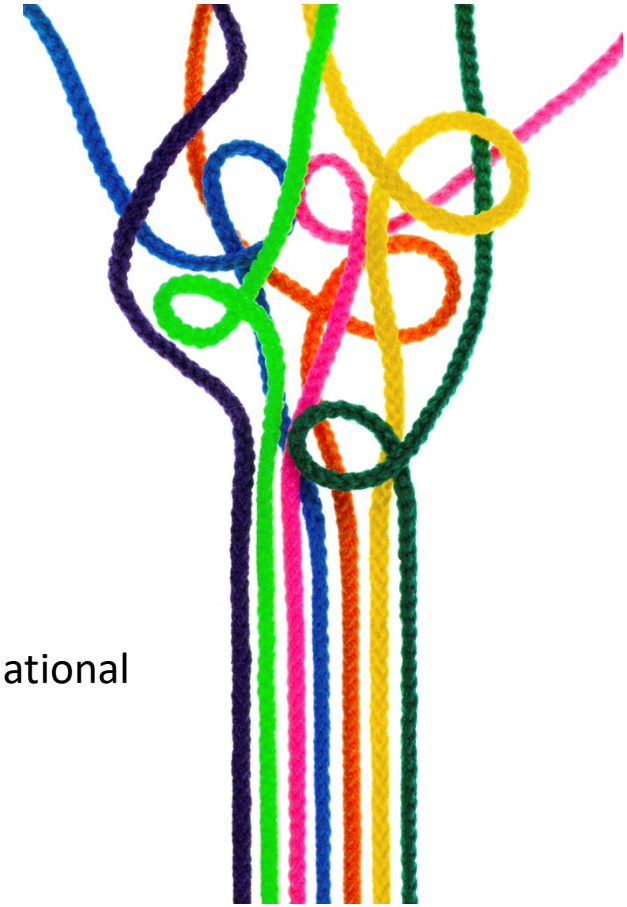
- Baseline = Risk management file
- Present = Updated RMF
  - Incorporates new information since approval/clearance



- When is “present risk” and/or “present benefit” no longer acceptable?

Making Sense of the Situation

- Choosing the right option
  - Outcomes?
  - B-R balance for each
  - Which is best?
  - New information and considerations
- Using the framework
  - Factors
  - Data and the sources
    - Real world evidence, off-label use, device history, class history, firm history
  - Confidence and uncertainty
    - Patient preferences, mitigations promised/accomplished, violations systemic/situational
  - New aspects
    - Mental health, privacy



Overarching Goal of a Benefit-Risk Assessment

- Minimize risk from problem while maintaining device benefit
- From: Firm's point of view
  - Corrections/removals, signals, complaints, inspectional observation responses
- From: FDA's point of view
  - Device availability, shortages, inspectional observations, signals, allegations, complaints

Recalls
Unapproved/Uncleared Devices
Incomplete/Inappropriate Mitigations
Shortages
PMA Pre-approval Inspections

EXAMPLES OF BENEFIT-RISK THINKING

Recalls

- Parts (21 CFR 7.41 – 7.55)
  - Classification
  - Strategy
  - User and patient communication
  - FDA public notification
  - Effectiveness checks
  - Audit checks
  - Monitoring
  - Termination

Recalls

Component	Risk	Benefit	Rationale
Classification	X		Risk-only
Strategy	X	X	Remove vs correct User and manufacturer mitigation(s) Staged/phased approach(es)
User and patient communication	X	X	Alarm vs inform Appropriate audience
FDA public notification	X	X	Alarm vs inform Appropriate audience
Effectiveness checks	X		Risk-only
Monitoring	X		Firm's history/performance
Auditing	X	X	Firm's history/performance
Termination	X		"Reasonable" efforts made

Recalls+

- Going beyond the parts: Regulatory interactions
  - When is a problem more than a problem?
  - Recidivism, repeat recalls, overarching quality issues
  - Lots of options
    - Consent decrees, civil money penalties, injunctions, seizures, import alerts, detention without physical examination, DWPE with surveillance, warning letters, untitled letters, It Has Come To Our Attention letters, formal regulatory meetings, informal meetings, telephone interactions, email interactions, criminal prosecution, criminal fines,...
  - "... All other things being equal ..."
    - B-R can fit the action to the situation
    - Keep the patient (and provider) foremost

Example Recall

Any resemblance to an actual stent, living or dead, is purely coincidental

- Vascular stent
  - 80% less thrombosis than any other
  - Designed for specific subpopulations
- Problem
  - 3 complaints of delivery system malfunction
  - All were <100mL blood loss
  - Anticipated failure, but occurring more frequently than expected
- Firm's proposed actions
  - Leave device on the market
  - Correction: Send customers an IFU supplement
  - Alert users to the increased risk and how to minimize blood loss
  - Continue monitoring

Factor Considerations

- Benefits
  - Vulnerable patient population
  - Malfunction did not reduce benefit
  - No substitute/alternative
- Risks
  - No serious adverse events
  - 0.1% incidence (0.05% RMF)
- Patient tolerance & perspective
  - Thrombosis a serious concern
  - Focus group, “We prefer to use”
- Uncertainty
  - Reported AE rate is “minimum”
  - But unlikely to reach “Class I”
- Mitigation
  - Communication explains issue, instructs how to address malfunction
- Patient impact (**of problem**)
  - Minor blood loss in a few cases
- Patient impact (**of removal**)
  - Delay surgeries?
  - Use less beneficial devices?
- Compliance picture
  - MDRs submitted for all complaints
  - 806 submitted within 10 days
  - No inspectional/regulatory issues

The Decision

Evaluations

Benefit	High
Additional risks	Low
Patient tolerance	High
Uncertainty	Low
Mitigations	Effective
Patient impact	Removal undesirable
Compliance picture	Favorable

Outcome

- Maintain access
- Continue active monitoring
- Continue root cause investigation
  - Formulate additional action as indicated
- Keep FDA updated
  - Regulatory submissions as needed
- No further action at this time

Unapproved or Uncleared Device

- A firm has made technical changes to their device without submitting notice to the FDA.
- The change was discovered on inspection
- The device is highly beneficial
- No signal of device problems
- Problem: No approval or clearance

Unapproved or Uncleared Device

- Regulatory violation: Misbranding
- What is the device benefit?
  - Life-saving/High/low, transient/durable, …
- What is the risk of use?
  - Serious/reversible/temporary, likely/not, …
- Is benefit > risk?
- Might removal cause a shortage?
- Options: Continue access while submitting application under time limit, remove device from the market, inspect the firm, …

Incomplete or Inappropriate Mitigation

- A firm submits a notice of a correction to a malfunctioning valve on a blood pump
  - 0.1% of the time the doesn't open
  - Tubing has ruptured and sprayed blood.
- The firm wants users to test the valve before each use.
- Problem: Incomplete mitigation

Incomplete or Inappropriate Mitigation

- Regulatory violation: Adulteration
- What is the device benefit?
  - Life-saving/High/low, transient/durable, …
- What is the risk of use?
  - Serious/reversible/temporary, likely/not, …
- Is benefit > risk?
- Might removal cause a shortage?
- Options: Continue access while addressing root case, remove device from the market, inspect the firm, …

Shortages

- 21 CFR 600.92(f)
  - A period of time when the demand or projected demand for the biological product within the US exceeds the supply of the biological product
- Sometimes “an analysis after the analysis”
- Would an action cause a shortage?
- Would a shortage be harmful to health?
  - Are there alternatives or mitigations?

Shortages

- If no alternatives/mitigations, how to meet the demand?
  - B-R of alternative devices, drugs, treatments
  - Allow continued availability: General population? Subpopulations?
  - Alter regulatory action: Enforcement discretion, import alert waiver, temporary clearance
  - Continued monitoring, reassessment
- B-R assessment for each scenario

PMA Preapproval Inspections

- A firm makes a device that treats a rare, incurable disease.
- IDE is completed, endpoints met successfully
  - Unanticipated adverse events during premarket study.
- Firm
  - Produces similar products using similar methods
  - Two Class II recalls in the past three years, terminated uneventfully
  - No allegations
  - No MDRs concerning other devices

PMA Preapproval Inspections

- Decision: PMA inspection prior to marketing? After? Never?
- Device benefit?
  - Breakthrough/life-saving/high/low, transient/durable, ...
- Device risk?
  - Serious/reversible/temporary, likely/not, …
- Firm's complexion?
  - Favorable, worrisome, ...
- Is benefit > risk? Unmet need?
- Strategy: Grant PMA approval first, inspect after market release

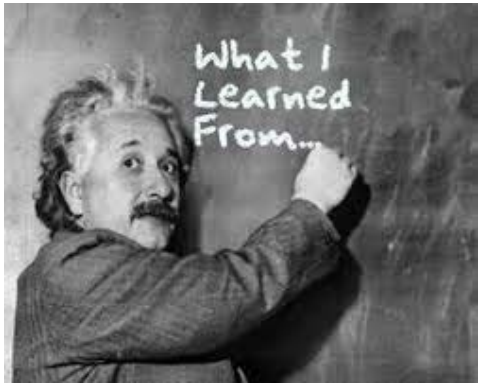
Key Points Covered

The Future with Benefit-Risk

SUMMARY

Objectives

- Understand why FDA is interested in the benefit-risk approach to medical device availability and compliance decisions
- Learn about CDRH's postmarket benefit-risk guidance document
- Understand when a formal postmarket benefit-risk evaluation could help decision-making
- Explore some example applications of benefit-risk thinking



Key Points

- B-R informs decision making to achieve a balance between **maximizing patient benefit** and **reducing patient risk**
  - Complements the premarket benefit-risk guidance documents
  - Covers a wide (unspecified) variety of compliance and enforcement decisions
  - Provides useful tools to promote uniformity and transparency
- Enables industry and FDA to “speak the same language”
- Enables industry to “make the case” for a chosen decision

The Purpose

Maximize patient benefit

Reduce patient risk

Improve overall medical device quality

The Purpose

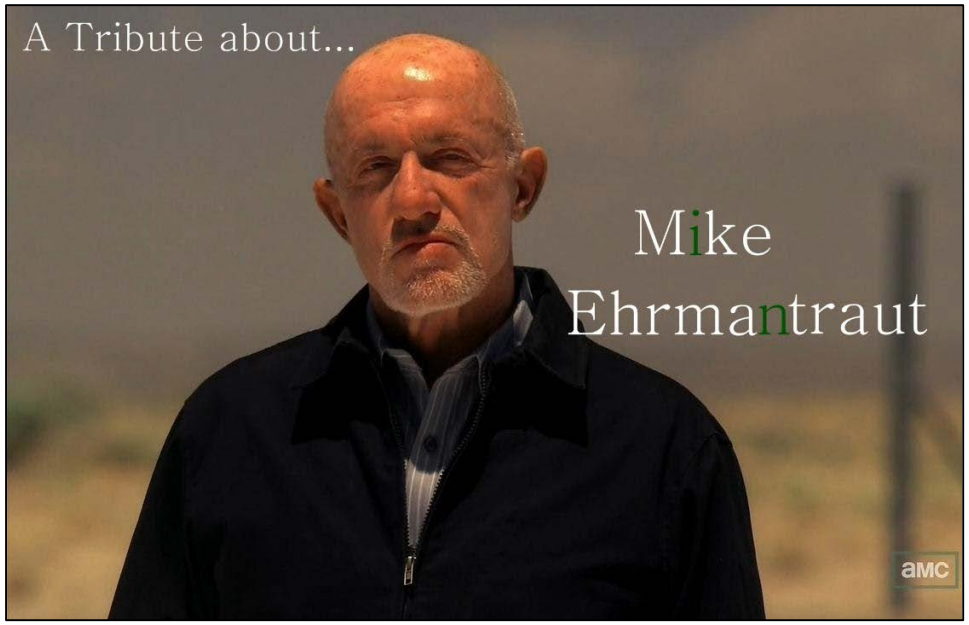
And who doesn't like quality?

Especially patients and the people who care for them

The Purpose

And who doesn't like quality?

Especially patients and the people who care for them



Contact Information

Adam E Saltman MD PhD
Medical Officer
Office of Compliance
FDA Center for Devices and Radiological Health
10903 New Hampshire Ave
Silver Spring, MD 20993

301-796-2909
Adam.Saltman@fda.hhs.gov

THANK YOU!