Benefit Loss and Risk in the Postmarket Environment
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Objective Today

- Principles and factors developed with public input could help bridge differences in understanding and create common terminology for use when considering actions such as recalls, warning letters, and other enforcement efforts that occur once a medical device is being marketed.
Focusing on Postmarket Risk
Focus

- Risk in addition to known risks for a cleared/approved device
- Clinical risk of injury to patients/users from defects or failure of marketed devices as well as false or misleading claims
- Risk due to lack of access to devices
  - First of a Kind
  - Shortage from CDRH or Industry action(s)
Changes in Understanding of Known Risk for Cleared/Approved Devices

• Identifying previously unrecognized hazards or hazardous situations
• Determining that the estimated risk(s) arising from a hazardous situation is/are no longer acceptable

Clause 9 ISO 14971 as well as CAPA subsystem in 21 CFR 820.
Current Thinking

• Regulations
• Standards
• Guidances and other literature
• Daily considerations in the regulatory environment
Harm and Hazard

• Harm: Physical injury or damage to the health of people, or damage to property or the environment. ISO 14971:2007 (E)

Safety

• Safety: Freedom from unacceptable risk  ISO 14971:2007 (E)

• Basic Safety: Freedom from unacceptable risk directly caused by physical hazards when equipment is used under normal conditions and single fault condition.  ANSI/AAMI E60601-1:2005

• Essential Performance: Performance necessary to achieve freedom from unacceptable risk.  ANSI/AAMI ES60601-1:2005
Risk

Combination of the probability of occurrence of harm and the severity of that harm. ISO 14971

Combination of the probability of an event and its consequences. ISO/IEC 73:2002 (E/F)
Effectiveness

Product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling. Federal Food, Drug, and Cosmetic Act.
Benefit

• Benefit: Helpful or good effect, or something intended to help. ISO 16439:2014(en), 3.7

• Health benefit: Likelihood of maintaining or improving health. ISO 10993-17:2002(en), 3.6
Proposal

• If Benefit is a helpful or good effect or something intended to help, it also needs to be safe or free of unacceptable risk.

• Loss of Benefit would occur when the risks are greater than expected, so the benefit to the patient may not be worth the increased risk.
Benefit Loss

Product 1

Maximum Benefit
Baseline set based on clearance or approval

Recovered

Product 2

Benefit

Start to market

Time

Harmful event

Removed from market
Loss of Benefit Concept

- Maximum benefit usually occurs at time of approval or clearance.
- Any defect, failure, or shortage postproduction is likely to reduce the benefit through loss of effectiveness and/or introduction of additional risk.
- This new risk may be in addition to the risk anticipated by the firm premarket.
Risk Benefit (R/B)Analysis

Risk Benefit Analysis is used to justify a risk once all practicable measures to reduce the risk have been applied...

ISO 14971:2007(E)
Benefit Loss Analysis

Benefit Loss Analysis or Residual Risk analysis?

• Will a shortage result if product is removed?
• Will attempts to recover benefit introduce new risk?
• Is there a way to modify the risk to make it tolerable, will patients tolerate no change?
Benefit Loss Analysis

Maximum Benefit
Baseline set based on clearance or approval

What to do with the product causing harm that is still on the market?

Shortage

Time
Risk Assessment

• Does how to perform risk assessment associated with a device malfunction or failure postproduction need to be clarified? Would more education be useful?
Risk Analysis

• Process that supports decision making by using science and evidence to identify what we know and what we don’t know. It integrates this knowledge and uncertainty with social values to meet objectives (public health) and avoid constraints and thereby to solve problems.

Charles Yoe,
Principles of Risk Analysis.
Risk Perception and Value

- **RP**: way in which a stakeholder views a risk based on a set of values or concerns. 
  ISO 73:2002 (E/F)

- **Value**: Importance that stakeholders attach to [libraries/devices] and which is related to the perception of actual or potential benefit. ISO 16439
Ethics Definitions
Ross et al. BMC Medical Ethics 2010, 11:14

• Beneficence: obligation to provide benefit to patients in part by ensuring that treatments are effective.

• Non-maleficence: obligation not to inflict harm on patients unless this is outweighed by potential benefit to patients in part by providing safe treatments.

• Autonomy: patients right of self-determination...to hold views, make choices, and take actions based on personal values and beliefs.

• Justice: fair, equitable, and appropriate treatment in light of what is due or owed to the person...relevant to fair access to treatment, responsible stewardship of scarce resources, and compensation for injury.
Situations Where Patient Perspective Impacts Balance

- Shortages
- Unmet medical needs
Risk Management
Spirit of Implementing Risk Management

• Risk Management by definition is the coordinated activities to direct and control an organization with regard to risk. ISO 73:2009

• Ideally, firms match sections of the design control regulations to their risk management processes.
Goal of Managing Risk

• Preproduction: Reduce risk
  – ID potential risk + prevent, minimize

• Production & Post production:
  – ID hazards and fully recover lost benefit if possible.
Phases of Risk Management

White Paper: PTC Quality in Medical Devices

• Establish levels of risk expected for the benefit provided
• Identify and analyze risk from all potential sources
• Evaluate risk in light of risk acceptability
• Implement measures to eliminate or mitigate risk
• Continuously monitoring including when outsourcing.
CDRH and Risk Management

CDRH does not always evaluate firm’s risk management plans

In premarket some devices:

– Are exempt from premarket review
– Are substantially equivalent to predicates
– Are higher risk devices e.g. PMA,
  • bench testing in laboratory conditions
  • clinical trials (controlled, idealized, small patient numbers)
  • quality system
When to Submit a 510(k)
May 8, 2013, Federal Register Vol. 89

- A company’s risk management processes are contained within its overall quality system and may not be specifically scrutinized by FDA during 510(k) reviews.
CDRH and Risk Management

- CDRH does not generally review sponsor risk management plans postmarket.
- In some cases a risk management plan may be reviewed during an inspection.
Different Perspectives

• Firms ID new hazard and implement appropriate risk control measures independently of CDRH.

• When CDRH becomes aware of a problem, risks may be reviewed without knowing the firm’s risk management plan.
Cannot Eliminate Risk

Understood risk can become uncertain when unforeseen harm or unexpected level of harm occurs:

- Design control failure
- Transport, storage, installation
- Clinical practices, regional or new
- Sensitive subpopulations
- Operator error
How is the Threshold for Actions Determined?

Both CDRH and the firm conduct risk analysis, weighing new risk and benefit profiles.
What Happens from a Risk Management Viewpoint?

Ideally a firm uses their experience gained when a product is being made or is being used in the marketplace to update their original risk management plan when new issues arise.
Risk Management Perspective

Baseline
Determined by preproduction risk assessment and risk management plan

Premarket Benefit

Sodium azide explosion

Contamination related to design issue

Known risk

Time
What Happens in a Regulatory Scenario?

• Routine inspection or other source identifies a postproduction deviation/violation.

• Assesses information submitted in the premarket submission generally without the additional risk information acquired under risk management.
Regulatory Perspective

- Maximum Benefit
- Baseline set based on clearance or approval
- Sodium azide explosion
- Contamination related to design control
- Possible shortage
Differences in usage of risk terms and concepts preproduction vs. postproduction may confound differences in expectations.
Some Examples of Terms Used Differently

• Probability vs Frequency
• Mitigation
• Risk-Benefit Analysis
Probability vs Frequency

Same Event

Viewpoints Differ

• One perspective - Risk was anticipated premarket and is acceptable since the frequency of the event occurs within the probability anticipated.

• Another perspective - Risk first occurred postmarket; the event occurs at some measurable frequency and was not prevented.
Mitigation and Risk Treatment

• Mitigation: Limitation of any negative consequences of a particular event. ISO/IEC Guide 73:2002 (E/F) also known as controlling risk.

• [preproduction- preventing something from happening]

• [postproduction-correcting something that happened]

• Risk Treatment: process for selection and implementation of measures to modify risk. ISO 31000:2009(E)
Overall Residual Risk Analysis or Benefit Loss Analysis

- It may be confusing to use the term “risk benefit analysis” when describing the process of figuring out what to do with a marketed product that is causing harm and is still in the marketplace.
Objective Today

Principles and factors developed with public input could help bridge differences in understanding and create common terminology for use when considering actions such as recalls, warning letters, and other enforcement efforts that occur once a medical device is being marketed.
We welcome your thoughts on today’s presentations and the questions posed in the Federal Register. Please send them to us through the open docket.

Please visit:  http://www.regulations.gov using docket number:  Docket No. FDA-2015-N-0620