SPECIAL REPORT

Postmarket Risk Management

A Framework for Incorporating Benefit-Risk Assessments into Correction and Removal Decisions

AAMI
Advancing Safety in Healthcare Technology

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A Framework for Incorporating Benefit-Risk Assessments into Correction and Removal Decisions

A SPECIAL REPORT

Developed by
AAMI

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NOTE: Participation by federal agency representatives in the development of this report does not constitute endorsement by the federal government or any of its agencies.

Foreword

In collaboration with the US Food and Drug Administration (FDA), AAMI launched an initiative and convened an informal working group in the fall of 2014. The group's goal was to address key issues in the area of postmarket device quality with particular emphasis on safety. The group was composed of representatives from the medical device industry, FDA, and industry trade associations. Two patient representatives provided the perspective of the patient along the way. The initial purpose of the initiative was to *develop a shared understanding of risk principles that would guide both the medical device industry and FDA in assessing and managing risk in the postmarket setting.* Fast forward to the fall of 2015, and AAMI published a white paper that memorialized the first deliverable from this ad hoc group[2].*

That first phase of what has become a much more significant initiative was successful in opening the dialogue between industry and FDA about the divide between manufacturers and regulators on postmarket device quality issues. The first phase also helped to inform recommendations to ISO Technical Committee 210, the committee responsible for maintaining ISO 14971. It also helped to inform the successful AAMI/FDA Risk Management Summit [1] held in October 2015.

More importantly, that first phase enabled work on deeper postmarket device quality issues where greater FDA and industry alignment would serve the public's interests. These include: how to conduct a risk assessment, how to use a risk assessment in determining the appropriate course of action in managing a recall[2], and the meaning of certain terms not used universally by FDA and industry (such as "baseline" and "worst case").

With greater clarity about what might improve the collective experience of industry and the FDA with postmarket device quality issues, phase two of this initiative began in April 2015. The original working group members agreed to continue, and brought the wisdom and expertise from phase one. Additional working group members brought in fresh perspectives and expertise. The emphasis of phase two was on how to incorporate benefit into correction and removal decisions. Conceptually, this is easy to understand but can be difficult to accomplish.

The objective of this report is to outline a framework that the members of the working group hope will be used by both the medical device industry *and* the FDA. The medical device industry can use this framework to incorporate benefit-risk assessments into correction and removal decisions once a medical device is on the market. It intended to support the FDA's draft guidance document [30] of June 16, 2016 (which is still a draft at the time of publication of this framework) on the same subject. Not all postmarket risk assessments lead to a recall decision. This particular framework, while emphasizing and supporting decisions that can lead to a recall, is intended to support a stronger analysis of the benefit aspects of a postmarket analysis of benefit and risk when deciding what type of action is most appropriate in this postmarket context.

In developing this report, the working group imagines and hopes that industry and the FDA will use the framework in their own independent analyses and processes, as well as in discussions that occur between a manufacturer and the FDA. If the FDA and a medical device manufacturer consistently use the same framework to do their assessments, and if the process that FDA and industry use is predictable and transparent, then it's much more likely that both will be aligned in arriving at decisions that clearly meet the public's best interests.

The more traditional risk assessments contemplated by ISO 14971 are well developed and built into existing processes within industry and the FDA. However, with more complex postmarket device quality issues, it was the consensus of the working group that the existing tools do not go far enough. This is especially the case when a manufacturer or the FDA is faced with the least certainty and thus

*The numbers in brackets refer to the Bibliography found on page 103. The superscripted numbers refer to the endnotes found on page 106.

the toughest decisions about what action to take regarding correction and removal. The working group envisioned that using *benefit* as a foundational principle in doing risk assessments will help achieving a stronger alignment between industry and FDA, most pointedly in those areas where an ISO 14971 analysis, with its primary focus on risk, is not enough.

As a framework, it includes, most importantly, a flow chart that maps the steps in a postmarket benefit-risk assessment, from the first look at the postmarket risk issue all the way through to the decision. Understanding the flow chart is a major clue to understanding everything else in the report.

The report includes several invaluable tools to support the analysis contemplated by the flow chart. The working group developed a new risk assessment form (and the steps for doing the assessment called for by the form). The new risk assessment form can provide a framework for a shared discussion of risk.

An extensive annex of examples helps illustrate the benefit-risk analysis and the use of the flow chart. The specific types of examples provided have historically been more challenging for industry and the FDA.

Another annex provides detail on using quantitative decision analysis tools to improve decision quality, for those who are ready to embark on using these tools. Some medical device companies are already using quantitative decision analysis tools, having the appropriate data and having learned from other high-reliability industries the value of such tools.

The final annex provides a concise summary of an informal "pilot" conducted by seven medical device manufacturers and staff from FDA's Center for Devices and Radiological Health (CDRH) to try out the new analysis prior to final publication of the framework.

During the public comment phase of this project, several important questions and comments were made that were beyond the objectives established for this report. These questions and suggestions are worthy of consideration for a future project(s) between CDRH and the medical device industry. These questions and suggestions are memorialized in Section 8.

The incredible volunteer leaders from industry and FDA who worked side by side on this initiative deserve many thanks for their dedication to developing these recommendations for a common framework to assess and make correction and removal decisions with *benefit* at the forefront of the decision-making process. When individual working group members were asked to identify measures for success for this effort, they identified the following as being important to them:

- When the FDA and a manufacturer sit down together, there will be a common understanding of risk for the situation being discussed;
- Industry and the FDA will be aligned on the steps and analysis encompassed in the new risk assessment form developed by the AAMI/FDA Ad Hoc Risk Working Group;
- It will be the unusual exception for industry and FDA to disagree about the postmarket risk assessment and decisions that need to be made as a result of that assessment;
- Industry and the FDA will have broadened their collective analyses to use benefit; and thus
- The FDA and industry will be more focused on taking actions that fit the best interests of patients; and
- Conversation between the FDA and a manufacturer will have patients as the top consideration in assessing the trade-offs of benefit/risk for patients.

We all have the same ultimate goal: to improve patient outcomes. This common goal will help bind us all together in working toward the alignment between industry and FDA that is envisioned in this report and by the working group that developed this material.

Now it's up to the community—both industry and the FDA—to test, adjust and implement these recommendations in their postmarket work. From AAMI, we are honored to have supported this learning process and look forward to toasting success in five years, when we look back and see how far we have all come.

Mary Logan, JD, CAE
AAMI President/CEO

NOTE

An extensive annex of examples helps illustrate the benefit-risk analysis and the use of the flow chart.

Introduction

0.1 Project intent

The AAMI/FDA Ad Hoc Risk Working Group has developed this special report to provide greater clarity regarding the process and the principal factors that should be considered when making benefit-risk assessments during postmarket surveillance. The AAMI/FDA Ad Hoc Risk Working Group focused its efforts on the postmarket issues surrounding the identification and management of medical device correction and removal events. The members of the AAMI/FDA Ad Hoc Risk Working Group believe that the uniform application of the process and factors listed in this special report can improve the predictability, consistency and transparency of this postmarket surveillance process.

The AAMI/FDA Ad Hoc Risk Working Group recognizes that the full implementation of the methodology described in this special report would require significant premarket and postmarket regulatory and process changes for FDA. For example, to implement the methodology as described, FDA and industry would need to agree on the adequacy of the initial risk management assessment, a decision that FDA does not currently make. However, the process and principles described in this special report represent a risk management methodology that utilizes an FDA recognized risk management standard and puts the benefits and risks the patient experiences at the heart of the correction or removal decision-making process.

0.2 Background

The use of medical devices in a real-world setting can provide a greater understanding of their risks and benefits. While devices are often approved based on data from specialized hospitals and narrow patient indications, less specialized hospitals may use the device on a wider spectrum of patients, once it is commercially available. Once a medical device is commercially available, its manufacturer is required to monitor the device's performance through its postmarket surveillance systems. The collected postmarket data may be utilized as a way to clarify the magnitude and effect of risk control measures, or as a way to develop additional information regarding benefits or risks for certain device types or in specific patient populations. Postmarket data that comes to light after the device is used in the real-world setting may

- alter the established risk assessment, especially if new risks are identified;
- confirm that certain risks have been adequately controlled;
- identify which patients are most likely to suffer adverse events; or
- identify, more specifically, how different groups of patients will respond

Data obtained through a postmarket surveillance system may indicate that a medical device is not performing as stated in its specification or labeling, because it is contributing to potential or actual injuries that are unexpected or occurring at a rate or with a severity that is considered unacceptable.

A medical device is considered "violative" if that device does not comply with the requirements of Federal Food, Drug and Cosmetic Act (FD&C Act) [45] or the associated regulations enforced by the FDA. A medical device can be considered violative if it fails to perform as stated in its specification or labeling. "Adulterated" is one term used to describe a violative medical device. A medical device can be considered violative if its labeling is false or misleading in any particular as set out

PROJECT GOAL

Greater industry-FDA alignment on incorporating benefit-risk assessments into correction and removal decisions.

in §502 of the FD&C Act. "Misbranded" is another term used to describe a violative medical device.

A medical device may also be violative because of some technical violation of the FD&C Act or the associated regulations.[3] In either case, if a product is found to be violative after commercial launch, its manufacturer has the obligation to consider actions that help manage the risk to patients and/or correct the technical violation.

A recall is an action that takes place because manufacturers and distributors appropriately carry out their responsibility to protect the public from products that present an unacceptable risk of injury or otherwise do not meet product specifications.

INFORMATION

Risk principles + context of use + Benefit = Stronger Analysis

There may be scenarios that arise in which a manufacturer would consider removing the medical device from the market to correct the violation. However, sometimes that removal could adversely impact public health. Examples of the way removing a product from the market could place patients at increased risk include explanting of implanted products, creating product shortages that delay treatment or necessitate the use of less appropriate therapies, etc. Currently there is little guidance on evaluating these scenarios in the postmarket setting. This report seeks to provide guidance to manufacturers as well as increase the transparency needed between FDA and manufacturers to reach a decision that is most beneficial to patients.

The process described in this report is not new. A number of manufacturers and the FDA have employed a similar methodology in the past to arrive at a consensus when recalling a medical device could present a greater risk to public health than keeping the device on the market with temporary mitigations while the manufacturer works to resolve the issues with the product. One of the purposes of this report is to provide structure around the process so it can be applied more consistently and transparently.

0.3 Risk factors

A significant part of the work underlying the AAMI White Paper 2015, *Risk Principles and Medical Devices: A Postmarket Perspective* [2], involved the development of the factors to consider when assessing risk and benefit on postmarket quality issues. Those factors are listed in Annex B to the White Paper and are reprinted again in Annex F to this report. They are flagged again here as a key reference for conducting the postmarket benefit and risk assessment because of the importance of context of use. One of the public review commenters asked the question of how the environment of care and use constructs play into the assessment. This question flagged for the reviewers that additional attention was needed in this report itself to connect readers back to that original AAMI White Paper 2015 [2].

The environment of care and use constructs are essential considerations, along with all of the other benefit/risk factors listed in Annex F from the AAMI White Paper 2015. When weighing the benefit of a device, the context of its use is always an important consideration. For example, a device that is being used in an emergency situation in an ambulance or emergency room is going to be viewed differently from a device that is used in more routine situations.

In short, the context is part of the assessment and plays out through those risk factors (Annex F). Those factors consider such things as the severity of harm (e.g., acute versus chronic; reversibility); frequency of harm; complexity of use and who is using it; the population at issue (e.g., age); current clinical practice (e.g., no other options are available; emergency versus routine use; home care versus intensive care unit); and environment of care (e.g., labeling; training).

Although not stated as such, the importance of these risk factors from the AAMI White Paper 2015 is implicit in the FDA's June 16, 2016 draft guidance document on *Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions* [30]. That draft guidance is heavily focused on the risk factors that are considered in a postmarket benefit and risk assessment.

Postmarket Risk Management: A Framework for Incorporating Benefit-Risk Assessments into Correction and Removal Decisions

1 Scope

1.1 The framework

The public health in the United States is best served when medical device manufacturers and the FDA's Center for Devices and Radiological Health (CDRH) understand, assess and approach benefit and risk consistently throughout the total product life cycle of a medical device. A good deal of work has already been done looking at the assessment of benefit and risk in the pre-market phase of the product life cycle. The FDA has published several guidance documents looking at the assessment of benefit and risk in pre-market submissions [28] [31], and additional guidance is contemplated. Work has been done by organizations, such as the Medical Device Innovation Consortium (MDIC), in such areas as incorporating information of patient preferences regarding benefit and risk into the regulatory assessment of new medical technology [20].

IMPORTANT

This report lays out a framework that medical device manufacturers and FDA can apply in assessing risk and weighing benefit when analyzing correction and removal decisions.

However, less work has been done on assessing benefit and risk in the postmarket phase of the product life cycle. In the AAMI White Paper, *Risk Principles and Medical Devices: A Postmarket Perspective* [1], the AAMI Ad Hoc Working Group on Risk Principles identified a number of issues that need to be addressed in more depth. This report addresses some of those topics identified under "Next steps" and "Recommendations from commenters" in the AAMI White Paper.

This report lays out a framework that medical device manufacturers and FDA can apply in assessing risk and weighing benefit when analyzing correction and removal decisions. The framework in this document applies to both diagnostic and therapeutic devices.

The medical device industry can use this framework to incorporate benefit-risk assessments into correction and removal decisions once a medical device is on the market. It intended to support the FDA's draft guidance document [30] of June 16, 2016 (which is still a draft at the time of publication of this framework) on the same subject.

Figure 1 provides a block-diagram overview of the process described in this report. The numbers in parentheses in the figure refer to the sections of this report where a particular topic is described in detail. Examples 1 through 4 in Annex D are intended to illustrate the application of the process steps in Figure 1.

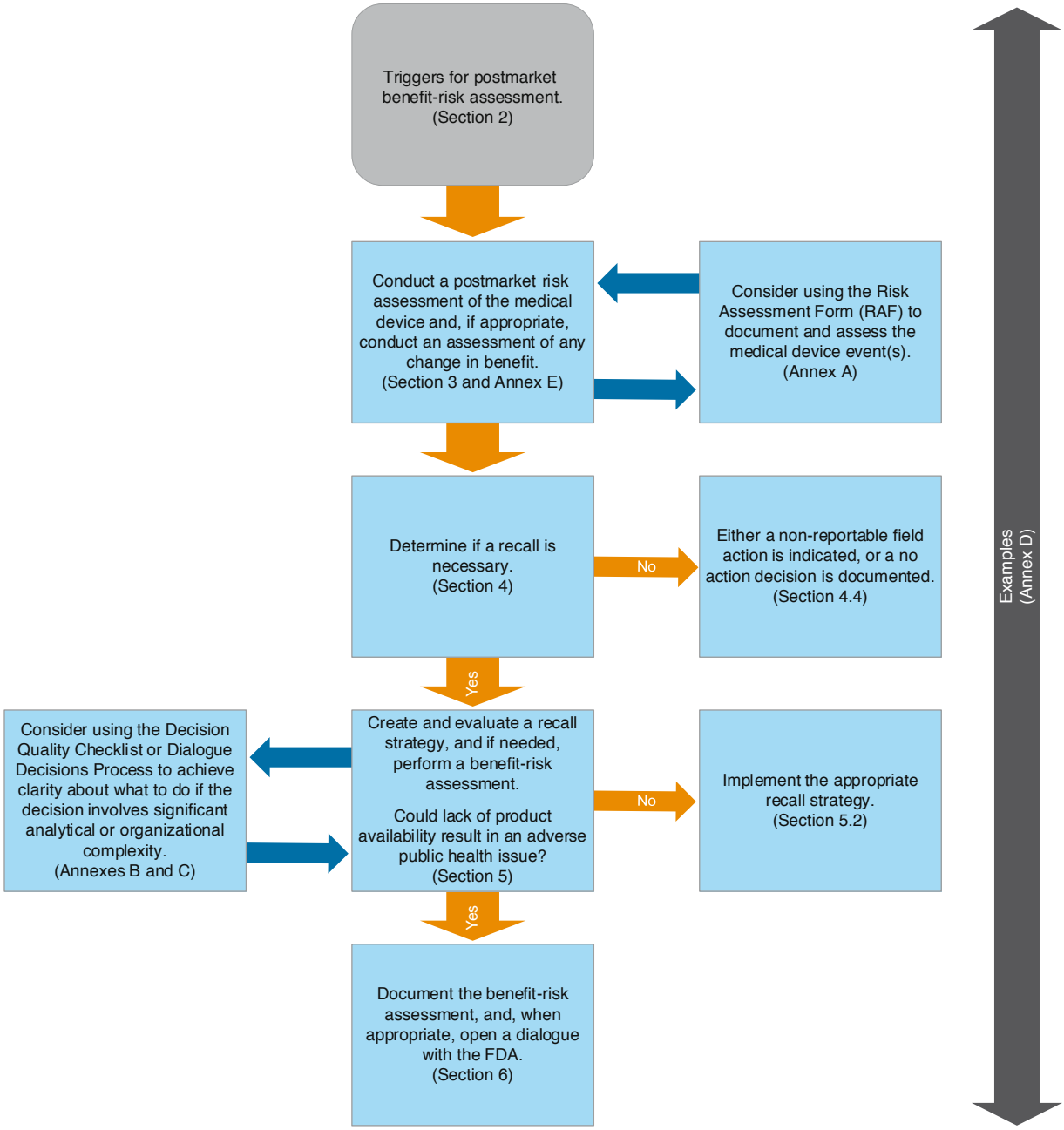

FIGURE 1—FRAMEWORK OVERVIEW

The framework in this report should be considered as a starting point for incorporating benefit and risk considerations into the postmarket decision-making process and must be applied within the legal and regulatory requirements set forth in 21 CFR Part 7 [37] and Part 806 [40] among others. This report does not purport to be a prescriptive how-to guide, nor does it purport to be a definitive document that addresses every situation a manufacturer or the FDA may encounter. Rather, it is intended to improve the understanding of manufacturers, FDA staff and others about how benefit and risk considerations can be incorporated into the postmarket decision process.

While full implementation of the methodology described in this report would require significant premarket and postmarket regulatory and process changes for FDA, much of the information provided is neither new nor revolutionary. The FDA has already

issued guidance on elements of the process, such as *Product Recalls, Including Removals and Corrections* [32] and *Recalls, Corrections and Removals* [33]. Under the requirements of the Quality System Regulation [44], manufacturers already have internal processes designed to monitor, collect and analyze postmarket data and, when necessary, take and document appropriate corrective action. However, this report attempts to bring the information together in a single document, with a particular focus on analyzing benefit and risk, and dealing with situations where there could be uncertainty regarding the adverse public health issues that might arise from implementing a particular field action.

While preparing this framework, teams working within the AAMI/FDA Ad Hoc Risk Working Group identified or developed:

a) The Risk Assessment Form (RAF)—A comprehensive, integrated engineering and clinical analysis tool for documenting and assessing medical device events that may have an impact on device quality (Annex A);
b) A field action decision-making process with a focus on assessment of risk, and, when appropriate, assessment of benefit, which includes consideration of the adverse public health issues from implementing a recall strategy;
c) The factors that are important for the manufacturer to consider to facilitate transparent communication between the manufacturer and the FDA when there is uncertainty about the adverse public health issues;
d) Illustrative examples to help build understanding of how the framework might be applied in those situations (Annex D); and
e) A "decision quality" approach that could facilitate good decision making, particularly when the decision involves significant analytical and organizational complexities (Annex B and Annex C).

1.2 Purpose

The purpose of this report is to improve predictability, consistency and transparency by providing a common framework that enables industry and FDA to arrive at decisions that are beneficial to patients in situations where decisions often have to be made with some urgency based on incomplete information in an environment of uncertainty.

IMPORTANT

Why This Report is Needed—To improve predictability, consistency and transparency by providing a common framework that enables industry and FDA to arrive at decisions that are beneficial to patients in situations where decisions often have to be made with some urgency based on incomplete information.

1.3 Terms and definitions used in this report

The consistent use of terminology is critical to understanding the process described in this report. To assist in understanding this report, a Glossary appears beginning on page 97. Some of the definitions of terms used in this report were taken from the section of US Code of Federal Regulation (CFR) dealing with regulatory enforcement actions[4], International Standards such as ISO 14971[5], and various FDA Guidance Documents listed in the Bibliography beginning on page 103. Where a term was taken from a source document, the source is noted in the Glossary.

2 Triggers for a postmarket benefit-risk assessment

2.1 Identification of an initiating device event

One of the measures of the effectiveness of a manufacturer's quality management system is feedback on whether the manufacturer is meeting customer and product requirements. The process for obtaining this information includes gathering data from production and post-production activities. Some sources of information about nonconformities related to manufacturing process issues include:

» Supplier controls.
» Environmental excursions.
» Calibration excursions.
» Alert limit excursions.
» Process parameter excursions.
» Compromised sterile barriers and/or other sterilization issues.

INFORMATION

Items to Consider

+ Supplier controls
+ Environmental excursions
+ Calibration excursions
+ Alert limit excursions
+ Process parameter excursions
+ Compromised sterile barriers and/or other sterilization issues
+ Inspection/test/validation failures
+ Failures to manufacture according to documented processes

» Inspection/test/validation failures.
» Failures to manufacture according to documented processes.

Other sources of internal information include:

» In-process testing.
» The Corrective and Preventive Action (CAPA) process.
» Observations from internal audits.
» Stability and reliability testing.
» Post-approval studies.
» Periodic reviews of safety and performance including adverse event reported in the scientific literature (e.g., preparation of a Premarket Approval (PMA) annual report).

Important sources of customer feedback include customer complaints, Medical Device Reporting (MDR), feedback from the sales force, and publications. Published medical literature may also be an additional source of information on postmarket experience including information on off-label uses. Other nontraditional sources, such as social media, should be taken into account while recognizing there can be issues including lack of accuracy and completeness.

The information gathered in these processes can serve as input into the quality system processes for monitoring and maintaining the product requirements as well as the product realization or improvement processes. In addition, these sources may indicate that the manufacturer potentially has a postmarket device quality problem that could adversely affect the benefit or risk associated with the product, i.e. an initiating event. In that case, additional steps, as detailed below, need to be taken to determine whether there is a nonconformance that would result in the medical device being considered "violative" and could require a field action. Such a process is the subject of this report.

Determining whether and when to commence an analysis on correction or removal is a critical and difficult decision. The "initiating event" as it is used in this Framework refers to the trigger or triggers that commence that correction/removal analysis. Every company needs a process to decide what it will consider to be an initiating event. Common initiating events are:

» Unanticipated adverse events or device malfunctions.
» Adverse events/device malfunctions that exceed the tolerances established for risks: more serious than anticipated or occurring at a higher frequency than anticipated.
» Data or information from internal testing that suggests an unexpected problem or a problem that exceeds expected thresholds.
» Labeling non-conformance or deficiency.
» Management discretion (e.g., reports in the news; social media).

However, these are just examples of common initiating events and every company needs to use its own judgment about what, for it, would be sufficient (alone or in combination with other triggers) to commence a correction/removal analysis.

Ultimately, any decision should always be made in the interest of what is best for public health and **should not be delayed** if a serious and imminent risk to public health is present, or is otherwise required by law. An appropriate field action should be initiated immediately.

INFORMATION

Common initiating events are:

+ Unanticipated adverse events or device malfunctions.
+ Adverse events/device malfunctions that exceed the tolerances established for risks: more serious than anticipated or occurring at a higher frequency than anticipated.
+ Data or information from internal testing that suggests an unexpected problem or a problem that exceeds expected thresholds.
+ Labeling non-conformance or deficiency.
+ Management discretion (e.g., reports in the news; social media).

2.2 Escalation of the initiating device event into a field action decision-making process

Following the procedures established in their quality system, the manufacturer determines, a field action decision-making process should ensue. Some questions to consider when evaluating the initiating device event can include:

- Is the medical device meeting all design outputs/product specifications contained in the Design History File (DHF)?
- Does the medical device perform to the specified requirements?
- Does a nonconformance exist that may affect product in distribution?
- Is there an increase in the overall failure rate beyond the expected rate?
- Is there an increase in a single failure mode rate beyond the expected rate?
- Has a new failure mode been identified?
- Is there an unanticipated patient outcome?
- Is the observed severity unanticipated?

Typically, the benefit of a device which is functioning as intended does not increase in the postmarket phase for FDA-cleared and approved indications beyond that anticipated pre-market. However, new benefits of a device which is functioning as intended are sometimes identified because of changes in clinical practice or through off-label use. It may be useful, in addition to looking at failure and risk, to also review the device benefit relative to that described in the DHF at the time of product launch (or most recent update) while taking account of any new or increased benefits discovered in the interim. For example, is there evidence gathered from sources such as postmarket clinical studies or the literature that demonstrate the medical device has proven to be useful in a broader population than originally intended? Is there a subset of the original patient population for whom the device benefit is greater or lower than anticipated? Is the benefit of the device for the original population greater or less than originally established? This assessment may be of use in determining the most appropriate corrective action. See Section 3.4.

3 Conduct a postmarket benefit-risk assessment

3.1 Gathering and recording the necessary data

Early in the process, the manufacturer needs to begin gathering and recording data that will support the event analysis and decision-making at various stages of the process described in this report. Annex A contains a Risk Assessment Form (RAF) that the manufacturer can consider using to begin assembling the appropriate data. All parts of the form need not be completed before moving to the next stage, but it does illustrate the breadth and depth of information that ultimately may be needed to support the event analysis and decision-making process.

3.2 Scope of products being impacted

It is important to understand the scope of the devices being investigated by considering such factors as device name, model, batch/serial numbers, design and manufacturing locations, production dates, quantities in the hands of users, software versions, countries where used, and so on. This information is captured in Part I(A) of the RAF. These factors establish the boundaries within which further analysis will be done and will support the probability calculations made when estimating the risk(s). It is important the manufacturer understand and document the rationale for these boundaries (for example, why only certain batches or serial numbers are involved).

3.3 Risk assessment

3.3.1 Characterize the risk(s)

3.3.1.1 Review the risk management documentation

The manufacturer's risk management file captures the criteria for risk acceptability and the established risk assessments for the medical device. It is against these criteria

and the established risk assessments that future evaluation of any new risk(s) or changes in the residual risk(s) will be made. This report is based on the assumption that the manufacturer has established and implemented appropriate risk management processes.

3.3.1.2 Risk was identified in the established risk assessment

First, the manufacturer needs to determine whether the device event falls within the expectations described in the established risk assessment for the medical device. The established risk assessment is usually made at the time the design is transferred to manufacturing. This assessment may be revised during final performance validation and may be updated until final device approval (or first sale).

If the medical device performance is within the expectations described in the established risk assessment, the data should be captured by the manufacturer's quality and risk management systems, so that the manufacturer can continue to monitor for trends and incorporate product improvements.

If the medical device performance exhibits a higher residual risk than is described in the established risk assessment for the medical device, further risk assessment as described in sections 3.3.2 through 3.3.5 need to be performed.

However, even if the medical device is performing within the expectations described in the established risk assessment, there could be a violation of one or more of the requirements in the FD&C Act or the associated regulations.

3.3.1.3 New hazard/hazardous situation is identified

For an event that was not identified in the established risk assessment for the medical device, the manufacturer's risk management process is to be followed. This is to include a formal risk evaluation described in this section (including identification of the intended use or any product characteristics that may have contributed to the event), identification of the specific hazard/hazardous situation, estimation of the risk, and consideration of the need for a risk management update.

INFORMATION

Postmarket risk assessment involves multiple steps and requires consideration of many factors. Broadly, the process will include estimating the severity and probability of occurrence associated with the hazardous situation.

To help in understanding the hazard/hazardous situation, the manufacturer may conduct a root cause analysis. For example, the root cause(s) may be found in the product realization processes, labeling, use error, clinical environment, the inherent risks associated with certain medical/clinical procedures where the particular medical device is being used, changes in the clinical environment/technologies, and interferences that were unforeseen (e.g., new drugs/devices interfering with an existing medical device).

In certain cases, root causes may not be immediately or readily available. The manufacturer should make every reasonable effort to avoid unnecessary delays in decision making to protect patients' or users' safety.

Once the hazard/hazardous situation is determined, an estimate of the severity and probability of occurrence of the device event is to be made by applying the manufacturer's risk process.

3.3.2 Estimate of the device risks

3.3.2.1 Estimating the severity and the probability of a hazardous situation

Postmarket risk assessment involves multiple steps and requires consideration of many factors. Broadly, the process will include estimating the severity and probability of occurrence associated with the hazardous situation, and evaluating the resulting risk against the established criteria for risk acceptability. When analyzing a medical device event and estimating risk, the factors discussed in the following sections and the information captured in Part I(B) of the RAF should be considered.

3.3.2.2 Severity of harm

Based on the patient impact, the severity of the harm associated with the medical device event being investigated may be categorized into one of three levels with proper rationale. Severity can be categorized as:

- Medical device-related deaths and serious injuries include those events, along with procedure-related complications, that may have been or were attributed to the use of the medical device and that caused or contributed to a death or injury or illness that is life-threatening, results in permanent impairment or damage to the body, or requires medical or surgical intervention to prevent permanent harm to the body.
- Medical device-related non-serious adverse events include those events, along with procedure-related complications, that may have been or were attributed to the use of the medical device and that caused or contributed to minor, temporary or medically reversible injuries that do not meet the criteria for classification as a medical device-related serious injury.
- Medical device-related events without reported harm include:
  - medical device nonconformities with no related harm;
  - medical device malfunctions with no related harm;
  - procedure related complications with no related harm; and
  - instances where a nonconformity or regulatory noncompliance was observed at the medical device manufacturing facility and no defective devices were released to the market.

A medical device nonconformity can include the failure of a medical device to meet its performance specifications even though the device still performs adequately to meet the needs of a given patient.

In the context of this report, a procedure-related complication is an unanticipated problem that arises during or following, and is a result of, a procedure employing a medical device. For example, anesthetic-related complications associated with the implantation of a medical device could be considered a procedure-related complication. If a procedure is lengthened, due to an unexpected device issue, complications due to the lengthened procedure could be considered a procedure-related complication.

A hazardous situation should be evaluated with a certain severity based on use/clinical settings, by considering such factors as the number of persons in the potentially affected patient population(s), the clinical practice, and the duration of harm to the patient. The treated or diagnosed condition, its clinical manifestation, how it affects the patients who have it, and the condition's natural history and progression (i.e., does it get progressively better or worse for the patient and at what expected rate) should be considered. This considerations can include:

- Whether the disease or condition is life-threatening; and
- Whether the disease is such that patients may be able to adapt and lead a relatively normal life, or the disease is a debilitating chronic condition.

IMPORTANT

Anesthetic-related complications associated with the implantation of a medical device could be considered a procedure-related complication. If a procedure is lengthened, due to an unexpected device issue, complications due to the lengthened procedure could be considered a procedure-related complication.

REMINDER

If the medical device performance is within the expectations described in the established risk assessment, the data should be captured by the manufacturer's quality and risk management systems, so that the manufacturer can continue to monitor for trends and incorporate product improvements.

If the medical device performance exhibits a higher residual risk than is described in the established risk assessment for the medical device, further risk assessment as described in sections 3.3.2 through 3.3.5 need to be performed.

Depending on circumstance, a medical device can cause harm to patients that is temporary, repeated but reversible, or permanent. Severity can vary over the duration of the harm. When relevant, severity and duration of the harm can be jointly considered.

Information on the medical device event and any complaints, death/injury reports and/or malfunction reports related to it are captured in Part 1(C) of the RAF.

3.3.2.3 Probability of occurrence

Applying the methodology in ISO 14971 [17], the probability of occurrence consists of two components: one is the probability of occurrence of a hazardous situation (P_1), which can be viewed as the probability of the failure, nonconformance or misuse. The other is the probability of occurrence of harm (P_2), which can be viewed as when the failure, defect or misuse happens, what is the probability of someone being injured.

INFORMATION

Factors that can affect the estimate of P_1 are:

+ Likelihood of the failure or nonconformity
+ Likelihood of detection
+ Availability of alternative devices

Factors that can affect the estimate of P_2 can include:

+ Potential for effective risk control measures;
+ Location of device;
+ Monitoring of patient; and
+ Patient population(s) with the greatest exposure.

The occurrence of the hazardous situation (P_1) is the first component to be considered when estimating risk. The estimate of P_1 is often determined by dividing the number of medical devices expected to exhibit the failure, nonconformance or misuse by the total number of devices manufactured under the same conditions (the at-risk devices). For instance, if a process capability-related manufacturing issue occurs randomly and infrequently, the probability of the hazardous situation occurring in a set of distributed medical devices may be quite small because the denominator of at-risk devices could be large. Conversely, a manufacturing issue that is bound to a specific lot may have a smaller denominator of at-risk devices.

Factors that can affect the estimate of P_1 can include, for example:

» Likelihood of the failure or nonconformity—what is the chance that a particular device in the set of at-risk device will exhibit the failure or nonconformance?
» Likelihood of detection—can the failure or nonconformance be identified by the manufacturer or the user or the misuse identified prior to exposing the patient to a hazard?
» Availability of alternative devices—are alternative medical devices available for easy exchange to avoid an unacceptable delay in treatment or diagnosis?

The second component to consider when estimating risk is the probability of the occurrence of harm (P_2). Given exposure to a hazard (i.e., a hazardous situation), what proportion of the intended patient population treated or diagnosed with a medical device exhibiting the failure, nonconformance or misuse are expected to experience harm. One method for calculating P_2 is to divide the number of patients treated with a medical device exhibiting the failure, nonconformance or misuse and who have experience harm by the total number of patients treated with at-risk devices.

Factors that can affect the estimate of P_2 can include, for example:

» Potential for effective risk control measures;
» Location of device;
» Monitoring of patient; and
» Patient population(s) with the greatest exposure.

Risk assessments may follow the RAF (see Annex A). In addition, other factors that may be considered include:

» Failure mode—Specify if it is related to manufacturing, design or use. Does the failure mode impact the function and/or safety of the device, or is it more compliance-related?

» Number of patients exposed—The proportion of the intended population that would be expected to experience the adverse event.
» The impact of a false-positive or false-negative result on the diagnostics—If a diagnostic device gives a false-positive result, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany the treatment, or might be incorrectly diagnosed with a serious disease. If a diagnostic device gives a false-negative result, the patient might not, for example, receive an effective treatment, thereby missing out on the benefits that treatment would confer, or might not be diagnosed with the correct disease or condition. The risks associated with false-positives and false-negatives can be multifold, but are considered in light of the probability of occurrence and the severity of the harm.
» Novel technology—Does the medical device represent or incorporate breakthrough technologies that contribute to a greater or lesser probability of occurrence than established technologies?
» Off-label use—Does off-label use of the medical device give rise to new hazardous situations?

Hazardous situations that are likely to be present prior to patient use, that are easily visualized, and that allow the user to act, are less likely to result in harm than hazardous situations that are not detectable and that do not allow the user time to act. Other potential factors to consider include: normal clinical workflow, patient anatomy and physiology in relation to the hazard, and company-specific instruction versus current known practice in the field.

Factors supporting a lower probability of the occurrence of harm can include:

» The user has the ability to detect and troubleshoot the failure or nonconformance.
» Normal/expected device use that may include device inspection, which prevents the device from failing or detects that it has failed, prior to use.
» No reports or complaints regarding the failure or nonconformance have been received. However, before lowering the estimate of the probability of occurrence of harm based on no reports or complaints, the manufacturer should take into account the total number of device uses in the patient population(s) with the greatest exposure.

Factors supporting an increased probability of the occurrence of harm can include:

» The failure or nonconformance is likely to manifest itself during patient use.
» The user does not have the ability to detect the failure or nonconformance and then troubleshoot or apply a workaround.
» The failure or nonconformance is likely to expose a secondary failure mode that has been associated with injuries.
» More reports of injury, as a result of the failure or nonconformance, have been received than were expected.

It is important to remember that the estimate of the probability of occurrence is only as reliable as the data on which it is based. The rationale for any probability estimate should reflect sound professional judgment including professional medical judgment that is focusing on the device and the population or specific subpopulation in which it is used. The rationale should include a review of relevant complaint data and/or clinical data, when available, as real-world examples demonstrate the potential clinical impact, timing of failure, and likelihood of mitigation. In-house engineering testing can also be used to add reliability/predictability to the assessment.

3.3.3 Evaluating risk acceptability

3.3.3.1 Comparison against the established criteria for risk acceptability

Once a risk has been estimated, it can be evaluated against the criteria for risk acceptability that were used to evaluate the risks in the established risk assessment for the medical device.

INFORMATION

Factors supporting a lower probability of the occurrence of harm can include:

+ The user has the ability to detect and troubleshoot the failure or nonconformance.
+ Normal/expected device use that may include device inspection.
+ No reports or complaints regarding the failure or nonconformance have been received.

Factors supporting an increased probability of the occurrence of harm can include:

+ The failure or nonconformance is likely to manifest itself during patient use.
+ The user does not have the ability to detect failure or nonconformance, then troubleshoot or apply workaround.
+ The failure or nonconformance is likely to expose a secondary failure mode associated with injuries.
+ More reports of injury as a result of the failure or nonconformance have been received than were expected.

IMPORTANT

Remember that an increased probability of occurrence does not in itself mean that a risk is unacceptable.

The risk will either:

- Have the same or lower probability of occurrence and/or severity than that documented in the established risk assessment and would remain acceptable; or
- Have an elevated probability of occurrence and/or severity above that documented in the established risk assessment and may exceed criteria for risk acceptability and thus be unacceptable; or
- Be new and not documented in the established risk assessment. When evaluated against the criteria for risk acceptability, this new risk may be acceptable or unacceptable. Regardless of that determination, when new risks are identified, their cumulative impact on the established risk assessment must be considered.

It is important to remember that an increased probability of occurrence does not in itself mean that a risk is unacceptable. In retrospect, the established risk assessment simply may have been incorrect, but the risk remains within the bounds established by the manufacturer's criteria for risk acceptability.

Each manufacturer maintains an ongoing assessment of risk for each device. The first established risk assessment is concluded prior to marketing the device. Original labeling reflects this initial assessment regarding safety and effectiveness. However, after the medical device has been in the market for some time, the periodic risk updates may significantly change the risk profile from the established risk assessment. Risk is assessed over the life cycle of the medical device, and as new risks are identified, their cumulative impact on the medical device's risk profile must be considered before the most current risk assessment is considered the acceptable version relative to safety and effectiveness.

3.3.3.2 Considering clinical acceptability

ALERT

Risk is assessed over the life cycle of the medical device, and as new risks are identified, their cumulative impact on the medical device's risk profile must be considered before the most current risk assessment is considered the acceptable version relative to safety and effectiveness.

The criteria for risk acceptability used to evaluate the risks can take into consideration factors such as the clinical acceptability associated with initiating device events and the practicality of further reducing the risks. The clinical acceptability can be viewed as generally acceptable by considering factors such as expert opinions and comparison to other generally accepted risks, sometimes referred to as the risks of daily living. However, for medical devices, clinicians may not necessarily place generally accepted risks in the same category as risks associated with identified medical device problems. For example, a laptop computer that is a part of a medical imaging system may have the same look, shape and weight as a laptop computer used by consumers. If the laptop in the medical imaging system has fallen from the desk and inflicted a minor injury on the operator's foot, the risk is similar to that for general consumer use, which is deemed to be an acceptable risk. Therefore, the laptop falling off the desk and hurting the operator may not require additional risk controls beyond that which would be expected for the consumer product. On the other hand, if due to the overall design of the medical imaging system, the laptop had fallen onto a patient lying on a bed, then the risk may not be clinically acceptable.

Consideration should also be given to whether other treatments or diagnostics, including non-device therapies, are available to treat the intended condition and patient population. When characterizing the availability of alternatives, important factors to be considered are treatment (or diagnostic) options, treatment strategy (if applicable, such as for chronic diseases), and the safety and effectiveness of alternatives, including their potential for adverse events. The availability of alternative devices/treatments should also be assessed. For a device with a known benefit and a well-defined risk that treats a condition for which no alternative treatments are available, the risk to the patient of having no treatment if the device were not available should be considered.

Finally, the risk to the patient from not receiving treatment even if there are alternative should be taken into consideration.

3.3.4 Risk is acceptable

If a known risk remains acceptable or a newly identified risk meets the manufacturer's criteria for risk acceptability, then the manufacturer could consider and document the practicability of additional risk controls that may further reduce the risks, by evaluating the effectiveness and completeness of the current risk controls regarding inherent safe design or protective measures. Additional risk controls could also include appropriate information within labeling (e.g., warnings, precautions, etc.), or to restrict the indication to a more limited use.

If further risk controls could reduce the risks without affecting the benefits, the manufacturer could consider making product or production changes.

3.3.5 Risk is unacceptable

If either a known risk or a newly identified risk does not meet the manufacturer's criteria for risk acceptability, then the manufacturer needs to determine what action may be appropriate *(see Section 4)*. To determine what is appropriate, the manufacturer may need to assess the benefit from using the medical device.

3.4 Assessment of the benefit for medical devices with an initiating device event

3.4.1 Change in the probable benefit(s)

Because benefit can change, regardless of whether the risk assessment indicates the risk is acceptable or unacceptable when compared to the manufacturer's criteria for risk acceptability, the manufacturer may need to assess whether the probable benefit from using the medical device has changed as a result of the initiation event. If the risk is reduced slightly, but the benefit is reduced significantly, then patient expectations based on the labeled intended use may influence risk acceptability.

When assessing a change in benefit(s), the following factors, individually and in aggregate may be taken into account:

- The type of benefit(s), e.g., is it a life-saving medical device or does it address a medically necessary situation.
- The magnitude of the benefit(s), e.g., the degree to which the patient experiences the treatment benefit of the effectiveness of the medical device.
- The probability of a patient experiencing one of more benefit(s), i.e., the chance that the patient will effectively treat or diagnose the patient's disease or condition.
- The duration of the effect(s), i.e., how long the benefit can be expected to last for the patient.

A few examples of when the benefit of a given device could change include:

- Changes in medical practice.
- Clinical data that establish additional benefits for patients.
- Changes in patient population treated/using device.
- A one-of-a-kind medical device when other comparable devices come onto the market.

INFORMATION

Because benefit can change, the manufacturer may need to assess whether the probable benefit from using the medical device has changed as a result of the initiation event.

3.4.2 Clinical benefit

3.4.2.1 Establishing the clinical benefit

The clinical benefit(s) to be considered in benefit-risk analyses are established in the context of the intended use of a medical device as stated in the labelling, and the clinical function of a medical device itself. Clinical benefits can be established through premarket and/or postmarket clinical trials. For medical devices for which there are no clinical trials, clinical benefits can be established from sources such as scientific literature that documents the impact of the medical device on patient management.

The intended clinical benefit(s) can include the effect of the medical device on the patient's health and clinical management. Examples of intended clinical benefit can include:

- The effect on patient treatment plans;
- Quality of life;
- Impact on survival; and
- How much the medical device can:
  - Aid in improving patient function
  - Prevent loss of function; or
  - Provide relief from symptoms of the disease or condition the medical devices is intended to treat.

Therefore, by determining the intended clinical benefit of a device, a baseline measure is established for comparison purposes in benefit-risk analyses.

To perform a benefit-risk analysis, a comparison needs to be made to the alternative treatments, therapies or diagnoses that would otherwise be followed if a particular medical device were withdrawn from the market. This is complicated by the fact that not all patient populations have the same view as to the acceptability of risk or have the same perception of benefit. These differences in views have many potential sources, including the patients themselves. As a result, some level of subjectivity is inherent in any benefit-risk comparison.

Risk is currently defined and assessed as a combination of the probability of occurrence of harm and the severity of that harm. Similarly, benefit may be considered as a combination of the likelihood and degree of intended clinical benefit. However, due to the differences in views of patient populations as well as other stakeholder, a third dimension should also be considered, and will be referred to as contextual factors *(see Section 3.4.2.4)*. By including this third dimension, it is possible to create a graduated scale of intended clinical benefit that will assist in the decision-making process.

INFORMATION

Benefit may be considered as a combination of the likelihood and degree of intended clinical benefit. However, due to the differences in views of patient populations as well as other stakeholder, a third dimension should be considered. This third dimension is referred to as contextual factors.

It has to be emphasized here that any such tool for assessing intended clinical benefit should not be viewed as a rigid structure from which answers will be strictly mathematically derived. Rather, this mechanism will serve to highlight and provide a focus point for discussion and decision making in an environment of uncertainty, where not all parties will have the same perception of risk and benefit.

The following paragraphs detail the elements and considerations that may comprise the three dimensional axes for assessing benefit in benefit-risk analyses. It should also be noted that intended clinical benefit should be expressed in terms that facilitate decision making—for example, using degree of benefit and probability scales and units that will mirror actual use.

3.4.2.2 Likelihood of intended clinical benefit

The likelihood of the intended clinical benefit is the percent of the intended population that would expect to experience a benefit. One method of calculating the likelihood of benefit, for a particular patient population, is to determine the number of patients treated or diagnosed effectively and divide this by the total number of patients treated or diagnosed with the medical device. In situations where sufficient data are available, it is sometimes possible to predict which patients may experience a benefit, but sometimes this cannot be well predicted. Where possible, a quantitative categorization of likelihood of benefit is preferred. For example, data from registries or electronic health records could support the quantitative categorization of the likelihood of benefit. Included with this assessment should be a discussion of the statistical variability of the estimate, as well as a definition of subpopulations'

expectations or results, if they differ significantly. That is, a benefit may be experienced only by a small portion of patients in the target population, or a benefit may occur frequently in patients throughout the target population.

If a quantitative categorization of the likelihood of the intended clinical benefit is not possible, the manufacturer should give a qualitative description. A good qualitative description is preferable to an inaccurate quantitative description. For a qualitative categorization of likelihood of benefit, the manufacturer should use descriptors appropriate for the medical device.

To categorize the contextual factors, the manufacturer should clearly identify those attributes that are most important to patients and other stakeholders, as well as the method by which this information is solicited.

3.4.2.3 Degree of intended clinical benefit

To categorize the degree of the benefit, the manufacturer should use descriptors appropriate for the medical device. Benefit is, in reality, a continuum; however, in practice, the use of a discrete number of benefit levels simplifies the analysis. In such cases, the manufacturer decides how many categories are needed and how they are to be defined. The levels can be descriptive and should be explicitly defined. Benefit levels will need to be chosen and justified by the manufacturer for a particular medical device under clearly defined conditions of use. Elements that should be considered for these categorizations include:

- **Type:** Examples include but are not limited to the device's impact on clinical management of the patient and the patient's physical and psychological health and patient satisfaction in the target population; and can range from significantly improving patient management or reducing the probability of death, to aiding in some improvement of management or reducing the probability of loss of function, to providing relief from minor symptoms. For diagnostics, benefits may be measured according to the public health impact of identifying and preventing the spread of disease, or the impact on individual patients. Other benefits of diagnostics include earlier diagnosis of disease and identification of patients more likely to respond to a given therapy.
- **Magnitude** (i.e., of the benefit in the individual patient)**:** The magnitude measures the size of the benefit. When postmarket data such as from registries or electronic health records are available, it may be possible to measure benefit along a scale or according to specific endpoints or criteria (types of benefits). The change in the patient's condition or clinical management as measured on that scale, or as determined by an improvement or worsening of the endpoint, is what allows us to determine the magnitude of the benefit for an individual patient. It is also possible that different patient subpopulations will experience different benefits or different levels of the same benefit.
- **Duration** (i.e., how long the benefit lasts for the patient)**:** Some medical device treatments are curative, whereas some may need to be repeated frequently over the patient's lifetime. Medical device treatments that are curative may be considered to have greater benefit than treatments that have to be repeated, because repetition may introduce greater risk or the benefit experienced may diminish over time. For many patients, cure of a disease involves treatment with multiple devices used in conjunction with other types of therapies. Quantifying the duration of benefit that can be attributed to a medical device with an identified event may require postmarket data or clinical data, although this data may not always be available.

3.4.2.4 Contextual factors

To categorize the contextual factors, the manufacturer should clearly identify those attributes that are most important to patients and other stakeholders, as well as the method by which this information is solicited. It is to be noted that patient preference attributes may be clinical or non-clinical; they can also be health states, time in a health state, probability of a health state or rate at which the health state occurs.

They can also be defined as a range of levels of a health state or a change in the levels of a health state. (Care should be exercised to ensure that the attributes identified do not overlap with the likelihood and degree of intended clinical benefit noted above.) The method for obtaining patient preference attributes should consider the time required for administration, given that the scenario may require a rapid response to an evolving and escalating situation. Contextual factors that can be considered include [2]:

- **Patient's perspective on benefit:** When determining if the device is effective or risky, any evidence relating to patients' perspectives of what constitutes a meaningful benefit should be described, noting that some set(s) of patients may value a benefit more than others. In many cases, it may be difficult for patients to make meaningful assessments about the relative benefits of the use of a medical device. Finally, it should be that if, for a certain device, the probable risks outweigh the probable benefits for all reasonable patients, use of such a device would be considered to be inherently unreasonable.
- **Patient:** Patient-centric metrics, such as validated quality-of-life measures, can be helpful to demonstrate benefit, to better quantify the impact of the medical device on the patient's well-being. Moreover, it may be appropriate to identify where only a minority of the intended patient population would expect a benefit. Patient-centric assessments should take into account both the patient's willingness and unwillingness to use a medical device or tolerate risk. Both preferences are informative and helpful in determining patient tolerance for risk and benefit and the benefit-risk profile of a medical device.
- **Healthcare professionals:** Benefits that healthcare professionals experience because of improved patient outcomes or improved clinical practice.
- **Caregivers:** Benefits to the experience of family members or other caregivers by improving the way they care for patients.
- **Unmet medical need:** Consider if a medical device provides benefits or addresses needs unmet by other medical devices of therapies. Consideration should be given to whether a medical device represents or incorporates breakthrough technologies that may address unmet medical need by providing a clinically meaningful advantage over existing technologies, providing a greater clinically meaningful benefit than existing therapy, or providing a treatment or means of diagnosis where no alternative is available.
- **Subpopulation:** Consider if there are groups of patients included in the FDA cleared indication for use that are at greater risk or receive greater benefit than the overall population. These subpopulations should be considered separately.

3.5 Documenting the benefit-risk assessment for medical devices with an initiating device event

3.5.1 Benefit-risk assessment process

The benefit-risk assessments process described above is intended to succinctly:

- Describe the problem.
- Identify alternatives.
- Identify benefit(s) of current device.
- Compare current device/alternatives.
- Identify concerns.
- Describe mitigation of concerns.

A structure for documenting the results of this process is contained in Table 1. Implicit in a benefit-risk assessment is a comparison of the device under consideration with any alternatives that may exist. In the structure below, the columns are to be completed for the medical device under consideration as the manufacturer conducts the risk assessment and, if appropriate, the benefit assessment described in Sections 3.3 and 3.4. To facilitate comparison, additional columns can be added, if additional

diagnostic or therapeutic alternatives are being considered. The RAF in Annex A and the worksheets in Annex E may be useful in completing the benefit-risk summary and assessment in Table 1.

TABLE 1—BENEFIT-RISK ASSESSMENT FOR MEDICAL DEVICES WITH AN INITIATING DEVICE EVENT

Consideration	Evidence and uncertainties	Conclusions and reasons
Analysis of condition		
Alternatives		
Clinical benefit		
Patient preference		
Risk		
Risk control		
Benefit-risk summary and assessment		

3.5.2 Explanation of framework elements

a) Columns:

» **Evidence and uncertainties:** A description of both what is known (facts) as well as what is not known (uncertainties and underlying assumptions). This includes a discussion on the quality of data used as the basis for statements provided.

» **Conclusions and reasons:** A statement summarizing the analysis of the data and uncertainties, and its clinical relevance. This is then followed with conclusions drawn for each consideration (row).

b) Rows:

The elements "Analysis of condition" and "Alternatives" are intended to provide information on the therapeutic area and to provide the clinical context for weighing benefits and risks. The elements "Clinical benefit," "Patient preference," "Risk," and "Risk control" are all product-specific information and are intended to allow for a direct comparison of alternatives.

» **Analysis of condition:** A description of the condition that is treated, diagnosed or monitored. This includes the clinical manifestations of the condition, what is known about its progression, and how severity may vary across subpopulations.

» **Alternatives:** A description of alternative approaches for treatment, diagnoses or monitoring of the condition. This includes an assessment of the effectiveness and tolerance for the alternatives, and evidence supporting the conclusions.

» **Clinical benefit:** A description of the clinical benefits that were used to establish efficacy. This includes identifying any endpoints that were evaluated and how they are clinically meaningful; can also include health states, time in a health state, probability of a health state or rate at which the health state occurs; can also be defined as a range of levels of a health state or a change in the levels of a health state; and additionally, identification of any differences that may exist across subpopulations. The premarket clinical trial data or other sources, such as scientific literature, may incompletely capture the remaining clinical benefit of the device. In such cases, the clinical benefit of the device may be best described using qualitative language or through the analysis of postmarket data sources such as registries or electronic health records.

» **Patient preference:** A description of attributes that matter to patients and the value the patient places on the use of the medical device.

INFORMATION

Implicit in a benefit-risk assessment is a comparison of the device under consideration with any alternatives that may exist.

» **Risk:** A characterization of the probability of occurrence and severity of the harm associated with the event(s) that triggered the benefit-risk analysis. This should include a summary of the analysis performed per Section 3.3 of this document, and should provide an overview of the incidence of risk to the patient population (and subpopulations as applicable), including whether there is a range in severity, whether the risk is reversible, and if additional work is needed to further characterize the risk.

» **Risk control:** A description of which risks (if any) require mitigation or further characterization, which risk control measures are recommended to address the risks, and the contribution of each risk control measure make to the mitigation of the associated risk. This should also include a description of what would be considered sufficient risk mitigation, methods for measuring success, and, if the desired result is not achieved, at what point the risk management activities need to be re-evaluated. This may also describe the residual risk that remains after the risk control measures have bene implemented.

c) Summary:

» **Benefit-risk summary and assessment:** A balanced written analysis of the factors and tradeoffs between each alternative diagnostic or therapeutic strategy, and a summary of the resulting regulatory recommendation and action.

NOTE: The manufacturer may choose any method to accomplish this goal, provided any alternative used addresses critical issues, captures expert views faithfully, represents the work and information transparently, is compatible with quantitative or qualitative analysis of clinical benefit and safety information, and facilitates communications (internal and external).

3.6 Other non-risk or benefit-related considerations

If it is likely that the device event is the result of a regulatory compliance problem, then the manufacturer needs to look at other factors that could result in the medical device being considered violative. For example, a product might not be correctly labeled as defined in 21 CFR Part 801 [38] or Part 809 [41]. There could be no impact on the risk or benefit associated with the medical device, but it could be technically violative.

4 Determine if a recall is necessary

4.1 Overview

When considering if a recall is necessary, the manufacturer needs to make a number of decisions. These decisions will be based on the circumstances associated with the event(s), the results of the postmarket benefit-risk assessment in Section 3, and the legal and regulatory requirements set forth in 21 CFR Part 7 [37] and Part 806 [40] among others. Figure 2 is an overview of the decision process that the manufacturer can employ to determine if a recall is necessary and what class FDA might assign to the recall, or other field action might be appropriate based on the circumstances and the benefit-risk assessment. The scenarios in Examples 5 through 11 in Annex D illustrate the recall classification decision steps in Figure 2.

NOTE: This decision chart is not all-encompassing and does not capture every possible situation. If a situation arises that is not captured, the manufacturer may contact the FDA to discuss the specific situation.

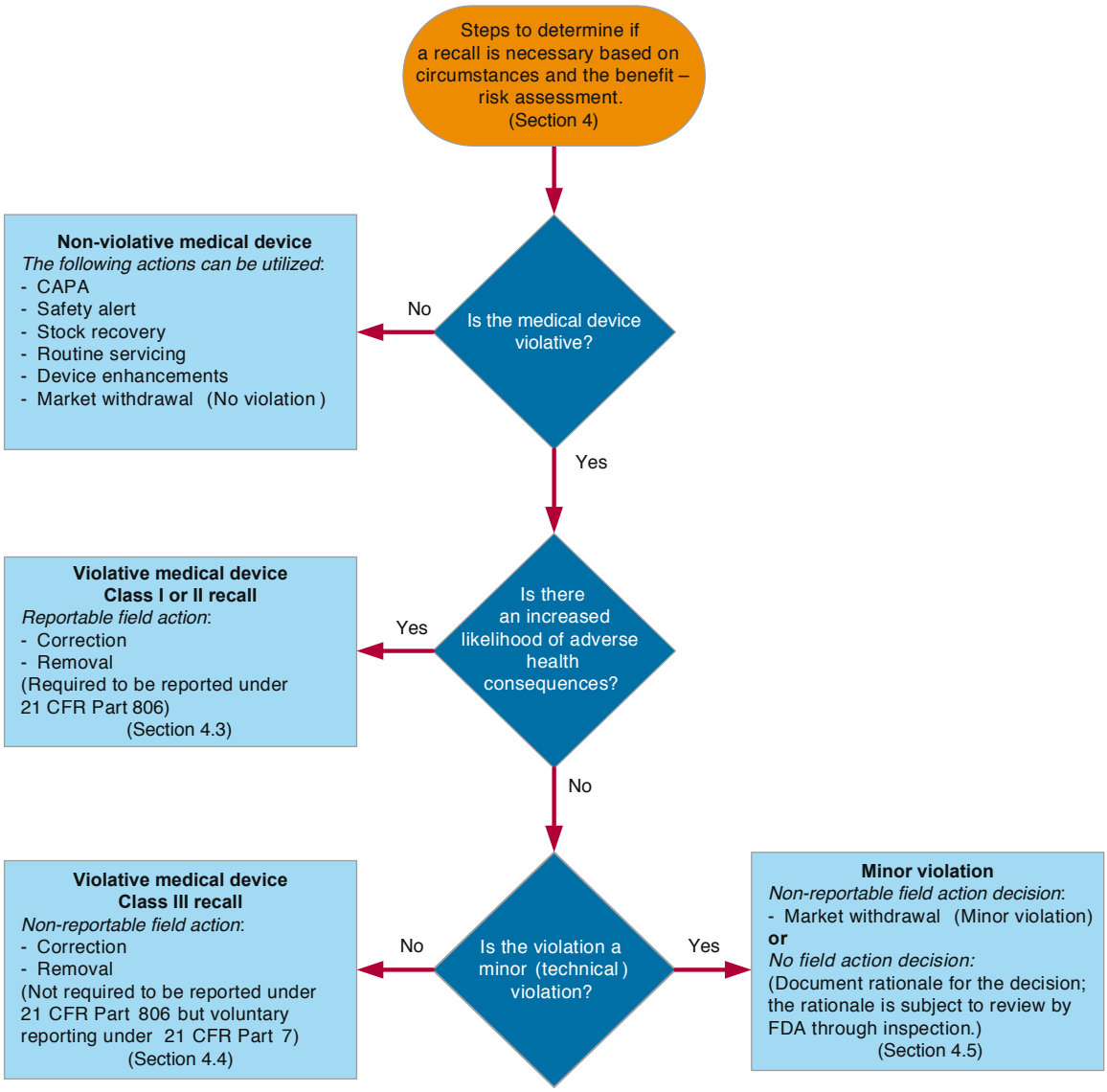

FIGURE 2—RECALL CLASSIFICATION DECISION STEPS

4.2 Is the medical device violative?

A medical device can be considered violative if it fails to satisfy of one or more of the requirements in the FD&C Act or the associated regulations. Some common violations that can result in a recall include:

- The medical device fails to meet specifications or fails to perform as represented. An increase in failure rate, single failure mode rate, or a new failure mode may suggest a failure to perform outside of specifications.
- The medical device is not in compliance with the standards to which compliance is claimed in regulatory filings.
- The medical device was not manufactured in compliance with the manufacturer's procedures or with the Quality System regulation in 21 CFR 820 [42].
- The medical device is not correctly labeled as defined in 21 CFR Part 801 [38] or Part 809 [41].

- The medical device has not been cleared or approved by the FDA or has been modified in a way that no longer complies with its clearance or approval.
- The medical device consists of any filth, putrid or decomposing substances, or it has been prepared, packaged or held under unsanitary conditions and may have become contaminated.
- The medical device labeling is false or misleading in any particular.
- The medical device is being used in accordance with its labeled instructions for use and intended use, but it has resulted in unexpected adverse events or deaths.
- The medical device is not properly listed and/or its manufacturing facility is not registered with the FDA.

The above list is not intended to be all-inclusive.

When seeking to differentiate a violative medical device from a non-violative medical device, the following factors can be considered:

- Only changes to devices to remedy a violation of the laws administered by FDA, and against which the agency would initiate legal action, fall within the definition of a medical device recall. For example, if a device is being corrected to address a quality system violation (see 21 CFR Part 820 [42]), then the correction would generally be considered a recall.
- Changes to non-violative devices are considered to be device enhancements and not medical device recalls. The following questions are intended to help clarify whether or not the device would be considered violative:
  - Are the changes intended to resolve a failure to meet specifications or failure of the device to perform as represented?
    FDA generally considers medical devices that fail to meet specifications or that fail to perform as represented to be of a device quality below that which they purport or are represented to possess, rendering them adulterated under section 501(c) of the FD&C Act [45]. Changes intended to resolve a failure to meet specifications or failure of the device to perform as represented would generally be considered a recalls.
  - Is the labeling for the device to which the manufacturer is considering making changes false or misleading, does it fail to bear adequate directions for use, or does it otherwise violate the FD&C Act or FDA regulations?
    Devices with false or misleading labeling are misbranded under section 502(a) of the FD&C Act [45]. Devices that fail to bear adequate directions for use as defined in 21 CFR 801.5 are misbranded under section 502(f)(1) of the FD&C Act (unless exempt). Devices that fail to meet applicable labeling requirements identified in 21 CFR Parts 801 [38] and 809, Subpart B [41], also violate the laws enforced by FDA.
    A change to a marketed device to address false or misleading labeling or other labeling violations would generally be considered a recall. If the device labeling was initially inadequate, a change to address the inadequacy could also be considered a recall. However, the addition of a new warning or other changes to the labeling of a non-violative device could be considered a device enhancement and not a recall.
  - Is the manufacturer otherwise out of compliance with FDA regulations?
    The manufacturer should conduct a careful, thorough, and adequate assessment for each proposed change to your device. If the result of your assessment indicates that the change is made to correct or remove a violative marketed device in order to bring it into compliance with the laws administered by FDA, then the change would likely be considered a recall.

IMPORTANT

If a device is being corrected to address a quality system violation (see 21 CFR Part 820 [42]), then the correction would generally be considered a recall.

The FDA has published guidance on distinguishing medical device recalls from medical device enhancements to clarify when a change to a device constitutes a medical device recall. [29]

If the medical device is determined to be violative, then the manufacturer need to determine if there is an issue that will cause an increased likelihood of adverse health consequences (see 4.3).

If the medical device is determined to be non-violative, the information gathered can be handled by the manufacturer's quality and risk management systems through activities such as trending and monitoring, and this process would end. If necessary and appropriate, the manufacturer has a range of options that can be utilized to deal with the issue under its quality management system:

- CAPA,
- Safety alert,
- Stock recovery,
- Routine servicing,
- Device enhancements, or
- Market withdrawal for non-violative products.

IMPORTANT

If the violation does not result in the increased likelihood of adverse health consequences, the manufacturer may still be faced with a technical violation of the FD&C Act or the associated regulations enforced by the FDA.

4.3 Does the violation increase the likelihood of adverse health consequences?

The manufacturer then determines if the identified risk or a change in probable benefit would result in an increase in the likelihood of adverse health consequences that could result in the FDA initiating legal action. If the answer to that question is yes, then a reportable field action is indicated. Depending on the likelihood of adverse health consequences up to and including death, the FDA is likely to classify the resulting field action as either a Class I or a Class II recall. The manufacturer needs to develop a recall strategy *(see Section 5.1)*.

Mandatory reporting of any correction or removal of a medical device initiated by the manufacturer is required if the correction or removal is initiated to:

- Reduce a risk to health posed by the medical device; or
- Remedy a violation of the FD&C Act caused by the medical device that may present a risk to health, unless the information has already been provided as described in 21 CFR 806.10(f) or the corrective or removal action is exempt from the reporting requirements under 21 CFR 806.1(b) [40].

If there is no increase in the likelihood of adverse health consequences that would cause the FDA to initiate legal action, the manufacturer must still deal with the technical violation *(see Section 4.4)*.

4.4 Is the violation a minor (technical) violation?

If the violation does not result in the increased likelihood of adverse health consequences, the manufacturer may still be faced with a technical violation of the FD&C Act or the associated regulations enforced by the FDA.

If the violation is assessed to be a minor technical violation, the manufacturer may institute a non-reportable field action or may document a "no action" decision following the processes set out in their quality management system *(see Section 4.5)*.

If there is no case to support assessing the issue as a minor technical violation, the manufacturer does need to take action, but that action is not required to be reported under 21 CFR Part 806 [40], and can be voluntarily reported under 21 CFR 7 [37]. The manufacturer needs to develop a recall strategy *(see Section 5.1).*

4.5 Actions not required to be reported to FDA

4.5.1 Non-reportable field actions

A manufacturer is not required to report certain correction or removal actions to the FDA. These are specified in 21 CFR 806.1 [40] and include:

- Actions taken by the manufacturer to improve device quality, but that do not reduce a risk to health posed by the medical device or remedy a violation of the Act caused by the device.
- Market withdrawals that involve the correction or removal of a distributed medical device that involves a minor violation of the Act, which would not be subject to legal action by FDA, or that involves no violation of the FD&C Act.
- Routine servicing, which includes any regularly scheduled maintenance of a device, including the replacement of parts at the end of their normal life expectancy (e.g., calibration, replacement of batteries, and responses to normal wear and tear).
- Stock recoveries that involve the correction or removal of a medical device that has not been marketed or that has not left the direct control of the manufacturer.

However, the manufacturer is required to maintain records of all corrections and removals, regardless of whether such corrections and removals are required to be reported to FDA.

4.5.2 No field action decision

In certain cases, the manufacturer may determine that the best course of action is to take no field action. The rationale for a "no field action decision" should be documented, and that documentation is subject to review by the FDA during a field inspection.

5 Create and evaluate the recall strategy

5.1 Recall strategy

5.1.1 What constitutes a recall?

As defined in the regulations, a recall is the removal or correction of a marketed product that the FDA considers to be in violation of the laws it administers, and against which the FDA would initiate legal action (21 CFR §7.3 (g) [37]). However, a recall can encompass a broad range of actions the manufacturer can take, including the repair, modification, adjustment, relabeling, destruction, or inspection of the device *in situ* or the physical removal of the device to another location where it can be for repaired, modified, adjusted, relabeled, inspected or destroyed.

5.1.2 Develop a recall strategy

Once it is determined that recall is necessary, the manufacturer has to develop a recall strategy, which is a planned course of action to be taken in conducting the specific recall. The recall strategy addresses:

- If the recall action is a correction or a removal;
- The depth of recall (i.e., how far into the distribution chain the recall goes; e.g., wholesale, retail or consumer levels);
- The need for public warnings to alert the public that a product being recalled presents a serious hazard to health; and
- The extent of effectiveness checks for the recall to verify that those affected have received notification about the recall and have the tools needed to take the appropriate actions.

The FDA has published guidance for medical device manufacturers on Recalls, Corrections and Removals (Devices) [33]. This guidance includes a detailed description of the factors to be taken into account in developing a recall strategy as they apply to the individual circumstances of the particular recall.

IMPORTANT

The rationale for a "no field action decision" should be documented, and that documentation is subject to review by the FDA during a field inspection.

5.2 Adverse public health issues

The potential for the recall to result in an adverse public health issue is a factor the manufacturer needs to consider when determining if a particular recall strategy is appropriate to the individual circumstances that led to the recall decision. In certain situations, the benefit to public health of a medical device recall may not outweigh the potential adverse public health issues caused by physical removal or lack of the ability to utilize the device in health care delivery. For example, adverse public health issues could result from:

- Product shortages (e.g., no adequate alternate product or treatment is available).
- Use interruption (e.g., treatment delays while product is under repair).
- Use of unqualified product (e.g., use of an alternative product that has not been properly qualified as a component of a system of devices).
- Absence of treatment due to cost or inconvenience of replacing or correcting the medical device.

In summary, the 'risk' created by a recall may be greater than the 'risk' being addressed by the recall.

IMPORTANT

The 'risk' created by a recall may be greater than the 'risk' being addressed by the recall.

Items to be considered in making this determination can include:

- The availability of device replacements or modifications in terms of time and quantity;
- The duration of the recall;
- The timeliness of communicating, replacing and modifying devices; and
- The quality or effectiveness of individual corrections and their impact on the available development, installation, or customer resources.

There are other factors that should be addressed when assessing the potential impact of a recall on public health. These include:

- The negative impact on the patient's mind-set of a recall involving an issue that cannot be corrected leading to significant mental and emotional anxiety.
- Unnecessary or medically inappropriate actions including explants or other medical procedures with their associated risks.
- Patients deciding not to receive therapy or have the device used.

The manufacturer should consider each potential recall strategy and evaluate whether implementing that strategy could lead to an adverse public health issue(s) (see 5.4).

5.3 Implement the appropriate recall strategy

If the evaluation of the recall strategy indicates there would be no adverse public health issue(s) resulting from its implementation[6], the manufacturer follows its recall procedures and implements an appropriate recall strategy. For voluntary recalls, the manufacturer follows 21 CFR Part 7 [37]; for mandatory device recalls, the manufacturer follows 21 CFR Part 810 [42].

The recall implementation actions may include the communication and the actual product correction or removal that may impact the healthcare providers, facilities and/or patients directly. FDA has published various training materials and guidance documents regarding recalls and the associated communications. These include such materials as:

- Training on *Customer Recall Notifications* [4].
- *Guidance for Industry: Product Recalls, Including Removals and Corrections* [33]., which contains a detailed description of the information that FDA recommends be included in the recall submission to FDA.
- *Guidance on Recalls, Corrections and Removals (Devices)* [33].

The timeframe for reporting mandatory device recalls is specified in §806.10(b) of 21 CFR Part 810 [42]. FDA urges the manufacturer to notify the appropriate District Recall Coordinator in FDA's Office of Regulatory Affairs (ORA) [22] as soon as a decision is made that a recall is appropriate, and prior to the issuance of press or written notification to customers.

5.4 Recall could result in adverse public health issue(s)

If a particular recall strategy could result in an adverse public health issue(s) (such as a medical device being unavailable when there is no alternate product available for treatment), then the manufacturer might need to do additional assessments of risk and benefit, applying a methodology such as that discussed in Section 3. At this stage of the process, however, the focus of the risk and benefit assessments would be on the risk(s) to public health and the benefit(s) to patients from implementing a particular recall strategy. In complex situations, the manufacturer might find the Decision Quality approach discussed in Section 5.5 helpful.

Consider the following example:

A drug-delivering device has an issue that can lead to an unexpected shortened battery life. The probability of occurrence of shortened battery life is estimated to be 1 out of 1 million applications (P_1). The battery failure may lead to an insufficient drug delivery and cause a serious harm. The device has alarms to warn the user of battery failure, and therefore it is estimated to have a very low probability of being undetected (part of P_1) and actually causing harm (P_2). It is estimated the risk is unacceptable following the manufacturer's risk acceptability criteria, and the manufacturer is able to identify the root cause (e.g., a software bug or manufacturing defect), as well as a correction to reduce the probability of shortened battery life and insufficient drug delivery.

Assuming there are 2 million devices in the field, the manufacturer estimates that it may take 3 months to replace the batteries for all devices, due to the constraints of battery production and personnel for services on the devices. During the 3-month period, it is estimated that 10 million applications would be performed by the device (e.g., 5 applications per device). There are no alternative drug delivery devices for this indication and no alternative treatments available. A high-level estimation of the impact may be:

a) **Strategy 1:** The manufacturer may advise all users to stop using the devices immediately and wait for the replacement of batteries. This may lead to the loss of 10 million applications to patients. Assuming it is difficult for the users to switch to an alternative drug delivery method in a short period of time, the potential serious injuries/harms to patients without the drug delivery applications are estimated to affect 1000 patients, based on scientific medical and clinical evaluation/assumptions.
b) **Strategy 2:** The manufacturer may communicate to all users to continue using the devices and remind them to be watchful of the alarms. The manufacturer is to replace the battery within a 3-month period. This strategy allows for continued use of the device. The potential harm, considering 10 million applications in a 3-month period of time, is less than 10 occurrences (1/1 million X 10 million usages with a low P_2 probability of harm) due to premature battery failure.
c) **Strategy 3:** The manufacturer may communicate to all users to continue using the devices and remind them to be watchful of the alarms. The manufacturer is to replace the battery within a 6-month period per the regular product maintenance schedule. This strategy allows for continued use of the device. The potential harm, considering 20 million applications in a 6-month period of time, is less than 20 occurrences (1/1 million X 2 x 10 million usages with a low P_2 probability of harm) due to premature battery failure.

NOTE

In complex situations, the manufacturer might find the Decision Quality approach discussed in Section 5.5 helpful.

Each of these recall strategies considers the factors of the use interruptions and the loss of benefits when the device is not available. By comparing the three options, Strategy 2 stands out as the better choice.

5.5 Decision quality

A manufacturer addressing the processes outlined in this report may encounter significant difficulty on the path to making a postmarket decision. One tool a manufacturer could employ is the Decision Quality Checklist (DQC) approach (Annex B). A DQC approach can provide a systematic framework for addressing the more challenging of these problems.

A manufacturer can consider using the DQC approach when creating and evaluating a recall strategy that involves significant analytical or organizational complexity.

What are the situations in which a detour to using the DQC approach will ultimately expedite achieving a high-quality decision? In general, decisions sort along two dimensions, as shown in Figure 3.

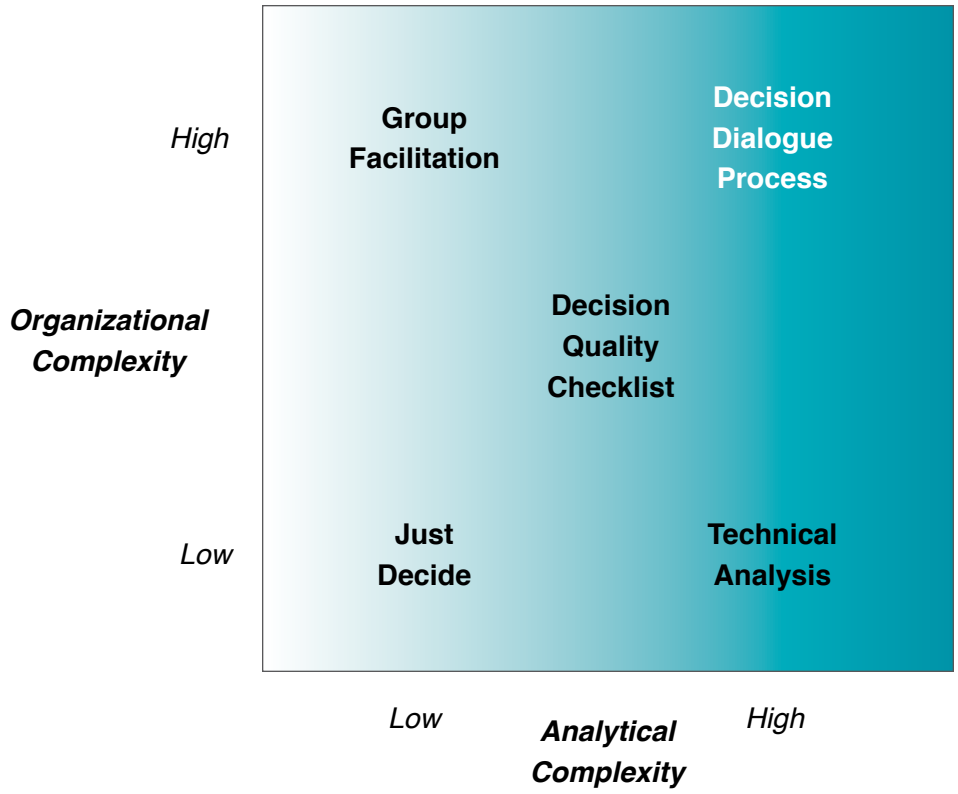

FIGURE 3—DIMENSIONS OF A DECISION PROBLEM

First, there is analytical complexity. Postmarket decisions have high analytical complexity where there are many relevant engineering and clinical factors, there is uncertainty, or things may be changing over time. Second, there is organizational complexity. High organizational complexity characterizes situations where departments have conflicting views or incentives, or there is a need to address outside stakeholders with different perspectives, such as regulatory bodies or customers.

Different decision-making approaches are effective for different combinations of organizational and analytical complexity. When both analytical and organizational complexity is low, then the manufacturer may simply arrive at a decision without

ALERT

The lack of obvious technical answers, the need to address medical, legal, and regulatory issues, and the need to simultaneously address conflicting organizational perspectives and beliefs, can lead to delays—even organizational paralysis.

Annex C contains a number of points to consider when evaluating the manufacturer's decision making in regard to corrective actions The purpose is to assist in identifying areas of potential disagreement between FDA and industry, and to facilitate detection of missing components of the decision making process.

employing a methodology such as the DQC approach. In cases where the analytical complexity is low, but organizational issues make deciding difficult, then group facilitation can promote recognition of, and then consensus around, the best alternative. In cases where the analytical complexity is high, but the organizational complexity is low, the decision will typically be amenable to technical analysis, with the resulting recommendation readily endorsed.

Postmarket benefit-risk evaluations, however, can have features of both increased analytical and organizational complexity. Even for situations where both features are increased only to a moderate degree, the lack of obvious technical answers, the need to address medical, legal, and regulatory issues, and the need to simultaneously address conflicting organizational perspectives and beliefs, can lead to delays—even organizational paralysis. For such situations where both dimensions of complexity are moderate, the Decision Quality Checklist (DQC) approach can be beneficial. Annex B presents the DQC methodology in detail, together with a set of questions that can facilitate its applications. DQC questions are introduced in boxed tables throughout the text. Annex C contains a number of point points to consider when evaluating the manufacturer's decision making in regard to corrective actions The purpose is to assist in identifying areas of potential disagreement between FDA and industry, and to facilitate detection of missing components of the decision-making process

In cases where the organizational and analytical complexity are both high, then the Dialogue Decision Process (DDP), presented in B.3.7, can be helpful. The DDP choreographs an efficient conversation between high-level managers and analysts in a way that clarifies the best decision for all stakeholders and leads to effective execution.

6 Document the benefit-risk assessment

6.1 The benefit-risk documentation

Good documentation practices are essential in recording and communicating a well-informed benefit-risk determination, as well as in supporting a robust risk management process. The documentation needs to satisfy regulatory and internal quality system requirements. Documentation of a specific benefit-risk evaluation should be clearly written, fact-based and comprehensively representative of the criteria used in decision making. For benefit-risk evaluations of medical devices, these criteria uniformly include a thorough, scientifically-based investigation of the issue, a knowledgeable clinical assessment of the implications to patients, and a regulatory analysis of the applicable laws, regulations, guidance and precedents that may influence FDA.[7]

When documenting a postmarket decision, it is recommended that the manufacturer collect and organize data about the event(s) and the medical device involved into a benefit-risk documentation package. Much of that data will have been captured or referenced in the Risk Assessment Form (RAF) (see Annex A) and in the benefit-risk assessment (*see Section 3.5)*.

The benefit-risk documentation package should contain information as complete and up-to-date as feasible, recognizing that decisions often have to be made with some urgency based on the available information. Regular updates to the benefit-risk documentation package are essential in many circumstances (e.g., incomplete root cause analysis, or information on potential clinical implications is evolving). In all cases, it is a good practice to update benefit-risk documentation packages through to resolution of an issue.

The overall objective of the documentation package is to facilitate the manufacturer reaching an appropriate decision on whether an issue(s) requires a product correction, removal, or other action. It can also be needed for legal, regulatory and CAPA

purposes and to facilitate the transparent communication between the manufacturer and the appropriate FDA Center/District to discuss benefit-risk scenarios associated with proposed recall strategy, or in some cases, the implications of different recall strategies. Depending on the depth of the benefit-risk analysis and the complexity of the issue under review, profiling the expert resources utilized in preparing the benefit-risk documentation package may be helpful in advancing a future dialogue with the FDA. These supplementary items could include:

- The device description,
- Root cause analysis,
- The RAF,
- Evaluation of device violation (if applicable),
- Benefits and risks associated with both the medical device and the potential field actions, and
- Optional recall strategies, mitigations, etc.

In cases where a manufacturer determines that a proactive FDA review is essential due to likely recall classification, complexity, or desire for agency input, the manufacturer should be well-prepared with the documentation described above, as well as any specific questions it may have for the agency. Even in those cases where the manufacturer is not required to report to FDA on the correction or removal of a medical device (e.g., Class III recall), the manufacturer is obligated to maintain records of all corrections and removals.[8] The manufacturer's records are subject to review by FDA personnel who will retrospectively assess the quality of the risk assessment process and any subsequent field action. Good documentation practices in this area enhance benefit-risk decision-making processes, risk management processes, and FDA communications.

6.2 Open a dialogue with the FDA

FDA and manufacturers have a shared goal to protect the public health by ensuring the availability of safe and efficacious products. In the case of a serious health issue potentially caused by a medical device, a manufacturer should err on the side of transparency and engage the FDA early in the process of its investigation and analysis.

As the manufacturer nears the end of the assessment and benefit-risk analysis, there may be some uncertainty about how the FDA will view the proposed recall strategy. This could be particularly true if the proposed strategy supports leaving a violative product on the market while a corrective action is being implemented. The manufacturer may favor this course of action because it will avoid a potential adverse public health consequence caused by removing the product from the field or limiting its availability for use. In this case, the manufacturer may wish to open a dialogue with the FDA prior to committing to a final recall strategy.

Factors such as the severity of the event, the particular recall strategy, and the clarity of the benefit-risk documentation package all impact the communication to the FDA. In general, the higher the severity and complexity of the situation, the greater the need for speed and early FDA involvement, to ensure good alignment of the manufacturer's assessment and plan with FDA expectations.

Once the manufacturer has gathered adequate information and assembled the documentation in the benefit-risk package, the manufacturer may contact the FDA. This should be done expeditiously.

The benefit-risk documentation package would serve as a starting point for the communication between FDA and the manufacturer. Based on the communication and understanding of the benefit-risk assessments with respect to both the medical

INFORMATION

The benefit-risk documentation package could include:

+ The device description
+ Root cause analysis
+ The RAF
+ Evaluation of device violation (if applicable)
+ Benefits and risks associated with both the medical device and the potential field actions
+ Optional recall strategies, mitigations, etc.

IMPORTANT

FDA and manufacturers have a shared goal to protect the public health by ensuring the availability of safe and efficacious products. In the case of a serious health issue potentially caused by a medical device, a manufacturer should err on the side of transparency and engage the FDA early in the process of its investigation and analysis.

ALERT

Currently, the District Recall Coordinator remains the initial point of contact for the manufacturer.

device and the potential recall strategies, the manufacturer and FDA may be able to reach a consensus on the most appropriate recall strategy before formally submitting the plan to the appropriate District Recall Coordinator.

FDA is currently evaluating CDRH and district office roles in recalls as part of their Program Alignment efforts and contact names and roles may change over time. Currently, a manufacturer would work through the district recall coordinator in the local district. Email addresses for ORA District and Headquarters Recall Coordinators can be found on the FDA website.[22] For questions related to CDRH recall guidance documents or related policy, a manufacturer may contact the CDRH Recall Branch at CDRHRecallGroup@fda.hhs.gov.

7 Conclusion

From the beginning, the AAMI/FDA Ad Hoc Risk Working Group recognized that greater clarity was needed regarding the process and the principal factors that should be considered when making benefit-risk assessments once a product is out in the market. A uniform understanding of the key consideration when making benefit-risk assessments can improve the predictability, consistency and transparency of this postmarket surveillance process. Born out of these considerations, this report lays out a framework that manufacturers and FDA can apply in assessing risk and weighing benefit when analyzing postmarket device quality and regulatory issues with a particular emphasis on decisions related to recalls.

While developing this report, the AAMI/FDA Ad Hoc Risk Working Group developed or identified:

- The comprehensive RAF in Annex A as a tool for documenting and assessing medical device events that may have an impact on device quality, safety and/or expected performance.
- The "decision quality" approach described in Annex B and Annex C, which can facilitate good decision making, particularly when the decision involves significant analytical and organizational complexities.
- A set of examples in Annex D to illustrate the proposed framework for incorporating benefit-risk assessments into the correction and removal decision-making process described in this report.
- A set of worksheets in Annex E to assist in compiling the benefit-risk summary and assessment to support the recall decision and to facilitate a discussion with FDA should the manufacturer wish to open a dialogue with the FDA prior to committing to a final recall strategy.

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Although not a prescriptive how-to guide, the framework is a starting point for incorporating benefit and risk considerations into the postmarket decision-making process, with enough detail to be a helpful, practical guide.

Although not a prescriptive how-to guide, the framework is a starting point for incorporating benefit and risk considerations into the postmarket decision-making process, with enough detail to be a helpful, practical guide. While not addressing every situation a manufacturer or the FDA may encounter, it is hoped that following the steps described in the framework may improve the understanding of manufacturers, FDA staff and others about how benefit and risk considerations can be incorporated into the postmarket decision process.

Prior to publication of this report, seven medical device manufacturers and staff from CDRH conducted an informal "pilot" to try out the new analysis. The results of that pilot are summarized in Annex G, and, when appropriate, modifications based on the pilot results have been incorporated into this report.

8 Recommendations for future work

During the public comment phase of this project, several questions and suggestions were made by commenters that were beyond the objectives established for this report. These questions and suggestions are worthy of consideration for a future project(s) between CDRH and the medical device industry and are listed here for purposes of memorializing their importance and expressing gratitude to the individuals and organizations that took the time to offer the suggestions:

1. **Multiple organization recall situations:** Many recalls involve multiple entities, such as suppliers, distributors, kits and multisource products. For example, a recall might involve a component made by a supplier and sold to multiple manufacturers for incorporation into products with different uses, risks and benefits. Other examples include contract sterilization activities, kits, and combination products. Challenges in these situations include dispersed and inconsistent information, multiple use environments, different risk/benefit calculus, multiple decision makers, and a variety of contract terms and responsibilities. These are difficult and complex situations but are increasingly common.
2. **Third-party Actions:** Manufacturers need to understand how they are expected to deal with recall situations involving counterfeit products, product theft or diversion, and misconduct by an unrelated third party.
3. **Off-label use:** The converse of intended use is off-label use. Off-label uses are considered in this report when identifying hazardous situations. However, off-label use can have an impact on benefit as well as risk and when considering alternative therapies. For example, can off-label, as well as well accepted uses, be considered in the analysis of alternative therapies?
4. **Qualifying the duration of benefit:** An issue with qualifying the duration of benefit is that over time the device in question may be replaced by a "corrected" device or new therapies may come to pass. This consideration should be addressed.
5. **FDA's role in recall classification:** This report does not address FDA's role in recall classification, oversight of recall strategy implementation and public communications. These are important matters and should be addressed.
6. **Jurisdictional Differences:** The medical device community assumes that a recall in one jurisdiction (word gets out fast) triggers a recall in all jurisdictions. Should this be the case?
7. **A refined and consolidated tool:** The individual tools in Table 1, Annex A and Annex E could be combined into a single streamlined tool to increase clarity and reduce or eliminate redundancy. The RAF described in Annex A encompasses considerable detail and completing the form could result in a labor intensive activity. The return or benefit from collecting all this detail may not be warranted for every issue. Guidance and/or examples should be provided that emphasize what is the 'relevant' data that may be used with an impact on decision making in various circumstances.

During the informal pilot described in Annex G, some additional recommendations were identified that are worthy of consideration for a future project(s) between CDRH and the medical device industry. These are:

8. **Customer communications:** During the pilot, FDA favored notifying the customer in virtually all cases. Industry, in some cases, was reluctant to do a customer notification particularly if the notification would not contain any actionable information. The industry perspective is that it can be confusing and stressful for customers to

INFORMATION

Future Work

+ Multiple organization recall situations
+ Third-party actions
+ Off-label use
+ Qualifying the duration of benefit
+ FDA's role in recall classification
+ Jurisdictional differences
+ A refined and consolidated tool
+ Customer communications
+ Factors considered by FDA when evaluating correction/removal strategies
+ Documenting changes in probable benefit(s)

receive a notification about something that calls for no action and possibly not even anything that would help inform them about something important. Further discussion on when a customer notification would not be considered necessary by the FDA could be valuable to both industry and CDRH reviewers.

9. **Factors considered by FDA when evaluating correction/removal strategies:** Additional information from FDA on the specific factors they take into consideration in their decision process would be valuable to industry and should be considered for inclusion in the FDA draft guidance
10. **Documenting changes in probable benefit(s):** The RAF in Annex A needs to be expanded to collect more information about changes in probable benefit(s) referencing Section B of the FDA draft guidance

Annex A:
Risk Assessment Form

This Risk Assessment Form (RAF) is a template that is intended to be used as a tool for documenting and assessing medical device events[9] that may have an impact on device quality. It may need to be adjusted to fit the needs of an individual case.

The RAF provides a comprehensive, integrated engineering and clinical analysis of potential safety issues. Its purpose is to present the most relevant data (i.e., risk file, CAPA files, complaint analysis, etc.), in order to assess what is known about the risk and to identify where more information is needed. The RAF helps inform decision makers; the form itself does not make decisions. It is expected that both FDA and industry would use the RAF for the purpose of cultivating alignment in event analysis and decision making.

Frequently, a final decision on the significance of and appropriate action for a given device event is made with incomplete data; therefore, it is understood that not all data requested in the RAF will necessarily be available. A decision should always be made in the interest of what is best for public health and should not be delayed if a serious and imminent risk to public health is present, or is otherwise required by law.

The RAF is not intended to address medical device emergencies where there is a clear need for action and no decision analysis is necessary. For example, consider proceeding directly to field action/withdrawal of product when:

- A "never event" (defined as an outcome that should never occur, such as death, serious injury, irreversible injury, etc.) occurs with a medical device that is not life-sustaining or medically necessary.
- A medical device with equivalently effective alternatives on the market is associated with serious harm.
- Without further analysis, it is clear that the benefits of the device do not outweigh the risks.

The objectives of the RAF are to:

- Describe the medical device;
- Describe the medical device event;
- Summarize and analyze any malfunctions and adverse events associated with the device event;
- Identify the inherent or expected risks associated with the medical device event, when possible;
- Assess if any new hazards are posed by the medical device event;
- Assess if any new hazardous situations are posed by the medical device event;
- Assess if any new harms are posed by the medical device event;
- Identify and rank the potential harms associated with the identified hazards or hazardous situations; and
- State any assumptions made during the course of completing the technical and clinical analyses.
- To document the information upon which a benefit-risk postmarket decision may be based.

The RAF facilitates an integrated technical and clinical understanding of the causes and consequences of the event to support decision making. The technical analysis section should be completed by qualified technical expert(s). The clinical analysis section should be completed by qualified clinical expert(s).

Risk Assessment Form

Summary: The summary outlines the most salient results of the analysis and explains how the event impacts the risk profile of the device. Because the audience for the summary includes medical device professionals with a range of clinical, technical and legal backgrounds, the summary should be expressed in terms that all members of the audience can understand.

The summary typically should consist of 1-2 paragraphs and include the following:

- The name of the device.
- A brief description of the event.
- Key points from the technical analysis.
- Key points from the clinical analysis.
- Summary statements about the integrated analysis of the impact to the risk profile.

Technical Reviewer Name/Signature/Date: _____

Clinical Reviewer Name/Signature/Date: _____

Part I: TECHNICAL ANALYSIS (to be completed by the Technical Reviewer)

Unique ID Number: Many organizations assign a reference number or a log number to their assessments. **Revision:** Risk assessments can be revised over time as additional information becomes available. This section can be used to differentiate different assessments of the same event.	**CAPA and/or Complaint Number:** If not applicable, put N/A.	**Date Opened:** Date this assessment was initiated. **Date Closed:** Date the final version of this assessment is completed.
Purpose/Source: What is the initiating event? (Examples include: nonconformance, CAPA, trending, postmarket vigilance.)		

Part I(A) Background Information

Manufacturer

a) Manufacturer Point of Contact Name and Address: (owner/operator/primary point of contact) *(This may vary from the actual manufacturing location of where the device is manufactured; the intent is to provide a contact for follow-up information, if needed.*

b) Manufacturer Establishment Registration Number:

c) Establishment Name and Address: *(location of manufacturing site optional)*

Product (Attach separate lists if needed)

a) Device Name:
Potentially more than one device design is affected by this event.

b) Unique Device Identifier (UDI): If not applicable, put N/A.

c) Device Model(s)/Catalog Number(s):
Provide information as appropriate.

d) Lot Number(s)/Serial Number(s):

e) Product Description (e.g., device description):
Provide a brief description of the device from labeling (inclusion of the product classification optional).

f) FDA Cleared or Approved Intended Use and Indication for Use (copy from IFU):
This can be copied from the IFU, or the IFU can be attached. Add additional detail regarding the use of the product as relevant, and clearly indicate which additional details are not captured in the FDA-cleared or -approved IFU. Note that the same device may have different intended uses or indications in other countries; it is recommended that these be evaluated separately.

g) Dates or Date Range of Device Manufacture:

h) Expected Lifespan of the Product (if known/available):
Expected lifespan could be expressed in a number of ways: by expiry date (e.g., 1/1/2018), by calendar time (e.g., 3 months after use/opening), by frequency of use (e.g., can be used 5xs before needing replacement), etc.

i) Regulatory Classification and Reference:

FDA Regulatory Status:	MDD Regulatory Class (optional):
510(k)/PMA Number:	FDA Product Code:

Product Distribution

a) Total Number of Devices Subject to Review or Field Action (for Industry):
List the numbers of devices impacted by the event that have been distributed, and the number of devices that are anticipated to be still in use. These estimates are used to help determine the extent of the event, and may also include the number of units that are still within the organization's control and/or are still in process. If hard numbers are not available, provide an estimate and explain how you arrived at the number(s). List source(s) (sales, manufacturing, supply chain, service records, etc.). Note that regions shown are examples only; it is expected that organizations will customize as appropriate.

TABLE I(A).1—PRODUCT DISTRIBUTION SUMMARY TABLE

Region	Devices in Distribution	Number of Devices Subject to Review or Recall
United States (US)		
Canada		
Europe/Middle East/Africa (EMEA)		
Asia Pacific (APAC)		
Latin America		
Other Regions		
Total		

Part I(B) Event Description and Analysis

This section is intended to define the event being assessed for risk (to health) and to present an explanation of what is known about the cause. It provides the basis for risk assessment.

Event Investigation

a) Trigger Event Date:

b) Initial Awareness Date:
Date the organization was first informed of this event. If awareness came from a trend, this would be the date that the trend was reviewed for action.

c) Describe How the Event, Defect, Malfunction, IFU/Labeling Error or Omission, or Use Error Leading to Risk Assessment Was Discovered:

d) Event Description:
An event may be caused by multiple reasons. Examples could include: design deficiency, manufacturing error, labeling error, servicing error, change in postmarket risk acceptability, etc.

A malfunction is a failure to meet a performance requirement/specification or intended use.

Use error is a "User action or lack of User action while using the Medical Device that leads to a different result than that intended by the Manufacturer or expected by the User" (ANSI/AAMI/IEC 62366-1:2015).

A risk assessment may be triggered when there is reason to believe that the original risk assessment may be incorrect, or there is a change in the level of seriousness of an adverse event, or when additional real-world use is or may be inconsistent with original expectations (e.g., off-label use, or on-label use that is different than originally expected).

This may include a description of the situation that occurred with as thorough a description as possible of the events and environmental elements. Methods to reproduce the event either at the customer site or at the manufacturing facility should be included, if these are known.

e) Preliminary/Immediate Cause/Root Cause:
S*ometimes the definitive root cause is not immediately known; for purposes of expediency, it is expected that organizations will perform an investigation and/or preliminary risk assessment to be revised later as more information becomes available. If the root cause is not available, describe what is known and indicate the investigation status. If the cause category is not listed below or is unknown, describe what is known. Check all that apply.*

- ☐ Design.
- ☐ Manufacturing/supply chain error.
- ☐ Use error.
- ☐ IFU/labeling.
- ☐ Change in use environment that increases risk.
- ☐ Change in public/user tolerance for inherent device risks.
- ☐ Change in rate or number of reported adverse events.
- ☐ Device meets specifications but is not performing optimally.
- ☐ Premature/wear-out failure.

Provide an explanation for each factor selected.
Design factors could include: selection of the wrong materials, interfaces that do not take into account the capabilities and limitations of the user, difficult calibration or maintenance procedures, etc.

Manufacturing errors could include: the use of inadequate raw materials, improper storage conditions, missed steps, quality release of out-of-specification products, labeling mix-ups, etc.

Use errors could include: a failure to follow instructions, taking shortcuts, not following calibration or maintenance procedures, use of untrained personnel, etc.

IFU/labeling could include: incorrect or incomplete labeling, such as incorrect expiry dates on packaging, missing warning or caution statements, or incorrect instructions.

Changes to the use environment could have the potential to impact product risk. For example, a product originally designed for use in a clinic may later be used in a home environment, which can introduce a wide variety of new risks that had not been considered in the original design.

Public/user tolerance for inherent device risks may change over time. For example, clinical practice changes over time, as does the public's expectations for safety. These changes could warrant a re-examination of a product's risk profile and current risk acceptability criteria.

Changes in the rate or number of reported adverse events may suggest that a device quality issue exists and should be examined.

"Device meets specifications but is not performing optimally" addresses continuous improvement issues.

1) What are the hazardous situations created or affected by this event (i.e., how are people exposed to this hazard)? *This information may be pulled directly from the risk file, if the event was previously identified.*
2) What are the reasonably foreseeable events that could result in exposing a person to these hazardous situations, could expose a person to harm, and could progress to actual injury? *This may be documented in the risk file at the pre-market stage, or may reflect an actual sequence of events that occurred, which is documented in the complaint or literature. Additionally, identify the probability for each step, if available.*
3) What are the potential harms due to this event (to patients, users and bystanders)? *This information may be pulled directly from the risk file, if the event was previously identified.*

    i) Current risk controls:
    Document any existing design elements that may help mitigate the risk. Examples could include: design redundancy, design margin, equipment self-diagnostics, protective features, etc. Specific user checks to prevent failures, if described in the IFU, should be mentioned; standard laboratory or hospital practices, however, should be excluded.

    ii) Is the user likely to recognize the impending risk to the patient or healthcare provider in time to prevent the occurrence from happening?
    Document any user actions that may help mitigate the risk. Examples could include: responding to a device alarm, notifications to user, and clinical intervention. Would the user know what to do, have time to take action, and take the correct action?

Part I(C) Adverse Events and Complaints Related to the Device Event

Complaints

Do not include complaints that are unrelated to the device event currently being evaluated.

NOTE: Regions shown are examples only; it is expected that organizations will customize as appropriate.

☐ No complaints reported.

TABLE I(C).1—COMPLAINT SUMMARY TABLE

Region	# of Relevant Complaints	Device Caused/ Contributed to Deaths (# of Complaints)	Device Caused/ Contributed to Serious Injuries (# of Complaints)	Device Caused/ Contributed to Temporary & Medically Reversible Injuries (# of Complaints)	Device Malfunctions But No Adverse Events (# of Complaints)
United States (US)					
Canada					
Europe/ Middle East/ Africa (EMEA)					
Asia Pacific (APAC)					
Latin America					
Other Regions					
Total					

Interval for complaint analysis: [dd/mm/yyyy] to [dd/mm/yyyy]. *Provide an explanation for the bracketed date range.*

Describe: The complaints received; any deaths, injuries and/or malfunctions that resulted from this event; and all related MDRs and vigilance reports. *Please attach any available supporting documents and/or reports.*

a) Complaints:
List relevant complaints (attach a list if there are many) or summarize the complaint analysis as part of the investigation, detailing the results.

b) Death/Injury Reports:
If any of the complaints involved injuries, or required medical intervention to preclude permanent injury, provide details. If qualified clinical experts determined that the device did not cause the event, provide a summary of the opinion.

c) Malfunction Reports:
Summarize reportable malfunctions that did not cause death or injury, including details of the potential for injury.

d) Were any adverse events from external sources? Yes/No. If yes, check all that apply and provide an analysis:

Ensure that events reported in this section do not duplicate complaints described above OR identify which of the specific adverse events are also included in the complaint information above.

- ☐ Adverse Events and Malfunctions Described in the Medical Literature.
- ☐ Adverse Events and Malfunctions Described in Other Media (newspapers, websites, television journalism, etc.).
- ☐ Adverse Events and Malfunctions Described in Trade Complaints.
- ☐ Adverse Events and Malfunctions Reported to the FDA by Foreign Governments.

1) Overview of External Adverse Event Reports.
2) Death/Serious Injury Reports—describe each.
3) Temporary/Medically Reversible Injury Reports—describe each.
4) Malfunction Reports.

e) Estimate the number of patient exposures that will occur (1) annually and (2) over the device's expected lifetime.

1) How many devices have or are expected to have the event?
Calculate or estimate the number of devices that may exhibit or be impacted by the event. Start with the number in Table I(C).1 above.

The calculation is based on the investigation results. If incomplete, base the estimates on the worst case. For design and labeling omission defects, the number generally will be all devices under evaluation. For manufacturing defects, the number may be limited by product/component lots, time of manufacturing, etc.

2) How many device failures are expected per year taking into consideration all the devices that are expected to exhibit the event?

Estimate the total number of devices that may fail, based on available data and expert judgment. Include the rationale.

3) Describe how the device event/hazard can cause harm to patients and/or users. Explain if there are circumstances that are required for the harm to occur, either with regard to the device or to the clinical setting of use.

If the device event/hazard, is not in the risk management file, a new risk assessment is necessary and the risk management file should be updated.

Different types of products will have different units of measure for an exposure event, depending on their clinical use. For example, an infusion pump may require a calculated risk based on the number of infusions that are delivered. A hip implant may require a calculated risk based on the number of implants currently in use. Other devices may require a calculated risk based on hours of usage. Therefore, describe the unit of measure, the justification for the appropriateness of that unit of measure, and how the organization determined the number of exposure events.

Consider a failure in which 1 in 1,000,000 uses may result in harm. To answer the question of whether this is a high or low risk to public health, you need to know how often the product is used.

Examples:

1. *Consider a specialized medical device in which there are only 100 devices in use, and each device is used 100 times a year; there would be 100 x 100 = 10,000 total uses in a single year. For a failure in which 1 in 1,000,000 exposures could lead to harm, the resulting risk to public health is relatively low (10,000 / 1,000,000 = 0.01 harm per year.)*
2. *In contrast, consider a more general medical device in which there are 100,000 devices in use, and each device is used 1,000 times in a year; there would be 100,000 x 1,000 = 100,000,000 total uses in a single year. For the same failure rate as above, in which 1 in 1,000,000 uses could lead to harm, the resulting risk to public health is much higher (100,000,000 / 1,000,000 = 100 harms per year.)*

Part I(D) INFORMATION FROM THE RISK MANAGEMENT FILE (If Available, for Industry)

☐ Information from the risk management file is not available.

The information in this section may be taken directly from the risk management file.

a) Has this hazard or hazardous situation previously been identified? Explain. [Clause 9, 14971:2007]
This question is intended to help clarify if a known risk has changed, or if a new risk has been discovered.

b) Has the estimated risk from the hazardous situation changed? Explain. [Clause 9, 14971:2007]
This question is intended to help clarify if a known risk has changed (e.g., severity or likelihood is different), or if a new risk has been discovered.

c) What are the inherent risks (related to the event under review) associated with this device when it is functioning as intended?
This question is intended to identify the inherent risks of the device that were anticipated during the premarket stage, and which may relate to the risks associated with the device event currently under review.

d) What are the hazardous situations created or affected by this event (i.e., how are people exposed to this hazard)?
Include if the event was previously identified in the risk management file.

e) What are the reasonably foreseeable events that would result in exposing a person to these hazardous situations and in progressing to actual injury/harm?
This may be documented in the risk file at the pre-market stage or may reflect an actual sequence of events that is documented in the complaint files or literature. Additionally, identify the probability for each event, if available.

f) What are the potential harms due to this event (to patients, users and bystanders)?
Include if the event was previously identified in the risk management file.

Technical Reviewer Name/Signature/Date: _____

Part II: Clinical Analysis (to be completed by the Clinical Reviewer)

Part II(A) POPULATIONS AFFECTED BY THE DEVICE EVENT

a) Describe the overall population that uses, or is exposed to, the device including the estimated size of the population.

b) Within the overall population of users, indicate if any significant subpopulations are at an increased risk of harm from the device event. Include the estimated size of each subpopulation.

All users have an equivalent risk of harm.

OR select from the following:

- ☐ Infants *[insert age group description].*
- ☐ Children *[insert age group description].*
- ☐ Elderly patients *[insert age group description].*
- ☐ Critically ill patients.
- ☐ Immunocompromised patients.
- ☐ Other subpopulations (e.g., chronically ill, chronic lung disease, arthritis, chronic renal disease, etc.). List:

c) Cumulatively, do all of the above selected subpopulations represent a majority of the users? Provide an explanation for your conclusion.

Clinical Analysis of Potential Harms

a) Describe the range of actual and potential harms that may occur as a result of exposure to the device event under review.
For example, consider a medical device failure that results in a fire. The range of potential harms could include: first degree burns, second degree burns, third degree burns, fourth degree burns, smoke inhalation injuries, and death resulting from a combination of these harms.

b) Of the devices expected to exhibit the event, what percentage is expected to cause harm? Please explain how this number was estimated. In the absence of data, assume that 100% of the affected devices are expected to cause harm.
The number of devices expected to exhibit the event are described in Table I(C).1 above.

c) Describe any clinical factors that might mitigate the risk.
Avoid using general statements, such as "It is common practice…".

d) Which of the harms identified above seem to be the most significant based on severity and probability of occurrence?

1) For the overall population of patients who may be exposed to the device that has or is expected to have the event, which harms identified above seem to be the most significant based on potential severity of harm?

2) For the overall population of patients who may be exposed to the device that has or is expected to have the event, which of the harms identified appear to be most significant based on potential probability of occurrence?

3) For the subpopulation of patients at greatest risk who may be exposed to the device that has or is expected to have the event, which of the harms identified seem to be the most significant based on potential severity of occurrence?

4) For the subpopulation of patients at greatest risk who may be exposed to the device that has or is expected to have the event, which of the harms identified seem to be the most significant based on potential frequency of occurrence?

The following examples of risk matrices are provided for illustrative purposes only. It is expected that organizations will complete an assessment appropriate for the medical device under evaluation.

Please complete the following assessments for each of the most significant harms identified above.

HARM: _____

PROBABILITY OF OCCURRENCE RATING SCALE			
Check	**Rating**	**Qualitative Description**	
☐	5	Very high: Failures likely/inevitable	1 in 5
☐	4	High: Repeated failures	1 in 50
☐	3	Moderate: Occasional failures	1 in 500
☐	2	Low: Relatively few failures	1 in 5000
☐	1	Remote: Failures unlikely	<1 in 500,000

Adapted from Department of Clinical Effectiveness and Quality Improvement, University of Pennsylvania Health System. The qualitative definitions may not be applicable to all device types.

SEVERITY RATING SCALE			
Check	**Rating**	**Description**	**Definition**
☐	5	Catastrophic event	Death or serious physical or psychological injury or the risk thereof. Serious injury specifically includes loss of limb or function. Must meet two of these three criteria: 1. Results in unanticipated death or major permanent loss of function. 2. Associated with a significant deviation from the usual process. 3. Has the potential for undermining the public confidence.
☐	4	Major event	Injury or permanent loss of bodily function (sensory, motor, physiologic, or intellectual), disfigurement, surgical intervention required, increased LOS, increased level of care.
☐	3	Moderate event	An event, occurrence, or situation involving the clinical care of a patient in a medical facility, which could have injured the patient but did not cause an unanticipated injury or require the delivery of additional healthcare services.
☐	2	Minor event	Failure is not noticeable to the patient and would not affect delivery of care. Failure can be overcome with modifications to the process; failure may cause minor injury.
☐	1	Near miss	A process variation that does not affect the outcome, but for which a recurrence carries a significant chance of a serious outcome. No injury, no increased LOS or level of care.

ABILITY-TO-DETECT RATING SCALE [a]			
Check	**Rating**	**Description**	**Definition**
☐	5	Absolute uncertainty	Potential failure mode and subsequent effect cannot be detected in time for adequate intervention.
☐	4	Remote	Remote chance that the potential failure mode and subsequent effect will be detected in time for adequate intervention.
☐	3	Low	Low chance that the potential failure mode and subsequent effect will be detected in time for adequate intervention.
☐	2	Moderately high	Moderately high chance that the potential failure mode and subsequent effect will be detected in time for adequate intervention.
☐	1	Almost certain	The potential failure mode and subsequent effect will be detected in time for adequate intervention.

[a]The concepts of detectability in this document are intended to reflect the clinical risk management concepts and not necessarily the risk management process in ISO 14971.

If the probability of an adverse event is estimated to be unlikely or less but adverse events have been reported, please explain how this affects the overall risk profile for the device with the identified event.

Clinical Summary/Comments:
Please provide a clinical assessment of the event, taking into consideration what was previously expected per the risk management file, and other information describing expected baseline performance-inherent expected risk. Include comments on device-related adverse events.

Clinical Reviewer Name/Signature/Date: _____

Annex B:

A Decision Quality Checklist for Postmarket Decisions

B.1 Introduction

This annex outlines a process for using Decision Analysis (DA) to illuminate postmarket decision making. DA is a powerful framework for making decisions where there is complexity, dynamics, and—most important—uncertainty. There are several references which describe the basic DA concepts, procedures and tools [1] [6] [12].

B.2 Relationship of Annex B to the process in this report

The Decision Quality Checklist (DQC) approach described in this annex can help a manufacturer facing recall strategy decisions, as detailed in Section 5. In reaching a situation in which this annex applies, the manufacturer will have experienced the following path through the flow chart shown in Figure 1:

- Encountered a trigger for postmarket benefit-risk assessment (Section 2);
- Determined that there is a change in risk and/or benefit compared to pre-market assessments (Section 3);
- Determined that a recall is necessary (Section 4); and
- Begun creating and evaluating a recall strategy (Section 5).

In many cases the specific actions to be taken will be clear. For example, suppose a manufacturer expects 1% of its life-support devices in the field to fail per year of use. The manufacturer receives reports indicating that 5% of its life-support devices are failing with dozens of patients already severely injured. In such a case, physical market removal of the device would be clearly indicated.

In other cases, the specific actions to take may be unclear. For example, suppose that a manufacturer has several hundred thousand devices in the field and the number expected to fail from the entire fleet over the next 10 years is estimated to range from 1 to 100. Severe injury to patients has not been reported, but the potential has clearly been demonstrated in the laboratory on patient simulators. Additionally, suppose that this device is unique, without ready substitution. Is physical market removal the best alternative?

As noted in Section 5.5, recall strategy decisions may present analytical complexity, such as in situations where:

- There is substantial uncertainty about the magnitude of increased risk or decreased benefit; and/or
- There is a combination of very low probability of harm but very high severity of harm;
- There are no precedents to refer to, and/or
- The interventions in recall strategies under consideration have potential for adverse consequences [11].

Recall strategy decisions may also confront a manufacturer with organizational complexity, such as when:

- Departments in the company (such as marketing, manufacturing, operations, quality, and legal) have conflicting views or incentives, and/or
- There is a need to address outside stakeholders who may have different perspectives (such as regulatory bodies, clinical users and, ultimately, patients).

This annex expands upon the process described in Section 5.1 through 5.4. In cases of analytic and/or organizational complexity, the application of DA methodology as described in this annex provides a systematic, comprehensive, and defensible approach for conducting the benefit-risk assessment and developing a recall strategy. (The DA approach also can address issues encountered with the risk matrix approach when used for risk screening, as described in ISO 14971, see [8] [9] [17] [26]).

This annex is organized as follows:

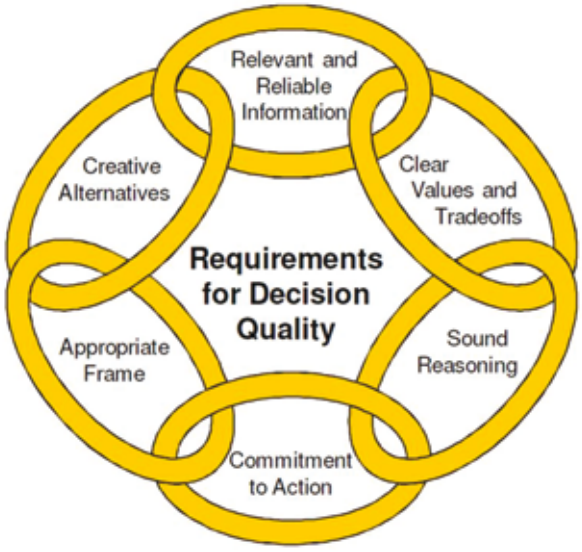
- Sections B.3.1 through B.3.6 detail the Decision Quality (DQ) approach.
- Section B.3.7 presents the Dialogue Decision Process (DDP), which adds additional steps to the DQ Checklist (DQC) pertinent to highly strategic and consequential decisions that hold the potential for organizational polarization and decision delays.

Medical device companies that would choose to adopt the approach described in this annex:

- May need to formalize the application with the addition of work instructions and other modifications to the quality system, and
- Will need to develop an analysis team, a cross-functional team that applies profound knowledge of product performance and clinical use, as well as decision modeling expertise, to generate insights into the decision problem.

B.3 Decision Quality Checklist

In general, the quality of any decision depends on six elements, as shown in the chain in Figure B.1 [1] [25] [13].



(From Strategic Decisions Group, www.sdg.com)

FIGURE B.1—DECISION CHAIN

The quality of a decision is only as strong as the weakest of these links. The Decision Quality Checklist (DQC) guides the members of the analysis team to consider the strength of each link as they formulate a recommendation for senior management regarding the postmarket decision situation. We will now consider each of the following links in turn:

- Appropriate frame.
- Creative alternatives (Options analysis in ISO 14971).
- Relevant and reliable information.
- Clear values and tradeoffs.
- Sound reasoning.
- Commitment to action.

B.3.1 Appropriate frame

The initial task for the members of the analysis team is to ensure that they are solving the correct problem. We use the term "framing" in the sense of "scoping," which the analysis team does with a conscious attempt to avoid cognitive biases [27]. In choosing an appropriate frame for the decision, they are determining "what's in and what's out." For example, a product postmarket issue found to have a design deficiency as the root cause may point to decisions not just for that product, but for the entire product family. It is important for the analysis team to think neither too broadly nor too narrowly about the scope of the problem. At this point the analysis team will consult with senior management to establish the decision body, which will ultimately make the decision in the best interest of public health. The decision body consists of representatives of senior management, as well as other external stakeholders selected by senior management.

Box 1 presents a list of questions for the analysis team members seeking an appropriate frame. Answering the questions in Box 1 will facilitate addressing the processes in Figure 1. Once the frame is determined, the analysis team can proceed to the next step, crafting creative alternatives.

QUESTIONS TO PROMPT AN APPROPRIATE FRAME

- Which external stakeholders are important? How would they like to see this decision framed? What would be their likely response to an adverse event? How should that influence our frame? Are the external stakeholders properly represented in the decision body?
- Which postmarket decisions do we need to focus on? What are we taking as givens? For example, are there commitments to regulators or customers that constrain what we can do? For example, is the medical device "violative" *(see Section 4.2)*?
- What are we deciding now and what will be decided later?
- Is this frame the same as the one we have always used for postmarket decisions? What aspects might we be missing? How can we think differently about the situation? How might things change if something we assume to be a given were actually something we could decide?
- If a simpler frame were chosen, what would we remove from our focus? How would that affect our approach to the postmarket problem?
- Have we included the right people in our framing discussion? Is there someone who should be included in the discussion who may allow us to see beyond our group's biases?
- Who will own and implement the final decision? Are implementers being included in the decision formulation and analysis, so that they will have insight to ensure high-quality execution?
- What is the appropriate timeframe for addressing the postmarket problem?
- Are there framing issues that would benefit from discussion with the FDA?

FIGURE B.2—QUESTIONS TO PROMPT AN APPROPRIATE FRAME (BOX 1)

B.3.2 Creative alternatives

Creative alternatives is an opportunity for brainstorming by the analysis team. It is tempting to reduce the decision in a postmarket situation to simply choosing between two options: physical market removal of all devices versus leaving all devices in the field. However, it is important to remember that physical market removal may entail disruption to clinical practice. So it is worthwhile for the analysis team to consider other ways to address the postmarket situation without creating shortages or otherwise adversely impacting patients.

Fault trees and event trees are examples of tools that are useful for creating alternative actions [7]. Fault tree analysis can highlight preventive measures that will block an initial undesired event from occurring. Event tree analysis can highlight opportunities for mitigation of the multiple possible consequences resulting from the initial undesired event.

Yet another useful tool to identify alternative strategies is the strategy table. The columns of the strategy table represent the different possible dimensions of a postmarket remediation activity, and the rows show the values that each activity can

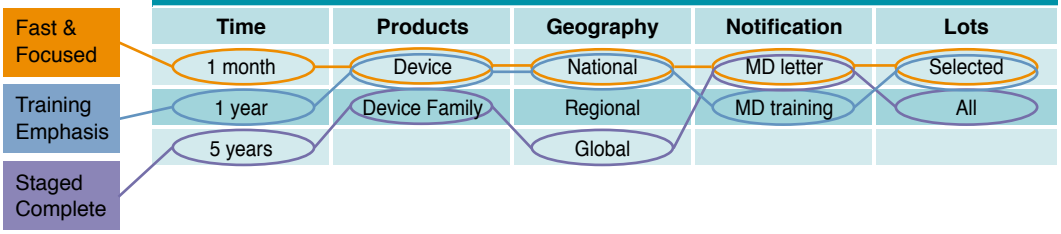
take. Table B.1 shows an example of a strategy table for a life-support medical device product line dealing with reports of an electrical failure, which could result in fires leading to electrical burns in patients. The company distributes the device globally. The failure rates are quite low, but vary according to several identifiable factors, including specific device, geography, and date of manufacture. The strategy table allows the analysis team to systematically envision the range of possible remediation alternatives by mixing and matching types of possible response elements.

TABLE B.1—STRATEGY TABLE (EXAMPLE)

Time	Products	Geography	Notification	Lots
1 month	Device	National	MD letter	Selected
1 year	Device family	Regional	MD training	All
5 years		Global		

For example, Table B.2 shows three possible strategies that can be constructed using the elements of the strategy table in Table B.1.

TABLE B.2—POSSIBLE STRATEGIES CONSTRUCTED USING THE STRATEGIES IN TABLE B.1



The "Fast & Focused" strategy is accomplished over a short time, with just the highest risk device in the device family. It is limited to the country where problems have already occurred and to the lots already known to be affected. Finally, it is accompanied by a letter to the physician users. The "Staged Complete" strategy is accomplished over a longer period of time, but encompasses the entire device family, is executed globally and covers all lots. Like Fast & Focused, this recall strategy involves a physician letter. Finally, we can imagine a strategy that has an emphasis on training the clinician users to manage the issue in a way that will avoid adverse consequences to the patient. The "Training Emphasis" strategy will limit the physical market removal to a focused set of devices and geography like Fast & Focused, but will take longer, 1 year.

Theoretically, with the strategy table in Table B.2 ,one could enumerate 72 possible strategies—the product of the number of items in each column (3 x 2 x 3 x 2 x 2). The analysis team does not need to consider every conceivable strategy. The goal of the table is to stimulate thinking about possible approaches so that the analysis team can generate a broad range of creative alternatives. From the large set of possibilities it may choose a smaller set that will be subjected to full analysis. Box 2 presents a list of questions for the analysis team to consider to enhance the quality of the alternatives.

Once the analysis team has created a set of alternatives, it can turn its attention to building a decision model. The decision model allows the analysis team to project the consequences of the alternatives so that the alternatives can be readily compared. Creating and analyzing the decision model will facilitate addressing the processes in Figure 1.

The analysis team will construct the model with mathematical rigor and precision, exposing assumptions and biases, facilitating the resolution of different observations, perspectives and opinions, and enforcing the correction of errors. As it builds the decision model and obtains illuminating insights from it, the analysis team will want to achieve high quality in the following DQ elements, to which we turn attention next:

» Relevant and reliable information.
» Clear values and tradeoffs.
» Sound reasoning.

QUESTIONS TO PROMPT CREATIVE ALTERNATIVES

- Have we fully considered a broad range of alternatives? Are the differences between the alternatives significant? What is the most outrageous idea with which we can challenge our thinking?
- Are the alternatives we are considering implementable? Are they reasonable? Are they adequate? Are they compliant with regulatory obligations? Should we check in with the FDA for input or guidance on the alternatives under consideration?
- Are we sure that the best possible alternative is in the group we have chosen?
- Who from outside our usual group has contributed to the generation of alternatives?
- Have we acknowledged disagreements between functional areas and used them as fuel for creatively generating alternatives?
- Have we incorporated the perspectives of all stakeholders?
- Have we honed the alternative set down to a manageable number?
- Have we considered both short-term actions (e.g., notification) together with long-term actions (e.g., update during service or preventive maintenance) to generate innovative strategies?

FIGURE B.3—QUESTIONS TO PROMPT CREATIVE ALTERNATIVES (BOX 2)

B.3.3 Relevant and reliable information

A decision model creates a chain that spans from device use, to hazardous situation, to hazard, to harm, to clinical outcome. Each of the links represents a different domain of expertise. For example, the link from use to hazardous situation may rely on the knowledge of quality engineers and draw on statistical analysis of postmarket surveillance data. The links from hazardous situation to hazard and harm will typically require input from clinicians with direct patient care experience and the ability to identify and interpret the relevant medical literature.

A relevance diagram is a useful tool for capturing the various factors and the web of relationships germane to how the outcomes depend on the postmarket alternatives under consideration. There are quite a few software tools available, such as Analytica™, which aid the structuring and analysis of such diagrams [19]. Figure B.4 shows a relevance diagram corresponding to the example of a device failure that may lead to an electrical burn and/or inhalation injury, as used for the strategy tables above (Table B.1 and Table B.2).

The relevance diagram shows the many factors that create the links between actions the medical device company can take for remediation, the strategy, and what will happen to the patient in terms important to him or her—the quality and length of survival. The different parts of the diagram are color-coded to show the different areas of expertise needed to detail the implications of the different possible remediation actions.

For example, engineers from functions in reliability and research and development will be experts on the factors and relationships shown in blue. Quality and regulatory team members will supply information about how the different strategies might impact device availability, shown in gray. Clinical experts will provide the information on the factors in green, which encompass not only the medical consequences of an electrical burn, but also the clinical impact of shortages or other consequences resulting from field actions under consideration.

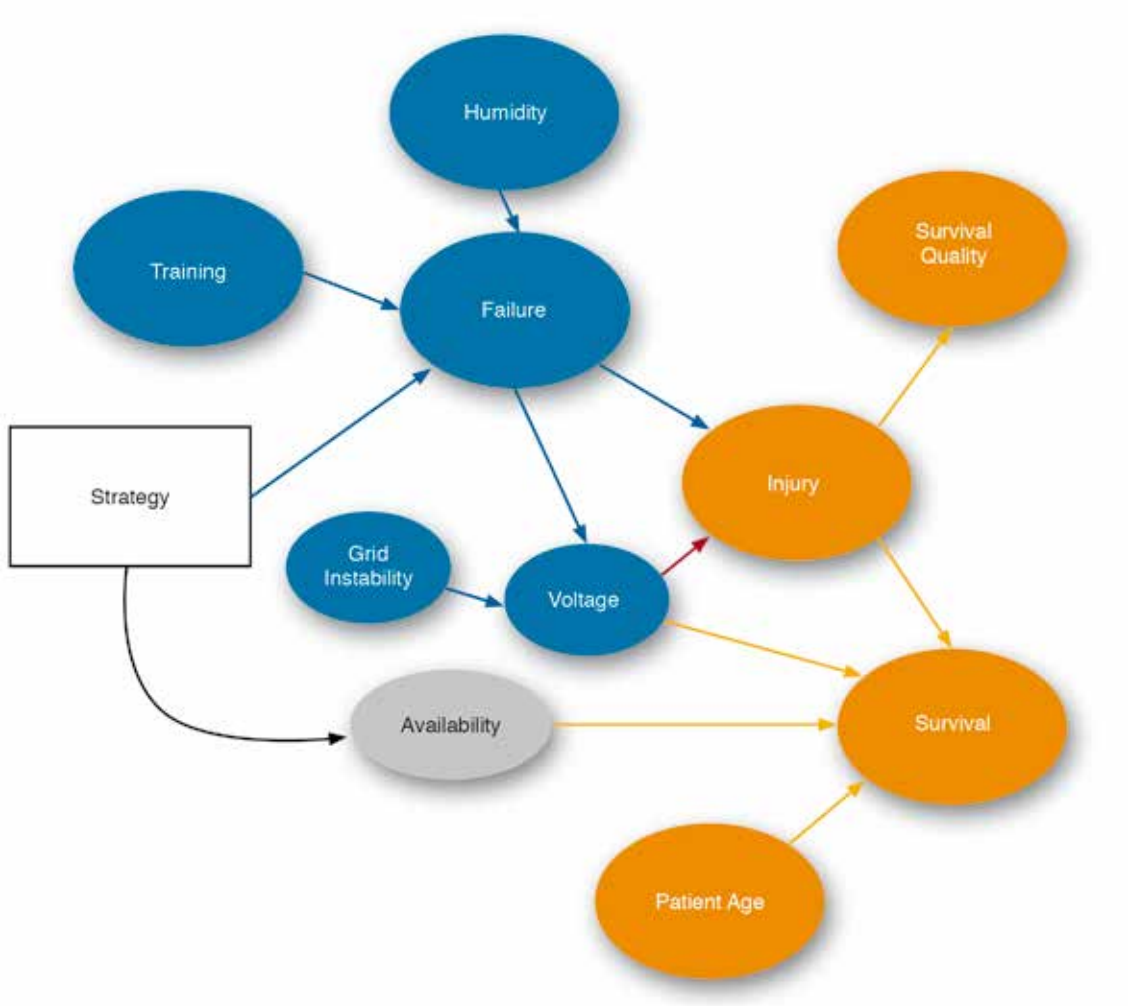


FIGURE B.4—RELEVANCE DIAGRAM

The diagram breaks the strategy's overall effect on survival and quality of life into a set of smaller relationships, which should be defined precisely for each diagram node or bubble. For example, the "Injury node" depends on "Voltage" and "Failure" nodes. "Voltage" can be readily characterized by a numerical value, and "Failure" modes may be readily categorized by the company engineers. It may be challenging, however, to clearly define the clinical entity "Injury" in unambiguous terms. The effort to work with clinicians and the medical literature, however, is well worthwhile

and might start, for example, with existing definitions of burn injury (such as arc, low voltage, high voltage, oral, flash and flame burns).

With clear definitions for the relevance diagram elements, it is possible to consult company surveillance data, as well as the clinical literature and medical experts, with such questions as:

» How likely are the particular failure modes?
» What is the likelihood of an arc burn after each device failure mode?
» What is survival from the different types of burn injury for the different age categories?

These are just a few of the questions that surface when encoding the model represented by Figure B.4. Answers to these questions are best expressed in terms of probabilities. There are well-developed techniques for eliciting this information from experts and other sources that encourage reliability and minimize bias [20].

The information in a relevance diagram provides a graphical representation that encourages meaningful discussion, allows attention to be focused efficiently on areas of disagreement, and facilitates discussion among the analysis team, the decision body, and regulators. In particular, use of the relevance diagram allows the evaluation of health hazards to go beyond simplistic, categorical representations of probability of harm and severity of harm. For example, the relevance diagram allows consideration of multiple possible harms and multiple severities, with likelihoods assessed using established probabilistic methods. Finally, there are software tools[10] that facilitate digital encoding of the relevance diagrams and enable the computational manipulations of the decision model, as discussed below. Whether or not the analysis team uses relevance diagrams, questions that it should consider in the information phase are given in Box 3.

QUESTIONS TO PROMPT RELEVANT AND RELIABLE INFORMATION

- Who has supplied the key relationships and estimates? Are the arguments underlying the formulations compelling?
- Are cited sources from the literature documented and authoritative?
- What data is available or can be gathered to validate the model?
- Have the perspectives of experts who may hold differing opinions been considered?
- What steps have been taken to ensure that biases are recognized and managed?
- Should the FDA review the model developed so far to provide feedback and guidance?

FIGURE B.5—QUESTIONS TO PROMPT RELEVANT AND RELIABLE INFORMATION (BOX 3)

The informational component forms a significant portion of the decision model. However, what is still missing is a way to value the outcomes of the decision. In the context of the medical device example diagrammed in Figure B.4, value modeling involves capturing the preferences about quality of life and quantity of life in comparable terms. We consider the matter of values and tradeoffs next.

B.3.4 Clear values and tradeoffs

Although there are several stakeholders for postmarket decisions, ultimately it is patients who bear the consequences. We thus find it reasonable to establish values

from the perspective of the population of patients. In other words, we take a public health perspective on valuing the consequences of the various actions the device company might take.

The ways to describe and value the consequences of any particular postmarket situation will vary. In general, we may need to capture preferences about the following outcome features: mortality, morbidity (including pain and loss of function), inconvenience, loss of dignity, and cost to the health care system. Patient preferences may vary widely, so it is important to consider a range of values. Work that has been done in medical DA and medical technology assessment is pertinent to eliciting patient values. For example, we can use the concepts of quality-adjusted life years (QALYs) and micromort valuation, which are concepts used in health services research [20] [10] [24] [15]. In particular, the project report from the Medical Device Innovation Consortium provides a framework and a catalogue of methods for the use of patient preferences in regulatory decision making [20].

Figure B.6 shows QALYs added to the relevance diagram as the value measure for the medical device example shown in Figure B.4.

In some cases, financial costs to the health care system will be a significant consequence of the alternative actions under consideration. Managing the clinical harm that a patient suffers from faulty device performance may result in large hospital and chronic care costs. There may also be large costs for a manufacturer to conduct physical recall or other remediation activities. Given that costs are ultimately borne by the public, it makes sense to include large costs in the model. Representing the costs explicitly in the model enables effective discussion, which may lead to resolution of differences of opinion.

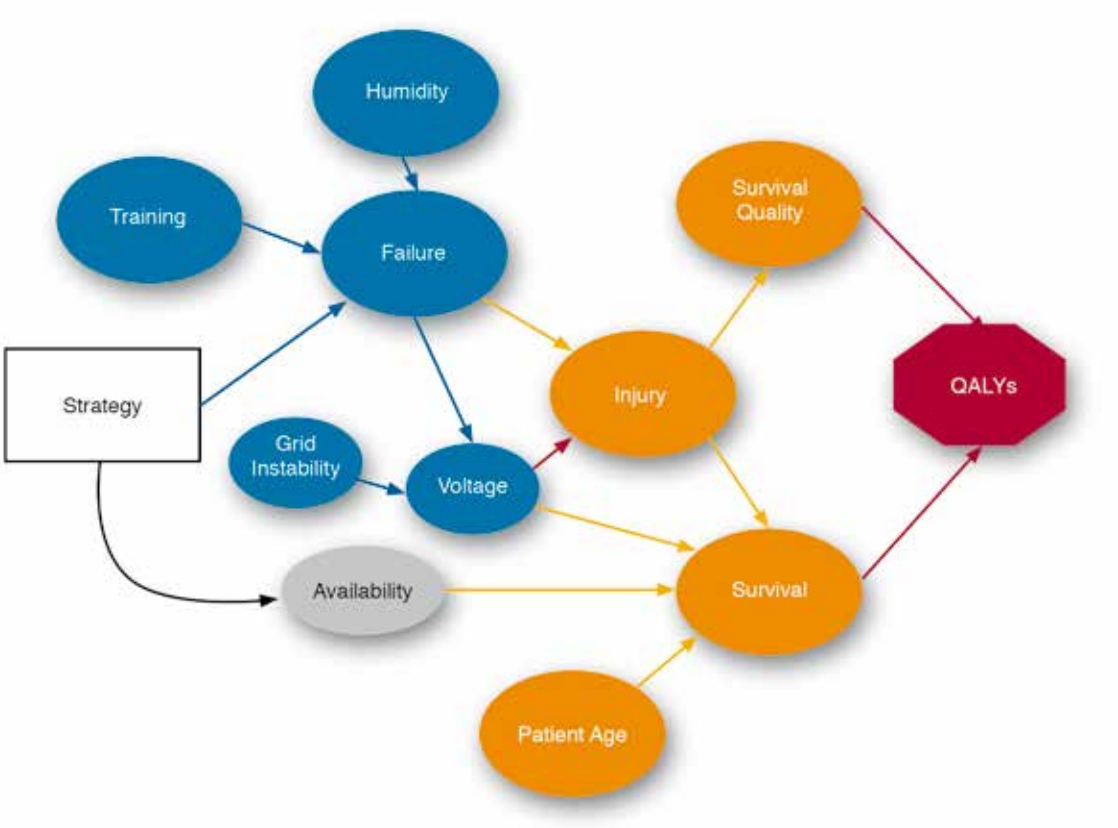


FIGURE B.6—RELEVANCE DIAGRAM WITH THE ADDITION OF QALYS

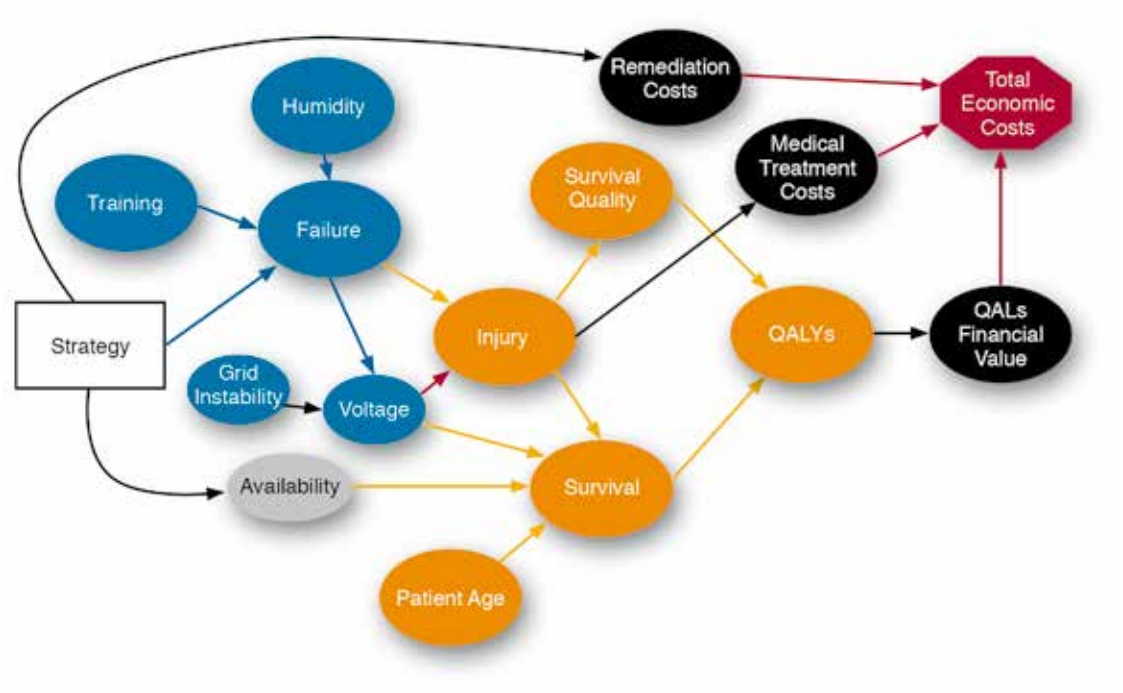


FIGURE B.7—RELEVANCE DIAGRAM WITH THE ADDITION OF NODES REPRESENTING REMEDIATION COSTS AND MEDICAL TREATMENT COSTS

Given the importance of cost control to the health care system, it is important to include costs and to explicitly represent tradeoffs between financial and clinical outcomes, as shown in Figure B.7. However, for simplicity of exposition, we will assume costs are not significant to the example company whose medical device has a fire hazard, and will use Figure B.6 as the model to proceed with analysis below. Box 4 provides questions the analysis team will want to keep in mind as it considers clear values and tradeoffs.

QUESTIONS TO PROMPT CLEAR VALUES AND TRADEOFFS

- How do we value intangibles, such as dignity and pain? Do they drive the decision, or will considerations of "life and limb" dominate?
- How do we account for variable preferences among patients? How sensitive is the decision to the range of preferences?
- Are costs large either for medical treatment or for field actions? If so, have we explicitly captured them in our model? Have we reviewed the model with healthcare services researchers who have expertise in the modeling of the economic implications of health care outcomes?
- How can we use patient-centered outcomes research to improve our understanding of values and tradeoffs?
- Should we request review by the FDA for input and guidance about our approach to values?

FIGURE B.8—QUESTIONS TO PROMPT CLEAR VALUES AND TRADEOFFS (BOX 4)

In technical terms, adding a value node to the relevance diagram converts it to an influence diagram. We can now use the influence diagram model from Figure B.6 to gain insights into the decision, as discussed in the next section on sound reasoning.

B.3.5 Sound reasoning

The model shown in Figure B.6 is fairly complicated, with many relationships that potentially require many assessments. The first insight we can glean from the model is to identify what is important—as opposed to what is merely relevant—in the influence diagram, which then will allow its simplification. A useful tool to start the study of how assessments for the different nodes impact the value (sensitivity analysis) is the tornado diagram, which can be readily generated by different software products.[11]

Figure B.9 shows a tornado diagram for the influence diagram shown in Figure B.6.

The tornado diagram shows the effect on QALYs of varying each of the variables, from the lowest plausible value to a mid-value to the highest value. The results are then stacked to put the variables with the highest "swing" at the top. As shown in Figure B.9, the variables of survival, survival quality, failure, and availability have the biggest impact on QALYs.

Using the tornado diagram as a guide, the analysis team can simplify the influence diagram, leading to the smaller diagram shown in Figure B.10.

FIGURE B.9—TORNADO DIAGRAM

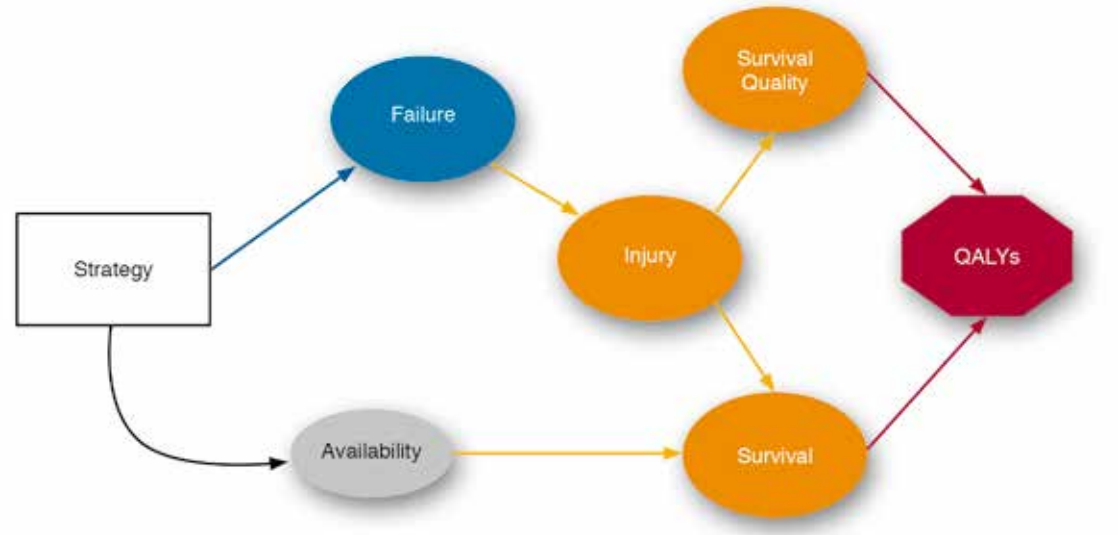


FIGURE B.10—SIMPLIFIED INFLUENCE DIAGRAM

We can readily transform the understanding gained from this smaller model into a spreadsheet, in which we can enter specific assessments and explore consequences numerically, as shown in Table B.3. In general, we will want to consider a wide range of alternatives for the "Strategy" node in Figure B.9. To simplify the exposition in this paper, however, we will consider only two alternatives:

» The device remains available, versus
» The device is removed from the field.

TABLE B.3—EXAMPLE ASSESSMENT

Item	Devices Available	Devices
Recalled		
Number patient device uses annually	1,750,000	1,750,000
Probability of survival	0.25	0.15
Probability of burn	0.5	0
Number of survivors with burns per year	218,750	
Number of survivors without burns per year	218,750	262,500
Number of non-survivors with burns per year	656,250	1,487,500
Number of non-survivors without burns per year		
Expected survival in years	10	10
Quality adjusted for burn years	0.5	
Quality adjusted life years (QALYs) per year	3,281,250	2,625,000

Note in Table B.3 that the entry for "Probability of survival" under "Devices Recalled" is 0.15, which is decreased from 0.25. This decrease reflects the fact that in this example, the medical device serves a life-sustaining function. Given the assessments in Table B.3, the decision model indicates that having the device available, even with the chance of a burn, leads to 3.3 million QALYs. Recalling the device is associated with only 2.6 million QALYs. Thus, leaving the device available is the preferred alternative.

The initial recommendation from the decision model is only a first step, since the goal is to obtain insights into not only what should be done, but also why, and under what range of assumptions. For example, suppose the probability of survival with the device is uncertain. One expert feels strongly that the probability is actually lower than 0.25 and should be assessed at 0.20. Another expert feels that it is higher than 0.25, at 0.30. This can be explored with a sensitivity analysis of the model.

Figure B.11 shows a graph of the QALYs for each of the two strategies, as the probability of survival, given the device, is varied from 0.15 to 0.3. Because there is no disagreement about the probability of survival without the device, that estimate is set to 0.15. The QALYs for the strategy of device removal are thus fixed at 2.6 million. The QALYs for the strategy whereby the device is left in the field varies from 1.97 million to 3.9 million, as the probability of survival varies over the range 0.15 to 0.30.

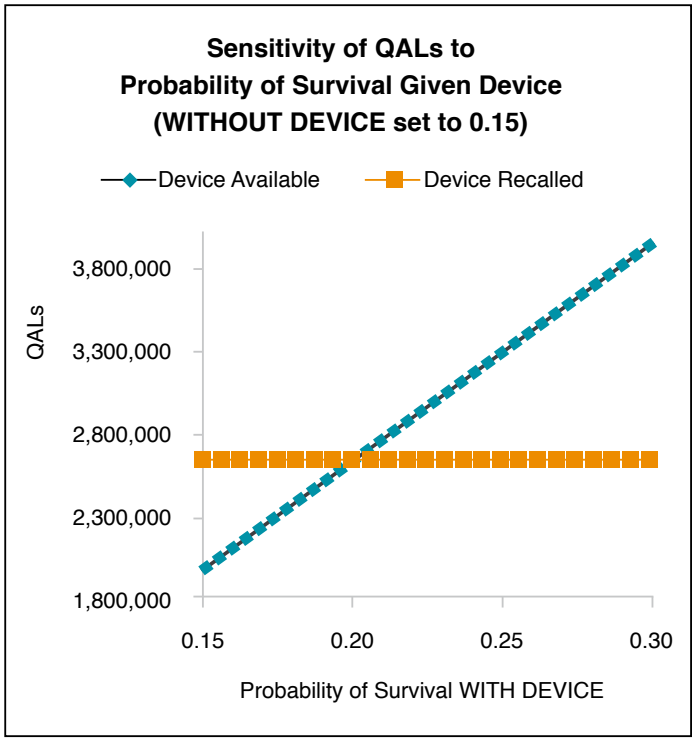


FIGURE B.11—SENSITIVITY OF QALYS TO PROBABILITY OF SURVIVAL GIVEN DEVICE

The graph in Figure B.11 shows how the strategies compare for different assessments of the probability of survival with the device. The crossover point for the two strategies occurs where the probability of survival with the device is 0.2. In other words, although the experts disagree about whether the probability of survival with use of the device is 0.2 or 0.3, they nevertheless both should agree on the best alternative. As long as the analysis team is confident that the change in survival with the device is an increase of at least 5% (from a 15% to a 20% chance of survival, at least), then leaving the device in the field, even with the risk of burn, will be the preferred strategy.

Suppose, however, that the analysis team is still uncertain about the assessment; perhaps there are opinions from other experts or data in the literature that support assessments pointing to a value for the probability of survival with the device both above and below the 0.2 crossover point. Such uncertainty can be rigorously captured using probabilistic methods.

Figure B.12 is an example of how the uncertainty about the probability of survival with the device could be expressed graphically. Figure B.12 shows that a probability of survival of 0.25 is considered most likely, but there is a 30% chance that the probability of survival value with the device could be less than 0.2, a 30% chance that it could be between 0.2 and 0.3, and a 40% chance that it is greater than 0.3.

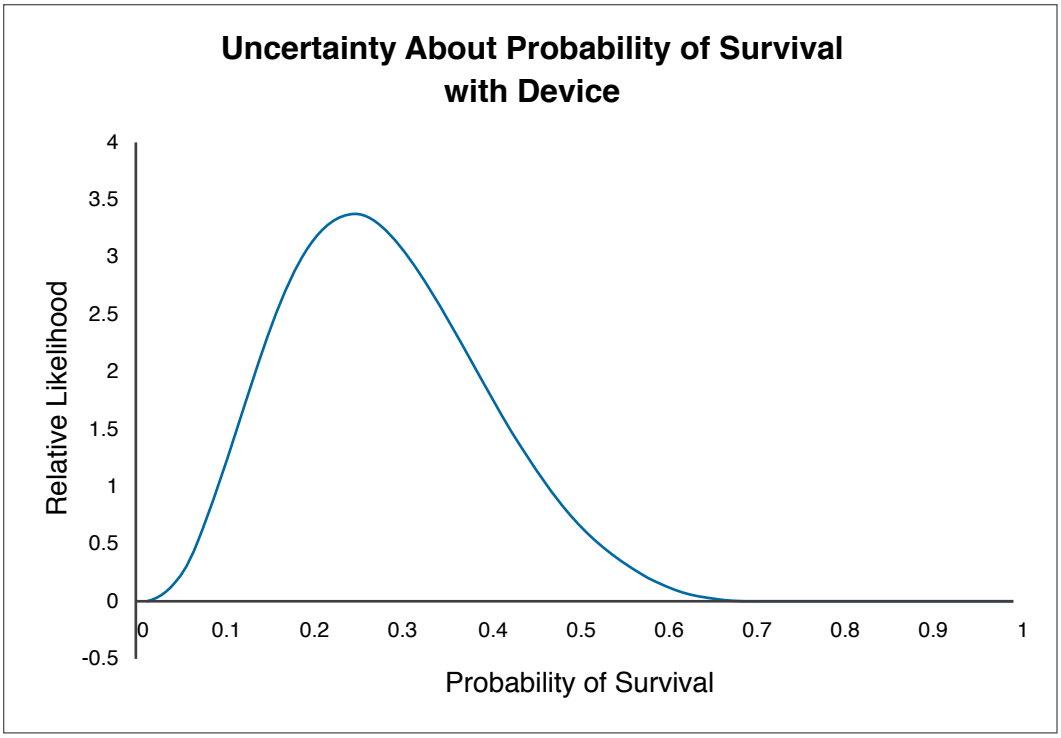


FIGURE B.12—UNCERTAINTY OF PROBABILITY OF SURVIVAL

Not surprisingly, uncertainty about the input to the decision model leads to uncertainty about the output of the decision model. Figure B.13 shows the degree to which the uncertainty about the probability of survival with the device will manifest as uncertainty about comparing the value of each of the two alternatives under consideration in QALYs. The alternative, leaving the device available, leads to a range of possible QALYs, with most of the likelihood between 2 million and 5 million QALYs. Because, in this example, there is no uncertainty about the probability of survival without the device, the alternative involving recalling the device is associated with the certain value of 2.6 million QALYs. There is thus a chance that the recall alternative would lead to greater QALYs, but also a chance that the recall would lead to fewer.

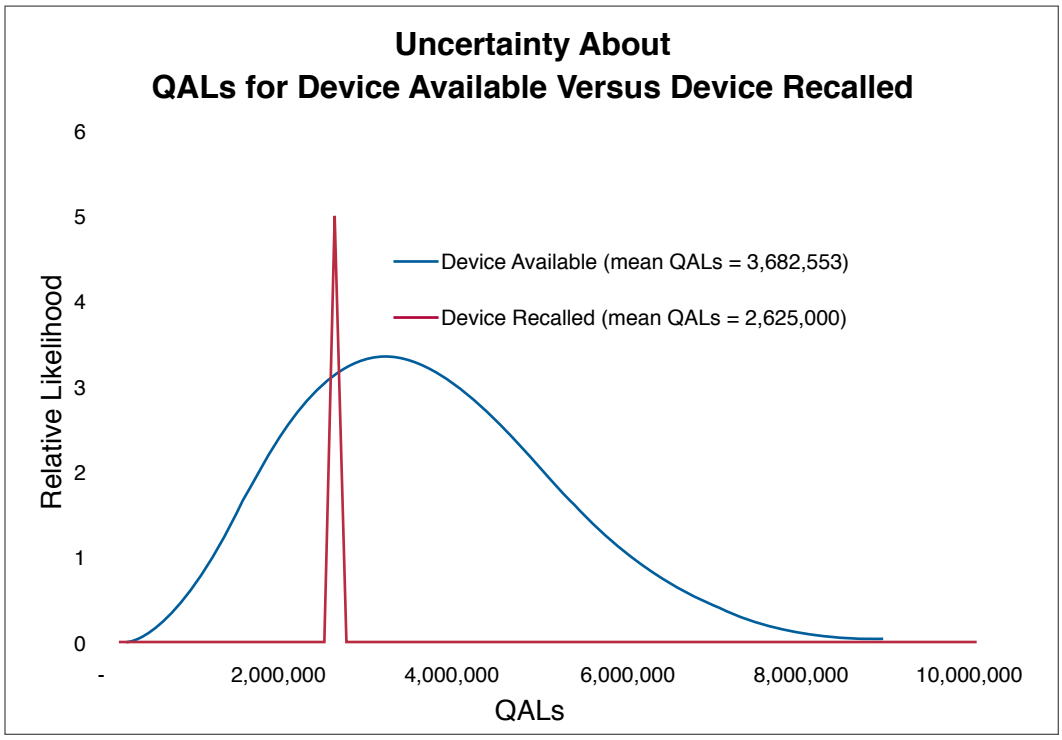


FIGURE B.13—UNCERTAINTY ABOUT QALYS FOR DEVICE AVAILABILITY

In general, comparison of probability graphs for life-and-death matters should be done cautiously. In this case, given that we are taking a public health perspective on consequences that are spread across a large population, it is reasonable to use the mean (average) value associated with each graph to compare the alternatives. As shown in Figure B.13, the mean for leaving the device available is approximately 3.7 million QALYs, while the recall mean is only approximately 2.6 million QALYs. The decision model thus provides clear guidance that, even in the face of the uncertainty and despite the risk of burns, not recalling the device is the preferred alternative.

As this point, the question might come up regarding the value of doing further research on the probability of survival with the device, to further reduce the uncertainty shown in the graphs in Figure B.12 and Figure B.13. The value of information (VOI) calculation technique can answer that question [14]. For example, we could calculate (in terms of QALYs) what a study would be worth to resolve uncertainty about the probability of survival with the device. This value could be used to decide whether a study is worthwhile and also to guide clinical study design, helping to determine sample size and duration.

We have seen how the analysis team can use decision analysis tools, including relevance, influence, and tornado diagrams, as well as sensitivity and probabilistic analysis, to gain insight into postmarket decision problems. As they use these tools, the analysis team should keep in mind the questions in Box 5 to prompt sound reasoning.

QUESTIONS TO PROMPT SOUND REASONING

- Is the level of analysis appropriate? Have we oversimplified? Or are we just procrastinating with a case of "paralysis by analysis"?
- Have we incorporated uncertainty using probabilistic modeling where appropriate?
- Can we clearly understand which alternative looks best, and why?
- Given what we have learned, is there another alternative that we can create that better serves public health?
- Should we review conclusions with the FDA to get feedback on analysis and proposed action?

FIGURE B.14—QUESTIONS TO PROMPT SOUND REASONING (BOX 5)

After the model has been analyzed, the analysis team will present the recommendation and insights to the decision body. The analysis may lead the decision body to request modifications to the model, additional assessments, further information-gathering, or even the inclusion of new alternatives. There may be several iterations to refine the model, but ultimately a clearly recommended alternative will emerge. The timeframe for this analysis may be flexible, as new insights appear. However, it is important to adhere to the deadlines established in the framing stage, as a delayed decision may actually be worse than the alternatives under consideration. In particular, there may be ongoing harm to patients while decisions are being made. We also emphasize that the model and the insights it provides do not replace senior management judgment, but rather it serves to highlight key uncertainties, focus attention, and improve efficiency and effectiveness of discussion, as the company seeks the best response to a postmarket issue.

B.3.6 Commitment to action

Choosing an alternative does not end the decision-making process. Decision implementation is as important for decision quality as decision making. An important factor for execution success is ownership of the decision by the implementers. Inclusion of the analysis team in regular updates will give the implementers the essential knowledge of how the decision was made and why. Such understanding will help the company monitor the accuracy of the assumptions and assessments that drove selection of the action being implemented. Box 6 lists questions to prompt the analysis team and senior management team about steps that will ensure high-quality commitment to action. Answering the questions in Box 6 will facilitate addressing the processes in Figure 1.

QUESTIONS TO PROMPT COMMITMENT TO ACTION

- Have all the functions aligned with the decisions that address the postmarket situation?
- Do the implementers understand the value drivers, so that they can execute details consistent with the decision intent?
- Do we have contingency plans in place to allow adjustment of the decision for unforeseen or unusual events, or for evidence that assumptions driving the decision are incorrect?

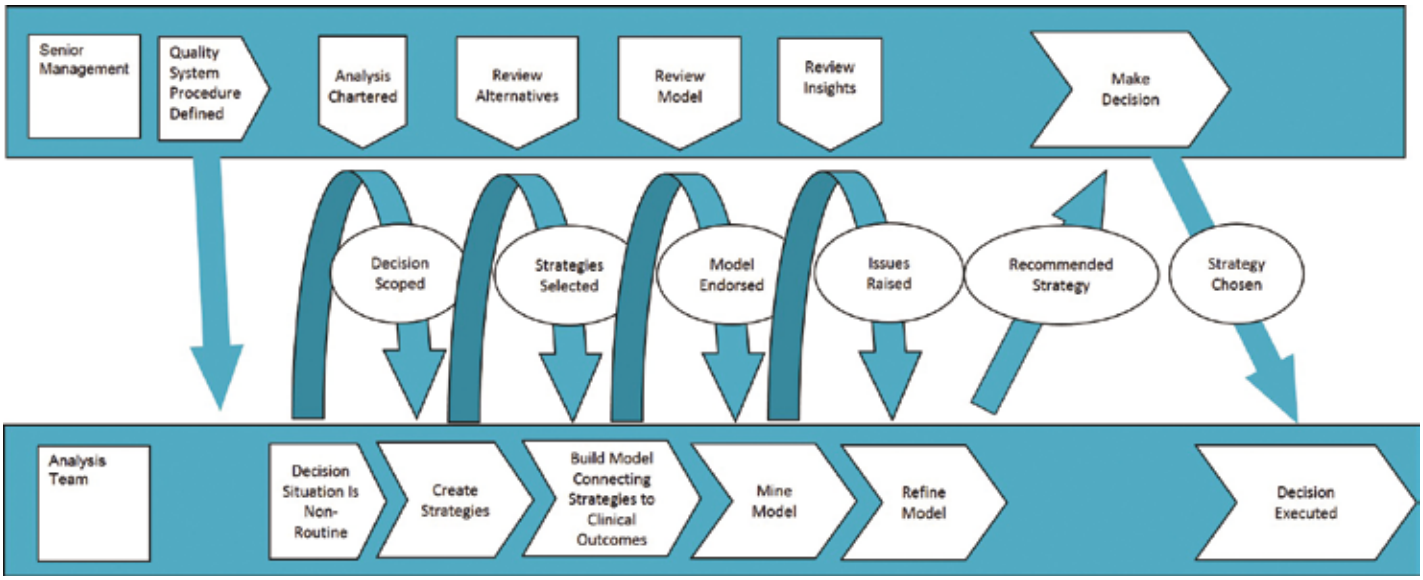
FIGURE B.15—QUESTIONS TO PROMPT COMMITMENT TO ACTION (BOX 6)

B.3.7 Dialogue Decision Process

One of a number of way to view the DA process is as a conversation between two groups. One group is the analysis team that represents various company functions and draws upon the expertise of subject matter experts, such as clinicians and other consultants, to conduct the analysis described above. The other group is the decision body, made up of senior management and other key stakeholder representatives, which will make the final decision based on insights developed by the analysis team. In general, the decision body can delegate the study of the decision to the analysis team, which identifies a preferred alternative and advocates to the decision body for its choice.

In some cases, particularly where there is a complex organization and disparate perspectives held by different stakeholders, the advocacy approach may lead to polarization of opinions and delays. There may be repeated requests to redo or extend the study of the decision, and ultimately there is a lack of alignment behind the decision. When the stakes are high and controversy is expected, the Decision Quality Checklist (DQC) approach may be modified to include regular review by the decision body, representing senior management, as the decision is framed and the decision model is developed and refined.

As a tool, the Decision Dialogue Process (DDP) is well grounded in both theory and practice [5] [18] [25]. Figure B.16 shows an application of DDP that structures the conversation between the analysis team and senior management. The DDP allows senior management to provide input at early stages of the modeling, to guide the decision study efficiently and to avoid "paralysis by analysis."



(Modified from Strategic Decisions Group, www.sdg.com)

FIGURE B.16—DECISION DIALOGUE PROCESS

B.4 Summary

This annex presents a Decision Quality Checklist (DQC) that is grounded in the philosophy, concepts and tools of decision analysis. Using the DQC, an analysis team can systematically define and scope the decision problem (framing); generate creative, actionable alternatives; and build a decision model that incorporates reliable information and explicit values. Ultimately, the medical device company can use the model to gain insight into which alternative, from a public health perspective, best manages the postmarket problem. Including implementers in the formulation and analysis of the decision will ensure the understanding and buy-in necessary for high-quality execution of the decision. Finally, it may be helpful in some circumstances to have the input of the regulators while building the decision model and doing the analysis.

In some organizations and for some problems, the creation and exploration of the decision model requires a step-wise conversation between the analysis team and senior management. The Dialogue Decision Process (DDP) provides a way to choreograph this conversation so that it will lead efficiently and effectively to insights into, and alignment behind, a best alternative.

Annex C:

Points to Consider when Evaluating Manufacturer Decision Making in Corrective Actions

C.1 Introduction

The Benefit-Risk Framework Project (BRFP) has recommended that manufacturers use specific tools and methods when arriving at a corrective action. This list of questions may be helpful to FDA personnel who are evaluating recall submissions, specifically with regard to the firm's chosen corrective action that resulted from these or other tools. Its purpose is to assist in identifying areas of potential disagreement between FDA and industry, and to facilitate detection of missing components of the decision-making process. It is not meant to be binding or prescriptive, but rather to help simplify and increase the transparency of the recall review process. It should also prove helpful when discussing deficiencies with the firm, should that become necessary.

C.2 The Decision Quality Checklist

A manufacturer is most likely to arrive at a corrective action that is in the best interest of public health if its decision-making process adheres to the principles of good decision quality. The BRFP-recommended model for decision quality includes six specific elements. If the manufacturer evaluates these elements to FDA's satisfaction, then agreement on corrective strategy is more likely. These six elements are:

- Appropriate frame.
- Creative alternatives.
- Relevant and reliable information.
- Clear values and tradeoffs.
- Sound reasoning.
- Commitment to action.

The FDA reviewer should determine whether the manufacturer has considered each of these elements, and has demonstrated that each is well-reasoned and well-supported. Each element is considered in turn, along with some focusing questions. Please note that this list is not all-inclusive. Additional questions and topics may arise, according to the specific situation.

C.3 Checklist elements

C.3.1 Appropriate frame

- Did the manufacturer scope the postmarket problem appropriately?
  - Example: Is this a design issue or a use issue?
  - Example: Is this problem specific only to this device, or to a family of devices?

» Did the manufacturer include appropriate subject matter experts?
  - Example: Have clinicians, engineers, patient advocates and others with understanding of the product and its use provided relevant input?
» Did the manufacturer identify a suitable precedent recall with similar benefit-risk profile? If so, what are the similarities and differences between the current situation and the precedent?
  - Examples: The anatomic area of use, the identified risk, and/or user workarounds might differ between the newly identified postmarket issue and those of the precedent.

C.3.2 Creative alternatives

» What specific alternatives were considered?
  - If only one alternative was considered, is any justification given why other alternative(s) was/were eliminated from consideration?
  - If more than one alternative was considered, did the manufacturer discuss how these alternatives were generated?
» What was the process by which the manufacturer accepted or excluded alternatives?
  - A brief discussion of how the company identified alternatives demonstrates that it was thoughtful and attempted to find a rich set of alternative actions based on fact, reason and experience.
    – Example: A chosen strategy might not reach every user, but it would avoid severe economic stress to the company, which might make the product unavailable.
    – Example: Patients may accept a higher risk than originally thought if the therapy remained available.
» Was a combination of actions considered?
  - Example: Instead of evaluating only market removal, perhaps the manufacturer considered a short-term action, such as notification, plus a long-term action, such as design modification. What tools did the manufacturer use to help it brainstorm or otherwise identify potential alternatives?
    – Examples of tools: Fault trees, event trees, strategy tables.

C.3.3 Relevant and reliable information

» Were the firm's information sources appropriate, reliable, bias-free and/or validated?
  - Examples: Information might come from engineering/R&D, clinical, quality, regulatory, literature, similar experiences/precedents, both internal and external to the manufacturer, outside experts, advisory boards.
» Did the manufacturer construct a model for device failure and impact?
  - Did the manufacturer sufficiently explore potential failure modes?
  - Did the manufacturer consider the likelihood of these modes?
  - Did the manufacturer consider the consequences of each mode? Did it incorporate this understanding into consideration or modeling of the consequences of each alternative under consideration?
    – Examples of modeling tools: Risk tables, probability models, relevance diagrams.
» How was uncertainty represented?
  - Were probabilities assessed?
  - Did the manufacturer attempt to minimize bias when accepting and incorporating information? How was bias managed?
» Were business/market considerations included?
» Were shortages or deprivation of therapy included?
» Was any model discussed with FDA previously? Were recommendations or suggestions incorporated?

C.3.4 Clear values and tradeoffs

- Did the manufacturer evaluate the consequences of the alternatives in a way consistent with protecting public health?
- How did the manufacturer value the consequences of the corrective strategies under consideration?
  - Examples of consequences: Mortality, morbidity, inconvenience, loss of dignity, cost to the health care system, cost to the manufacturer, patient preferences.
  - Did the manufacturer quantify these?
    - Examples of quantifications: Quality-adjusted life years (QALYs), micromorts, economic costs to the health care system and the firm.
- Has the manufacturer discussed these components of its strategy with FDA previously? Has it incorporated any suggestions or criticisms?

C.3.5 Sound reasoning

- Has the manufacturer attempted to rank the model components? What does it rank most important and why?
  - Example: Did the manufacturer perform a sensitivity analysis based on the model inputs (mortality, device availability, failure mode, etc.)?
  - Example: Did the manufacturer use tornado diagrams to display input influences and rank them?
- Has the manufacturer attempted to simplify the model by removing components of little or no impact?
- Has the manufacturer identified and attempted to quantify uncertainty in the model inputs?
  - Example: Are ranges put around possible values, such as likelihood of specific modes of failure or likelihood of certain injuries?
- Has the manufacturer identified specific inputs that should be studied further, in order to better define them and reduce uncertainty?
  - Example: Did the manufacturer perform mechanical failure analyses on representative samples of the device, in order to determine more precisely the likelihood of a specific failure mode?
- Has the manufacturer offered evidence of a dialogue between decision makers and data and modeling experts, to be sure that the correction strategy has been reviewed from all angles?

C.3.6 Commitment to action

- Has the manufacturer included associates who will implement the corrective action in the decision-making process?
- Has the manufacturer detailed specific corrective action(s) and a timeline for those action(s)?
- Has the manufacturer detailed which business units and/or personnel will be responsible for carrying out those actions?
- Has the manufacturer offered contingency plans that allow for unforeseen/unusual events, or for evidence that assumptions driving the decision are incorrect?

Annex D:
Examples

D.1 Introduction

This annex contains several examples constructed to illustrate the proposed framework for incorporating benefit-risk assessments into the correction and removal decision-making process described in this report. The examples are hypothetical, but are based on the real-world experience of the industry members of the AAMI/FDA Ad Hoc Risk Working Group. They are not necessarily accurate assessments of the current premarket and postmarket requirements for managing corrections or removal events. These examples are illustrative of a proposed regulatory paradigm that does not exist at this point and has the potential to be in conflict with the current regulatory paradigm.

Examples 1 through 4 were created around a single scenario to illustrate the application of the process steps in Figure 1. Examples 5 through 11 each contain multiple scenarios intended to illustrate the recall classification decision process steps in Figure 2.

The first part of each example provides some background on the example device, outlining its intended use and describing in broad terms the issue that has come to the manufacturer's attention. The example then presents one or more scenarios, and describes how the manufacturer might react to that scenario, following the process steps in this report. Each scenario is organized into several parts, following the sections of this report. They are:

Escalation and assessment—Corresponding to Section 2, this step determines whether the evaluation of the initiating device event, either in terms of a potential change in the established risk assessment, or device benefit relative to that described in the Design History File (DHF) and the FDA approved labelling at the time of product launch (or most recent update), supports continuing with a postmarket benefit-risk assessment. For purposes of these examples, that answer is always yes.

Postmarket risk and benefit assessment—Corresponding to Section 3, the manufacturer gathers data (see Annex A), reviews the risk management file, and analyzes the circumstances associated with the scenario to determine whether: the risk is known and within established parameters; is previously unknown; or has become unacceptable because it does not meet the manufacturer's criteria for risk acceptability. Although not always appropriate, the manufacturer may need to assess whether the probable benefit(s) from using the medical device has changed as a result of the event under investigation. In any case, the manufacturer needs to document the results of the investigation and may need to update the risk management file.

Recall decision: Corresponding to Section 4, the manufacturer needs to determine whether the product is violative because it fails to satisfy of one or more of the requirements in the FD&C Act [45] or the associated regulations. The recall decision needs to be based on the legal/regulatory conclusion that the product is violative taking full account of the requirements set forth in 21 CFR Part 7 [37] and Part 806 [40]. Even if the medical device is not violative, the manufacturer may choose, in the interest of the patient, to take some remedial actions that it does not have to report to the FDA.

If the medical device is violative, the manufacturer needs to assess likelihood of serious health consequences, up to and including death. FDA would likely take legal action if the manufacturer did not voluntary initiate a reportable recall, and is likely to classify the resulting field action as either a Class I or Class II recall.

Even if the violation does not result in the increased likelihood of serious health consequences, the manufacturer may still be faced with a technical violation of the FD&C Act or the associated regulations. In this case, the FDA may still take legal action if the manufacturer did not voluntarily take steps to correct the violation. The FDA is likely to classify the resulting field action as a Class III recall.

Finally, if the issue is a minor technical violation, the FDA might consider not taking legal action. The manufacturer may institute a non-reportable field action or may document a "no action" decision, following the processes set out in their quality management system. The documentation supporting these decisions is subject to review by FDA during an inspection.

Recall strategy: Corresponding to Section 5.1, the manufacturer has determined that recall is necessary. The manufacturer then has to develop a recall strategy, which is a planned course of action to be taken in conducting the specific recall.

Evaluate recall strategy: Corresponding to Section 5.4, the manufacturer has to determine whether a particular recall strategy is appropriate to the individual circumstances that led to the recall decision, if there is a potential for the recall to result in an adverse public health issue. For instance, if a particular recall strategy could result in an adverse health issue(s), such as a medical device being unavailable when there is no alternate product available for treatment (a shortage situation), then the manufacturer might need to do additional assessments of risk and benefit. It is during this analysis that the manufacturer might consider using the Decision Quality (DQ) approach described in Annex B.

Communicate with FDA: Corresponding to Section 6.2, the manufacturer may have some concern about how the FDA will view the proposed recall strategy. This could be true particularly if the proposed strategy involves leaving a violative product on the market while corrective action is being implemented because of potential adverse public health issue(s). In this case, the manufacturer may wish to open a dialogue with the FDA prior to committing to a particular recall strategy.

D.2 Example 1—Reusable Medical Device

D.2.1 Background

A manufacturer is making a type of medical device that is reusable, with a certain service life and use life. Some products may have been in the field for more than 18 years. The medical device has a screen that displays certain critical parameters. The medical device has a specified life and requires regular maintenance. In this case, the risk may increase when the medical device ages beyond its specified life and/or necessary maintenance is missed.

D.2.2 Scenario 1—Scenario with risk, non-violative product, no recall

Escalation and assessment: Recently, the manufacturer receives an increasing rate of complaints regarding unstable, fading, or missing segments in the screen readings for certain critical parameters.

Postmarket risk and benefit assessment: The missing-segment screen reading may cause misreading and or misdiagnosis—a serious hazardous situation. It was determined that the root cause is a typical electric component aging issue. The products associated with complaints are already out of the manufacturer's warranty and/or product-specified use life in the labeling, by a large margin (e.g., 15 years).

The manufacturer reviewed the original design, manufacturing, labeling data, and conducted a new investigation. It was determined that this is an aging issue. The display cannot be repaired due to discontinued parts. The only option is to replace the whole display system.

Recall decision: Non-violative product. FDA would not consider taking action because no technology will allow a manufacturer to make products that last forever. Given an aging issue for a product that meets the original product design/use/service life, the manufacturer could consider potential non-reportable actions, including:

- Not doing a field action (i.e., no recalls, no communications to users) as the product is non-violative and well past its expected service life; or
- A non-reportable field action to communicate to users, reminding them to follow the original instructions for use regarding the service life of the device, the potential safety issues, and the potential solution of replacing the unit or replacing the component.

Recall strategy: Not required.

Evaluate recall strategy: No further analysis required.

Communicate with FDA: No discussion with FDA is required.

D.3 Example 2—A Biological Indicator

D.3.1 Background

A manufacturer is making a type of biological indicator used by healthcare providers to produce evidence that a sterilization process has achieved the required sterilization assurance level for the surgical environment. During a CAPA investigation, deterioration of the machinery used to manufacture the biological indicator was found. A recall was initially conducted, but a product shortage occurred. A subsequent communication between the manufacturer and FDA resulted in a new strategy for the recall and the new product registration.

D.3.2 Scenario 2—Scenario with unacceptable risk, violative product, recall, conversation with FDA

Escalation and assessment: The manufacturer identified the root cause of product issues as the deterioration of the manufacturing machinery.

Postmarket risk and benefit assessment: The deterioration of the manufacturing machinery may lead to inaccurate assessments of whether the required sterility assurance level was attained.

Recall decision: Violative product. FDA would consider taking legal action if the manufacturer did not address the violation.

Recall strategy: As the medical device is violative and reporting is required, the manufacturer decides to initiate a reportable field action to remove products in the field and fix the manufacturing machinery issues for future products.

Evaluate recall strategy: The manufacturer determined that there was the potential for decreased production for some time with reduced availability of the biological indicators (i.e., a product shortage). It was understood the recall was necessary and may bring more benefits to the patients, due to infections caused by inadequate sterilization.

Communicate with FDA: The manufacturer discusses the strategy with the FDA to confirm that this solution is in the best interest of patients. However, a few months later, the manufacturer became aware that some surgeries were being delayed due to the lack of biological indicators. The manufacturer did not expect to return to full production for some time. There was a greater risk of adverse public health issues (including delayed surgeries, prioritization of critical surgeries, and rationing of indicators) versus the risk of using instruments without confirmation of sterility. The manufacturer proposed a temporary change in the instructions for use that would allow monitoring of fewer loads. After review of data from the manufacturer, FDA agreed that the risk of less frequent testing was acceptable until adequate supplies of the indicator were available. FDA agreed to the change in the instructions for use to allow monitoring of fewer loads until the manufacturer was able to return full production.

One of the challenges faced was coordination of response to the shortage between offices. Another challenge was timely review of additional scientific data to support the manufacturer's proposed strategy.

D.4 Example 3—A Class III Implantable Device

D.4.1 Background

A manufacturer is making a Class III implantable device for critically ill patients. Complaints from the field may indicate some malfunction of the device. Because few options are available for the patients if the product is removed from the market, a strategy is developed and communicated to FDA.

D.4.2 Scenario 3—Scenario with unacceptable risk, violative product, recall, conversation with FDA

Escalation and assessment: The manufacturer received three field complaints related to a malfunction. Medical Device Reports (MDRs) were filed for the malfunctions. Loss of blood was reported, but no serious injuries occurred.

Postmarket risk and benefit assessment: The failure rate of 0.08% exceeds the expected rate of 0.01%. The root cause was found to be design-related. The investigation determines it is a low level, randomly occurring component failure that cannot be confirmed while it is happening, partially due to the low occurrence rate. A benefit-risk assessment of explanting devices was conducted with the conclusion that product removal (device explant) is not justified.

Recall decision: Violative product. FDA would consider taking legal action if the manufacturer did not address the violation.

Recall strategy: As the medical device is violative and reporting is required, the manufacturer needs to initiate a field action. Actions the manufacturer could consider include removal of product from the field or issuing a communication to the field to alert the users of the low frequency malfunction. The field communications

need to take into account the risks associated with unnecessary explants. The manufacturer decides to initiate a reportable field action to alert users of the low frequency malfunction. The manufacturer would continue monitoring the complaints and trending in the field.

Evaluate recall strategy: The manufacturer has determined that an adverse public health issue could exist if the medical device were removed from the market, because it will result in cancellation of surgeries for hundreds, perhaps thousands, of critically ill patients, and leave them with few options.

Communicate with FDA: The manufacturer discusses the proposed notification with the FDA to confirm that this solution is in the best interest of patients. FDA may agree with the manufacturer on an alert to users, rather than removing the medical device from the market, assuming there are no other options to prevent a product shortage.

D.5 Example 4—A Class II IVD Device

D.5.1 Background

A manufacturer is making a Class II glucose monitoring system. By design, the glucose value will show "HI" (or "High") when the actual value is greater than 600 mg/dL. For example, if an actual glucose value equals 599 mg/dL, then the glucose meter will display "599 mg/dL". If an actual value is equal to 601 mg/dL, the glucose meter will display "HI."

Due to software issues, the device is not performing according to its specification at the high level of glucose.

D.5.2 Scenario 4—Scenario with unacceptable risk, violative product, recall, conversation with FDA

Escalation and assessment: The manufacturer identified a software issue during internal testing. The postmarket data shows there are no complaints from the field. The software issue is causing a 25% low bias at values greater than 700 mg/dL level. The 25% bias is higher than the product specification of 20%. For example, the display may be "525 mg/dL" instead of "HI" when the glucose value is actually 700 mg/dL. A glucose value of greater than 700 mg/dL is a severe condition and affects the brain or other body functions with obvious symptoms. The patient would have been treated based on the symptoms without relying on or solely relying on the testing value of > 700 mg/dL.

Postmarket risk and benefit assessment: The severity of harm of low bias is estimated to be serious if a patient's decision to take medicines may be affected by the value. However, in this case, 525 mg/dL would require medical treatment, such as insulin injection, as it is well above the normal range of glucose value. The manufacturer decides the probability of occurrence (P_1: probability of a patient with actual glucose values greater than 700 mg/dL) is low (e.g., 0.1%), and probability of harm (P_2: a patient may be harmed due to insufficient medical treatment, e.g., insulin injection) is remote. The overall probability is very low; however, the glucose monitoring system is not meeting the product specification.

NOTE: This example contains hypothetical estimates of the patient population.

Recall decision: Violative product. FDA would consider taking legal action if the manufacturer did not address the violation.

Recall strategy: As the medical device is violative and reporting is required, the manufacturer is considering two recall strategies:

- **Strategy 1—**Advise the users to immediately cease using the device and wait for a replacement meter to arrive, or
- **Strategy 2**—Advise the users to continue using the device, but to be mindful of this issue when the test value is > 525 mg/dL; advise to retest after taking medical treatment, such as insulin injection; and the manufacturer will send the replacement meter with the software issue corrected.

For recall Strategy 1, the software fix, manufacturing and shipping of the new meter, takes a minimum of two months. It was estimated that about 10% of the population among those who stop using the devices would not be able to or willing to get alternative testing. The severity of not conducting routine testing for certain patients is evaluated to be critical (i.e., more than serious). For recall Strategy 2, the manufacturer determines that patients would have taken necessary medical treatments when the glucose value is greater than 525 mg/dL; and the suggested follow-up retest would confirm the effectiveness of the treatment and further reduce the risks. The manufacturer determines that the temporary use of the affected devices with further instructions would present low risks to the patients. Therefore, the manufacturer chooses Strategy 2: communication first and replacement later.

Evaluate recall strategy: In this case, there are no adverse public health issues because of a shortage of glucose monitoring systems (i.e., there are plenty of different glucose meters available). However, some users may not always be ready or willing to go to the store and get a new meter.

Communicate with FDA: The manufacturer discusses the two-step strategy with the FDA to confirm that this solution is in the best interest of patients.

D.6 Example 5—Class 1 Medical Device—Surgical Tray

D.6.1 Background

A company manufactures reusable surgical trays that are intended for the storage and transportation of reusable surgical instruments. The trays and the instructions for use are labeled "For transportation only. Not intended for sterilization or for maintaining sterility." The company has become aware that some hospitals are using the trays for holding instruments during steam sterilization. An instrument that is inadequately sterilized can become the source of cross-contamination or cross-infection when used in multiple surgical procedures.

D.6.2 Scenario 5 (a)—Scenario with acceptable risk, non-violative product, no recall

Escalation and assessment: The manufacturer has not received any complaints to indicate there have been any reports of inadequate sterilization cycles (i.e., cycle failures) or adverse events (infections) caused by inadequate sterilization of instruments in the subject instrument trays.

Postmarket risk and benefit assessment: The manufacturer reviews the risk management file and determines that this cross-infection hazard was identified. As a control measure, the product labeling stated the intended use as "For transportation only. Not intended for sterilization or for maintaining sterility." There is no change in the assessment of adverse consequences from the established risk assessment documented in the risk management file.

There is little or no increase in risk and the benefit of the use of the surgical tray under the FDA-cleared indications for use has not changed. The investigation file documents that:

» The benefit of the surgical tray when used according to the FDA-cleared indications for use remains unchanged.
» The risk remains acceptable.

Recall decision: Non-violative product. FDA would not consider taking legal action for this use, which the manufacturer was not promoting. Trending and monitoring are deemed appropriate. No reportable recall is needed.

Recall strategy: Not required.

Evaluate recall strategy: No further analysis required.

Communicate with FDA: No discussion with FDA is required.

D.6.3 Scenario 5 (b)—Scenario with acceptable risk, minor violation, no recall

Escalation and assessment: The manufacturer has not received any complaints to indicate inadequate sterilization cycles (i.e., cycle failures) or adverse events (infections) caused by inadequate sterilization of instruments in the subject instrument trays.

The company reviews the risk management file and determines that this cross-infection hazard was identified. The company determined that the tray is clearly labeled as not intended to be used for sterilization. However, the instructions for use did not contain the necessary warning.

Postmarket risk and benefit assessment: The reported event does not change the assessment of adverse consequences from the established risk assessment documented in the risk management file. The benefit of the use of the surgical tray under the FDA-cleared indications for use has not changed. The investigation file documents that:

» The benefit of the surgical tray when used according to the FDA-cleared indications for use remains unchanged.
» The risk remains acceptable.

Recall decision: Violative product, minor violation. However, FDA would probably not consider taking legal action. However, potential action for the manufacturer to consider would include issuing a letter to customers to identify the issue and/or correcting the instructions for use. The manufacturer's actions are not required to be reported under 21 CFR Part 806 [40]; however, internal documentation is maintained.

Recall strategy: Not required.

Evaluate recall strategy: No further analysis required.

Communicate with FDA: No discussion with FDA is required.

D.6.4 Scenario 5 (c)—Scenario with unacceptable risk, violative product, recall

Escalation and assessment: The manufacturer received several complaints of reported inadequate sterilization cycles (i.e., cycle failures). One hospital reported several cases of postoperative surgical infections that appear to be linked to waterborne organisms, suggesting inadequate sterilization of instruments in the subject instrument trays. The patient was promptly treated and recovered.

The company reviews the risk management file and determines that this hazardous situation and cross-infection harm were identified. However, trays manufactured from the same batches associated with the recent complaints identified a manufacturing error, revealing that the warning labels were not applied. The manufacturer updates the risk management file.

Postmarket risk and benefit assessment: The reported event does change the assessment of adverse consequences from the assessment documented in the risk management file. However, the established risk assessment of the reusable surgical tray has changed, due to this newly identified and confirmed hazardous situation/harm in use. The benefit of the device under the FDA-cleared indication for use has changed. The investigation file documents that:

- The benefit of the surgical tray when used according to the FDA-cleared indications for use has changed.
- The risk is unacceptable.

Recall decision: Violative product. FDA would consider taking legal action if the manufacturer did not address the violation.

Recall strategy: Potential actions for the manufacturer to consider would include a correction or removal. As the medical device is violative and reporting is required, the manufacturer decides to initiate a customer letter and update product labeling. This letter will describe the correction or removal method, as determined by the manufacturer. The manufacturer will also report the recall action in compliance with 21 CFR Part 806 [40].

Evaluate recall strategy: As the proposed recall strategy would not result in a product shortage or use interruption, there would be no adverse public health issue resulting from this recall strategy.

Communicate with FDA: No discussion with FDA is required.

D.7 Example 6—Class I Catheter Accessory: Guidewire

D.7.1 Background

A Class I guidewire intended to be used in gastro-urologic procedures typically consists of two major components: a core wire with an extruded plastic covering over the length of the wire, to provide steerability and ease of advancement; and a tip component, designed for shaping and atraumatic patient contact. These components are typically bonded together using different means of adhesive. Product labeling instructs the user to not advance the guidewire if resistance is met, and to remove/replace if resistance occurs. Risk management documents have identified tip detachment as potentially related to improper user handling, manufacturing damage, and improper adhesive bonding. Potential patient harm probability and severity is identified at specified expected rates for each of these potential failure modes in the established risk assessments. Customer complaint(s) as detailed below were received and escalated to field action decision-making process, based on the manufacturer's predetermined criteria.

D.7.2 Scenario 6 (a)—Scenario with acceptable risk, non-violative product, no recall

Escalation and assessment: The manufacturer receives one complaint noting that the tip of the guidewire was partially detached from the length of the wire. The wire was withdrawn from the patient when resistance to advancement was detected.

Visual examination of the product found that the extruded plastic surface of the wire showed areas of scratched and compressed plastic, possibly due to use error from improper handling. Sampling from same lot did not identify similar damage.

Postmarket risk and benefit assessment: The reported event does not change the assessment of adverse consequences from the established risk assessment documented in the risk management file. The nonconformance is accurately captured in the established risk assessment. The benefit of the use of the guidewire under the

FDA-cleared indications for use has not changed. The investigation file documents that:

- The benefit of the guidewire when used according to the FDA-cleared indications for use remains unchanged.
- The risk remains acceptable.

Recall decision: Non-violative product. FDA would not consider taking action. Trending and monitoring are deemed appropriate. No reportable recall is needed.

Recall strategy: Not required.

Evaluate recall strategy: No further analysis required.

Communicate with FDA: No discussion with FDA is required.

D.7.3 Scenario 6 (b)—Scenario with acceptable risk, non-violative product, no recall

Escalation and assessment: The manufacturer receives numerous complaints noting that the tip of the guidewire was partially detached from the length of the wire when removed from the patient, upon feeling resistance during insertion.

Visual examination of the product found that the extruded plastic surface of the wire showed areas of scratched and compressed plastic. Sampling from the same manufacturing lots identified similar scratched and compressed areas in a portion of the lots. The root cause is identified as attributable to manufacturing process equipment; however, manufacturing was conducted in accordance with the firm's procedures. The guidewires all met the manufacturer's product specifications and performed as intended. The scratches and compressed areas on the devices were considered to represent lot-to-lot variations in the product.

Postmarket risk and benefit assessment: The reported events do not change the assessment of adverse consequences from the assessment documented in the risk management file. The nonconformance is accurately captured in the established risk assessment. There is little or no increase in risk, and the benefit of the use of the guidewire under the current intended use has not changed. The investigation file documents that:

- The benefit of the guidewire when used according to the FDA-cleared indications for use remains unchanged.
- The risk remains acceptable.

Recall decision: Non-violative product. FDA would not consider taking action. However, the manufacturer should consider potential non-reportable actions, such as a corrective action to address the manufacturing equipment defect output rate, while continuing complaint trending and monitoring. No reportable recall is needed.

Recall strategy: Not required.

Evaluate recall strategy: No further analysis required.

Communicate with FDA: No discussion with FDA is required.

D.7.4 Scenario 6 (c)—Scenario with acceptable risk, minor violation, no recall

Escalation and assessment: During the pre-market phase, the manufacturer documented projected adverse event rates attributable to expected potential failure modes. After a year on the market, the reported adverse events for the guidewire are occurring at a rate (3%)above the documented expected rate (2.5%) for a minor-severity patient harm.

Postmarket risk and benefit assessment: The reported occurrence of adverse device events is higher than that projected during the pre-market phase. The investigation file documents that:

- The technical manufacturing defect is slightly higher than expected; however, the severity of the impact on patients (procedural delay) and detectability are unchanged. The slight increase in rate is not significant enough to impact user concern and/or expectations regarding benefit risk profile. No changes are required to the instructions for use and the medical device continues to meet performance specifications for its intended use. No new risk types have been identified and no changes to expected rates of higher-severity harms have occurred.
- The benefit of the guidewire when used according to the FDA-cleared indications for use remains unchanged.

Recall decision: Violative product, minor violation. FDA would probably not consider taking legal action. The manufacturer should take appropriate actions consistent with its quality system. The manufacturer could consider a non-reportable market withdrawal to replace product in the field with new product runs in which the root cause is corrected. This field action is not required to be reported under 21 CFR Part 806 [40], however, internal documentation is maintained.

Recall strategy: Not required.

Evaluate recall strategy: No further analysis required.

Communicate with FDA: No discussion with FDA is required.

D.7.5 Scenario 6 (d)—Scenario with unacceptable risk, violative product, recall, conversation with FDA

Escalation and assessment: In addition to the reported events occurring at a rate (3%) above the documented expected rate (2.5%) for a minor-severity patient harm, three additional complaints were received for a major-severity harm that resulted in severe injuries. The investigation confirmed that the same manufacturing root cause of scratched and compressed plastic on the guidewire caused the higher-severity harm. In this case, this is the only guidewire device cleared for this type of surgery.

Postmarket risk and benefit assessment: The investigation file documents an increase in likelihood to cause adverse health consequences, based on a major (i.e., significant) increase in probability of occurrence in a major-severity patient harm. The benefit of the device under the FDA-cleared indications for use has not changed. Potential action to consider would include a risk management documentation update to include higher occurrence of failure mode. The investigation file documents that:

- The technical manufacturing defect is slightly higher than expected; however, the severity of the impact on patients (i.e., procedural delay) and detectability are unchanged. The slight increase in rate is not significant enough to impact user concern and/or expectations regarding benefit risk profile. No changes are required to the instructions for use and the medical device continues to meet performance specifications for its intended use. No new risk types have been identified and no changes to expected rates of higher-severity harms have occurred.
- The benefit of the guidewire when used according to the FDA-cleared indications for use remains unchanged.

Recall decision: Violative product. FDA would consider taking legal action if the manufacturer did not address the violation.

Recall strategy: As the medical device is violative and reporting is required, the manufacturer decides to initiate a reportable field action to address the medical device not meeting its specifications and the associated severe risk. The manufacturer implements a product removal or correction by alerting customers to perform a visual check of the guidewire prior to use, and to request replacements as necessary.

Evaluate recall strategy: As this is the only guidewire device cleared for this type of surgery, removal of the device would delay surgery until an alternative was available. As the removal action could result in adverse public health issue(s), further analysis is required.

Communicate with FDA: The manufacturer discusses the strategy with the FDA to confirm that this solution is in the best interest of patients.

D.8 Example 7—Class I Software—Powered Exerciser

D.8.1 Background

A Class I powered exercise bicycle is used as therapy for several orthopedic conditions as well as general physical therapy. The bicycle is intended to be used under licensed therapist supervision and includes programmable software to program speed(s), elevation(s) or selection(s) of pre-programmed scenarios. The manufacturer receives several customer complaints that the exercise bike, which can be used in a forward or backwards motion in several speeds, is operating at a speed that was not selected/programmed. The speed when the equipment is malfunctioning is typically three times the expected speed. Customer complaint(s) were escalated to field action decision making process based on the manufacturer's predetermined criteria (e.g., not meeting specifications).

D.8.2 Scenario 7 (a)—Scenario with acceptable risk, non-violative product, no recall

Escalation and assessment: The use of the medical device is determined to be used within intended use, including instructed proper supervision. However, the root cause is identified as a result of use error. The user is not following instructions to stop pedaling while selecting/programming speed(s) on the bicycle. No injuries have been reported.

Postmarket risk and benefit assessment: The reported events (foreseeable misuse and potential patient harm—severe injury) do not change the assessment of adverse consequences from the established risk assessment documented in the risk management file. The nonconformance is accurately captured in the established risk assessment. The investigation file documents that:

- The benefit of the powered exerciser when used according to the FDA-cleared indications for use remains unchanged.
- The risk remains acceptable.

Recall decision: Non-violative product. FDA would not consider taking action. Trending and monitoring are deemed appropriate. No reportable recall is needed. However, the manufacturer could consider potential non-reportable actions, such as a safety alert to customers, to reinforce the instructions for use, and a future design change (product enhancement) to the software, to not allow selecting/programming speeds while pedaling.

Recall strategy: Not required.

Evaluate recall strategy: No further analysis required.

Communicate with FDA: No discussion with FDA is required.

D.8.3 Scenario 7 (b)—Scenario with unacceptable risk, violative product, recall, no availability concerns

Escalation and assessment: The exercise bike is determined to be used within intended use, including instructed supervision. The root cause is identified as a software anomaly that manifests itself when the exercise bike is pedaled backwards. The exercise bike automatically switches to an incorrect programmed speed after the patient begins pedaling. Three injuries have been reported (fractures).

Postmarket risk and benefit assessment: The risk management file did have the risk type (wrong selected/programmed speed) and patient harm (fractures) identified, but not, however, as due to software failure. As a result of root cause being identified as software anomaly, the assigned probability of occurrence rate is no longer applicable. The investigation file documents that:

- The benefit of the powered exercise bike when used according to the FDA-cleared indications for use remains unchanged.
- The risk is unacceptable based on increased likelihood of adverse health consequences due to a software anomaly not currently captured in the product labeling.

Recall decision: Violative product. FDA would consider taking legal action if the manufacturer did not address the violation.

Recall strategy: Potential actions for the manufacturer to consider would include a communication alerting customers to not allow user to pedal backwards until the correction (software change) has been implemented. Temporary warning labels could also be sent to customers to reemphasize the hazard associated with the anomaly.

Evaluate recall strategy: As the proposed recall strategy would not result in a product shortage or use interruption, there would be no adverse public health issue resulting from this recall strategy.

Communicate with FDA: No discussion with FDA is required.

D.9 Example 8—Class II Software—IVD Chemistry Analyzer System

D.9.1 Background

A Class II IVD automated and random access clinical chemistry system is used to measure chemical analytes (such as glucose electrolytes, kidney function, cardiac enzymes, and liver enzymes in blood serum) utilizing photometric and potentiometric technology. The system can simultaneously process samples and analyze and manage data. The system is typically utilized in a clinical laboratory of a hospital or medical clinic or in a reference laboratory. Intended users for the system are trained clinical laboratory technologists and technicians. Analyte results from the system are used by physicians or clinicians to help diagnose illnesses and diseases and determine therapy for patients.

The system consists of:

- A data center that provides the human interface and online operations manual;
- Analyzer module(s) that perform all sample processing, from aspiration to result generation; and
- A transport module that delivers specimens in sample tubes from the loading area to the processing area.

Specimens are aliquoted into sample tubes that contain customer-generated barcode labels for specimen identification. The sample tubes are loaded into transport carriers, then placed on the transport loader and transferred to the transport module for automated processing on an analyzer module. If a sample tube does not have a barcode or if a barcode label is not properly read by the system, the analyzer will

process the sample tube, generate results, and system software will assign a specimen identifier of "no label" to the result record. The operations manual instructs users to not report an analyte result with a specimen identifier of "no label."

The manufacturer received several customer complaints against the chemistry analyzer system for reporting erroneous results. Customer complaint(s) were escalated to a field action decision-making process based on company predetermined criteria (e.g., not meeting specifications).

D.9.2 Scenario 8 (a)—Scenario with acceptable risk, non-violative product, no recall

Escalation and assessment: The IVD chemistry analyzer system is determined to be used within its intended use and included adequate instructions for use. However, the root cause is identified as use error. The user was not following instructions to not report an analyte result with a specimen identifier of "no label" and had manually entered specimen identifiers for several tubes that were identified as "no label." Lab staff reported that the barcode label printer was overdue for maintenance. No injuries were reported.

Postmarket risk and benefit assessment: The reported events (incorrect results and potential patient harm—severe injury) do not change the assessment of adverse consequences from the established risk assessment documented in the risk management file. The nonconformance is accurately captured in the established risk assessment. The investigation file documents that:

- The device was operating within specifications.
- The benefit of the chemistry analyzer when used according to the FDA-cleared indications for use remains unchanged.
- The risk remains acceptable.

Recall decision: Non-violative product. FDA would not consider taking action. Trending and monitoring are deemed appropriate.

Recall strategy: Not required.

Evaluate recall strategy: No further analysis required.

Communicate with FDA: No discussion with FDA is required.

D.9.3 Scenario 8 (b)—Scenario with unacceptable risk, violative product, recall, conversation with FDA

Escalation and assessment: The IVD chemistry analyzer system is determined to be used within its intended use as described in the instructions for use. The root cause is identified as a software anomaly that allows results from one sample to be reported for a different sample. After two or more consecutive "no label" samples, the software reports erroneous results for the next sample that has a valid specimen identification. Two injuries have been reported for delayed treatment, and three injuries have been reported for unnecessary treatment.

Postmarket risk and benefit assessment: The risk management file did have the risk type (sample mis-association) and patient harm (injury to patient due to incorrect patient results) identified due to a software failure. As a result of the number of incidents reported for this issue, the assigned probability of occurrence of severe patient harm is no longer applicable, and is increasing. The investigation file documents that:

- The benefit of the chemistry analyzer system when used according to the FDA-cleared indications for use remains unchanged.

» The risk is unacceptable based on increased likelihood to cause adverse health consequences (an increase in probability of occurrence of severe patient harm) due to a software anomaly not currently captured in the product labeling.

Recall decision: Violative product. FDA would consider taking legal action if the manufacturer did not address the violation.

Recall strategy: As the medical device is violative and reporting is required, the manufacturer decides to implement a correction by alerting customers to check integrity of barcode samples and repeat any samples that followed two consecutive "no label" barcode reads, until the software change has been implemented.

Evaluate recall strategy: The benefit from using the device and mitigated risk supports the decision to apply a temporary correction and to not remove the devices.

Communicate with FDA: The company discusses the temporary correction with the FDA to confirm that this solution is in the best interest of patients.

D.10 Example 9—Surgical Navigation Device

D.10.1 Background

A company manufactures surgical navigation devices that are used to enable or improve placement of surgical instruments during procedures. One of its devices is designed and intended specifically for sinus surgery.

The manufacturer received three complaints that the navigation device had intermittent performance problems, but in all cases the procedure was completed as intended.

An extensive investigation did not reveal any device malfunction, but discovered that in each case, a specific light, made by a different manufacturer and intended for use in surgical suites, was placed in the surgical field within two feet of the surgical navigation device.

D.10.2 Scenario 9 (a)—Scenario with acceptable risk, non-violative product, no recall

Escalation and assessment: The manufacturer procured the specific light and ran tests. It confirmed that electrical interference was being observed above what would normally be expected from an appropriately shielded light, and that this electrical interference was causing the navigation error. Testing confirmed that the surgical navigation device is performing as intended and meeting all required product performance specifications.

Postmarket risk and benefit assessment: The manufacturer reviewed the risk management file and determined that electrical interference causing a navigation error had been identified. As a control measure current labeling for the navigation equipment includes a general instruction making users aware that possible interference may occur when electronic equipment is used in or near the surgical field. The investigation file documents that:

» The benefit of the surgical navigation device when used according to the FDA-cleared indications for use remains unchanged.
» The risk remains acceptable.

Recall decision: Non-violative product. FDA would not consider taking action. However, the manufacturer could consider potential non-reportable actions, including notifying the light manufacturer, and/or sending a safety alert to customers to reinforce the instructions for use.

Recall strategy: Not required.

E**valuate recall strategy:** No further analysis required.

Communicate with FDA: No discussion with FDA is required.

D.10.3 Scenario 9 (b)—Scenario with acceptable risk, minor violation, no recall

Escalation and assessment: The manufacturer procured the specific light and ran tests. It confirmed that electrical interference was being observed above what would normally be expected from an appropriately shielded light, and that this electrical interference was causing the navigation error. Testing confirmed that the surgical navigation device is performing as intended and meeting all required product performance specifications.

However, during testing, a manufacturing issue with the surgical navigation devices was identified. The manufacturing issue related to an assembly error that impacted the effectiveness of the electrical shielding of the surgical navigation device for a particular product.

Postmarket risk and benefit assessment: The manufacturer reviewed the risk management file and determined that electrical interference causing a navigation error had been identified. No additional complaints were received, and based on the failure modes replicated during testing, no adverse health consequences are expected. Additionally, a Health Hazard Evaluation was conducted and no additional clinical hazards were identified. The investigation file documents that:

- The benefit of the surgical navigation device when used according to the FDA-cleared indications for use remains unchanged.
- There is no increase in likelihood to cause adverse health consequences based on a minor (i.e., non-significant) increase in probability of occurrence of a minor-severity patient harm and no change in probability of a major-severity harm.

Recall decision: Violative product. However, FDA would probably not consider taking legal action, although the medical device is not performing as intended. Potential action for the manufacturer to consider would include product removal for the affected products, or a customer notification to identify the issue and describe corrective actions. As the risk assessment has determined there is no increased likelihood of adverse health consequences , the manufacturer's actions are not required to be reported under 21 CFR Part 806 [40]; however, internal documentation is maintained.

Recall strategy: Not required.

E**valuate recall strategy:** No further analysis required.

Communicate with FDA: No discussion with FDA is required.

D.10.4 Scenario 9 (c)—Scenario with unacceptable risk, violative product, recall

Escalation and assessment: The manufacturer procured the specific light and ran tests. It confirmed that electrical interference was being observed above what would normally be expected from an appropriately shielded light, and that this electrical interference was causing the navigation error. Testing confirmed that the surgical navigation devices are not performing as intended and are not meeting all required product performance specifications.

Postmarket risk and benefit assessment: The manufacturer reviewed the risk management file and determined that electrical interference causing a navigation error had been identified. However, during the investigation of the manufacturing

assembly issue, six additional complaints were received. In two complaints, the device malfunctioned in a way that caused the improper placement of instruments and resulted in patient injuries. The investigation file documents that:

- The benefit of the surgical navigation when used according to the FDA-cleared indications for use has changed.
- Complaints and injuries have been reported, and the medical device is not performing as intended.
- The risk is unacceptable due to this newly confirmed hazardous situation/harm in use.

Recall decision: Violative product. FDA would consider taking legal action if the manufacturer did not address the violation.

Recall strategy: Potential actions the manufacturer could consider would include a correction by alerting customers of the shielding issue, with mitigation steps outlined.

Evaluate recall strategy: No further analysis required.

Communicate with FDA: No discussion with FDA is required.

D.11 Example 10—Prescription Glucose Meter

D.11.1 Background

A company manufactures a glucose meter that is intended for home use and self-monitoring of a patient's glucose level. The manufacturer's labeling contains warnings about interfering substances, proper handling and storage instructions for glucose strips, and addresses error codes. Incorrect glucose values may lead to serious adverse health consequences or death.

D.11.2 Scenario 10 (a)—Scenario with acceptable risk, non-violative product, no recall

Escalation and assessment: Complaints were reported that some customers were receiving no results or error messages, indicating that the device was unable to produce a value. Upon further investigation, the manufacturer has determined that users were not following the instructions for storage of the glucose strips, and the device was functioning properly. The company elects to reiterate its current labeling and warnings. It also reiterates its warnings regarding error codes and how to address them.

Postmarket risk and benefit assessment: The manufacturer reviews the risk management file and determines that the failure mode/rate and potential patient harm are identified in the established risk assessment. No new hazards have been identified. This foreseeable misuse is accurately captured in the established risk assessment. The investigation file documents that:

- The benefit of the glucose meter when used according to the FDA-cleared indications for use remains unchanged.
- The risk remains acceptable.

Recall decision: Non-violative product. FDA would not consider taking action. Trending and monitoring are deemed appropriate. However, the manufacturer could consider potential non-reportable actions, such as issuing a safety alert to customers to reinforce the instructions for use.

Recall strategy: Not required.

Evaluate recall strategy: No further analysis required.

Communicate with FDA: No discussion with FDA is required.

D.11.3 Scenario 10 (b)—Scenario with unacceptable risk (cause: poor instructions), violative product, recall

Escalation and assessment: The manufacturer receives numerous complaints that the glucose meter is giving erroneous results due to interfering substances. A list of interfering substances is included in the current labeling. However, the instructions for retesting and when to see a physician are misleading.

An extensive investigation was conducted and product testing identified similar erroneous results. The root cause is identified as inadequate troubleshooting instructions. The current instructions list recommendations for the user to follow. However, the steps are not intended to be followed sequentially.

Postmarket risk and benefit assessment: The manufacturer reviews the risk management file and determines that the complaint type (failure mode/rate and potential patient harm) is not identified in the established risk assessment. The investigation file documents that:

- The benefit of the glucose meter when used according to the FDA-cleared indications for use remains unchanged.
- The risk is unacceptable because this newly identified failure mode/rate and potential patient harm is not identified in the established risk assessment.

Recall decision: Violative product. FDA would consider taking legal action if the manufacturer did not address the violation.

Recall strategy: As the medical device is violative and reporting is required, the manufacturer decides to initiate a reportable field action to address the inadequacies in the labeling. The manufacturer will communicate to customers and provide new labeling.

Evaluate recall strategy: As the proposed recall strategy would not result in a product shortage or use interruption, there would be no adverse public health issue resulting from this recall strategy.

Communicate with FDA: No discussion with FDA is required.

D.11.4 Scenario 10 (c)—Scenario with unacceptable risk (deaths; cause: software), violative product, recall

Escalation and assessment: The manufacturer receives numerous complaints that glucose meters were not producing error codes for falsely elevated patient results, which led to multiple serious adverse health consequences and deaths. The potential severity of harm to patients is increased. An extensive investigation was conducted and the manufacturer finds that the latest software release for certain glucose meters has caused the problem.

The root cause is identified as a software issue. Specifically, the glucose meter does not provide the expected warnings. Manufacturing was conducted in accordance with the firm's procedures. The product does not continue to meet previously established performance specifications.

Postmarket risk and benefit assessment: The manufacturer reviews the risk management file and determines that the complaint type (failure mode/rate and potential

patient harm) is not identified in the established risk assessment. The investigation file documents that:

- The benefit of the glucose meter when used according to the FDA-cleared indications for use remains unchanged.
- The risk is unacceptable because of an increase in likelihood to cause adverse health consequences, based on a major patient harm and an increase in probability of that harm.
- The risk management file is updated to include this newly identified failure mode/rate and potential patient harm.

Recall decision: Violative product. FDA would consider taking legal action if the manufacturer did not address the violation.

Recall strategy: As a software patch is available to correct the software problem, the manufacturer decides to undertake a correction. As the medical device is violative and reporting is required, the manufacturer decides to issue a communication with recommendation that the software patch be installed or the meter be returned for a replacement.

Evaluate recall strategy: As the proposed recall strategy would not result in a product shortage or use interruption, there would be no adverse public health issue resulting from this recall strategy.

Communicate with FDA: No discussion with FDA is required.

D.12 Example 11—Implantable Cardiac Pacemaker

D.12.1 Background

A company manufactures an implantable cardiac pacemaker that is intended as a substitute for the heart's intrinsic pacing system, to correct both acute and chronic cardiac rhythm disorders. The manufacturer's labeling claims that the typical life of this type of battery is 60 months. Internal validation supports that battery failure does not occur until 84 months. A failing pacemaker may lead to serious adverse health consequences or death.

D.12.2 Scenario 11 (a)—Scenario with acceptable risk, non-violative product, no recall

Escalation and assessment: Additional internal validation testing and clinical information from patients show that the battery failure rate is well within expectations of 84 months. The manufacturer elects to change the labeling and instructs the practitioners to change the battery every 72 months.

Postmarket risk and benefit assessment: The manufacturer reviews and updates the risk management file and determines that the failure mode/rate and potential patient harm are identified in the established risk assessment. No new hazards have been identified. The investigation file documents that:

- The benefit of the pacemaker when used according to the FDA-cleared indications for use remains unchanged.
- The risk remains acceptable.

Recall decision: Non-violative product. FDA would not consider taking action. Trending and monitoring are deemed appropriate. No reportable recall is needed. The manufacturer could consider submitting the required pre-market information to the FDA for review.

Recall strategy: Not required.

Evaluate recall strategy: No further analysis required.

Communicate with FDA: No discussion with FDA is required.

D.12.3 Scenario 11 (b)—Scenario with acceptable risk, minor violation, recall

Escalation and assessment: The manufacturer receives numerous complaints that the pacemaker is giving off erroneous battery end-of-life indicator warnings, under certain circumstances, as early as 48 months post-implantation, in a much higher than expected frequency.

Postmarket risk and benefit assessment: An extensive investigation was conducted, and product testing identified similar erroneous battery end-of-life indicator warnings. Manufacturing was conducted in accordance with the firm's procedures. However, the root cause is identified as a software issue. The manufacturer reviews the risk management files and determines that the complaint type (failure mode/rate and potential patient harm) is identified in the established risk assessment. The investigation file documents that:

- There is no increase in likelihood to cause adverse health consequences based on a minor (i.e., non-significant) increase in probability of occurrence in a minor-severity patient harm, and no change in probability of a major-severity harm.
- The benefit of the pacemaker when used according to the FDA-cleared indications for use remains unchanged.
- The risk is acceptable, but the risk management file is updated to include the higher probability of the failure mode.

Recall decision: Violative product, minor violation. However, FDA might consider taking legal action if the manufacturer did not address the violation.

Recall strategy: Potential actions for the manufacturer to consider would include issuing a communication and a software update. The manufacturer decides to issue a communication and software update to advise patients and physicians to get the devices checked for battery life if battery end-of-life indicator warnings are seen, but concludes this would be a non-reportable field action.

Evaluate recall strategy: As the proposed recall strategy would not result in a product shortage or use interruption, there would be no adverse public health issue resulting from this recall strategy.

Communicate with FDA: No discussion with FDA is required.

D.12.4 Scenario 11 (c)—Scenario with unacceptable risk, violative product, recall

Escalation and assessment: The manufacturer receives numerous complaints that the pacemaker did not provide the necessary therapy, resulting in multiple serious adverse health consequences and deaths in a much higher than expected frequency. The potential severity of harm to patients is increased. An extensive investigation was conducted and the manufacturer finds that the software alarm system did not warn of impending battery failures in many cases.

The root cause is identified as a software issue. Specifically, the pacemaker battery is not giving the expected end-of-life indicator warnings. Manufacturing was conducted in accordance with the firm's procedures. The product does not continue to meet previously established performance specifications.

Postmarket risk and benefit assessment: The manufacturer reviews the risk management files and determines that the complaint type (failure mode/rate and potential

patient harm) is identified in the established risk assessment. The investigation file documents that:

» The benefit of the pacemaker when used according to the FDA-cleared indications for use has changed. Based on the failure mode, the expected benefit of the device is reduced.
» Risk is unacceptable because of an increase in likelihood to cause adverse health consequences based on a major (i.e., significant) increase in probability of occurrence in a major patient harm and a change in probability of that harm.

Recall decision: Violative product. FDA would consider taking legal action if the manufacturer did not address the violation.

Recall strategy: As the medical device is violative and reporting is required, the manufacturer decides to initiate a reportable field action. The characteristics of the field action could depend on whether a pacemaker had been implanted or not:

» If the product is already implanted: Issue a communication with additional risk mitigations and an expedited software update.
» If the product is not implanted: Product removal.

Evaluate recall strategy: If the removal could result in a product shortage situation, where patients requiring implantable cardiac pacemaker would not be treated, other potential mitigation approaches should be considered.

Communicate with FDA: The manufacturer discusses the strategy with the FDA to confirm that this solution is in the best interest of patients.

Annex E:
Benefit-Risk Worksheets

The worksheets in Table E.1 are intended to assist in completing the benefit-risk summary in Section 3.5. The questions in these worksheets are prompts and may not apply to all situations.

TABLE E.1—BENEFIT-RISK WORKSHEETS

Factor Questions to Consider	Notes
Assessment of Benefits of Devices[a]	
Type of benefit(s)	» What primary endpoints or surrogate endpoints were evaluated? » What key secondary endpoints or surrogate endpoints were evaluated? » What value do patients place on the benefit?
Magnitude of the benefit(s)	» For each primary and secondary endpoint or surrogate endpoint evaluated: • What was the magnitude of each treatment effect? » What scale was used to measure the benefit? • How did the benefit rank on that scale?
Probability of the patient experiencing one or more benefit(s)	» Was the study able to predict which patients will experience a benefit? » What is the probability that a patient for whom the device is intended will experience a benefit? » How did the benefits vary across subpopulations? (If the study was sufficiently powered for subpopulations, note specific subpopulations, nature of difference, and any known reasons for these differences.) » Was there a variation in public health benefit for different populations? » Even if the benefit is in a small portion of the population, would those patients who would experience the benefit value it?
Duration of effect(s)	» Could the duration, if relevant, of each treatment effect, including primary and secondary endpoints, be determined? If so, what was it? » Is the duration of the benefit achieved of value to patients?

[a]For medical devices without identified events and postmarket data sources such as registries, electronic health records, or clinical trial data.

TABLE E.1—BENEFIT-RISK WORKSHEETS (CONTINUED)	
Factor Questions to Consider	**Notes**
Assessment of Risks of Devices ***Severity, types, number and rates of harmful events (events and consequences):***	
Device-related serious adverse events	» What are the device-related serious adverse events for this product?
Device-related non-serious adverse events	» What are the device-related non-serious adverse events for this product?
Procedure-related complications	» What other procedure-related complications may a patient be subject to?
Probability of a harmful event	» What percent of the intended patient population would be expected to experience a harmful event? » What is the incidence of each harmful event in the study population? » How much uncertainty is in that estimate? » How does the incidence of harmful events vary by subpopulation (if applicable)? » Are patients willing to accept the probable risk of the harmful event, given the probable benefits of the device?
Duration of a harmful event	» How long does the harmful event last? » Is the harmful event reversible? » What type of intervention is required to address the harmful event?
Risk from false-positive or false-negative results for diagnostics	» What are the consequences of a false positive? » What are the consequences of a false negative? » Is this the only means of diagnosing the problem, or is it part of an overall diagnostic plan?

TABLE E.1—BENEFIT-RISK WORKSHEETS (CONTINUED)	
Factor Questions to Consider	**Notes**
Additional Factors in Assessing Probable Benefits and Risks of Devices[a]	
Uncertainty:	
+ Quality of the study design	» How robust were the data?
+ Quality of the conduct of the study	» How was the trial designed, conducted and analyzed? » Are there missing data?
+ Robustness of the analysis of the study results	» Are the study results repeatable? » Is this study a first of a kind? » Are there other studies that achieved similar results?
+ Generalizability of results	» Can the results of the study be applied to the population generally, or are they more intended for discrete, specific groups?
Characterization of the disease	» How does the disease affect the patients that have it? » Is the condition treatable? » How does the condition progress?
Patient tolerance for risk, and perspective on benefit:	» Did the sponsor present data regarding how patients tolerate the risks posed by the device? » Are the risks identifiable and definable?
+ Disease severity	» Is the disease so severe that patients will tolerate a higher amount of risk for a smaller benefit?
+ Disease chronicity	» Is the disease chronic? » How long do patients with the disease live? » If chronic, is the illness easily managed with less invasive or difficult therapies?
+ Patient-centric assessment	» How much do patients value this treatment? » Are patients willing to accept the risk of this treatment to achieve the benefit? » Does the treatment improve overall quality of life? » How well are patients able to understand the benefits and risks of the treatment?
Availability of alternative treatments or diagnostics	» What other therapies are available for this condition? » How effective are the alternative treatments? » How does their effectiveness vary by subpopulation? » How well-tolerated are the alternative therapies? » How does their tolerance vary by subpopulation? » What risks are presented by any available alternative treatments?
Risk mitigation	» Could you identify ways to mitigate the risks (such as using product labeling, establishing education programs, providing add-on therapy, etc.)? » What is the type of intervention proposed?

[a]For medical devices without identified events and postmarket data sources such as registries, electronic health records, or clinical trial data.

TABLE E.1—BENEFIT-RISK WORKSHEETS (CONTINUED)		
Factor Questions to Consider	**Notes**	
Additional Factors in Assessing Probable Benefits and Risks of Devices[a]		
Postmarket data	» Are there other devices with similar indications on the market? Are the probabilities for effectiveness and rates of harmful events from those devices similar to what is expected for the device under review? » Is postmarket data available that change the risk/benefit evaluation from what was available when the previous devices were evaluated? » Is there reason to consider evaluation of any of the following elements further in the postmarket setting, due to the risk/benefit evaluation as described above? • Longer-term device performance. • Effectiveness of training programs or provider preferences in use of device. • Subgroups (e.g., pediatrics, women). • Rare adverse events. » Is there reason to expect a significant difference between real-world performance of the device and the performance found in pre-market experience with the device? » Is there data that otherwise would be provided to support approval, which could be deferred to the postmarket setting? » Is there off-label use, or on-label use that is different than originally expected?	
Novel technology addressing unmet medical need	» How well is the medical need this device addresses being met by currently available therapies? » How desirable is this device to patients?	
Summary of the Benefit(s)	**Summary of the Risk(s)**	**Summary of Other Factors**
Summarize as Appropriate in Each Column Below		

Annex F:

Factors to consider when applying the principles and assessing risk and benefit

(This annex is reprinted from Annex B of the AAMI White Paper 2015, Risk Principles and Medical Devices: A Postmarket Perspective [2]*)*

This annex contains a list of factors that can be considered when applying the risk principles described in the white paper while assessing both risk and benefit in the context of postmarket quality and safety issues. Although lengthy, this list is still incomplete as there are many factors that should be considered when applying these risk principles. This list is a starting point that is intended to help stimulate a thorough analysis.

These factors should apply as they are relevant to the postmarket event. Not every risk factor is applicable to every situation.

F.1 Factors having an impact on the severity of harm

- Duration of exposure
- Acute versus chronic
- Reversibility of harm (e.g., death, injury)
- Body part impacted
- Pain intensity and duration of recovery
- Known and immediate injury versus reasonably foreseeable future injury
- Immediacy of the onset of harm
- Patient, operator or others—who is harmed?
- Patient preferences (quality of life) context of benefit given known harm (consider alternatives)

F.2 Factors having an impact on the probability of occurrence of harm (also sometimes referred to as frequency of harm)

- Not all exposures to a hazard result in harm
- Extent of event needed to cause injury or disease
- Consider both the probability of future occurrence (fraction) and the number of patients who may plausibly experience the harm (numerator).

NOTE: For example, the probability of occurrence of the hazard can be identified first, and feeds the probability of occurrence of harm. Quantitative analysis is often thought of as a fractional probability. The numerator can take into consideration customer complaints (understanding that complaints may be underreported). The denominator can take into consideration sales or distribution data, estimated or known use cases, device log file analysis, etc.

F.3 Factors having an impact on the complexity of the risk and benefit assessments

- Complexity of use (human factors use error / usability of the device)
- Systemic versus randomly occurring
- Unexpected or uncertain hazard versus known prior adverse events
- Chronic harm may take time to become evident
- Failure detectability / user awareness of an existing problem
- Single versus multiple use device
- Single versus multiple patient use device
- Intended use of the device
- Software dependency
- How many other devices are likely to be in use with this particular device—is there an additive nature of multiple devices used at the same time on the patient (environment of care considerations)

F.4 Factors having an impact on risk management process

- Acceptable risk (rationale)
- Extent of change needed to recover lost benefit/reduce risk
- Impact on the health system
- Impact of defect or failure on other devices
- Does a risk control option introduce another unacceptable risk?
- If a newer product has increased benefit, does previously acceptable risk ever become no longer acceptable?
- Balance between benefit versus probability and severity of harm
- Nature of the defect or failure relative to societal values and preferences
- Availability of products and suitable replacements or alternatives, percent of market share, delay in treatment. This is a consequence of device defect not a defect itself. (This is a postmarket factor not considered in ISO 14971).
- Cumulative history of repeated malfunctions/failure modes
- Level of risk may influence level of documentation by the manufacturer and level of FDA intervention.
- Consistent application of the risk management framework (ISO 14971) across the total product life cycle

NOTE: ISO 14971 does not require that a manufacturer have a quality management system, but risk management can be an integral part of a quality management system.

F.5 Factors arising from the affected population

- Clinical impact on patients
- Health status of patients (increased sensitivity to particular defect or failure)
- Age of population impacted
- Size of population involved
- Amount of benefit or harm in different populations (small benefit large population or large benefit in small population)
- Impact on other patient populations
- Known versus reasonably affected sensitive populations

F.6 Factors arising from current clinical practices

- Actions taken or planned to recover lost benefit based on clinical practice
- Lifesaving / life sustaining uses for devices
- Where is the device being used and by whom (e.g., home care versus ICU); what is the skill level of the user?
- Other options available

- Effectiveness of communication to users (who is the user; what will they understand; who is interpreting the information for the patient; etc.)
- Unmet medical needs
- Risks with alternative choices
- Use in emergency / crisis situations
- Duration of device exposure
- Implanted
  - location
  - patient age
  - weight
  - level of physical activity
  - device aging
- Patient tolerance for risk
- Clinical understanding in evaluating risk
- Current expectations in clinical use
- Any changes in medical practice that could affect risk

F.7 Factors arising from the environment of care

- Causes of and interactions among various failures and faults and the potential impacts of multiple concurrent hazards or actual events resulting in harm
- Available medical device service information
- Labeling
- Training
- Experience with the device
- Mode of availability
- Overall use environment
- Clinical work flow patterns
- Age of the device and its estimated remaining shelf life or useful life
- How long on market without updates / change
- Do other products have similar issues
- When use occurs in a device life
- Multiple patient use or single patient use
- Multiple use or single use / disposable
- Consumables and incompatible consumables
- Evolution of the practice of medicine as it relates to the evolution of products, e.g., a new drug or device enters the market that interferes with old product already marketed.
- Other impacts, e.g., antibiotic coating and bacterial drug resistance

Annex G:

Summary of an informal pilot conducted by seven medical device manufacturers and staff from CDRH

G.1 Overview

A repeated discussion thread during the development of the *Framework for Incorporating Benefit-Risk Assessments* into *Correction and Recall Decisions* was the desire by industry and CDRH staff to "pilot test" what they were developing. A dedicated group of seven industry participants and FDA staff agreed to do just that, once the draft was out for public review over the summer of 2016. With an agreed upon process coordinated by AAMI, work began in early fall 2016 to assess both the framework and the FDA draft guidance on *Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance and Enforcement Decisions*.

The major goals of this pilot project were to:

- Continue the positive and open dialogue between industry and CDRH and to test the work they have done together before finalizing the draft documents.
- Determine whether using the AAMI draft framework and the FDA draft guidance document helps to minimize differences in the assessment of benefit and risk between FDA and industry (do the documents help industry and FDA reach similar conclusions regarding appropriate remedial actions when incorporating elements from the AAMI and FDA documents into the recall review process).
- Determine ease of use and identify gaps, areas of concern, and opportunities for improvement in both documents.

Although developing quantitative measures of success were difficult because of the small number of test cases and a rather compressed timescale to develop and analyze the hypothetical recall events, industry and FDA alike viewed success as:

- **Increasing Harmony**—Did industry and FDA reach the same or a very similar outcome utilizing the FDA draft guidance and AAMI draft framework?
- **Building Confidence**—Will using these processes improve relationships, resulting in a more efficient and collaborative environment when postmarket issues arise?
- **Identifying Areas for Improvement**—Were gaps, areas of concern, and opportunities for improvement in both documents identified?

The industry partners were 3M Healthcare, Boston Scientific, Edwards Lifesciences, GE Medical, Johnson & Johnson, Medtronic, and Phillips Medical. Participating from the FDA were representatives from CDRH's Office of Compliance (OC) and the Office of In Vitro Diagnostics and Radiological Health (OIR).

G.2 Process

Each industry partner developed one or more hypothetical recall events based, to the extent possible, on previous real events properly sanitized.

When constructing the hypothetical recall events, the industry participants and FDA agreed that:

- They would not base the hypothetical recall event on real events that were controversial at the time;
- As the hypothetical recall event will be modified from reality and not necessarily representative of reality, neither industry or FDA is to expect that this pilot will reopen already finalized decisions or result in a request from FDA for a field action; and
- Nothing from this pilot will be used against an industry participant in real life if the facts in the hypothetical recall event happen to occur in real life in the future.

Eleven hypothetical recall events were developed by the industry participants. Nine involved devices that entered the US market through the Premarket Notification (510(k)) process, one was approved through the Premarket Approval (PMA) process, and one was unclassified because of being intended for export only.

Before each hypothetical recall event was finalized, FDA had clinical and regulatory staff, not otherwise involved in the pilot, examine the recall event and suggest possible modifications to the circumstances to ensure variety in the expected outcomes.

Once any modifications were agreed, the industry partner utilized the event(s) to challenge their process for evaluating nonconforming/regulatory non-compliant products and developed a Report of Corrections and Removals (mock Part 806 report). FDA, in turn, received the firm's mock Part 806 report, followed its internal procedures, and completed a recall review. For each hypothetical recall event, the analysis resulted in an FDA determination, including the recall classification and proposed corrective action.

The process engaged a designated medical officer, compliance officer and branch chief from the following groups within CDRH:

- **Office of Compliance (OC)**
  - Immediate Office
  - Division of Manufacturing and Quality (DMQ)
    - Cardiovascular Devices Branch
    - Physical Medicine, Orthopedic, Neurology & Dental Device Branch
    - Abdominal and Surgical Device Branch
    - Respiratory, ENT, General Hospital and Ophthalmic Device Branch
  - Division of Analysis and Program Operations (DAPO)
    - Recall Branch
  - Division of International Compliance Operations (DICO)
    - Foreign Enforcement Branch

- **Office of In Vitro Diagnostics and Radiological Health (OIR)**
  - Division of Radiological Health (DRH)
    - Mammography, Ultrasound and Imaging Software Branch
    - Diagnostic X-Ray Systems Branch

Once the FDA had completed its review of the mock Part 806 report, the FDA and the individual manufacturer convened to discuss the rationale, findings and tools utilized during the decision-making process for each hypothetical recall event. The lessons learned were discussed during two conference calls. The first was with only FDA staff and the second with both FDA and industry participants. The lessons learned are captured in this Annex.

G.3 Limitations

As an informal pilot project, this effort has several inherent limitations. First, in order to maintain confidentiality there was limited sharing of information among the manufacturer participants during the development of the hypothetical recall events. In this way, each participant had some freedom to determine what information would be provided and how it would be presented. Also because of confidentiality concerns by some of the manufacturers, the review of the results was restricted to the FDA and the responsible manufacturer. Because the hypothetical recall events were developed by the manufacturer who would submit them, even though they were critiqued by an independent party at FDA prior to being finalized, they were not truly blinded. The primary goal of this effort was to thoroughly discuss rationales, findings, and tools utilized rather than developing statistically significant measurements. The participants focused on qualitative rather than quantitative data Finally, the compressed timescale for designing and executing the pilot put all parties under a good deal of pressure that complicated, and in some cases limited, the interactions between the manufacturer participants and the FDA staff.

G.4 Lessons learned

In spite of the limitations outlined in the preceding section, the effort did produce results that were both worthwhile and instructive to the industry and FDA participants. The participants agreed that overall the pilot did lead to a greater understanding of the points of view of the parties and provided some insight into the internal processes that both the industry participants and FDA apply when assessing recall strategies. Most significantly, applying the framework and the draft guidance increased the participants' focus on the benefit to patients in a process that traditionally has been primarily focused on changes in patient risk.

The FDA participants reported that all the manufacturers wanted more feedback throughout the process. The manufacturers, in turn, found the opportunity to exchange information with the people at FDA was very valuable. All agreed that open and constructive communications between the parties led to a better understanding of what makes a good Part 806 report. From the FDA perspective, the best reports contained a concise, carefully constructed justification supporting the proposed correction/removal strategy, explaining why the proposed corrective action is superior to available alternatives.

This justification was particularly important when the manufacturer proposed leaving the device in the market with or without a customer notification. In general, FDA reviewers favored notifying the customer in virtually all recall cases. In some of the hypothetical recall events, however, the manufacturer proposed not doing a customer notification, particularly if the notification would not contain any actionable information. The industry perspective is that customer notifications can be confusing and stressful if they call for no action on the part of the recipient. Further discussion with CDRH on when a customer notification would or would not be considered necessary could increase alignment between industry and FDA. It was also noted in that further information from FDA on the specific factors taken into consideration in the decision process would be valuable to industry, and should be considered for inclusion in the FDA draft guidance.

The pilot used the Risk Assessment Form (RAF) in Annex A as a tool for capturing the basic information from which the manufacturer participants developed their mock Part 806 reports. However, participants felt that the RAF did not capture all of the information that was ultimately needed. One recommendation is that the RAF needs to be expanded to collect more information about changes in probable device benefits as a result of the non-conformity, following the outline in Section B of the FDA draft guidance.

For these hypothetical recall events, the application of the framework and the FDA draft guidance document did not greatly affect the recall classification itself, but it did have an effect on the assessment of the correction/removal strategy. Of the eleven hypothetical recall events:

» Seven resulted in aligned thinking with FDA and the industry participant;
» Two were not initially aligned but the lessons learned session resulted in a mutual understanding; and
» Two resulted in no alignment between the industry participant and FDA.

All involved agreed that good, carefully constructed examples add value to both the framework and the FDA draft guidance. It was also suggested that open discussion of software-focused examples would be useful, and that examples on special circumstances when a device might or might not be considered violative would add value. Two potential cases were highlighted:

» A device is performing as intended but there have been changes in the environment that affect the benefit-risk balance.
» The device is in use well beyond its intended useful life and is subject to wear-out (obsolescence).

As noted in the report, FDA is currently evaluating CDRH and ORA district office roles in the recall process as part of their Program Alignment efforts. At the conclusion of the pilot, CDRH staff noted that, although this pilot was a joint effort between AAMI and CDRH:

» ORA continues to partner throughout development and implementation of the benefit-risk approach;
» The District Recall Coordinator remains the initial point of contact for the manufacturer; and
» Post-pilot efforts will include broader communication and training for CDRH and ORA personnel.

G.5 Conclusions

The pilot, even with its limitations, was useful both to industry and to the FDA participants. The most instructive conclusion that can be made and emphasized to the entire medical device industry and also to everyone at FDA who has any role with postmarket correction and removal decisions is: Increased communication, with a collaborative intent and approach, is key to achieving the best outcome for patients. More communication and more detail about the context and "why" someone is viewing a situation in a certain way, or why a proposed outcome is better than another one, or even why the dialogue isn't going well, is helpful and greatly increases the likelihood that FDA and a manufacturer will achieve alignment in their thinking and in their decisions.

Frameworks and guidance documents do not change organizational culture either at the manufacturer or the FDA. People change cultures though open and collaborative dialog. The pilot indicated that more discussion is warranted in these situations, and more opportunities to work collaboratively will continue to support the trust that both the regulator and the regulated want to build. In short, the industry and CDRH participants in the pilot have a heightened awareness of the potential for both the FDA and industry to shift how they think about and approach correction and removal decisions. To some extent the participants have already begun to change their approaches to be more collaborative. This shift in thinking needs to continue to be nurtured and expanded across CDRH and throughout industry before real success can be realized.

The industry participants benefited from being able to have a real-time exchange of information with the CDRH staff who evaluate recall strategies and classify recalls. More opportunities for this real-time exchange of information would enhance the process itself, as well as the outcomes.

Finally, two recommendations for future work are worth repeating in these concluding remarks:

1) Further discussion on when a customer notification would not be considered necessary by the FDA could be valuable to both industry and CDRH reviewers.
2) Additional information from FDA on the specific factors they take into consideration in their decision process would be valuable to industry and should be considered for inclusion in the FDA draft guidance.

GLOSSARY:
Terms Used in This Report

Term	Definition
Adverse event	Any undesirable experience associated with the use of a medical product in a patient. NOTE: The event is serious and should be reported to the Food and Drug Administration (FDA) when the patient outcome is: • Death; • Life-threatening; • Hospitalization (initial or prolonged); • Disability or permanent damage; • Congenital anomaly/birth defect; • Required intervention to prevent permanent impairment or damage (devices); • Other serious (important medical events). • See the MedWatch guidance on what is a serious adverse event [35] for more descriptions of patient outcomes.
Benefit	The combination of the likelihood and degree of intended clinical benefit.
Class I recall	A situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death. [SOURCE: 21 CFR §7.3 (m)(1)]
Class II recall	A situation in which use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences, or where the probability of serious adverse health consequences is remote. [SOURCE: 21 CFR §7.3 (m)(2)]
Class III recall	A situation in which use of, or exposure to, a violative product is not likely to cause adverse health consequences. [SOURCE: 21 CFR §7.3(m)(2)]
Clinical benefit	Favorable effect or desirable outcome of a diagnostic procedure or therapeutic intervention. NOTE: Clinical benefits include prolongation of life, reduction in pain, improvement in function, or an increased sense of well-being.
Complaint	Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a device after it is released for distribution. [SOURCE: 21 CFR §820.3(b)]
Correction	The repair, modification, adjustment, relabeling, destruction, or inspection (including patient monitoring) of a device without its physical removal from its point of use to some other location. [SOURCE: 21 CFR §806.2(d)]

Term	Definition
Corrective and preventive action (CAPA)	Process for investigating, understanding and correcting discrepancies while attempting to prevent their recurrence.
Decision analysis (DA)	A discipline encompassing philosophy, theory, tools and professional practices useful for thinking clearly about what to do when facing complex, uncertain and dynamic situations.
Decision quality (DQ) approach	A practical and systematic framework for assessing how good or bad the thinking is about a choice of action.
Defect	Imperfection, flaw or deficiency.
Dialogue decision process (DDP)	In complex organizations facing difficult decisions, a method for choreographing conversations between a management team and an analysis team to efficiently achieve decision quality.
Design History File (DHF)	A compilation of records which describes the design history of a finished device. [SOURCE: 21 CFR §820.3(e)]
Established risk assessment	The baseline risk assessment that was established at the time of medical device approval, plus the addition of periodic updates made through life cycle management, and that is reflected in the current risk management file.
Event	An issue that may adversely impact the risk associated with the use of a medical product. NOTE: While an event often may be due to a malfunction or nonconforming product, there are other circumstances that can impact the risk profile.
Exposure event	An event that results in someone being exposed to a hazard(s) resulting in a hazardous situation(s).
Field action	Action taken by the manufacturer or registration holder of a health product, in order to reduce the risk of occurrence of the adverse event related to the use of an already marketed health product.
Frame	The purpose, scope and perspective that the analysis team uses to focus its efforts when addressing a decision problem.
Health state	A system of classifying the current clinical situation or state of a patient's health.
Harm	Physical injury or damage to the health of people, or damage to property or the environment. [SOURCE: ISO 14971:2007, definition 2.2]
Hazard	Potential source of harm. [SOURCE: ISO 14971:2007, definition 2.3]
Hazardous situation	Circumstance in which people, property or the environment is/are exposed to one or more hazards. [SOURCE: ISO 14971:2007, definition 2.4]
Indications for use	A general description of the disease or condition that the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for whom the device is intended. [SOURCE: 21 CFR §814,20(b)(3)(i)]
Influence diagram	A graphical representation of a decision, which includes not just a relevance diagram that represents relevant information, but also includes nodes that represent alternatives and values.

Term	Definition
Intended clinical benefit	A favorable effect on a meaningful aspect of how a patient feels (e.g., symptom relief), functions (e.g., improved mobility) or survives as a result of the intended use of a medical device.
Intended use	Use for which a product, process or service is intended, according to the specifications, instructions and information provided by the manufacturer. [SOURCE: ISO 14971:2007, definition 2.5]
Malfunction	The failure of a device to meet its performance specifications or otherwise perform as intended. NOTE: Performance specifications include all claims made in the labeling for the device. [SOURCE: 21 CFR §803.3(k)]
Manufacturer	Any person who designs, manufactures, fabricates, assembles or processes a finished device. Manufacturer includes but is not limited to those who perform the functions of contract sterilization, installation, relabeling, remanufacturing, repacking or specification development, and initial distributors of foreign entities performing these functions. [SOURCE: 21 CFR §830.3(o)]
Market withdrawal	A correction or removal of a distributed device that involves a minor violation of the Act, which would not be subject to legal action by FDA or involves no violation of the Federal Food, Drug and Cosmetic Act (FD&C Act) (e.g., normal stock rotation practices). [SOURCE: 21 CFR §806.2(i)]
Medical device	Instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of: » Diagnosis, prevention, monitoring, treatment or alleviation of disease; » Diagnosis, monitoring, treatment, alleviation of or compensation for an injury; » Investigation, replacement, modification or support of the anatomy or of a physiological process; » Supporting or sustaining life; » Control of conception; » Disinfection of medical devices; » Providing information by means of in vitro examination of specimens derived from the human body; » and does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means. NOTE: Products that may be considered medical devices in some jurisdictions but not in others include: • Disinfection substances; • Aids for persons with disabilities; • Devices incorporating animal and/or human tissues; • Devices for in vitro fertilization or assisted reproduction technologies.[SOURCE: ISO 13485:2016, definition 3.11]
Medical Device Reporting (MDR)	A mechanism for the FDA and manufacturers to identify and monitor significant adverse events involving medical devices, so that problems may be detected and corrected in a timely manner.
Mitigation	The action of reducing the severity, seriousness, or painfulness of something.

Term	Definition
Never event	An event that should never occur, such as death, serious injury or irreversible injury.
Nonconformity	The non-fulfillment of a requirement. [SOURCE: ISO 9000:2015, definition 3.6.9]
Novel medical device	A medical device featuring unique technology that provides an unmet medical need.
Off-label use	Used for an intended use other than that in the approved labeling.
Product realization	Encompasses all processes that a manufacturer employs to create a medical device. NOTE: Clause 7 of ISO 13485:2016 describes product realization as encompassing: • planning and development of the processes needed, including the risk management process; • Determining customer requirements related to the product; • Establishing design and development inputs, outputs and design controls; • Establishing purchasing controls to ensure purchased product conforms to requirements; • Monitoring and controlling production and service provisions to ensure product conforms to specifications; and • Controlling of monitoring and measuring equipment needed to provide evidence of conformity.
(device) Quality	The totality of features and characteristics that bear on the ability of a device to satisfy fitness-for-use, including safety and performance. [SOURCE¨: 21 CFR 820.3(s)]
Quality adjusted life year	A measurement of the value of a health outcome that aggregates the time of survival in various health states, weighted by the desirability of those health states.
(QALY)	The organizational structure, responsibilities, procedures, processes and resources for implementing quality management. [SOURCE: 21 CFR 820.3(v)]
Quality system	The organizational structure, responsibilities, procedures, processes and resources for implementing quality management. [SOURCE: 21 CFR 820.3(v)]
Recall	A firm's removal or correction of a marketed product that the FDA considers to be in violation of the laws it administers and against which the agency would initiate legal action (e.g., seizure). NOTE: Recall does not include a market withdrawal or a stock recovery. [SOURCE: 21 CFR §7.3 (g)]
Recall classification	The numerical designation (i.e., I, II or III) assigned by the FDA to a particular product recall to indicate the relative degree of health hazard presented by the product being recalled. [SOURCE: 21 CFR §7.3 (m)]
Relevance diagram	A graphical representation using nodes and arrows that show the probabilistic relationship between uncertain quantities or events. NOTE: The absence of an arrow between two nodes asserts probabilistic independence between the entities represented by the nodes.

Term	Definition
Removal	The physical removal of a device from its point of use to some other location for repair, modification, adjustment, relabeling, destruction or inspection. [SOURCE: 21 CFR §806.2(j)]
Residual risk	Risk remaining after risk control measures have been taken. [SOURCE: ISO 14971:2007, definition 2.15]
Risk	The combination of the probability of occurrence of harm and the severity of that harm. [SOURCE: ISO 14971:2007, definition 2.16]
Risk analysis	Systematic use of available information to identify hazards and estimate the risk. [SOURCE: ISO 14971:2007, definition 2.17]
Risk assessment	Overall process comprising a risk analysis and a risk evaluation. [SOURCE: ISO 14971:2007, definition 2.18]
Risk control	Process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels. [SOURCE ISO 14971:2007, definition 2.19]
Risk evaluation	Process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk. [SOURCE: ISO 14971:2007, definition 2.21]
Risk matrix	A table with probability of harm categorized on one axis and severity of harm along the other axis, with the entries in the table providing risk ratings (such as acceptable or unacceptable).
Risk management	Systematic application of management policies, procedures and practices to the tasks of analyzing, evaluating, controlling and monitoring risk. [SOURCE: ISO 14971:2007, definition 2.22]
Risk management file	Set of records and other documents that are produced by risk management. [SOURCE: ISO 14971:2007, definition 2.23] NOTE: The records and other documents that make up the risk management file can form part of other documents and files required, for example, by a manufacturer's quality management system. The risk management file need not physically contain all the records and other documents; however, it should contain at least references or pointers to all required documentation. The manufacturer should be able to assemble the information referenced in the risk management file in a timely fashion.
Risk to health	(1) A reasonable probability that use of, or exposure to, the product will cause serious adverse health consequences or death; or (2) That use of, or exposure to, the product may cause temporary or medically reversible adverse health consequences, or an outcome where the probability of serious adverse health consequences is remote. [SOURCE: 21 CFR §806.2(k)]
Routine servicing	Any regularly scheduled maintenance of a device, including the replacement of parts at the end of their normal life expectancy (e.g., calibration, replacement of batteries, and responses to normal wear and tear). Repairs of an unexpected nature, replacement of parts earlier than their normal life expectancy, or identical repairs or replacements of multiple units of a device are not routine servicing. [SOURCE: 21 CFR §806.2(l)]

Term	Definition
Safety alert	A communication voluntarily issued by a manufacturer, distributor, or other responsible person (including FDA). A safety alert informs health professionals and other appropriate persons of a situation which may present an unreasonable risk to the public health by a device in commercial distribution. [SOURCE: FDA Investigations Operations Manual 2016 [34] §7.1.1.9] NOTE: If the device is violative, a safety alert becomes a recall. If the device is non-violative, the action remains a safety alert.
Sensitivity analysis	A technique to identify what is important in a model, as opposed to what is merely relevant, by varying a model input through a plausible range and assessing how much the model output varies.
Severity	Measure of the possible consequences of a hazard. [SOURCE: ISO 14971:2007, definition 2.25]
Stock recovery	The correction or removal of a device that has not been marketed or that has not left the direct control of the manufacturer (i.e., the device is located on the premises owned, or under the control of, the manufacturer, and no portion of the lot, model, code or other relevant unit involved in the corrective or removal action has been released for sale or use). [SOURCE: 21 CFR §806.2(m)]
Strategy table	A tool for crafting alternatives by combining selected choices for different aspects of what can be done. NOTE: The different aspects are the columns of the strategy table; the choices for each aspect are arrayed as entries in the row for each column.
Total product life cycle	All of the processes that lead to the creation of a product, the actual use of the product, and what happens after the product is discarded.
Trade complaint	An allegation of inappropriate trade practice such as promotion or advertising of a device outside the FDA-cleared or approved indications for use or marketing a medical device without the appropriate FDA clearance (510(k)) or approval (PMA).
Unmet medical need	Medical need that is not addressed adequately by an existing therapy.
Use error	A situation in which the outcome of device use was different than intended, but not due to malfunction of the device. NOTE: The error may have been due to a poorly designed device, or it may have been used in a situation that promoted incorrect usage.
Violative	Does not comply with the FD&C Act or the associated regulations enforced by the FDA. NOTE: A medical device can be considered violative if it fails to perform as represented by its specification or labeling.

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Endnotes

1. Karen Smith, patient representative, participated in the initiative actively in April 2015 and then on an as-needed basis throughout the remainder of the process. Her participation was supported by the Parkinson's Disease Foundation.

2. Throughout this report the word recall is used in a broad sense to describe activities that involve a violative device. FDA would refer to any action taken by a manufacturer prior to the determination that there is a violation as a "correction or removal."

3. This report uses the terms minor or technical violations in the same sense as minor violation and technical violation are used in the preamble to the final rule for the recall regulation (21 CFR 7 *Federal Register*, Vol 43, No. 117-Friday, June 16, 1978).

   "For example, in reviewing a firm's product removal or correction or the need to request a firm to recall, the agency must exercise its judgment as to whether the evidence could support a judicial determination that the product in question is violative. The exercise of judgment can prevent removals and corrections of products because of minor violations or for non-violative reasons from being classified as recalls." (43 FR 26207-26208.)

   [The expression "minor violation"] "serves a vital purpose in the definition. The agency has long recognized that minor or so-called technical violations occur. In accordance with its discretionary authority under section 306 of the Federal Food, Drug, and Cosmetic Act, FDA may forego legal action in such cases. This exercise of enforcement discretion also has long been part of the agency's policy on recalls. In short, although a product being removed or corrected by a firm may be violative, the action is not considered by FDA to be a recall unless the agency would be prepared to initiate court action." (43 FR 26009-26010.)

4. 21 CFR Part 7, Enforcement Provisions, §7.3, Definitions [37].

5. ISO 14971:2007, Clause 2 [17].

6. During the public comment period, a commenter suggested establishing the level of confidence needed to make this judgement. The working group chose to not try and establish a specify confidence level for deciding when a particular recall strategy might or might not result in an adverse public health issue(s). The level of confidence that is appropriate will depend on the particular circumstances and results of the benefit and risk analyses.

7. It is assumed a manufacturer will consult with legal counsel on complex matters that might need an analysis of applicable laws and regulations or a discussion of confidentiality and issues around attorney/client privilege.

8. See §20 of 21 CFR Part 806 [40].

9. An event is an issue that may adversely impact the risk associated with a medical product. While often an event may be due to a malfunction or nonconforming product, other circumstances can impact the risk profile.

10. An example of a software tool for digital encoding of the relevance diagrams is Analytica™ [19]

11. Software products that can readily generate tornado diagrams include Microsoft Excel™ and Analytica™ [19].

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