AAMI has circulated this draft for public review and comment. Consensus on this draft will be developed by AAMI/FDA Ad Hoc Risk Working Group.

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COMMENT DEADLINE: August 11, 2016

INSTRUCTIONS FOR COMMENTING:
Comments should be received by AAMI by the above deadline (earlier if possible) to ensure their consideration by the Ad Hoc Risk Working Group. Comments should be set forth as follows:
 a. Line number;
 b. Section number of document, and if appropriate, additional identification such as table or figure number;
 c. The type of comment (technical, editorial or general);
 d. Comments/objection; and
 e. Suggested alternative text to resolve comment/objection.

NOTE: All the above is not required for comments concerning typographical errors; simply identify the nature and location of the error (e.g., line number). Failure to comply fully with these instructions may cause comments to be considered non-persuasive.

An electronic Public Reviewer form is available from the AAMI website:


Comments not submitted using the electronic Public Reviewer form will not be accepted.

Please be sure to identify the document by the designation "Special Report – Postmarket Risk Management", and include your name, address, phone number and email address, in the event we need to contact you about your comments.

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Postmarket Risk Management:
A Framework for Incorporating Benefit-Risk Assessments into Postmarket* Decisions

A Special Report
Version 4.0
2016-06-10

During the internal committee review it was noted that the report does not cover all of the
decisions made postmarket. The contents of the report is more narrowly focused on applying
benefit-risk assessment to recall decisions. Reviewers are particularly asked to consider if it
would be appropriate to replace "postmarket" in the title with either "recall" or "correction and
removal"?

Developed by
Association for the Advancement of Medical Instrumentation
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Committee representation

Association for the Advancement of Medical Instrumentation

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

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.
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, to address key issues in the area of postmarket quality and safety with medical devices. The group was comprised 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.

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 quality and safety issues. The first phase also helped to inform recommendations to ISO Technical Committee 210, the standards committee responsible for maintaining the ISO 14971 family of risk management standards. It also helped to inform the successful AAMI/FDA Risk Management Summit held in October 2015.

Even more importantly, that first phase opened the door to working on deeper postmarket quality and safety issues where greater FDA and industry alignment would serve the public’s interests. Those deeper issues included: how to conduct a risk assessment, how to use a risk assessment in determining the appropriate course of action in managing a recall, and the meaning of certain terms not used universally by FDA and industry (such as “baseline” and “worst case”).

With clarity about what would have the biggest impact to improve the collective experience of industry and the FDA with postmarket quality and safety 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 risk assessment. Conceptually, this is easy to understand: why wouldn’t we always want to incorporate benefit into postmarket analyses and decisions? The devil, of course, is in the details.

This special report articulates those details. It outlines a framework that the members of the working group hope will be used by both the medical device industry and the FDA. 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 company and the FDA. If the FDA and a medical device company 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 quality or safety issues, the existing tools do not go far enough, especially when a company or the FDA is faced with the least certainty and thus the toughest decisions about what action to take. The working group envisioned that using benefit as a foundational principle in doing risk

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3 Throughout this special report the word recall is used in a broad sense to describe activities which may or may not 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".
assessments will help achieve a stronger alignment between industry and FDA, most pointedly in
the grey areas where an ISO 14971 analysis alone is not enough.

The report itself is more concise than it first appears. 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 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 decisions about postmarket issues with benefit at the forefront of
all decisions. When asked how we will know we have been successful when we look back in five
years, individual working group members identified what was 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 tradeoffs 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
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

Once a medical device is commercially available, its manufacturer is required to monitor the device's performance through its postmarket surveillance systems. Data obtained through a postmarket surveillance system may indicate that a medical device is not performing as represented by 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) [43] or the associated regulations enforced by the Food and Drug Administration (FDA). A medical device can be considered violative if it fails to perform as represented by its specification or labeling. "Adulterated" is a 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. 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.

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4 This special 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.)
A recall is an effective method of removing or correcting medical devices that are violative. A voluntary 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.

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 by creating product shortages or otherwise delaying treatment. Currently there is little guidance on evaluating these scenarios in the postmarket setting. This special report seeks to provide guidance to manufacturers as well as increase the transparency needed between FDA and manufacturers to reach a decision most beneficial to patients.

The process described in this special 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 special report is to provide structure around the process so it can be applied more consistently and transparently by both the industry and FDA.

1 Scope

1.1 The framework

The public health in the United States is best served when medical device manufacturers and the US Food and Drug Administration’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 [8] [10], 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 [24].

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 special report addresses some of those topics identified under "Next steps" and "Recommendations from commenters" in the AAMI White Paper.

This special report lays out a framework that medical device manufacturers and FDA can apply in assessing risk and weighing benefit when analyzing postmarket quality, safety and regulatory issues with a particular emphasis on decisions related to recalls. The framework in this document applies to both diagnostic and therapeutic devices.

Figure 1 provides a block-diagram overview of the process described in this special report. The numbers in brackets in the figure refer to the sections of this special 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.

The framework in this report should be considered as a starting point for incorporating benefit and risk considerations into the postmarket decision making process. 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.

Much of the information provided in this special report is neither new nor revolutionary. The FDA has already issued guidance on elements of the process, such as Product Recalls, Including Removals and Corrections [11] and Recalls, Corrections and Removals [12]. Under the requirements of the Quality System Regulation [42], manufacturers already have internal processes designed to monitor, collect and analyze postmarket data and, when necessary, take and document appropriate corrective action. However, this special 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.
Triggers for post-market benefit-risk assessment.  
(Section 2)

Conduct a post-market risk assessment of the medical device and, if appropriate, conduct an assessment of any change in benefit.  
(Section 3 and Annex E)

Consider using the Risk Assessment Form (RAF) to document and assess the medical device event(s).  
(Annex A)

Determine if a recall is necessary.  
(Section 4)

Either a non-reportable field action is indicated, or a no action decision is documented.  
(Section 4.4)

Consider using the Decision Quality Checklist or Dialog Decisions Process to achieve clarity about what to do if the decision involves significant analytical or organizational complexity.  
(Annexes B and C)

Create and evaluate a recall strategy, and if needed, perform a benefit-risk assessment.  
Could lack of product availability result in an adverse public health issue?  
(Section 5)

Implement the appropriate recall strategy.  
(Section 5.2)

Document the benefit-risk assessment, and, when appropriate, open a dialogue with the FDA.  
(Section 6)

Figure 1 – Framework overview

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, safety and/or expected performance (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 special 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.

1.3 Terms and definitions used in this special report

The consistent use of terminology is critical to understanding the process described in this special report. To assist in understanding this special report, a Glossary of Terms appears beginning on page 78. Some of the definitions of terms used in this special report were taken from the section of US Code of Federal Regulation (CFR) dealing with regulatory enforcement actions\textsuperscript{5}, International Standards such as ISO 14971\textsuperscript{6}, and various FDA Guidance Documents listed in the bibliography beginning on page 83. Where a term was taken from a source document, the source is noted in the Glossary of Terms.

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.
- 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.


\textsuperscript{6} ISO 14971:2007, Clause 2 [21].
Stability and reliability testing.
Post-approval studies.
Periodic reviews of safety and performance (e.g., preparation of a PMA annual report).

Important sources of customer feedback include customer complaints, MDR reports, feedback from the sales force, publications, and other nontraditional sources, such as social media.

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 quality or safety problem. 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 special report.

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. An appropriate field action should be initiated immediately while the benefit-risk assessment described in this special report proceeds in parallel.

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

Once an initiating device event is identified by the manufacturer’s quality system and predetermined escalation criteria have been met, 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 acceptable rate?
- Is there an increase in a single failure mode rate?
- Has a new failure mode been identified?
- Is there an unanticipated patient outcome?

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. The However, new benefits of device which is functioning as intended are sometimes identified 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). For example, has the device 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 special 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, use countries, and so on. This information is captured in Part I(A) of the RAF. These factors will further support the probability calculations made when estimating the risk(s).

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 changes in the residual risk(s) will be made.

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 of device approval or clearance. This document is generally based on the assumption that the manufacturer has established and implemented appropriate risk assessment processes.

If 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.

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. In the past, such a technical violation could well have resulted in the recall of the medical device, as discussed in Section 4.

A manufacturer's management may, for business reasons (such as customer good will), decide to still go through the recall decision making process for a non-violative medical device.

However, 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 this section needs to be performed.

3.3.1.3 New hazard/hazardous situation is identified

For a device 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 and an estimate of the risk.

To identify 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 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 associated with the hazardous situation, and evaluating the resulting risk against the established criteria for risk acceptability. When analyzing postmarket events and estimating risk, the factors that may be considered include the following, taken individually and in aggregate:

- **Severity**, types, numbers and rates of harmful events associated with the use of the medical device:
  - Device-related serious adverse events.
  - Device-related temporary or medical reversible adverse events.
  - Procedure-related complications.
- **Probability** of a harmful event.
- Populations at greatest risk.
- Likelihood of detection.
- Duration of harmful events.
- Impact of a false-positive or false-negative result on the diagnosis.

#### 3.3.2.2 Severity

Based on the patient impact of a particular device issue, the device event being investigated may be categorized as either a non-hazardous or a hazardous situation, with proper rationale (see Part I(B)(e) of the RAF). A hazardous situation should be evaluated with a certain severity based on use/clinical settings, by considering such factors as the affected populations and the clinical practices.

Information on the device event and any adverse events and complaints related to it are captured in Part 1(C) of the RAF. In addition, other factors that may be considered include:

- **Device-related adverse events** – Those events that may have been or were attributed to the use of the device and produce an 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.
- **Procedure-related complications** – Harms to the patient that would not be included under serious or non-serious adverse events, and that do not directly result from use of the device. (For example, anesthetic-related complications associated with the implantation of a device. Similarly, FDA would factor risks associated with the collection of human biological materials into the benefit-risk determination.) Note that if a procedure is lengthened, due to an unexpected device issue, complications due to the lengthened procedure could be considered as a device-related adverse event.

#### 3.3.2.3 Probability

The probability of occurrence may consist of two subcategories: one is the probability of occurrence ($P_1$) of a hazardous situation, and it can be viewed as the probability of the failure, nonconformance or misuse. The other is the probability of occurrence of harm ($P_2$), and it can be viewed as when the failure, defect or misuse happens, what the probability is of someone being injured. A description of this concept can be found in ISO 14971 [21].
Occurrence of the hazardous situation \((P_1)\) in a population of affected devices should be considered when considering risk. For instance, if a process capability-related manufacturing issue occurs randomly and infrequently, the probability of the hazardous situation occurring in a population of distributed devices may be quite small. Conversely, a manufacturing issue bound to a specific lot may have a smaller denominator of affected devices, and the risk evaluation should be limited to the affected devices.

Factors used to assess probability of injury resulting from a hazardous situation \((P_2)\) should include assessment and documentation of:

- Timing (anticipated/potential);
- Potential for mitigation;
- Location of device;
- Likelihood of detection;
- Monitoring of patient; and
- Patient population at the greatest risk.

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?
- Probability of adverse event – The proportion of the intended population that would be expected to experience a harmful event. This could be based on a single adverse event or on multiple adverse events.
- Duration of harmful events – Some devices can cause temporary minor harm; some devices can cause repeated but reversible harm; and other devices can cause permanent debilitating injury. Severity and duration of the harm can be jointly considered.
- 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.

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 flow of procedure, patient anatomy and physiology in relation to the hazard, and company-specific instruction versus current known practice in the field.

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

- Detection of the hazard/hazardous situation prior to use.
- Availability for easy exchange.
- The user has the ability to detect and troubleshoot and/or mitigate the hazardous situation.
- 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 hazard/hazardous situation and its potential injuries have been received.

Factors supporting a more likely probability of the occurrence of harm can include:
The hazard is likely to cause device failure during patient use.

The user does not have the ability to detect a hazardous situation and then troubleshoot, mitigate or apply a workaround.

The hazard/hazardous situation is likely to expose a secondary failure that has been associated with prior injuries.

Reports of injury as a result of the hazard/hazardous situation have been received.

The rationale for any probability estimate should reflect sound professional medical judgment, 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.

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

### 3.3.2.4 Additional factors

In addition to the factors listed in 3.3.2.2 and 3.3.2.3, the following may be considered when appropriate:

- Disease or condition being treated or diagnosed – The treated or diagnosed condition, its clinical manifestation, how it affects the patients who have it, how and whether a diagnosed condition is treated, 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). This should include:
  - **Severity** – In particular, whether the disease or condition is life-threatening; and
  - **Chronicity** – In particular, 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.

- Availability of alternative treatments or diagnostics – When making risk determinations, consideration should 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 market share and 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.

- Other postmarket data – The use of 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 approved. When making a benefit-risk determination, the collection of postmarket data may be utilized as a way to clarify the magnitude and effect of mitigations, 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 of certain devices, especially if new risks are identified, or if the information can be used to confirm that certain risks have been mitigated, to identify which patients are most likely to suffer adverse events, or to identify, more specifically, how different groups of patients will respond.

- Novel technology addressing unmet medical need – In assessing benefit and risk, consideration should be given to whether a device represents or incorporates breakthrough
technologies and addresses an unmet medical need. A device may address unmet medical
need by providing a clinically meaningful advantage over existing technologies, providing a
greater clinically meaningful benefit than existing therapy, posing less risk than existing
therapy, or providing a treatment or means of diagnosis where no alternative is available.

During subsequent iterations of the medical device, its established risk assessment may change
(e.g., the benefits may increase or the risks may be reduced), the expected level of safety and
effectiveness may change, and later versions may offer significant advantages over the initial
device.

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
following the manufacturer’s risk management process. The device issue/hazardous situation will
either:

– Have the same or lower severity/probability than that documented in the established risk
assessment and would remain acceptable; or

– Have an elevated severity/probability 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.

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 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

Additionally, risk acceptability can be evaluated by considering factors of 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 devices with initiating events, clinicians may not necessarily place
generally accepted risks in the same category as risks associated with identified device
problems. For example, a laptop for medical image use may have the same look, shape and
weight as a consumer laptop computer. If the laptop falls from the desk, it may injure the user’s
foot with a minor severity and low probability. This risk is similar to that of the general consumer
use, which is deemed to be an acceptable risk. Therefore, the laptop falling off the desk and
hurting someone may not require additional mitigations beyond that of the consumer product,
unless otherwise justified. On the other hand, for example, if due to the overall design of the
medical imaging system, the laptop has the potential of falling onto a patient lying on a bed and
hitting the patient’s face/eyes, then the risk and the need for additional risk controls may need to
be reassessed.

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 should consider and document the practicability of
additional mitigations that may further reduce the risks, by evaluating the effectiveness and
The completeness of the current mitigations regarding inherent safe design or protective measures (e.g., alarms). The mitigations may also include appropriate information within labeling (e.g., warnings, precautions, etc.), or to restrict the indication to a more limited use.

If further mitigations may reduce the risks without affecting the benefits, the manufacturer could consider taking a field action or 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 type of recall action may be appropriate (see Section 4).

3.4 Assessment of the benefit

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 since the last assessment of benefit. If the risk is reduced slightly, but the benefit is reduced significantly, patient expectations based on the labeled intended use, raise risk acceptability issues.

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

– The type of benefit(s).
– The magnitude of the benefit(s).
– The probability of a patient experiencing one of more benefit(s).
– The duration of the effect(s).

Examples of where the perception of the benefit(s) of the medical device could change include:

– A device shortage situation.
– A one-of-a-kind medical device if other devices come onto the market.
– Life-saving medical device.
– Medically necessary situation.

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.

3.4.2 Benefit factors

3.4.2.1 Establishing the benefit factors

The benefit factors to be considered in benefit-risk analyses are established in the context of the intended use of a medical device, and the clinical function of a medical device itself.

For the purposes of determining the benefit of a medical device, it is frequently helpful to consider the converse of its intended use. For example, if the device does not properly perform the intended use of diagnosis, prevention or monitoring, would the patient and/or affected population experience a reduction in health, quality of life, satisfaction or other positive clinical outcome? If the answer is yes, these are the benefits (hereafter referred to as intended clinical benefit) to be considered. 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, a third dimension should also be considered, and will be referred to as contextual factors. 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.

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. 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 benefit probability levels is preferred. For example, data from registries or electronic health records could support the quantitative categorization of benefit probability levels. Included with this assessment should be a discussion of the statistical variability of the estimate, as well as a definition of subpopulations’ expectations, 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. It is also possible that different patient subgroups will experience different benefits or different levels of the same benefit.

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, the manufacturer should use descriptors appropriate for the medical device.

### 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 severity 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 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. 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.

- **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 each time the treatment is repeated. 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 requires postmarket data.

### 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[1]:

- **Tolerance for risk, and perspective on benefit** – When determining if the device is effective, 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. Additionally, consideration should be given to input from stakeholders other than the patient; they may also have an objective perspective on the benefit to be realized from 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.

- **Clinician** – The expert judgment of experienced and knowledgeable individuals.

- **Others** – Benefits to caregivers or family members may also indirectly benefit the patients.

### 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:
665  – Define the problem.
666  – Identify alternatives.
667  – Identify benefit(s) of current device.
668  – Comparison of current device/alternatives.
669  – Identify concerns.
670  – Describe mitigation of concerns.
671  A structure for addressing this process is described in Table 1. Implicit in a benefit-risk
672  assessment is a comparison of the device under consideration with any alternatives that may
673  exist. In the structure below, the columns are to be completed for the medical device under
674  consideration as the manufacturer conducts the risk assessment and, if appropriate, the benefit
675  assessment described in Sections 3.3 and 3.4. To facilitate comparison, additional columns can
676  be added, if additional diagnostic or therapeutic alternatives are being considered. Annex E
677  contains worksheets that may be useful in completing the benefit-risk summary and assessment
678  in Table 1.
679
680 Table 1 – Benefit-risk assessment for medical devices with an initiating device event

<table>
<thead>
<tr>
<th>Consideration</th>
<th>Evidence and uncertainties</th>
<th>Conclusions and reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis of condition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmet medical need</td>
<td></td>
<td></td>
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<tr>
<td>Clinical benefit</td>
<td></td>
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<tr>
<td>Patient benefit</td>
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<td></td>
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<tr>
<td>Risk</td>
<td></td>
<td></td>
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<tr>
<td>Risk management</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Benefit-risk summary and assessment</td>
<td></td>
</tr>
</tbody>
</table>

681 3.5.2 Explanation of framework elements

682 a) Columns:
683  – Evidence and uncertainties – A description of both what is known (facts) as well as what
684  is not known (uncertainties and underlying assumptions). This includes a discussion on
685  the quality of data used as the basis for statements provided.
686  – Conclusions and reasons – A statement summarizing the analysis of the data and
687  uncertainties, and its clinical relevance. This is then followed with conclusions drawn for
688  each consideration (row).
689  – Benefit-risk summary and assessment – A balanced written analysis of the factors and
690  tradeoffs between each alternative diagnostic or therapeutic strategy, and a summary of
691  the resulting regulatory recommendation and action.

692 b) Rows:
693  The elements “Analysis of condition” and “Unmet medical need” are intended to provide
694  information on the therapeutic area and to provide the clinical context for weighing benefits
and risks. The elements “Clinical benefit,” “Patient benefit,” “Risk,” and “Risk management” 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.

- **Unmet medical need** – 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 premarket and/or postmarket clinical trials (including strengths and weaknesses) that were conducted to establish efficacy. This includes identifying the 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. For medical devices with initiating device events, premarket clinical trial data 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 benefit** – A description of attributes that matter to patients. The methodology used to establish the benefits of devices with sufficient postmarket data such as registries or electronic health records and any weighting applied should be described and validated. It may not always be feasible to use such methodologies to evaluate the benefits of medical devices with initiating device events) particularly if a correction or removal has taken place. In such cases, the relative patient benefits associated with the device can be described qualitatively.

- **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 management** – A description of which risks (if any) require mitigation or further characterization, what tools are recommended to address the risks, and the contribution of each tool to the overall risk management plan. This should also include a description of what would be considered to constitute a successful risk management plan, methods for measuring success, and, if the desired result is not achieved, at what point the risk management plan should be re-evaluated. This may also describe the residual risk that remains after mitigation, if mitigation is not total.

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 [36] or Part 809 [39]. 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 based on the circumstances associated with the event(s) and the results of the postmarket benefit-risk assessment in Section 3. Figure 2 is an overview of the decision process that the manufacturer can employ to determine if a recall is necessary and what class of recall or other field action might be appropriate based on the circumstances. 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.

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**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 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:

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– The medical device fails to meet represented 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 as represented.

– 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.7

– The medical device is not correctly labeled as defined in 21 CFR Part 801 [36] or Part 809 [39].

– 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 is being used in accordance with its labeled instructions for use and intended use, but it has resulted in unexpected adverse events or deaths.

– Appropriate notification has not been provided prior to placing the medical device into interstate commerce.

– 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 [40]), 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 questions in this section 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 devices that fail to meet represented specifications or that fail to perform as represented to be of a quality below that which they purport or are represented to possess, rendering them adulterated under section 501(c) of the FD&C Act [21 U.S.C. 351(c)]. Changes intended to resolve a failure to meet specifications or failure of the device to perform as represented would generally constitute recalls.

  – Is the labeling for the device to which you are 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 [21 U.S.C. 352(a)]. 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 [21 U.S.C. 352(f)(1)] (unless exempt). Devices that fail to meet applicable labeling requirements identified in 21 CFR Parts 801 and 809, Subpart B, also violate the laws administered by FDA.

7 21 CFR Part 820 [40]
A change to a marketed device to address false or misleading labeling or other labeling violations would generally constitute a medical device recall. If the device labeling was initially inadequate, this could also constitute a medical device recall. However, the addition of a new warning or other changes to the labeling of a non-violative device would not meet the definition of a recall.

- Are you otherwise out of compliance with FDA regulations?

You 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 constitute a medical device 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.[9]

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,
- Product advisory, or
- Market withdrawal for non-violative products.

4.3 Is there an increased likelihood of adverse health consequences?

The manufacturer determines if the identified risk or a change in probable benefit could result in the increased likelihood of adverse health consequences. If the answer to that question is yes, then a reportable field action is indicated. If the medical device is violative, depending on the likelihood of serious 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) [38].

4.4 Is the violation a minor (technical) violation?

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 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 [38], and can be voluntarily reported under 21 CFR 7 [35]. 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 [38] and include:

- Actions taken by the manufacturer to improve the performance or quality of a medical device, 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) [35]). However, a recall can encompass a broad range of actions the manufacturer can take, including product withdrawal, replacement, modification, communication, services, etc.

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 is a correction or 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 taken the appropriate action.
The FDA has published guidance for medical device manufacturers on *Recalls, Corrections and Removals (Devices)* [12]. 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.

### 5.2 Adverse public health issues

The potential for the recall to result in an adverse public health issue is a factor for the manufacturer 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 medical device.

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, and the timeliness of communicating, replacing and modifying devices.

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

### 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, the manufacturer follows its recall procedures and implements an appropriate recall strategy that is commensurate with the medical device's benefits and risks to the patients and users. For voluntary recalls, the manufacturer follows 21 CFR Part 7 [35]; for mandatory device recalls, the manufacturer follows 21 CFR Part 810 [40].

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* [3].
- *Guidance for Industry: Product Recalls, Including Removals and Corrections* [11], 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)* [12].

FDA urges the manufacturer to notify the appropriate District Recall Coordinator in FDA's Office of Regulatory Affairs (ORA) 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 health issue(s)

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), then the

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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 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 mitigations of alarms to warn the user of battery failure, and therefore it is estimated to have a very low probability of being undetected 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 all 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 in 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.

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 special report may encounter significant difficulty on the path to making a postmarket decision. A Decision Quality approach can provide a systematic framework for addressing the more challenging of these problems.

A manufacturer can consider using the Decision Quality 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 Decision Quality approach will ultimately expedite achieving a high-quality decision? In general, decisions sort along two dimensions, as shown in Figure 3.

![Figure 3 – Dimension of a decision problem](image)

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 medical device company can simply decide; the answer is obvious. 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, 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. The worksheet to evaluate manufacturer decision
making corrective actions in Annex C collects and summarizes these questions for ready application.

In cases where the organizational and analytical complexity are both high, then the Dialogue Decision Process (DDP), presented 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. 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.

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 (such as where root cause analysis is incomplete, 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 for manufacturers the reaching of an appropriate decision as to whether an issue(s) requires a product correction, removal, safety communication or some other action. It can also 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. 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 is 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 as much information as feasible 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 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. 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 special report lays out a framework that manufacturers and FDA can apply in

9 21 CFR Part 806, Medical devices; reports of corrections and removals, §20, Records of corrections and removals
not required to be reported [38].
10 ORA District and Headquarters Recall Coordinators,
assessing risk and weighing benefit when analyzing postmarket quality, safety and regulatory
issues with a particular emphasis on decisions related to recalls.

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

- The comprehensive Risk Assessment Form (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
special 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.

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.
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\(^\text{11}\) that may have an impact on device quality, safety or expected performance. 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.

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.

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).

\(^{11}\) 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.
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)

<table>
<thead>
<tr>
<th>Unique ID Number:</th>
<th>CAPA and/or Complaint Number:</th>
<th>Date Opened: Date this assessment was initiated.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Many organizations assign a reference number or a log number to their assessments.</td>
<td>If applicable; if not applicable, put N/A.</td>
<td>Date Closed: Date the final version of this assessment is completed.</td>
</tr>
</tbody>
</table>

**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.

**Purpose/Source:** What is the initiating event? (Examples include: nonconformance, CAPA, trending, postmarket vigilance.)

### Part I(A) BACKGROUND INFORMATION

**Manufacturer**

a) Manufacturer Contact: *(owner/operator/primary point of contact)*

b) Name and Address:

   *(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.)*

c) Manufacturer Establishment Registration Number:

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

e) Manufacturer Point of Contact Name and Address:

**Product**

a) Device Name: Potentially more than one device design is affected by this event. Attach a separate list if lengthy.

b) Unique Device Identifier (UDI): Attach a separate list if lengthy; if not applicable, put N/A.

c) Device Model(s)/Catalog Number(s) Provide information as appropriate. Attach a separate list if lengthy.

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. If the IFU statement is not sufficient, add additional detail 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:

<table>
<thead>
<tr>
<th>FDA Regulatory Status:</th>
<th>MDD Regulatory Class (optional):</th>
</tr>
</thead>
<tbody>
<tr>
<td>510(k)/PMA Number:</td>
<td>FDA Product Code:</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Region</th>
<th>Devices in Distribution</th>
<th>Number of Devices Subject to Review or Recall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worldwide (WW)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States (US)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe/Middle East/Africa (EMEA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia Pacific (APAC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latin America</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Regions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**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.

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:  
*Sometimes 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 product 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

<table>
<thead>
<tr>
<th>Region</th>
<th># of Relevant Complaints</th>
<th>Device Caused/Contributed to Deaths (# of Complaints)</th>
<th>Device Caused/Contributed to Serious Injuries (# of Complaints)</th>
<th>Device Caused/Contributed to Temporary &amp; Medically Reversible Injuries (# of Complaints)</th>
<th>Device Malfunctions But No Adverse Events (# of Complaints)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worldwide (WW)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States (US)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe/ Middle East/ Africa (EMEA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia Pacific (APAC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latin America</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Regions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

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

- 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.

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

i. 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.

ii. How many of the devices that have or are expected to have the event are likely to exhibit it annually over the lifetime of the product?

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

iii. Of the devices that have or are expected to have the event, how many are likely to cause harm to patients or users?

Not all events lead to a harm. Consult the Risk Management File (RMF) if available.

iv. 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 RMF, a new risk assessment is necessary and the RMF 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 file is not available.

a) Has this hazard or hazardous situation previously been identified? Explain.

[Clause 9, 14971:2007]
This information may be pulled directly from the risk file. 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 information may be pulled directly from the risk file. 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 information may be pulled directly from the risk file. This question is intended to identify the inherent risks of the device that were anticipated during the premarket stage, and which are separate from 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)?

This information may be pulled directly from the risk file, if the event was previously identified.
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)?

This information may be pulled directly from the risk file, if the event was previously identified.

Technical Reviewer Name/Signature/Date:____________________________________

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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.

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

- 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 frequency 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 occurrence?

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 frequency 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: ___________________________________________________________________

### Likelihood Rating Scale

<table>
<thead>
<tr>
<th>Check</th>
<th>Rating</th>
<th>Qualitative Description</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>5</td>
<td>Very high: Failures likely/inevitable</td>
<td>1 in 5</td>
</tr>
<tr>
<td>☐</td>
<td>4</td>
<td>High: Repeated failures</td>
<td>1 in 50</td>
</tr>
<tr>
<td>☐</td>
<td>3</td>
<td>Moderate: Occasional failures</td>
<td>1 in 500</td>
</tr>
<tr>
<td>☐</td>
<td>2</td>
<td>Low: Relatively few failures</td>
<td>1 in 5000</td>
</tr>
<tr>
<td>☐</td>
<td>1</td>
<td>Remote: Failures unlikely</td>
<td>&lt;1 in 500,000</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Check</th>
<th>Rating</th>
<th>Description</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>5</td>
<td>Catastrophic event</td>
<td>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.</td>
</tr>
<tr>
<td>☐</td>
<td>4</td>
<td>Major event</td>
<td>Injury or permanent loss of bodily function (sensory, motor, physiologic, or intellectual), disfigurement, surgical intervention required, increased LOS, increased level of care.</td>
</tr>
<tr>
<td>☐</td>
<td>3</td>
<td>Moderate event</td>
<td>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.</td>
</tr>
<tr>
<td>Check</td>
<td>Rating</td>
<td>Description</td>
<td>Definition</td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>-------------</td>
<td>------------</td>
</tr>
<tr>
<td>☐</td>
<td>2</td>
<td>Minor event</td>
<td>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.</td>
</tr>
<tr>
<td>☐</td>
<td>1</td>
<td>Near miss</td>
<td>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.</td>
</tr>
</tbody>
</table>

### Ability-to-Detect Rating Scale a)

<table>
<thead>
<tr>
<th>Check</th>
<th>Rating</th>
<th>Description</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>5</td>
<td>Absolute uncertainty</td>
<td>Potential failure mode and subsequent effect cannot be detected in time for adequate intervention.</td>
</tr>
<tr>
<td>☐</td>
<td>4</td>
<td>Remote</td>
<td>Remote chance that the potential failure mode and subsequent effect will be detected in time for adequate intervention.</td>
</tr>
<tr>
<td>☐</td>
<td>3</td>
<td>Low</td>
<td>Low chance that the potential failure mode and subsequent effect will be detected in time for adequate intervention.</td>
</tr>
<tr>
<td>☐</td>
<td>2</td>
<td>Moderately high</td>
<td>Moderately high chance that the potential failure mode and subsequent effect will be detected in time for adequate intervention.</td>
</tr>
<tr>
<td>☐</td>
<td>1</td>
<td>Almost certain</td>
<td>The potential failure mode and subsequent effect will be detected in time for adequate intervention.</td>
</tr>
</tbody>
</table>

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] [5] [17].

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

We start with a discussion of issues found with the existing approach to risk management for medical devices. We then outline a Decision Quality Checklist (DQC) that can help an analysis team apply decision analysis to postmarket problems. The 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 receives reports indicating that 5% of its thousands of life-support devices in the field fail per year of use, 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; and/or
- The interventions in recall strategies under consideration have potential for adverse consequences [16].

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 [6] [7] [21] [28]).

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 will
need to:
– Formalize the application with the addition of work instructions and other modifications to the
quality system, and
– 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] [27] [18].

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.
– 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 [29]. 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 the company and 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 checklist 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 useful tools for creating alternative actions [30] [31]. 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)

<table>
<thead>
<tr>
<th>Time</th>
<th>Products</th>
<th>Geography</th>
<th>Notification</th>
<th>Lots</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month</td>
<td>Device</td>
<td>National</td>
<td>MD letter</td>
<td>Selected</td>
</tr>
<tr>
<td>1 year</td>
<td>Device family</td>
<td>Regional</td>
<td>MD training</td>
<td>All</td>
</tr>
<tr>
<td>5 years</td>
<td></td>
<td>Global</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Time</th>
<th>Products</th>
<th>Geography</th>
<th>Notification</th>
<th>Lots</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month</td>
<td>Device</td>
<td>National</td>
<td>MD letter</td>
<td>Selected</td>
</tr>
<tr>
<td>1 year</td>
<td>Device family</td>
<td>Regional</td>
<td>MD training</td>
<td>All</td>
</tr>
<tr>
<td>5 years</td>
<td></td>
<td>Global</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 communication 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 checklist of questions for the analysis team to ask, 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 preventative 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 [23]. 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 [24].

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, tools like Analytica™ allow 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 [24][14][32][20]. 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 [24].

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 direct costs for a medical device company to conduct physical recall or other remediation activities, as well as intangible costs, such as loss of market share, brand impairment, and disruption of research initiatives. Given that costs are ultimately borne by the public, it makes sense to include large costs in the model. Different stakeholders may have different perspectives on what costs to include and how to trade them off against public health benefits. Representing the costs explicitly in the model enables effective discussion, which may lead to resolution of the differences of opinion. Inclusion of industry-focused factors can also help to eliminate unconscious bias against inaction and improve alignment with regulatory organizations, such as the FDA.
Figure B.6 – Relevance diagram with the addition of QALYs

Figure B.7 shows the addition to Figure B.6 of nodes representing remediation costs and medical treatment costs. The node labeled "QALYs Financial Value" represents the translation of QALYs into corresponding financial terms, using, for example, dollars per QALY, as is done in the health technology assessment literature [25]. (Alternatively, the model could be built using willingness-to-pay for micromorts [20]). Finally, the costs are added, so that the node "Total Economic Costs" completes the economic model.

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 health care 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?

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 is readily generated by software such as Excel™ and Analytica™ [33].

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.

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

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.
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.

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.
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 [19]. 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?

B.3.7 Dialogue Decision Process

One 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, comprised 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.

Figure B.16 shows an application of the Decision Dialogue Process (DDP), which structures the conversation between the analysis team and senior management [4] [22] [27]. 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)
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. Finally, including implementers and regulatory bodies in the formulation and analysis of the decision will ensure the understanding and buy-in necessary for high-quality execution of the decision. 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

Worksheet to Evaluate 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 worksheet 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 special 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 special report. Each scenario is organized into several parts, following the sections of this special 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) 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 [43] or the associated regulations. 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, by a large margin (e.g., 15 years). There is no log evidence to show these devices were properly maintained annually and/or that a check-up was performed prior to use, as required by the instructions for use.

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 for providing evidence that a sterilization process has achieved the required sterilization assurance level for the surgical environment. During a CAPA investigation, deterioration of the manufacturing machinery 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 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.

One of the challenges faced was coordination of response to the shortage between offices. Another challenge was rapid 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 products are removed from the market, a new 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 complaint rate is 0.08%. The root cause was found to be design-related. The investigation determines it is a low level, randomly occurring event that cannot be confirmed while it is happening, partially due to the low occurrence rate.

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 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 the design protocol, 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. A removal may be required, but new risks may present due to new product availability and the users’ responses. The manufacturer, with proper evidence, rationale and documentation, may choose to conduct a phased recall—sending out communication with temporary solutions and then replacing the product as a later phase. Communication with FDA may not be needed, assuming the evidence and rationale are valid.

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 [38]; 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 [38].

**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 (e.g., not meeting specifications).

**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 [38], 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. The exercise
bke 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 is comprised 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.

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 misassociation) 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.

**Evaluate 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 [38]; 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.

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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: Potential actions for the manufacturer to consider would include removal or corrections, dependent on risk mitigations and available software update. As the medical device is violative and reporting is required, the manufacturer decides to issue a communication with recommendation for device removal or corrections, dependent on risk mitigations and available software update.

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, 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

<table>
<thead>
<tr>
<th>Factor Questions to Consider</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Assessment of Benefits of Devices</strong> a)</td>
<td></td>
</tr>
</tbody>
</table>
| 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)

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

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

<table>
<thead>
<tr>
<th>Factor Questions to Consider</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Postmarket data</strong></td>
<td>– 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?</td>
</tr>
<tr>
<td></td>
<td>– Is postmarket data available that change the risk/benefit evaluation from what was available when the previous devices were evaluated?</td>
</tr>
<tr>
<td></td>
<td>– 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?</td>
</tr>
<tr>
<td></td>
<td>– Longer-term device performance.</td>
</tr>
<tr>
<td></td>
<td>– Effectiveness of training programs or provider preferences in use of device.</td>
</tr>
<tr>
<td></td>
<td>– Subgroups (e.g., pediatrics, women).</td>
</tr>
<tr>
<td></td>
<td>– Rare adverse events.</td>
</tr>
<tr>
<td></td>
<td>– 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?</td>
</tr>
<tr>
<td></td>
<td>– Is there data that otherwise would be provided to support approval, which could be deferred to the postmarket setting?</td>
</tr>
<tr>
<td><strong>Novel technology addressing unmet medical need</strong></td>
<td>– How well is the medical need this device addresses being met by currently available therapies?</td>
</tr>
<tr>
<td></td>
<td>– How desirable is this device to patients?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Summary of the Benefit(s)</th>
<th>Summary of the Risk(s)</th>
<th>Summary of Other Factors</th>
</tr>
</thead>
</table>
# Glossary of Terms Used in This Special Report

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event</td>
<td>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:</td>
</tr>
<tr>
<td></td>
<td>— Death;</td>
</tr>
<tr>
<td></td>
<td>— Life-threatening;</td>
</tr>
<tr>
<td></td>
<td>— Hospitalization (initial or prolonged);</td>
</tr>
<tr>
<td></td>
<td>— Disability or permanent damage;</td>
</tr>
<tr>
<td></td>
<td>— Congenital anomaly/birth defect;</td>
</tr>
<tr>
<td></td>
<td>— Required intervention to prevent permanent impairment or damage (devices);</td>
</tr>
<tr>
<td></td>
<td>— Other serious (important medical events).</td>
</tr>
<tr>
<td></td>
<td>See the MedWatch guidance on what is a serious adverse event [13] for more descriptions of patient outcomes.</td>
</tr>
<tr>
<td>Benefit</td>
<td>The combination of the likelihood and degree of intended clinical benefit.</td>
</tr>
<tr>
<td>Class I recall</td>
<td>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)]</td>
</tr>
<tr>
<td>Class II recall</td>
<td>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)]</td>
</tr>
<tr>
<td>Class III recall</td>
<td>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)]</td>
</tr>
<tr>
<td>Clinical benefit</td>
<td>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.</td>
</tr>
<tr>
<td>Complaint</td>
<td>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)]</td>
</tr>
<tr>
<td>Correction</td>
<td>Repair, modification, adjustment, relabeling, destruction or inspection (including patient monitoring) of a product without its physical removal to some other location. [SOURCE: 21 CFR §7.3 (h)]</td>
</tr>
<tr>
<td>Corrective and preventive action (CAPA)</td>
<td>Process for investigating, understanding and correcting discrepancies while attempting to prevent their recurrence.</td>
</tr>
<tr>
<td>Decision analysis (DA)</td>
<td>A discipline encompassing philosophy, theory, tools and professional practices useful for thinking clearly about what to do when facing complex, uncertain and dynamic situations.</td>
</tr>
<tr>
<td>Decision quality (DQ) approach</td>
<td>A practical and systematic framework for assessing how good or bad the thinking is about a choice of action.</td>
</tr>
<tr>
<td>Defect</td>
<td>Imperfection, flaw or deficiency, often so great that the medical device cannot be used.</td>
</tr>
<tr>
<td>Dialogue decision process (DDP)</td>
<td>In complex organizations facing difficult decisions, a method for choreographing conversations between a management team and an analysis team to efficiently achieve decision quality.</td>
</tr>
<tr>
<td>Design History File (DHF)</td>
<td>A compilation of records which describes the design history of a finished device. [SOURCE: 21 CFR §820.3(e)]</td>
</tr>
<tr>
<td>Established risk assessment</td>
<td>The baseline risk assessment that was established at the time of medical device approval, plus the addition of periodic updates made...</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>through life cycle management, and that is reflected in the current risk management file.</td>
<td></td>
</tr>
<tr>
<td>Event</td>
<td>An issue that may adversely impact the risk associated with 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.</td>
</tr>
<tr>
<td>Exposure event</td>
<td>An event that results in someone being exposed to a hazard(s) resulting in a hazardous situation(s)</td>
</tr>
<tr>
<td>Field action</td>
<td>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.</td>
</tr>
<tr>
<td>Frame</td>
<td>The purpose, scope and perspective that the analysis team uses to focus its efforts when addressing a decision problem.</td>
</tr>
<tr>
<td>Hazard</td>
<td>Potential source of harm. [SOURCE: ISO 14971:2007, definition 2.3]</td>
</tr>
<tr>
<td>Hazardous situation</td>
<td>Circumstance in which people, property or the environment is/are exposed to one or more hazards. [SOURCE: ISO 14971:2007, definition 2.4]</td>
</tr>
<tr>
<td>Indications for use</td>
<td>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)]</td>
</tr>
<tr>
<td>Influence diagram</td>
<td>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.</td>
</tr>
<tr>
<td>Intended clinical benefit</td>
<td>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.</td>
</tr>
<tr>
<td>Intended use</td>
<td>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]</td>
</tr>
<tr>
<td>Malfunction</td>
<td>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)]</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>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)]</td>
</tr>
<tr>
<td>Market withdrawal</td>
<td>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&amp;C Act) (e.g., normal stock rotation practices). [SOURCE: 21 CFR §806.2(ii)]</td>
</tr>
</tbody>
</table>
| 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; |
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>— Investigation, replacement, modification or support of the anatomy or of a physiological process;</td>
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<tr>
<td>— Supporting or sustaining life;</td>
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<tr>
<td>— Control of conception;</td>
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<tr>
<td>— Disinfection of medical devices;</td>
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</tr>
<tr>
<td>— 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.</td>
<td></td>
</tr>
<tr>
<td>NOTE: Products that may be considered medical devices in some jurisdictions but not in others include:</td>
<td></td>
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<tr>
<td>— Disinfection substances;</td>
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<tr>
<td>— Aids for persons with disabilities;</td>
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<tr>
<td>— Devices incorporating animal and/or human tissues;</td>
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<tr>
<td>— Devices for in vitro fertilization or assisted reproduction technologies.</td>
<td></td>
</tr>
<tr>
<td>Medical Device Reporting (MDR)</td>
<td>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.</td>
</tr>
<tr>
<td>Never event</td>
<td>An event that should never occur, such as death, serious injury or irreversible injury.</td>
</tr>
<tr>
<td>Nonconformity</td>
<td>The nonfulfillment of a specified requirement.</td>
</tr>
<tr>
<td>Novel medical device</td>
<td>A medical device featuring unique technology that provides an unmet medical need.</td>
</tr>
<tr>
<td>Product realization</td>
<td>Encompasses all processes that a manufacturer employs to create a medical device.</td>
</tr>
<tr>
<td>NOTE: Clause 7 of ISO 13485:2016 describes product realization as encompassing:</td>
<td></td>
</tr>
<tr>
<td>— Planning and development of the processes needed, including the risk management process;</td>
<td></td>
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<tr>
<td>— Determining customer requirements related to the product;</td>
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<tr>
<td>— Establishing design and development inputs, outputs and design controls;</td>
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<tr>
<td>— Establishing purchasing controls to ensure purchased product conforms to requirements;</td>
<td></td>
</tr>
<tr>
<td>— Monitoring and controlling production and service provisions to ensure product conforms to specifications; and</td>
<td></td>
</tr>
<tr>
<td>— Controlling of monitoring and measuring equipment needed to provide evidence of conformity.</td>
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<tr>
<td>Quality adjusted life year (QALY)</td>
<td>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.</td>
</tr>
<tr>
<td>Quality system</td>
<td>The organizational structure, responsibilities, procedures, processes and resources for implementing quality management.</td>
</tr>
<tr>
<td>[SOURCE: 21 CFR 820.3(v)]</td>
<td></td>
</tr>
<tr>
<td>Recall</td>
<td>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).</td>
</tr>
<tr>
<td>NOTE: Recall does not include a market withdrawal or a stock recovery.</td>
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<tr>
<td>[SOURCE: 21 CFR §7.3 (g)]</td>
<td></td>
</tr>
<tr>
<td>Recall classification</td>
<td>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.</td>
</tr>
<tr>
<td>[SOURCE: 21 CFR §7.3 (m)]</td>
<td></td>
</tr>
<tr>
<td>Relevance diagram</td>
<td>A graphical representation using nodes and arrows that show the probabilistic relationship between uncertain quantities or events.</td>
</tr>
<tr>
<td>NOTE: The absence of an arrow between two nodes asserts probabilistic independence between the entities represented by the nodes.</td>
<td></td>
</tr>
<tr>
<td>Removal</td>
<td>The physical removal of a device from its point of use to some other location for repair, modification, adjustment, relabeling, destruction or</td>
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<table>
<thead>
<tr>
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<tr>
<td>Residual risk</td>
<td>Risk remaining after risk control measures have been taken. [SOURCE: ISO 14971:2007, definition 2.15]</td>
</tr>
<tr>
<td>Risk</td>
<td>The combination of the probability of occurrence of harm and the severity of that harm. [SOURCE: ISO 14971:2007, definition 2.16]</td>
</tr>
<tr>
<td>Risk analysis</td>
<td>Systematic use of available information to identify hazards and estimate the risk. [SOURCE: ISO 14971:2007, definition 2.17]</td>
</tr>
<tr>
<td>Risk assessment</td>
<td>Overall process comprising a risk analysis and a risk evaluation. [SOURCE: ISO 14971:2007, definition 2.18]</td>
</tr>
<tr>
<td>Risk evaluation</td>
<td>Process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk. [SOURCE: ISO 14971:2007, definition 2.21]</td>
</tr>
<tr>
<td>Risk matrix</td>
<td>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).</td>
</tr>
<tr>
<td>Risk management</td>
<td>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]</td>
</tr>
<tr>
<td>Risk management file (RMF)</td>
<td>Set of records and other documents that are produced by risk management. [SOURCE: ISO 14971:2007, definition 2.23]</td>
</tr>
<tr>
<td>Stock recovery</td>
<td>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).</td>
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</table>

**Terms and Definitions**

- **Inspection**: [SOURCE: 21 CFR §806.2(j)]
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Strategy table</td>
<td>A tool for crafting alternatives by combining selected choices for different aspects of what can be done.</td>
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<tr>
<td></td>
<td>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.</td>
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<tr>
<td>Total product life cycle</td>
<td>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.</td>
</tr>
<tr>
<td>Unmet medical need</td>
<td>Scenario in which no device/therapy exists to treat life-threatening or debilitating diseases or conditions.</td>
</tr>
<tr>
<td>Use error</td>
<td>A situation in which the outcome of device use was different than intended, but not due to malfunction of the device.</td>
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<tr>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>Violative</td>
<td>Does not comply with the FD&amp;C Act or the associated regulations enforced by the FDA.</td>
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<tr>
<td></td>
<td>NOTE: A medical device can be considered violative if it fails to perform as represented by its specification or labeling.</td>
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</tbody>
</table>
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