Risk Principles and Medical Devices:
A Postmarket Perspective

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Introduction

History of the work

In collaboration with the U.S. Food and Drug Administration’s Center for Devices and Radiological Health (CDRH), the Association for the Advancement of Medical Instrumentation (AAMI) convened an informal working group in the fall of 2014, whose purpose was to develop a shared understanding of risk principles that would guide both the medical device industry and CDRH in assessing and managing risk in the postmarket setting.

This white paper and the risk principles and risk factors and it identifies are focused on postmarket quality and safety issues and related activities by industry and CDRH. Representatives from industry and CDRH participated in the project, and this white paper is a synthesis of their work.

In the short run, the project was successful if for no other reason than to nurture open discussion between industry and CDRH staff. The open discussions served to build a more collaborative approach to tackling issues that both industry and CDRH have in common but see from very different perspectives. Longer term, this work will inform more discussion between industry and CDRH about additional postmarket compliance issues where it would be helpful to have industry and CDRH alignment.

It is also anticipated that this white paper may influence the future work by ISO Technical Committee 210, the standards committee responsible for maintaining ISO 14971 [3] and its companion guidance document, ISO/TR 24971:2013 [5]. ISO 14971 and ISO/TR 24971 are important resources for both the industry and CDRH on an accepted risk management process including requirements for collecting and reviewing information about the medical device or similar devices in the production and the post-production phases. During this work on developing risk principles and risk factors, industry experts noted that ISO 14971 and ISO/TR 24971 include some guidance about managing risk in the postmarket setting. They noted that it would be helpful for ISO/TC 210 to consider the work done here to help further expand that guidance on managing risk postmarket.

NOTE Figure B.1 of ISO 14971:2007 illustrates the risk management process described in ISO 14971 including how the analysis of information generated in the postmarket setting is fed back into the risk management process.

An additional goal of this joint industry-CDRH activity was to foster open discussion. The participants had deep academic and practical expertise on the subject of risk, and the discussions benefitted greatly from this collaborative atmosphere of mutual respect.

This white paper is a starting point in helping industry and CDRH develop a shared understanding of risk management in the postmarket setting. As such, it is a snapshot in time on a continuum of building on that shared understanding. As that shared understanding continues to grow, the participants in the work no doubt will revisit the principles and factors that were developed in this first phase. It’s possible that what is learned later will call for re-shaping some of the principles and factors. As such, this work should not be construed as being etched in stone but rather part of a continuum of work that will continue to be developed and refined at future points in time.

Why work on risk principles

The public health in the United States is best served when industry and CDRH understand, assess and approach risk consistently throughout the total product life cycle of a medical device.

If industry and CDRH have a shared view based on a common risk management process, then less time should be lost resolving differences in understanding between CDRH and industry. It is hoped that a shared view will minimize the differences in the assessment of risk and resulting conclusions reached by industry and CDRH related to appropriate remedial actions. This work will be considered successful in the long-term if it: 1) increases the consistency of postmarket risk assessments; 2) speeds recognition and response to postmarket quality and safety issues; and 3) facilitates access to needed products.

Barriers to optimizing risk management for medical devices

There are a number of barriers to achieving optimal risk management for medical devices, such as:

- the legal/tort system in the United States, which may limit learning from adverse incidents because of concerns about openly sharing mistakes and lessons learned out of fear of the potential legal implications;
- the difficulty in measuring and interpreting both the qualitative and quantitative dimensions of risk;
- the use of medical devices beyond their labeled indications for use or beyond their useful life;
• the related practice of using multiple generations of the same medical device, which in some cases can add to risk in the environment of care;
• the complex societal and political views about how much risk we are willing to tolerate as a society and as individuals;
• the difficulty of learning about device issues in the field from service data on equipment that is serviced in hospitals, by third-party servicing organizations, or by other original equipment manufacturers (OEMs), and due to gaps in event reporting from healthcare providers for devices that are not equipment.

These barriers all directly or indirectly affect risk and device users but are difficult to specify and quantify in the limited scope of this paper. Manufacturers of medical devices also must address many other complex issues in their assessment and management of risk across the total product life cycle of medical devices (e.g., supply chain; quality and adequacy of sample size of the data for purposes of evaluating risk; and other regulatory challenges). The existence of these complexities are acknowledged here because they impact how the risk factors and risk principles are applied for any given product or circumstance. In short, the application of risk principles and risk factors in real life is much more complex than it may appear from a simple reading of this white paper.
Risk Principles and Medical Devices: A Postmarket Perspective

1 Scope

1.1 In scope

The risk principles and risk factors described in this white paper are intended to be useful when assessing risks for medical devices with postmarket quality and safety issues. It includes assessment of risk above and beyond the baseline risk profile for a device (acknowledged in marketing clearance or approval). These risk issues arise in situations of device non-conformance, malfunctions or failures, use errors, or in limited availability (shortage) situations. Postmarket quality and safety issues include but are not limited to recalls.

1.2 Out of scope

The risk principles and risk factors described in this white paper are not intended to address:

- risk and benefit decisions made during premarket review, except for basic understanding and definitions;
- quality system management in device design and manufacturing;
- detailed implementation of specific compliance activities by FDA or industry;
- academic theory about risk; or
- regulation or business risk.

2 Definitions of risk and benefit

For purposes of this white paper, risk is defined as in ISO 14971: 2007 [3]: Risk is the combination of the probability of occurrence of harm and the severity of that harm.

The term 'benefit' is not explicitly defined in ISO 14971:2007. However, for the purposes of this white paper, benefit is defined as in ISO 16439: 2014 [4]: Benefit is a helpful or good effect, or something intended to help.

3 Decision analysis

Decision analysis (DA) is a management technique in which tools are applied to discover the most advantageous alternative under the circumstances particularly where uncertainty figures as a prominent element. Consideration of risk principles and the factors that support them is only one part of the decision analysis in which risk is assessed and then managed. The ultimate goal for industry and CDRH is to make high-quality decisions about medical device risk. However, a good decision is not the same as a good outcome.

Annex A provides a brief description of the Decision Quality (DQ) chain which one of the industry experts provided the working group as an example of a practical framework for decision analysis.

4 Risk throughout the total product life cycle

Risk principles provide the foundational underpinning for risk management throughout the total product life cycle. Without alignment between industry and CDRH on the risk principles, achieving harmonization on the risk management processes will not be possible.
Even so, an even deeper analysis and discussion between industry and CDRH will be needed for purposes of coming much closer to a shared understanding of how the principles are applied in real life when postmarket examples of hazards and hazardous situations resulting in harm occur. From an industry perspective, risk is characterized for a product as part of total product life cycle and is neither a premarket nor postmarket specific concept. However, just as unexpected new infectious and contagious diseases come to North America and we don’t have drugs or vaccines to deal with them, a hazard or hazardous situation can arise when a product is marketed that was not foreseen at the time of device creation or market clearance. A manufacturer may have even identified a hazard or hazardous situation, but they anticipated the probability or severity was so low that it was not considered a risk requiring risk control measures. Again, infectious and contagious diseases are useful illustrations of how this happens.

Identifying the baseline risk profile prior to market release can be difficult. When patients are harmed in a way or with a probability or severity not anticipated, the original risk assessment will likely require revision. A new risk evaluation is needed to determine if the risk remains acceptable or if additional risk control measures are required to reduce that risk to a level that would satisfy the original risk acceptability criteria. For example, there may be a particular scenario where the manufacturer decides the benefit of having a device on the market outweighs the residual risk. When the device is marketed, however, patients experience the predicted harm at a rate or with a severity that is not readily comparable to the premarket residual risk assessment. When the rate of occurrence or severity of the predicted harm is significantly different from the baseline risk profile, an updated risk assessment is needed to determine if the benefits to patients still outweigh the risks, given the new understanding probability of occurrence of harm or its severity.

Additionally, when considering responses to a revised risk assessment it may be necessary to consider the harm that may occur due to other consequences, such as a shortage caused by a recall. In such cases, industry and CDRH may need to evaluate the postmarket risk in the context of actions that could make the product unavailable in the marketplace resulting in a shortage that affects the public health.

### 5 Setting the foundation for risk assessment and risk management

In preparation for thinking about risk principles, it is important to consider several philosophical points that are fundamental to any consideration and thus management of risk for medical devices with postmarket quality and safety issues:

1. It is impossible to eliminate all risk. Consequently, one of the elements of the risk management process is evaluating the overall residual risk that is acceptable using the criteria for risk acceptability established for the device.

2. Risk assessments often are conducted without all of the information or data that would help in the assessment, e.g., the results of a root cause analysis (RCA) for a device failure or a use error. The performance of the device may also be considered in light of similar devices in use. Delaying a decision in order to continue to gather more information may be a bad decision associated with greater risk than proceeding with incomplete information. At the same time, it is important to consider a variety of investigative approaches to identify the root cause(s).

3. Compliance with applicable laws and regulations is a minimum requirement. Risk principles do not govern all regulatory decision making, which must take into account the law and regulations. That said, it is important to note that regulatory reliability and quality issues may arise that are not associated with clinically significant safety issues. There may not always be reasonable actions that address these issues as well as those that reduce risk.

4. ISO 14971:2007 lays out the risk management process that virtually all medical device companies doing business in the U.S. use for managing risk from a total product life cycle perspective. Risk management for a particular medical device begins with the development of a risk management plan. The process flow, as illustrated in Figure B.1 of ISO 14971:2007, then starts with a risk analysis, and ISO 14971 states that identifying hazards and determining the probability of occurrence and severity of harm is fundamental to assessing risk. Risk evaluation involves deciding if risk reduction is required by comparing the estimated risk against the criteria for risk acceptability given in the risk management plan. Together these two process steps form the risk assessment phase of the risk management process.
Assessing the probability of occurrence of harm typically involves structuring the relationships between hazards (in both normal and fault condition), the hazardous situations that can arise due to particular sequences of events, and the harm that could ensue. This activity is termed a “qualitative” analysis. At some point in the analysis, numerical quantities (including but not limited to probabilities) may be useful. This activity is termed a “quantitative” analysis. Both qualitative and quantitative thinking are important to risk analysis. Sometimes risk analysis requires nothing more than a written characterization (“qualitative”), but often the assessment will be characterized by both written formulations and increasingly detailed mathematical models (“quantitative”). However, one should never lose sight that the conversion of qualitative data into quantitative values can be nothing more than a “quantification of subjectivity.” As such, it is essential to be mindful of bias and preconceived notions. Techniques have been developed, such as those described in the paper by Soll, et. al [8], to reduce the effect on bias in decision analysis.

Risk evaluation is reviewing the output of the risk analysis and making a judgment of whether a risk is acceptable or unacceptable, applying the criteria for risk acceptability given in the risk management plan.

Ultimately, the risk evaluation—whether based on a quantitative or qualitative risk analysis—is intended to support and not replace judgment as part of the decision analysis. The goal of risk assessment is to clarify a complex decision such that the judgment about what should be done is readily made, easily understood, and defensible. For example, a risk assessment can help the decision makers understand how the probability of the occurrence of harm and thus risk varies with factors such as when the use occurs in the life of the device, whether it is used with multiple patients, and other clinical and nonclinical application characteristics. When striving for a high-quality risk assessment, people may naturally experience difficulty in the risk evaluation part of the overall risk process. This is because when dealing with patient needs, sometimes, the risk is greater when the product is not available than the risk arising from the fault or defect. This does not make the risk or residual risk arising from the fault or defect “acceptable.” However, when used alone, judgment can be subject to widely recognized biases and thus is difficult to defend.

Risk management principles should also help deter criticism of the decisions and actions made by others by providing standards for good risk management decision making. While easier said than done, decisions should not be judged solely by the outcome. Embedded in the ISO 4971 risk management process is the realization that two reasonable people looking at the same data may reach different conclusions about the level of acceptable risk. The standard should be: Was the risk management decision consistent with what a reasonable person, using reasonable methods, would conclude, given what was known or what could be reasonably foreseen about the uncertain harms and benefits of various potential actions at the time the decision was made?

5. Judgments on acceptable or unacceptable risk made by industry should be supported by analysis that assesses key uncertainties using experience, historical data, etc. This type of analysis can enable a more defensible judgment that goes beyond just citing standards, data, or conventional practice/experience for those situations that warrant a more comprehensive approach. A well done risk assessment can help demonstrate that the alternative chosen best balances the risk and benefit given what was known at the time the risk management decision was made.

However, there are times when conformance with standards can be sufficient to demonstrate that risk and benefit is appropriately balanced. For example, conformance with ISO 10993-1 [1] and with other appropriate parts of the ISO 10993 series such as ISO 10993-3 [2] is sufficient to demonstrate a medical device is biocompatible. No additional analysis is needed.

Some experts would contend that it is important to distinguish “known” risks from “reasonably foreseeable” risks. When considering what risks are “reasonably foreseeable” the manufacturer needs to consider those sequences or combinations of events that can result in a hazardous situation that a reasonable person would be able to predict or expect under the given conditions. The manufacturer needs to exercise due diligence in constructing those sequences or combinations of events to avoid missing scenarios that a reasonable person would have predicted or expected while also avoiding the cascading (sometimes referred to as stacking) of events that results in an unreasonable prediction leading to a false conclusion.

Both know and reasonably foreseeable risks, however, can be characterized by probability of occurrence of harm and severity of harm. Identifying “immediate” risks, on the other hand, may be
relevant. Given adequate information, people generally prefer present benefits over future benefits, and prefer future harms over present harms. Therefore, the so-called time-preference may need to be captured when risks and benefits occur at different times. Known and immediate risks may or may not require intervention; reasonably foreseeable and delayed risk may or may not require intervention. With respect to the rationale to intervene to make changes to a product, the principle of balancing risks and benefits is the key, not distinctions about known versus reasonably foreseeable or delayed risks.

6. Risk should be assessed from a holistic perspective, looking at it in the entire context of the environment of use and considering evolving circumstances that could change the baseline risk profile.

For example, would the risk change with the introduction of some new device into the environment of care, or how would device integration impact risk? IEC 80001-1 [6] defines the roles, responsibilities and activities that are necessary for risk management of IT-networks incorporating medical devices to address safety, effectiveness and data and system security.

In another example, consider a catheter that is used to invasively monitor cardiac function. Typically, such a catheter is placed through a sheath into the cardiac chambers, usually for 1 to 3 days. It is connected to a monitor that contains software that calculates and displays cardiac output and pressures in the heart. The catheter, sheath and monitor represent a system and the accuracy of the values used to make clinical decisions requires that each of the components of the system meet their performance specification. In addition, the catheter can be used with sheaths and monitors from different manufacturers. The postmarket risk assessment needs to consider the function of each of the devices and how they interact.

7. Knowledge of the state of the art in clinical-understanding and clinical workflows should be a part of the overall risk assessment: e.g., what are the current expectations of the clinical use; are there any changes in medical practice that could increase risk.

6 Risk principles

While ISO 14971 provides the overall framework that the medical device industry uses for risk management of medical devices across the total product life cycle, it does not specify what risk principles should be used to guide risk assessment or the management of risk. In the context of postmarket quality and safety issues, the industry and CDRH experts who worked together on this project agreed that the following risk principles should guide both CDRH and industries' postmarket risk assessment. Again, it is hoped that if both CDRH and industry share the same view about the risk principles, then postmarket risk assessments and subsequent decisions should be more closely aligned.

6.1 Informed judgment in risk and benefit evaluations

All risk and benefit decisions require the use of informed judgment. Information to be considered in a postmarket environment should include relevant information such as:

- experience with the device, similar devices and the general type of product,
- historical data,
- community standards, and
- potential planned product mitigations.

Risk and benefit evaluations should be conducted by teams with expertise, including but not limited to qualified medical / clinical professionals and subject matter experts (e.g., engineers; scientists; etc.).

NOTE 1 Community standards, that can reflect a society's tolerance for risk, may include: international standards, national norms, other technical standards, and local standards of care.

NOTE 2 The use of experience, insight and judgment is discussed in several places in ISO 14971 including in the introduction and in Annex D.3 and D.6.

6.2 Loss-of-benefit assessment

A loss-of-benefit assessment needs to be considered as part of the overall decision analysis for issues that emerge postmarket. "Loss-of-benefit assessment" means that the overall postmarket risk assessment needs to include whether the particular postmarket issue would change the benefit-risk ratio, as well as...
whether the options for action or inaction would change the benefit-risk ratio. In other words, in determining the appropriate action or inaction, the evaluator should consider multiple risk and benefit scenarios. Each scenario should consider any changes in the baseline risk profile as well as the potential introduction of new risk and the consequent effect of either on benefit. Examples include:

- the same benefit with increased risk;
- decreased benefit with increased risk; or
- the loss of benefit with increased risk from product withdrawal.

Product withdrawal could increase the potential for field shortages, cancellations of procedures, and other ripple effects that can result in the loss of benefit in the absence of alternative products or procedures.

NOTE 1 This is not the same risk/benefit analysis or overall residual risk/benefit analysis described in Subclause 6.1 or Clause 7 of ISO 14971.

NOTE 2 Loss-of-benefit assessment is not currently addressed in ISO 14971. A suggestion that ISO 14971 include a discussion of loss-of-benefit assessment and guidance be added to ISO/TR 24971 is one of the suggested enhancements which might be considered in a future revision of these documents.

6.3 Populations

In conducting the risk assessment in response to a device failure, an unanticipated problem, or a field shortage due to a recall, the evaluator should determine if there are subpopulations included in the indication for use that are at greater risk or receive greater benefit than the overall population. These subpopulations should be considered separately.

NOTE 1 Annex C of ISO 14971:2007 contains questions and descriptions that include areas such as patient population to consider if the risk may be different based on patient population aspects.

NOTE 2 Abnormal use on subpopulations excluded in the indication for use are outside the scope of the assumed benefit. Postmarket problems occurring during off-label use need to be addressed in a different industry - CDRH forum.

In conducting the risk assessment, the evaluator should focus on individual risk to the patient and/or user with balanced consideration to the impacted population. In some cases, it may be that postmarket quality and safety issues raise possible harm to the overall population (including clinicians) either directly or indirectly, e.g., spread of infectious disease, fire, and explosion. In such cases risk assessment must consider harm beyond harm just to the patient, but also to the wider population.

NOTE 3 Population considerations are included in the questions in Annex C, in Annex D.3.4.2 and in Annex H of ISO 14971.

6.4 Use environment and clinical assessment

The risk assessment should include the context of the environment in which the device will be used. The risk assessment and the loss-of-benefit assessment outlined above should be conducted considering the total clinical system within which the device will be used, including but not limited to, transport, hospital use, home use, backup systems, interaction with other devices and systems, impact of multiple device environments or multiple device use.

NOTE 1 Annex C of ISO 14971:2007 contains a list of questions that can help understand the total clinical system within which the device will be used during both the pre- and postmarket risk assessment.

A qualified clinical professional should participate in the postmarket risk assessment and the loss-of-benefit assessment. The clinical risk and benefits or reduction in benefits should be evaluated with a knowledge of current clinical practices, expectation of clinical use, alternative products and procedures, and how changes in medical practice may change the assessment.

NOTE 2 The use of expert opinion is discussed in several places in ISO 14971 including subclause 4.4, Annex A.2.3.3 and Annex D.

6.5 Communication

Important device risks and/or any reduced or loss of benefits to patients due to a failure, unanticipated problems, or a field shortage due to a recall that occur once the device is marketed should be
communicated effectively to relevant stakeholders. In certain circumstances, postmarket risk can be managed effectively through communications, sometimes reducing the need to remove the affected device from the market. Communications with relevant stakeholders may be useful both in cases involving a device failure and when new risk information is obtained from postmarket surveillance systems.

NOTE 1 It is important that communication be effectively made to relevant stakeholders given that too much communication can cause audiences to stop listening, thereby increasing risk. Too little communication, on the other hand, can prevent the user from making an informed decision that weighs the residual risk against the benefits of using the device.

NOTE 2 It's also important to consider cultural diversity and health disparities in determining communication strategies.


Stakeholders input needs to include physicians and others such as:
- patients
- users
- regulators
- healthcare facilities
- healthcare providers
- hospital biomedical engineering, service providers, and technicians
- community partners

6.6 Risk control and recovering loss of benefit

After risks are identified and assessed postmarket, risk control is used to reduce the risk. In addition, the decision analysis will need to address potential actions if the benefit has been reduced and the full benefit cannot be recovered. Effective decision analysis in a postmarket environment requires understanding the potential impact of the loss of benefit from the device, risks to the patient caused by the defect or failure, and potential harm from other devices that may be used in place of the device. In determining the measures for controlling the risk arising from a postmarket event, it is important to consider the various options available for minimizing or preventing re-occurring risks. In addition, it is important to assess the impact of the options on healthcare delivery.

NOTE 1 The occurrence of a postmarket event that was not identified in the premarket risk management activities could indicate a certain inadequacy or failure of the premarket risk management process. It could also indicate other changes that affect the product’s baseline risk profile such as changes in the use environment, the standard of care, or other new knowledge unknown to the device manufacturer at the time the baseline risk profile was developed. This underscores the need of periodical review of the risk management files against the postmarket data.

NOTE 2 The Swiss-cheese model of risk management proposed by Professor James Reason [7] is one well known and accepted model for identifying risk control measures. This model shows that no single method of defense can protect individuals or organizations. The model helps to reduce the risk to an acceptable level by deploying multiple layers of defense and managing carefully the probability of occurrence of harm in each one.

NOTE 3 Risk control option analysis is described in subclause 6.2 of ISO 14971:2007. This analysis is required when risk reduction is required for risks identified either premarket or postmarket.

7 Factors to consider when applying the principles while assessing risk and benefit to postmarket quality and safety issues

There are many factors that can be considered when applying these risk principles while assessing both risk and benefit in the context of postmarket quality and safety issues. These factors should apply as they are relevant to the postmarket event. Not every risk factor is applicable to every situation. The list in Annex B is a starting point that is intended to help stimulate a thorough analysis. From the perspective of CDRH, disagreements may require justification / documentation. It is noted that the list in Annex B is long and the items are categorized but not explained. There were too many possible factors to explain each one. It is still worth sharing the list because it represents the thinking of the industry and CDRH experts who did this work together.
8 Risk principles in context

In this section of the white paper, several representative examples are provided from the set of examples that the working group used to help set the context for developing the above risk principles and risk factors.

The purpose of including these examples and the discussion points is to put the risk principles into real and meaningful context. They are illustrative only, with the caveat that every risk scenario is unique.

Example 1: A biological indicator was recalled; and during the CAPA investigation, the manufacturing machinery was found to have deteriorated. The firm notified FDA that there would be a decrease in product available for some time.

A few months later, the firm contacted FDA about reports that surgeries were being delayed due to lack of biological indicators. The firm did not expect to return to full production for some time.

The risk considerations included the risk of delayed surgeries / prioritization of critical surgeries / rationing of indicators versus the risk of using instruments without sterility confirmed. The firm proposed a temporary change in the Instructions for Use that would allow monitoring of fewer loads. After review of data from the firm, CDRH agreed that the risk of less frequent testing was acceptable until adequate supplies of the indicator were available. FDA also accelerated review of an in-house 510(k) from the manufacturer of an alternate indicator.

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

This example is considered an excellent model of industry and CDRH working well together to solve a practical problem with a shared discussion of the risk and ways to solve that risk to minimize problems in the market. It is included here for that reason.

Example 2: A Class III implantable device has three (3) field complaints for a malfunction: a complaint rate of 0.08%. Medical Device Reports (MDRs) are filed for malfunctions. They report that blood loss occurs but no serious injuries occur. The root cause was found to be design related. The investigation determines it is a low level, randomly occurring event that cannot be bounded. Removal of the product from the field will result in hundreds/thousands of cases being cancelled in critically ill patients with few options.

This example illustrates the issue of potential “shortage” and the importance of including potential harm to patients from removing a product in the overall postmarket risk and benefit assessments.

Example 3: At extremely high blood glucose levels of 1024 mg/dL and above, the blood glucose meter will display and store in its memory an incorrect test result that is 1024 mg/dL below the measured result. Device is a Class II device.

The manufacturer assessment of risks as follows:

- Severity = High
- Probability of occurrence of Harm = Rare – no change from initial assessment
- Overall Risk = Low
- Risk control = The probability of experiencing extremely high blood glucose levels such as 1024 mg/dL and above is rare. For users of this meter, it is likely that a user would be testing on a regular basis. Hyperglycemia would likely be recognized prior to reaching levels above 1023 mg/dL. In addition, a user would be experiencing hyperglycemic symptoms which would prompt them to test more frequently and/or seek medical attention.

Several factors made this risk assessment difficult. While the severity associated with such an elevated blood glucose reading was high, the probability of such a reading actually occurring was extremely low due to known factors of use. The overall risk to the user was determined to be low and the probability of occurrence of harm did not change, though a new hazardous situation was identified. However the issue was deemed high risk (Class I recall) by FDA.

This illustrates the real life difficulty of postmarket decisions when industry and CDRH do not have a shared view on how to prioritize the overall risk to patients when the severity is high and the probability of occurrence is very low.
Example 4: A manufacturer initiated a global mailing to remind patients and healthcare providers about a feature in its drug delivery device that allows the user to scroll continuously from the maximum set amount to the minimum set amount, without having to scroll back in the other direction. This particular feature has been, by default, in every drug delivery device produced since the 1980s.

This example illustrates why industry experts see “communication” as an important risk principle. It also illustrates the importance of evaluation and judgment in the risk assessment, as well as a deep understanding of the use environment and total clinical system in which the device will be used (in order to understand the implications of the options).

Example 5: A sample of catheters failed an FDA import visual exam due to small clumps of debris on them. However, the inspection was performed using a microscope providing 20X magnification or more. The FDA was concerned that the catheters did not comply with:

- ISO 10555-1:2013, Intravascular catheters — Sterile and single-use catheters — Part 1: General requirements, Subclause 4.4, and

Both standards state: “When examined by normal or corrected to normal vision, with a minimum 2.5x magnification, the external surface of the effective length of the catheter shall appear free from extraneous matter.”

The manufacturer maintained that this was innocuous material with no risk to the patient, and it would meet the manufacturer’s specification for cosmetic defects.

This example illustrates several issues, especially the importance of good documentation of the risk assessment. Without strong documentation, it was not clear whether the manufacturer used ISO 10555-1 for their manufacturing specifications and, if so, had failed to meet it. Second, it was not clear whether debris seen at more than 2.5x magnification would pose a significant risk to the patients.

Challenges included: (1) Documentation of how a test method in an external standard is used in order to assess manufacturing compliance to the standard. (2) The lack of clearly stated criteria such as level of magnification for examinations. (3) Assessment of risk with incomplete information about effects of intravascular introduction of small particles into the circulatory system, and impact of size of particles on safety. If the assessment was done, it was not documented well, which raised the question of whether the risk had even been considered.

9 Next steps

A number of issues surfaced in the working group discussions that will need to be addressed in more detail during the next phase of this project. Those issues are mentioned in the context of this white paper simply to provide context to the reader about the additional topics that the working group members acknowledged will need further work. As of the time of this writing, no determination has been made about when or how that work will be done, unless otherwise noted.

1. How will the risk principles be weighted, and how will the weighting criteria be evaluated to determine the “correct” results?
2. Issues that arise in determining if a recall should be classified as a Class I, Class II or Class III recall.
3. Recalls of products with compliance issues that either have low or no significant impact on safety.
4. How to conduct a risk assessment.
5. How to interpret and use the risk assessment.
6. To what extent ISO 14971 would benefit from being augmented to address more postmarket issues than it currently includes. For example, the standards committee might consider weaving in the use of the risk principles and factors in the section on evaluation of overall residual risk acceptability. The ISO committee might also want to tie the risk factors into Annex C of ISO 14971, which includes questions to help identify risk. It would also be useful for the ISO committee to evaluate how else the risk factors and principles could interact with ISO 14971 in the future.
7. Issues around whether (if ever) to apply a worst case assessment versus overall risk on a continuum. The industry experts in the working group found the notion of “worst case” to be problematic because it
may ignore probability and the fact that the risk assessment should be looking at the potential range of possible outcomes and related probabilities.

8. How to make precedents more transparent so industry can learn from them.

9. Several of the industry experts expressed that they would like to carry the risk principles further to provide standards for risk evaluation by codifying what are defensible judgments, in order to harmonize industry and regulatory perspectives on this important point. This was not discussed at any length and may or may not become part of further work. It is included here to memorialize the request from industry to address it.

10. Some industry experts would like to work on a definition of “baseline,” which is a term used by CDRH but not by industry. The industry experts think it must mean “the premarket risk file,” because this would clearly delineate the scope to only unexpected risks or new risk inputs, which either drive revisions to 1) the risk management file (to define and evaluate the risk), or 2) the device (to further control and bring the risk back in line with the premarket risk profile). More work appears to be needed to gain a shared view of this.

10 Recommendations from commenters

A number of thoughtful comments and suggestions were made by commenters that were beyond the scope of the assignment given to this informal working group. Consequently, comments and suggestions could not readily be addressed in the white paper itself, which represents the collective work done by the working group. However, the working group wanted to memorialize these comments and suggestions because they bring up issues that are worthy of consideration by future industry-CDRH ad hoc groups like this one. These comments and suggestions are captured in this section with encouragement to the greater community to continue the dialogue started here.

1. Global harmonization: Several commenters were concerned with the US-centric perspective of the white paper, when risk management for global companies is a global responsibility. Others suggested that the working group find ways to coordinate the project with existing global harmonization efforts and engage with organizations such as the International Medical Device Regulators Forum (IMDRF). The working group had a limited scope that was focused on US regulatory considerations because CDRH is the US regulator and the disconnects being addressed were between CDRH and manufacturers who are doing business in the United States. It is the challenges faced by industry and CDRH when assessing risks for medical devices with postmarket quality and safety issues that this project was set up to address. The working group agrees that global harmonization is an important goal and driver, and simply notes that it is beyond the scope of this project. The working group hopes that the issues raised in this project help in some way to further inform the efforts of experts who are involved in global harmonization work.

2. Involvement of qualified clinical professionals: Commenters observed that greater involvement of qualified clinical professionals is needed in postmarket risk assessment, as well as in the premarket risk assessment. This is addressed in Subclause 3.2 of ISO 14971:2007 by reference to “known stakeholder concerns” but is not explicit about the intent. Some guidance on determining stakeholder concerns is given in ISO/TR 24971, but perhaps that guidance could be expanded.

3. Off-label uses: Several commenters made the comment that the issue of off-label uses is very important and deserves consideration beyond a mere mention in the white paper. The comments collectively suggest that more industry-CDRH collaboration would be beneficial just on this topic alone.

4. Product shortages affecting public health: One commenter suggested that regulatory bodies may have more global understanding of when a product shortage can affect public health. The comment suggested that industry and CDRH need to collaborate on developing guidance that would describe where the information is expected to come from to determine if a recall will result in a product shortage that will affect public health.

5. Interaction between industry and CDRH: While agreeing that the next steps identified in the white paper are a good start, one commenter suggested the following items should be addressed in future phases of this project:

   a) Industry and CDRH should continue to explore ways to encourage, rather than penalize, proactive communication by manufacturers of new risk information obtained from postmarket surveillance systems. This recommendation builds on the concept that risk assessment and decision analysis necessarily relies
on using best judgment of the information available at the time the decision is made; hindsight and second-guessing reasonable risk decisions made at an earlier time that were based on the best available evidence is not appropriate.

b) CDRH should provide guidance and examples on the appropriate use of safety alerts to communicate new risks, or to manage existing risks, as an alternative to disruptive product removals.

c) The use of probability assessments in the risk evaluation process should be encouraged to better align with regulatory requirements and definitions. The relevant stakeholders should be encouraged to enter into a joint effort to determine acceptable methods, documentation, and use of probability calculations in evaluating safety and health risks that CDRH will find reliable and acceptable.

d) CDRH should continue to work with stakeholders on appropriate approaches to account for international differences in risk assessments, such as differences in approaches to assessing and managing postmarket risk and to benefit-risk calculations (see also recommendation 1 above).

6. **More and better examples:** A number of commenters wanted to hear more details about the examples provided, and to see even more examples. The comments collectively suggest that it would be very beneficial to manufacturers to learn even more deeply from the experiences of others (CDRH and industry). Another commenter suggested tying the examples back to the specific risk principles and factors. One commenter went so far as to note that the analysis of failures can be just as valuable for current risk assessments as for future predictions, and that more consideration is needed on risk improvement through design changes. “New” hazards always exist in real life so an important discussion topic is how we should acknowledge and monitor that these failures can come about and what we should do about them. Another commenter suggested it is key to understand what aspects of the design must be controlled, and which have the potential for significant impact on safety i.e., components that are relied upon to preserve safety.

Additional discussion regarding the significance of the facts and resolution also would be useful, in addition to an explanation of FDA’s decision-making process for the particular case and the facts and circumstances warranting product action, if any.

7. **Publish CDRH recall policies:** In this regard, greater transparency and dialogue with FDA will lead to a better understanding and alignment between industry and the agency. We believe the white paper should call on FDA to publish its policies that determine the types of recalls that are considered Class I. Having a better understanding of FDA’s rationale for these policies will facilitate more consistent decision making for industry, and allow for an open dialogue about whether certain FDA policies and procedures should be reconsidered.

8. **Guidance on postmarket risk monitoring:** More specific guidance is needed on monitoring risk in the postmarket phase. This conclusion came across in a number of comments and is, to a certain extent, related to recommendation 4 above. The need for industry and regulators to work together (and with healthcare delivery) to try to solve this major problem was aptly summarized by one commenter in these insightful thoughts: “Risk monitoring . . . is an important subject and the source of much confusion today. The ISO standard is ambiguous in how the probability of harm should be estimated, so manufacturers can view risk in different ways and still comply with the standard. Ultimately, however, their approach will be subject to interpretation by regulatory authorities when a field issue occurs, and thus often leads to contentious audits and inspections, as well as emotional debates that the manufacturer rarely wins. For example, the probability scales given as examples in Annex D of ISO 14971:2007 are based on the likelihood that an individual exposed to a medical device will be harmed, whereas the probability scales used in the FDA’s HHE [Health Hazard Evaluation] form are based on the likelihood that harm will occur in the overall population exposed to the device AND in the subpopulation at greatest risk. Both approaches are reasonable from an individual patient’s perspective as well as a public health perspective. The probability scale used in the AAMI risk management course actually includes both probabilities. However, a consensus among those charged with protecting the public health and the industry would be helpful to standardize the approach and avoid surprises.”

“There is also considerable confusion in the interpretation and application of risk acceptability criteria in the postmarket phase. In effect, the standard requires a manufacturer to define an acceptable probability of harm for a given type of injury, so for monitoring and trend analysis some companies translate that acceptable probability level to an acceptable (i.e., unavoidable) inherent rate of deaths and serious injuries. But since few manufacturers have access to sufficient reliable data to detect adverse trends based on statistical analysis, how should risk monitoring work in practice?”
9. **ISO 14971 and ISO/TR 24917:** Some commenters had specific suggestions for the committee responsible for ISO 14971 and ISO/TR 24917 to consider in future revisions. Those suggestions have been collected below and in Annex C to facilitate the communication with the ISO committee.

- Consider including the concept of “mission criticality” in the components that define risk. Mission criticality characterizes how critical is the function of a medical device to the global mission of the healthcare organization, not just to an individual patient.
- Expand the guidance ISO/TR 24917 on determining stakeholder concerns (see also recommendation 2 above).
- Expand guidance in ISO/TR 24917 on managing risk postmarket.
- Create a methodology for analyzing device benefits systematically and consistently across medical devices. Add guidance to ISO/TR 24917 on conducting a loss-of-benefit assessment.
- Provide additional guidance in ISO/TR 24917 on calibration of premarket estimates of risk to postmarket reality.

Earlier drafts of the white paper recognized ISO 14971 but, based on comments from ISO 14971 experts, did not adequately incorporate the terminology or concepts expressed in the standard. While some commenters noted that there were important points coming out of this project that should be forwarded by AAMI to the committee responsible for ISO 14971 for future consideration, others seemed to express that ISO 14971 adequately addresses all aspects of risk management that industry and regulators globally need in order to harmonize the process of risk management itself. The fact that the white paper generated so much conversation about what ISO 14971 already answers and where it might be expanded seems proof enough on its face that those responsible for ISO 14971 have much food for thought about potential topics worthy of expansion, clarification, or greater applied consensus.

11 **Conclusion**

FDA has stated publicly that it is dedicated to being more predictable, consistent, and transparent across the agency. Embedded in this goal is a dedication to seek input from stakeholders about its approach to risk and risk assessment and how they relate to continued benefit in postmarket situations where new hazards or hazardous situations develop that were not present, not known, or not addressed at the time of clearance or approval.

As applied to the compliance area, there is a strong shared desire by both FDA leadership and industry to harmonize expectations of FDA, industry, and other stakeholders. The first step has been achieved through this collaborative process that allowed for the development of mutually agreeable risk principles developed jointly by FDA staff and industry. The next steps will be even more important, as subgroups begin to tackle harder questions around the application of the risk principles in various compliance scenarios where industry and FDA in recent years have not been aligned with a shared view of risk.

12 **Working group**

The three national industry trade associations (AdvaMed, Medical Imaging & Technology Alliance [MITA], and Medical Device Manufacturers Association [MDMA]) were invited to name three representatives each to the working group. As convener, AAMI also named three representatives to the working group. Additionally, FDA provided several representatives. The working group members are listed on page iv. Dr. Kimber Richter served as the FDA co-chair and project lead. Ginger Glaser served as the industry co-chair.

The draft white paper was submitted for public review and comment on February 6, 2015. The deadline for comments was May 20, 2015. Comments were submitted by 26 individual and organizations. A total of 285 comments related to specific line(s) within the draft were submitted along with an additional nine general comments related to the overall document. The comments were thoroughly reviewed by an independent editor and then by the working group.
Annex A
Decision Quality (DQ) chain

A.1 The DQ chain

One of the industry experts provided the working group with a practical framework for decision analysis, called the Decision Quality (DQ) Chain. It is illustrated here:

Source: Decision Education Foundation (www.decisioneducation.org)
For more information, the brief video on the DEF home page explains each link in the DQ chain.
Copyright Decision Education Foundation. Used with permission.

Within each link of the DQ Chain we can identify the best practices and standards for medical device risk decisions. The DQ Chain thus serves as one organizing principle for thinking through risk. The DQ Chain is used here solely for purposes of illustrating the usefulness of some type of decision analysis tool. It certainly is not the only such tool.

The distinction between a good decision and a good outcome is very important. When we face uncertainty, a good decision can still have a bad outcome. Good decisions do not guarantee good outcomes, but—on average—consistently better decisions lead to consistently better outcomes.

A.2 The elements of decision quality

A.2.1 Helpful frame

Framing is clarifying the decision to be made. To properly frame a decision, the decision maker needs to define what is being decided, what is not being decided, what can be taken as given, and what goal is to be achieved.

The decision frame has three components:
- Purpose: what the decision maker hopes to accomplish by the decision;
- Scope: what to include and exclude in the decision; and
- Perspective: the decision maker's point of view about this decision.
A.2.2  Clear values

Values are what the decision maker cares about—wants, needs, likes, and dislikes. They cause the decision maker to prefer the consequences of one alternative decision over another.

A.2.3  Creative alternative

An alternative is one of the possible courses of action available. Without alternatives, there can be no decision. Good alternatives are (1) under our control, (2) significantly different, (3) potentially attractive, and (4) achievable.

A.2.4  Useful information

Useful information is anything the decision-maker knows, would like to know, or should know that might influence the decision-making process but that is not under the control of the decision maker. This includes factual information from the past and judgments about current or future situations that help anticipate the consequences of acting on the alternatives.

A.2.5  Sound reasoning

Reasoning is the process of combining alternatives, information, and values to arrive at a decision. It completes the sentence, “I am choosing this alternative because....”

A.2.6  Commitment to follow through

Commitment to follow through means purposeful execution of the decision. If the execution is only half-hearted, the execution may not achieve the best results.
Annex B
Factors to consider when applying the principles and assessing risk and benefit

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

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

B.1 Factors having an impact on the severity of harm
- Duration of exposure
- Acute versus chronic
- Reversibility of harm (e.g., death, injury)
- Body part impacted
- Pain intensity and duration of recovery
- Known and immediate injury versus reasonably foreseeable future injury
- Immediacy of the onset of harm
- Patient, operator or others – who is harmed?
- Patient preferences (quality of life) context of benefit given known harm (consider alternatives)

B.2 Factors having an impact on the probability of occurrence of harm (also sometimes referred to as frequency of harm)
- Not all exposures to a hazard result in harm
- Extent of event needed to cause injury or disease
- Consider both the probability of future occurrence (fraction) and the number of patients who may plausibly experience the harm (numerator).

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

B.3 Factors having an impact on the complexity of the risk and benefit assessments
- Complexity of use (human factors use error / usability of the device)
- Systemic versus randomly occurring
- Unexpected or uncertain hazard versus known prior adverse events
- Chronic harm may take time to become evident
- Failure detectability / user awareness of an existing problem
- Single versus multiple use device
- Single versus multiple patient use device
- Intended use of the device
- Software dependency
- How many other devices are likely to be in use with this particular device—is there an additive nature of multiple devices used at the same time on the patient (environment of care considerations)
B.4 Factors having an impact on risk management process

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

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

B.5 Factors arising from the affected population

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

B.6 Factors arising from current clinical practices

- Actions taken or planned to recover lost benefit based on clinical practice
- Lifesaving / life sustaining uses for devices
- Where is the device being used and by whom (e.g., home care versus ICU)—what is the skill level of the user?
- Other options available
- Effectiveness of communication to users (who is the user; what will they understand; who is interpreting the information for the patient; etc.)
- Unmet medical needs
- Risks with alternative choices
- Use in emergency / crisis situations
- Duration of device exposure:
- Implanted
  a) location
  b) patient age
  c) weight
  d) level of physical activity
  e) device aging
• Patient tolerance for risk
• Clinical understanding in evaluating risk
• Current expectations in clinical use
• Any changes in medical practice that could affect risk

B.7 Factors arising from the environment of care
• Causes of and interactions among various failures and faults and the potential impacts of multiple concurrent hazards or actual events resulting in harm
• Available medical device service information
• Labeling
• Training
• Experience with the device
• Mode of availability
• Overall use environment
• Clinical work flow patterns
• Age of the device and its estimated remaining shelf life or useful life.
• How long on market without updates / change
• Do other products have similar issues
• When use occurs in a device life
• Multiple patient use or single patient use
• Multiple use or single use / disposable
• Consumables and incompatible consumables
• Evolution of the practice of medicine as it relates to the evolution of products, e.g., a new drug or device enters the market that interferes with old product already marketed.
• Other impacts, e.g., antibiotic coating and bacterial drug resistance
Annex C
Suggested items that might be considered by ISO/TC 210 when revising ISO 14971 or ISO/TR 24971

When developing this white paper, the risk principles working group identified items that merit consideration by ISO/TC 210 at the next revision of ISO 14971 or ISO/TR 24971. In addition, some commenters had specific suggestions for enhancements to ISO 14971 or ISO/TR 24971 to consider in a future revision. The suggestions are summarized in the following table to facilitate the communication with ISO/TC 210.

<table>
<thead>
<tr>
<th>Document</th>
<th>Comment</th>
<th>Suggested change</th>
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<tbody>
<tr>
<td>ISO 14971 or ISO/TR 24971</td>
<td>Consider weaving in the use of the risk principles and factors described in this white paper in the section on evaluation of overall residual risk acceptability.</td>
<td></td>
</tr>
<tr>
<td>ISO 14971</td>
<td>Consider tying the risk factors described in this white paper into Annex C of ISO 14971.</td>
<td>Include mission criticality as an additional element in the definition of risk.</td>
</tr>
<tr>
<td>ISO 14971</td>
<td>Consider including the concept of &quot;mission criticality&quot; in the components that define risk.</td>
<td>Mission critically characterizes how critical is the function of a medical device to the global mission of the healthcare organization, not just to an individual patient. This reasoning has led the United States Joint Commission to define risk as composed of: (i) proximity to patient, (ii) probability of harm, (iii) severity of harm, and (iv) number of patients at risk.</td>
</tr>
<tr>
<td>ISO/TR 24971</td>
<td>Expand the guidance in ISO/TR 24971 on determining stakeholder concerns.</td>
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<tr>
<td>ISO 14971 or ISO/TR 24971</td>
<td>Expand guidance in ISO 14971 and/or ISO/TR 24917 on managing risk postmarket to address more issues including the effect of shortages created by removal of a device from the market.</td>
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</tr>
<tr>
<td>ISO 14971 or ISO/TR 24971</td>
<td>Another important fundamental element missing in ISO 14971 is the loss of benefit.</td>
<td>Create a methodology for analyzing device benefits systematically and consistently across medical devices.</td>
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<tr>
<td></td>
<td>Well before the postmarket example #1 mentioned on page 11, this concept was clearly demonstrated during the Y2k paranoia in late 1999. At that time, several healthcare leaders and safety organizations recommended the sequestration of medical devices for which it was not possible to either obtain manufacturers’ certification of Y2k compliance or test the devices thoroughly. This recommendation would have precluded access of patients to numerous medical devices, including some life-support equipment, during the</td>
<td>Include a discussion of loss of benefit in ISO 14971 and add guidance on assessing loss of benefit in ISO/TR 24971.</td>
</tr>
<tr>
<td>Document</td>
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<tr>
<td>ISO/TR 24971</td>
<td>Transition. The loss of benefit would have been catastrophic if such recommendation were followed.</td>
<td></td>
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</tbody>
</table>
Bibliography


### Glossary of terms used in this white paper

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>Source</th>
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<tbody>
<tr>
<td><strong>Baseline risk profile</strong></td>
<td>premarket estimates of the actual residual risks from using a properly designed, manufactured and labeled medical device</td>
<td>ISO 16439:2014, definition 3.7</td>
</tr>
<tr>
<td><strong>Benefit</strong></td>
<td>helpful or good effect, or something intended to help</td>
<td>ISO 14971:2007, definition 2.2</td>
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<tr>
<td><strong>Decision analysis</strong></td>
<td>a management technique in which tools are applied to discover the most advantageous alternative under the circumstances particularly where uncertainty figures as a prominent element</td>
<td>ISO 14971:2007, definition 2.3</td>
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<tr>
<td><strong>Harm</strong></td>
<td>physical injury or damage to the health of people, or damage to property or the environment</td>
<td>ISO 14971:2007, definition 2.2</td>
</tr>
<tr>
<td><strong>Hazard</strong></td>
<td>potential source of harm</td>
<td>ISO 14971:2007, definition 2.3</td>
</tr>
<tr>
<td><strong>Hazardous situation</strong></td>
<td>circumstance in which people, property, or the environment are exposed to one or more hazard(s)</td>
<td>ISO 14971:2007, definition 2.4</td>
</tr>
<tr>
<td><strong>Postmarket</strong></td>
<td>phase of the total product life cycle following market clearance until the product is removed from the market.</td>
<td>ISO 14971:2007, definition 2.11</td>
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</table>
| **Postmarket quality and safety issue** | an unexpected situation that arises postmarket which negatively impacts the performance or safety of the medical device  
NOTE: A “situation” could include issues with the device’s design or manufacture, unexpected uses, or factors arising in the environment of care | ISO 14971:2007, definition 2.15      |
<p>| <strong>Post-production</strong>                     | part of the life cycle of the product after the design has been completed and the medical device has been manufactured | ISO 14971:2007, definition 2.15      |
| <strong>Residual risk</strong>                       | risk remaining after risk control measures have been taken                                            | ISO 14971:2007, definition 2.15      |
| <strong>Residual risk assessment</strong>            | process of evaluating the risk that remains after risk control measures have been taken and comparing the estimated residual risk against given risk criteria to determine the acceptability of the residual risk | ISO 14971:2007, definition 2.21      |
| <strong>Risk</strong>                                | combination of the probability of occurrence of harm and the severity of that harm                     | ISO 14971:2007, definition 2.16      |
| <strong>Risk analysis</strong>                       | systematic use of available information to identify hazards and to estimate the risk                  | ISO 14971:2007, definition 2.17      |
| <strong>Risk assessment</strong>                     | overall process comprising a risk analysis and a risk evaluation                                        | ISO 14971:2007, definition 2.18      |
| <strong>Risk control</strong>                        | process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels | ISO 14971:2007, definition 2.19      |
| <strong>Risk control measure</strong>                | action or means to eliminate hazards or reduce risks                                                  | ISO 14971:2007, definition 2.21      |
| <strong>Risk evaluation</strong>                     | process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk | ISO 14971:2007, definition 2.21      |</p>
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<tr>
<th>Term</th>
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<tr>
<td><strong>Risk management</strong></td>
<td>systematic application of management policies, procedures and practices</td>
<td>ISO 14971:2007, definition 2.22</td>
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<td>to the tasks of analyzing, evaluating, controlling and monitoring risk</td>
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<td><strong>Risk management file</strong></td>
<td>set of records and other documents that are produced by risk management</td>
<td>ISO 14971:2007, definition 2.23</td>
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<td><strong>Risk management plan</strong></td>
<td>a document prepared by the manufacturer that includes:</td>
<td>ISO 14971:2007, Subclause 3.4</td>
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<td></td>
<td>a) the scope of the planned risk management activities, identifying and</td>
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<td>describing the medical device and the life-cycle phases for which each</td>
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<td>element of the plan is applicable;</td>
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<td>b) assignment of responsibilities and authorities;</td>
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<td>c) requirements for review of risk management activities;</td>
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<td>d) criteria for risk acceptability, based on the manufacturer’s policy</td>
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<td>for determining acceptable risk, including criteria for accepting risks</td>
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<td>when the probability of occurrence of harm cannot be estimated;</td>
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<td>e) verification activities;</td>
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<td>f) activities related to collection and review of relevant production</td>
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<td></td>
<td>and post-production information.</td>
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<td><strong>Risk factor</strong></td>
<td>factor to be considered when applying risk principles while assessing</td>
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<td></td>
<td>both risk and benefit</td>
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<td><strong>Risk principle</strong></td>
<td>principle used to guide risk assessment and management of risk</td>
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<td><strong>Root cause analysis</strong></td>
<td>a method of problem solving used for identifying the root causes of</td>
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<td></td>
<td>faults or problems</td>
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<tr>
<td><strong>Severity</strong></td>
<td>measure of the consequences of a hazard</td>
<td>ISO 14971:2007, definition 2.15</td>
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<td><strong>State of the art</strong></td>
<td>the current stages of development of a practical or technological subject</td>
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<td><strong>Total product life cycle</strong></td>
<td>all of the processes that lead to the creation of a product, the actual</td>
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<td>use of the product, and what happens after it is discarded</td>
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<td><strong>Use error</strong></td>
<td>user action or lack of user action while using the medical device that</td>
<td>IEC 62366-1:2015, definition 3.21</td>
</tr>
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<td></td>
<td>leads to a different result than that intended by the manufacturer or</td>
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<td></td>
<td>expected by the user</td>
<td></td>
</tr>
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