

Risk Management Series – Article 7: Determining Risk Acceptability – Part B

Foreword

MEDICEPT presents this ongoing series of articles focused on the implementation and practical conduct of risk management in the medical device industry to provide practitioners with insight into how to apply risk management principles and tools to improve the performance and safety of their devices; and, as an added benefit, to maintain compliance with risk management standards.

Our team at MEDICEPT publishes these articles to capture best practices, to explore the more challenging aspects of maintaining risk management systems over the long term, and to elicit discussions among practitioners.

To this last point, if you have questions or comments on the issues discussed, or if you have recommendations for topics to consider in the future, please let us know: 508-231-8842.

In our last two articles, *RM 5 - Assessing Severity* and *RM 6 – Estimating Probability of Occurrence of Harm*, we discussed approaches to develop values for these two elements of risk and the challenge of completing these assessments/estimates. This article takes the next step to address the question: *Are we, as a company, willing to accept the risks associated with our device given the benefits that a patient is likely to receive?* This first part of this article (Part A) provided a review of the standard approach. This article (Part B), provides our thoughts on the challenges of applying that approach.

Assessing Risk Acceptability – The Challenges

In Part A of this article, we provided an overview of the key elements of the standard approach assessing risk acceptability as described in ISO 14971, *Medical Devices – Application of Risk Management to Medical Devices* (we'll just refer to it as "the standard"). While this approach establishes a solid framework for building your internal risk acceptability processes, there are a few aspects of the approach that remain a bit murky and require some interpretation. The most challenging issues to deal with when applying this approach are:

- ***The role of Benefits in the Risk Acceptability Criteria***
- ***Independent Risks vs. Overall Risk***
- ***Residual Risk Evaluation vs. Risk-Benefit Analysis***

The role of Benefits in the Risk Acceptability Criteria

When risk analysis team members think about "risk acceptability" they typically focus solely on comparing one risk to another and forget that you can only judge the acceptability of a risk when you compare it to the benefits of the device. To some extent, this disconnect is driven by the language in the standard where they present two separate activities – first the "evaluation of risk acceptability" and then the "risk/benefit analysis". This separation implies that the consideration of benefits is not included

in the evaluation of risk acceptability. That's clearly not true. If a medical device had no benefits, you wouldn't be willing to accept any level of risk. Your RPN criteria would be "RPN > 0 = Unacceptable" and your Risk Acceptability Matrix would be a solid block of "Unacceptable".

The benefits of a device are implied in the structure of the risk acceptance criteria. This implicit consideration of the benefits of a device is a very important concept to understand when you are developing and using acceptance criteria. When developing risk acceptance criteria, the benefits of the device should be explicitly documented in your Risk Management Plan (RMP) so that you have a baseline against which the acceptability of risks can be judged.

Consider, for example a fictitious company that manufactures two very different medical devices. The first is an OTC disposable heating pad intended for the relief of minor muscular aches and pains for up to four hours. The second is a line of Automatic External Defibrillators (AEDs) designed to be used by individuals with limited training to treat patients in an emergency situation suffering from cardiac arrest. With the first device, the benefit is four hours of minor pain relief, while the second could save a life. Should the same risk acceptability criteria be used for both devices? Not likely. The benefits associated with the AED are so much greater than the heating pad, that there is a much greater tolerance for the potential risk of harm.

Continuing with the example, the company may decide that for the heating pad, any risk with a Severity of 3 or more (a "3" is typically defined as "major harm") is considered "Unacceptable", while the only "Unacceptable" risk for the AED might be a risk with a Severity 5 and a high likelihood of occurrence. Both devices could cause serious burns. For the heating pad, that risk may be "Unacceptable", for the AED, that may be a generally accepted part of applying the treatment.

Therefore, if properly designed, your risk acceptability criteria (either RPN or Matrix) are in fact "risk – benefit" criteria. You are assessing explicit risks against sometimes implied benefits. By making those benefits explicit in your RMP, your rationale for why the identified risks are acceptable will be much clearer.

Independent Risks vs. Overall Risk

As we've discussed in earlier articles (e.g., *RM 3: Using Fault Trees to Focus and Simplify Risk Analysis*), one of the weaknesses of the Hazard Analysis and FMEA structures (or a least one of the issues that you need to keep top-of-mind when working with these tools) is that they treat each hazard/failure as a separate event. In fact, they treat each individual cause as a separate event. This fact has a major impact on how you evaluate risk acceptability.

Just to review . . . for each hazard/failure you may have multiple causes. The Severity rating associated with each cause will be the same since all the causes are linked to the same harm. For example, consider the following example.

Hazard Analysis Rev A

Hazard Category	Hazard	Failure Mode	Effect (Harm)	Severity	Cause	POH ⁽¹⁾	Risk
Energy Hazard: Thermal	High Temp.	Out-of-Spec Device	Burn to hand	4	Device failure	4 (1/4,000 uses)	Unacceptable
-	-	Use Error	Burn to hand	4	User does not follow IFU	3 (1/50,000 uses)	ALARP

1: Probability of Occurrence of Harm (POH) values are based on the example table provided in ISO 14971 (Table D.4) and reproduced in Attachment A.

In this example, we have a generic device that has the potential to cause a serious burn to the user’s hand. The risk analysis team has not done a very detailed job of describing the potential causes of the identified failure modes. Only one cause is identified for the “Out-of-Spec Device” failure mode and one is identified for the “Use Error” failure mode. We’ll accept this limited analysis for now, but let’s assume that they did a good job of estimating the Probability of Occurrence of Harm (POH). In the POH column provided above, we include the estimate for the rate at which users would be harmed by each failure mode/cause. Using the criteria provided in Attachment A, the Probability of the Occurrence of Harm is “Probable” (a rating of “4”) for the device failure; and “Occasional” (a rating of “3”) is assigned to “User does not follow IFU”.

Both failure modes/causes need to be investigated to identify methods to reduce the level of risk, but the “Device Failure” issue is the highest priority given its status as an “Unacceptable” risk. So the team goes back to work, and as a first step they look at each of the five major components of the device to assess the relative impact of each component on the probability of causing a burn. As it turns out, they find that each component has an equal impact on device failure, so they prepare Revision B to the Hazard Analysis, see below.

Hazard Analysis Rev B

Hazard Category	Hazard	Failure Mode	Effect (Harm)	Severity	Cause	POH ⁽¹⁾	Risk
Energy Hazard: Thermal	High Temp.	Out-of-Spec Device	Burn to hand	4	Comp. A failure	3 (1/20,000 uses)	ALARP
-	-	-	-	-	Comp. B failure	3 (1/20,000 uses)	ALARP
-	-	-	-	-	Comp. C failure	3 (1/20,000 uses)	ALARP
-	-	-	-	-	Comp. D failure	3 (1/20,000 uses)	ALARP
-	-	-	-	-	Comp. E failure	3 (1/20,000 uses)	ALARP
-	-	Use Error	Burn to hand	4	User does not follow IFU	3 (1/50,000 uses)	ALARP

1: Probability of Occurrence of Harm values are based on the example table provided in ISO 14971 (Table D.4) and in Attachment A.

Did you see what happened? By completing a more detailed analysis of the “Out-of-Spec Device” failure mode (and without implementing any controls) we’ve moved from one “Unacceptable” risk to five “ALARP” risks. From a mathematical perspective it makes sense ($1/4,000 \div 5 = 1/20,000$), and logically it makes sense (one “Probable” harm occurs as a result of five “Occasional” causes). However, the result doesn’t fit with the spirit of the analysis. Taken to an extreme, you can imagine a serious harm with so many potential causes that the risk associated with any one cause is “Broadly Acceptable”. In this extreme case, if you keep your blinders on and don’t think about the overall risk of all these causes, you could say that the risk is acceptable.

What to do? . . . Well the first thing is to recognize that this can happen. Unlike a fault tree analysis, there is no “Top Fault” in a Hazard Analysis or FMEA where the overall probability for a particular harm is captured. As a result, the overall risk associated with a particular harm may never be presented. Depending on how your analysis is structured, the individual risks associated with a particular harm may not even be presented together in one section of the analysis. They may be scattered throughout the analysis, essentially burying the overall risk in the analysis.

To see how this problem affects your company, take a look at one of your Hazard Analyses / FMEAs and pick a significant harm described in the analysis. Then build a fault tree with that harm as the “Top Fault” (if you’re not sure how to do this, take a look at our article *RM 3: Using Fault Trees to Focus and Simplify Risk Analysis*). Go through the analysis and include every cause in the analysis that is associated with the particular harm. What is the probability of occurrence for that Top Fault? Is the classification

for this overall risk different from the individual risks in your FMEA? The results of this exercise could change your perspective on the risk of your device.

One way to deal with this challenge is to include lines in the body of your Hazard Analysis or FMEA for the overall risk of particular harms – there’s no rule against it, it’s just not often done. In the “Cause” column, you’ll just need to write “see below” or “see Fault Tree Ref. XXX”. This approach will allow you to capture the overall risk in your standard format.

Residual Risk Evaluation vs. Risk-Benefit Analysis

The standard discusses the use of Residual Risk Evaluation and Risk-Benefit Analysis at two different stages of the Risk Management process. These two activities are first applied during Phase 6, *Risk Control*, and they are applied again during Phase 7, *Evaluation of overall residual risk acceptability*. The challenge is to understand the differences between the two activities and the different ways that they are applied during the two phases.

1. During the **Risk Control Phase (Section 6)**, the standard is focusing on **individual** risks and describes:
 - Residual risk evaluation (section 6.4)
 - Risk/benefit analysis (section 6.5)

As we discussed above, both the RPN and Risk Evaluation Matrix approaches implicitly include the benefits of the device in the assessment. So the difference between the “residual risk evaluation” and “risk/benefit analysis” is not that one considers benefits and the other doesn’t. The difference is in the approach taken to determine acceptability.

When conducting a “residual risk evaluation”, each individual risk is re-evaluated using the original acceptance criteria (i.e., typically the RPN or Risk Evaluation Matrix approach). These approaches are fairly blunt tools. They are designed to determine the acceptability of a wide variety of risks - from use errors to material failures and software bugs – and plug them into one of 25 cells (if you’re using a typical 5 x 5 matrix). If you’ve gone through this exercise a few times, you may remember looking at a group of risks that all received the same Severity and Occurrence scores and saying to yourself, “A couple of these seem like much bigger risks than the others”. You were probably right – like we said, these criteria are pretty blunt tools.

Given the lack of precision in the standard acceptability criteria, the residual risk evaluation may not address the subtleties associated with the causes and effects of particular hazards / failure modes. That’s why the standard also allows for the use of a risk/benefit analysis.

The standard devotes a fair amount of text to describing how to conduct a risk/benefit analysis (see section D.6). This approach is less structured than a residual risk evaluation and can, therefore, be

designed to address the specific issues most relevant to the particular risk being assessed. In a risk/benefit analysis, you can consider a wide range of detailed information about a specific risk and weigh that risk against the device's benefits. The result is a qualitative judgment by experts based on a review of clinical data. Given that a risk/benefit analysis is less structured, you will want to be sure that individuals with clinical expertise (in addition to those on the analysis team) are actively involved in the review.

One odd element of this stage of the assessment is that you are comparing a single, unacceptable risk to the full list of potential device benefits. Yes, that's how the standard is structured. Each individual residual risk is to be evaluated against all device benefits. If there is only one unacceptable risk, there's no problem. But when there are multiple unacceptable risks, the approach makes less sense.

For example, take a manufacturer that identifies two unacceptable risks during the residual risk review of their device and, following the standard, conducts two separate risk/benefit analyses. Considering each risk on its own, experts find that each risk is acceptable when weighed against all device benefits. However, if they had considered both risks (or all risks), the combined risks would have outweighed the benefits.

In practice, this doesn't (or at least shouldn't) happen. Risk analysis teams faced with multiple, significant risks generally do not put their blinders on at this stage knowing that the very next step in the process is to conduct an overall analysis of residual risk. So, this is one area where it's advisable to stray a bit from the standard.

The bottom line is that it's important to clearly define the scope and approach of your risk evaluation activities. If the focus is on individual risks, make sure that's what you're doing. But if it's more appropriate to be considering overall risks (even at a preliminary level), make sure that you've described that in your RMP and identify that you've taken that approach in your report of risk acceptability.

2. During the **Evaluation of Overall Residual Risk Acceptability Phase (Section 7)**, the standard focuses on **overall** risks, stating that:
 - The manufacturer shall decide if the overall residual risk posed by the medical device is acceptable using the criteria defined in the RMP; and
 - If the overall residual risk is not acceptable, the manufacturer may review data to determine if the medical benefits of the intended use outweigh the overall residual risk

The standard provides somewhat conflicting guidance at this point, by stating that "the manufacturer shall consider how to evaluate the remaining residual risk with respect to the acceptability criteria" (section D.7.1). The problem is that the established acceptability criteria are typically set up to assess individual risks, not overall risks. So unless you have also established "super-criteria" such as "No more

that X% of risks shall be categorized as ALARP” in the RMP, you don’t have any way to judge overall residual risk using the established criteria.

The writers of the standard basically acknowledge this conflict by ignoring any discussion of how to use the acceptability criteria to assess all risks and quickly point to a set of other tools that could be useful for the overall residual risk assessment including:

1. Event tree analysis – to assess the relationships among risks
2. Fault tree analysis – to assess combined probability of harm
3. Review for conflicting requirements
4. Review of warnings – to identify if there is an over-reliance on warnings
5. Review of operating instructions – to identify information that is inconsistent or difficult to follow
6. Compare risks to similar existing devices
7. Review by application experts

These methods are described in sections D.7.2 to D.7.8 of the standard.

Unfortunately, the first five methods on this list are not very helpful. The first two are good tools, but they are not designed to compare risks to benefits. Both Event Tree and Fault Tree Analyses help you to learn more about specific events and faults, but they don’t tell you much about their acceptability. Methods 3 through 5 are all important things to do, but while they might help you identify additional risks they won’t shed much light on the overall residual risk acceptability.

Methods 6 and 7, however, are very appropriate. They are also, arguably, important components of a risk/benefit analysis and don’t have much to do with the established acceptability criteria. Comparing risks to similar existing devices makes a lot of sense, especially when you have detailed information about the effectiveness of these other devices and their safety risks. The review by application experts is hopefully something that you’ve done all along, but bringing in folks with clinical expertise to provide their judgment about risks and benefits would be very valuable.

The FDA has recently weighed in on the question of how to conduct a risk/benefit analysis with their draft guidance titled “Factors to Consider when Making Benefit-Risk Determinations in Medical Device Premarket Review” (August 15, 2011). Like section D.6 of the standard, the FDA’s draft guidance acknowledges that to be effective, “benefit-risk determinations” require experts to make complicated judgments that include a variety of factors. To that point, the FDA does a good job of breaking the risk/benefit analysis down into three sets of factors that need to be considered to complete a comprehensive evaluation. These factors are outlined below:

- Extent of the probable benefit(s)
 - Type of benefit(s)

- Magnitude of the benefit(s)
- Probability of the patient experiencing a benefit
- Duration of effect(s)

- Extent of the probable risk(s)/harm(s)
 - Number, severity, and types of harmful events associated with the use of the device
 - Device-related serious adverse events
 - Device-related non-serious adverse events
 - Procedure-related or indirect harms
 - Probability of a harmful event
 - Duration of harmful events
 - Risk from false-positive or false-negative for diagnostics

- Additional factors for Weighing Probable Benefits and Risks of Devices
 - Uncertainty
 - Characterization of the disease
 - Patient tolerance for risk
 - Disease severity
 - Disease chronicity
 - Availability of alternative treatment/diagnostic options
 - Risk mitigation¹
 - Novelty of technology

The FDA then provides three examples of how these factors can be used to determine the acceptability of a device based on risks and benefits. They also provide examples of how FDA has ruled on device risk/benefit questions that they have faced in the past. Finally, they provide a worksheet (based on the factors outlined above) that they recommend be used to structure risk/benefit arguments.

So, where does that leave us? The bottom line is that there really is no difference between an “overall residual risk evaluation” and a “risk/benefit analysis” as suggested in ISO 14971. Unless the risk and the benefit have the same clinical effects (e.g., surgery with the risk of causing back pain to alleviate chronic back pain), you are always forced into an apples and oranges comparison: X-rays can damage cells, but aid diagnosis; IVDs can aid early detection of a disease, but a false-positive could lead to unnecessary treatment, etc., etc., etc. Any time that a detailed review is needed to weigh risks and benefits, experts with experience in the appropriate clinical field are needed to make an effective judgment.

¹ Be careful when you read this paragraph in the draft guidance, it includes language like “The most common form of risk mitigation is to include warnings in labeling . . . [*and much later*] . . . Finally, some harms can be mitigated through changing device design features”. They got it exactly backwards: improving the design comes first, and labeling is a last resort. Hopefully that will be cleaned up in future versions.

The format recommended by FDA is very helpful. Explicitly documenting the anticipated device benefits and summarizing the device risks (outside of the FMEA format) in a single document along with any assessment considerations, is a great aid to anyone trying to determine risk acceptability. The format is structured enough to ensure that information is captured in a consistent manner, but flexible enough to allow for the consideration of issues that are specific to particular devices.

Conclusion

The key points that you should take away from this article are:

- **Make benefits explicit:** Whether you follow FDA's format (recommended) or one of your own, explicitly state the anticipated benefits of your device in the RMP so that when you're determining risk acceptability everyone on the team has a shared understanding of the benefits.
- **Consider benefits in your acceptance criteria:** Make sure that the level of benefit implied in your risk acceptability criteria matches the anticipated benefits for your device.
- **Don't let overall residual risk get lost in your FMEA:** Whether you summarize overall risk of specific harms in your FMEA or conduct a separate assessment of overall risk, don't let the FMEA tool trick you into thinking your overall risk is low just because multiple individual risks are low.
- **Structure your risk/benefit analysis:** Recognize that the "Evaluation of Overall Residual Risk" is a risk/benefit analysis and structure the analysis in a way that the risks, benefits, and assessment considerations are all clearly presented.
- **Involve clinical experts:** At the end of the day, the determination of risk acceptability is a judgment call based on the evaluation of potential harm, probabilities, alternative treatments, potential health benefits, and other considerations that don't fit neatly into a scoring table. Experts with experience with the disease condition and treatment options are needed to review the assembled clinical data and make the final determination of acceptability.

Next Steps

While there are other elements of risk acceptability that could be explored further, in our next article we will focus on Risk Control – i.e., what to do when you find you have unacceptable risks.

If you've missed any of the previous articles look them up on www.medicept.com/blog/.

Attachment A: Example of Semi-Quantitative Probability Levels (based on ISO 14971, Table D.4)

Rating	Common Term	Probability of Occurrence of Harm	Layman's terms
5	Frequent	$\geq 10^{-3}$	More than 1 per 1,000
4	Probable	$\leq 10^{-3}$ and $\geq 10^{-4}$	Between 1 per 1,000 and 1 per 10,000
3	Occasional	$\leq 10^{-4}$ and $\geq 10^{-5}$	Between 1 per 10,000 and 1 per 100,000
2	Remote	$\leq 10^{-5}$ and $\geq 10^{-6}$	Between 1 per 100,000 and one in a million
1	Improbable	$< 10^{-6}$	Less than one in a million