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Risk-Based Decision-Making – using knowledge of risk throughout the lifecycle

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Risk-Based Decision-Making – using knowledge of risk throughout the lifecycle

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Contents

ICH Q9R1 regarding Risk-Based Decision-Making

What is risk-based decision making? That is the big question many people in the industry and with regulators have been asking themselves for some time. The concept paper for revising ICH Q9 into the R1 version that we see now describes that there was a lot of discussion and a lack of clarity around risk-based decision-making. Most people knew they needed to make risk-based decisions – but what is it and how do you do it?

A definition of Risk-Based Decision-Making

One of the major changes that was made in ICH Q9R1 was the introduction of a definition for risk-based decision-making. This should be seen as a good thing because when people said risk-based decision-making they were often actually talking about different things. Nobody really agreed on what it was because there was no official definition. The Expert Working Group put together an official definition which is now in the guideline, and forms how the concept should be understood and used.

> ***Risk-Based Decision-Making:***
>
> *An approach to, or a process of, making decisions that considers knowledge about risks relevant to the decision and whether risks are at an acceptable level.*
>
> *ICH Q9R1*

This definition goes back to and plays into the very definition of Quality Risk Management. So contrary to what some people believed, you will not have risk assessments on one side, and on the other side risk-based decisions as something completely different. All throughout any quality risk management decision that you are making, you are making decisions based on your knowledge of risk. The entire quality risk management process is a set of risk-based decisions.

For some this may be a little academic, but it is very fundamental in understanding what risk-based decisions are and how they should be used. It also means that whenever you talk about quality risk management in anything that you do – and Q9R1 does that in abundance – you are basically talking about risk-based decisions. And that also means that all the principles around formality, subjectivity, etc. apply as well.

It is also worth noting that the guideline talks about knowledge management. That is because basing your decisions on risk requires knowledge of those risks. So, knowledge is a key component and that is why the guideline is now emphasizing that. ICH Q9R1 is not meant to be a knowledge management guideline, but it does require knowledge.

Different Levels of Structure for RBDM

The guideline talks about how there can be varying degrees of structure for a variety of approaches. This is because you should start applying some of the other principles in the guideline – formality especially. You should investigate how to work with structuring your knowledge and using it in the best possible way to work with the concept of formality.

This is how the Expert Working Group arrived at the structures. The revised guideline describes that you should work with formality, and it also mentions three different types of approaches:

- Highly structured approaches
- Less structured approaches
- Rule-based approaches.

These different levels of structure are closely related to how formality is being applied.

Talking about these three categories is a simplification and probably a little bit too simple. But it is quite helpful to understand the concept and realize that this is more of a spectrum – just as in formality. You cannot really use these boxes very rigidly. But this simple point of view can help you address the shortcomings you might have.

The different levels of structure help you based on how much you know already, and how much rigor you would need in your data search. How much structure you would need to combine different pieces of knowledge, to take care of the complexity that you have in what you are looking at, etc. The different approaches to risk-based decision-making are beneficial because they address uncertainty through the use of knowledge, and that leads to more informed decisions.

Depending on where you are in terms of the three fundamental things that the guideline talks about in formality:

- Importance
- Uncertainty
- Complexity.

You will actually end up in one of the structured approaches, working your way into a position where the decision process and the tools in your plan will help you work with whatever you have to work with.

In general, higher levels of formality in Quality Risk Management require higher levels of structure in relation to risk-based decision-making.

Highly structured approaches

- Highly structured that can involve formal analysis of available options before decision
- In depth consideration of relevant factors
- Typicaly used for high importance and high uncertainty and/or complexity

Less structured approaches

- Simpler approaches used to lead decisions
- Primarilly uses existing knowledge
- Typically used where uncertainty and complexity is lower

Rule based approaches

- SOPs, policies or rules in place to guide decisions into predetermined outcomes
- No new risk assessment is needed – uses previously obtained understanding of risk
- Typically used for quick response when uncertainty and/or complexity is low

Figure 1: Different structured approaches to risk-based decision making

Highly structured approaches, are fairly complicated – more structured on tools, etc. In less structured approaches, we can use simpler approaches, a well written rationale on the back of an envelope could actually be a thing here, because it to a large extent uses existing knowledge. With rule-based approaches, you have already set limits. And of course, this is based on your current knowledge of risks, and that somebody has already analysed those risk scenarios for you. That way you can set up rules in order to control the risks and base your decisions on that.

It is a way to categorize and talk about the different methods, and to mention that it does not always have to be this big FMEA. Simpler approaches can be used and are sometimes more appropriate. You can use decision trees or simple rationales describing why a decision was taken based on the knowledge you have. All depending on where you are in terms of importance, uncertainty, and complexity. It was quite important to get this into the guideline, as people were struggling with this.

And the official ICH Q9R1 training material will contain examples of these structured approaches and some principles on how you can work with it, providing more detail than the guideline does.

Examples of different Risk-Based decisions using knowledge across the QMS

In Novo Nordisk we strive to set up and define different types of risk-based decisions, making sure we use the knowledge already available. This section will contain some examples of how they were defined.

Some years ago, we realized we were not getting the effect from Quality Risk Management that we would have liked to see. We started looking at how knowledge really flows because that was one of the problems we identified. People were not really using the knowledge that should otherwise have been available, and we wanted to know how we could connect the dots even better.

We started looking at what information was needed to make the different risk-based decisions in the different Quality Risk Management activities. And what information should be sent on to other decision or to other assessment. As a result, we are building what some will call a Quality Risk Management Architecture or blueprint, but many names have been used.

It is an attempt at creating a picture of what the information flow should really be, and also show what the different decisions are, and how they are connected into one lifecycle of risk management knowledge for a product.

Up until that time, we had been so used to looking at these activities individually - looking at them as singular events, or silos you might say. What we realized was we needed to alter that. We needed them to function together and to have information flow to and from each of them. A high level illustration is found in Figure 2.

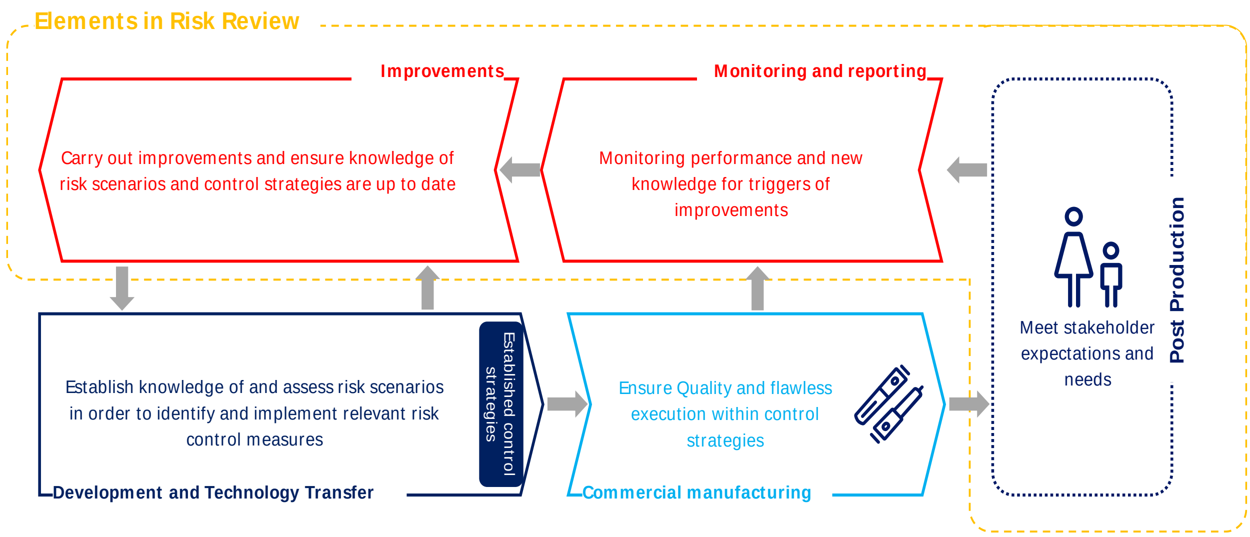


Figure 2: High level Quality Risk Management architecture and lifecycle

Throughout development and technology transfer, a lot of knowledge of different risk scenarios is created. A lot of things are investigated trying to be wiser about what are the risks, how they can be controlled - what the scenarios are that we want to manage, etc. We end with verified control strategies

In commercial operation, that knowledge can be used for decisions to make sure that we stay within that controlled space and make sure we are actually in control. But a lot of new knowledge is also generated about how things are working.

The monitoring of these new data might, trigger some interesting findings. And that will sometimes trigger improvements – and those improvements might trigger us to update that original knowledge base that we had from the original assessments. Some of this lifecycle is actually what the guideline would call risk review.

Transport Risk Management model

The first example is a model that was created for transporting different products across the world from one warehouse to another warehouse or directly onto wholesalers or similar in order to make sure that the products are still good when they arrive.

The whole model was built on a fundamental understanding of what would these individual products be able to tolerate in terms of temperature, humidity, etc. as adequate transport conditions considering their specifications and stability. This was an understanding of what were the risks of undergoing transport and what the boundaries were. This included what were the qualified setups of transporting vessels and limits etc. i.e., an in-depth understanding of the science behind the different scenarios.

Because of that understanding, a decision model could be set up to define what the immediate risk level is for a particular transport with a particular combination of a product, transport vessel, duration of time, route, and if this is acceptable or if something needed to be done about it.

The model is based on a number of parameters that talk about the risk scenarios. Although they are not called probability or severity, some of these parameters are an expression of the severity of harm, and some of the probability of occurrence of harm. The model brings the risk management to a much more practical level where users select options they can directly relate to, and each option has a defined score. The model makes use of an RPN score, and based on the results, you know whether the product is good or bad and what you need to do.

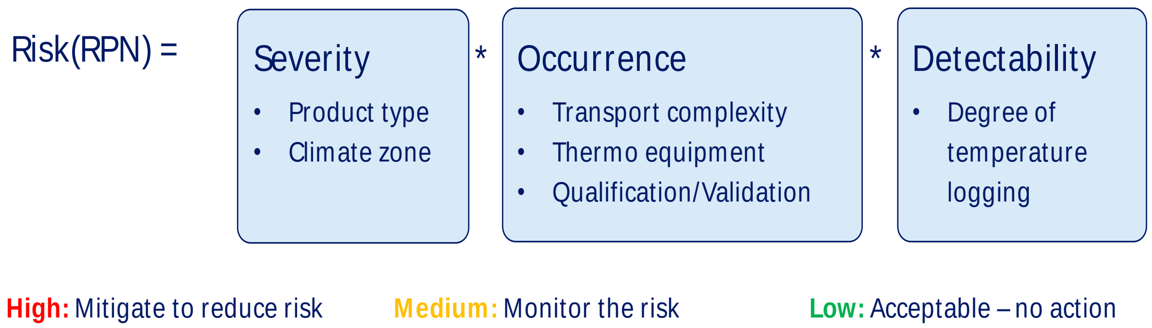


Figure 3: Overview of the parameters used in the risk-based transportation model.

Warehouse validation setup

The next example is a warehouse decision setup looking at what to include in the validation and monitoring of that warehouse. In fact, this model is used for making four different decisions:

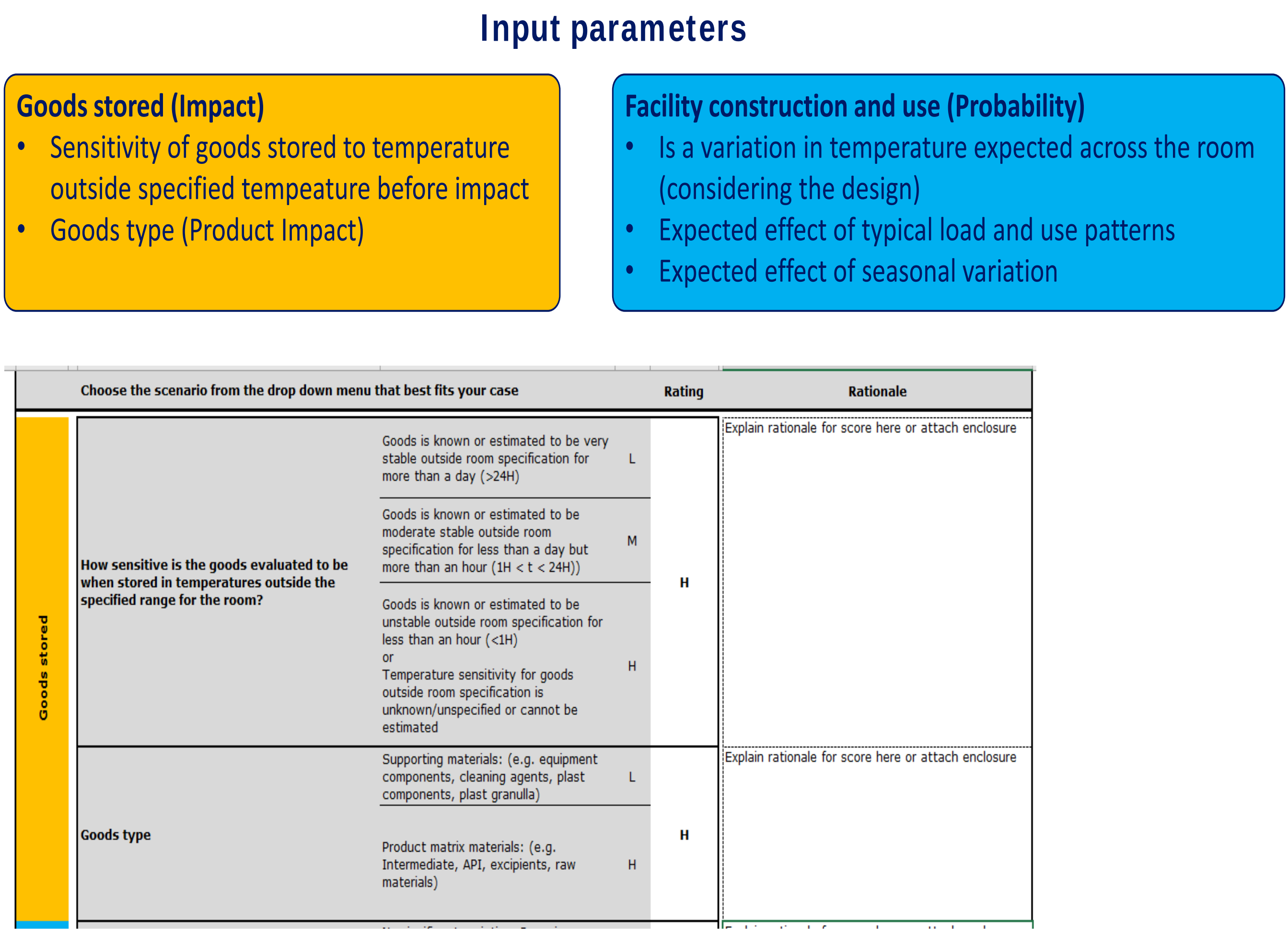
1. What is the effort to be used for temperature distribution testing during the validation study?

2. What is the amount of load and use pattern testing to be performed during the validation setup?
3. What is the need for seasonal variation testing (-because this might apply, or it might not apply)?
4. How should you keep monitoring this warehouse once in operation?

These decisions be taken based on the knowledge available on the design of that warehouse.

A couple of parameters are expressions of the importance or the severity of what might go wrong here. There is the temperature or humidity sensitivity of the goods stored. There is also the goods type relating to “What is the product impact based on this material being wrong or faulty?”

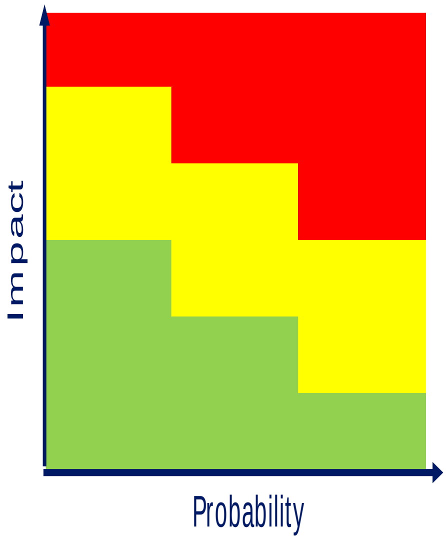
Then, there are some facility construction pieces. Is temperature variation across the room, based on the room design? Would we expect an effect of any load changes, etc., considering that design, and what is the expected effect of seasonal variation? The illustration in Figure 4 contains the input parameters and a cut out what it looks like in the template. This gets described in a lot more detail in the actual model.



	Choose the scenario from the drop down menu that best fits your case			Rating	Rationale
Goods stored	How sensitive is the goods evaluated to be when stored in temperatures outside the specified range for the room?	Goods is known or estimated to be very stable outside room specification for more than a day (>24H)	L	H	Explain rationale for score here or attach enclosure
		Goods is known or estimated to be moderate stable outside room specification for less than a day but more than an hour (1H < t < 24H))	M		
		Goods is known or estimated to be unstable outside room specification for less than an hour (<1H) or Temperature sensitivity for goods outside room specification is unknown/unspecified or cannot be estimated	H		
	Goods type	Supporting materials: (e.g. equipment components, cleaning agents, plast components, plast granulla)	L	H	Explain rationale for score here or attach enclosure
		Product matrix materials: (e.g. Intermediate, API, excipients, raw materials)	H		

Figure 4: Warehouse decision model with input parameters and a cut out of the input template

Each of the parameters will have an input from a list of pre-defined options. When varying the input factors, the model will provide you with the most appropriate action. In the background different risk acceptability grids or a decision model for each of those four questions based on the input were set up based on the already available understanding of the risk scenarios (see Figure 5).



Effort used for temperature distribution testing

Low	No temperature mapping needed in empty state
Med	Temperature mapping with a few sensors to identify hot and cold spot for monitoring - could be done in connection with load and use test
High	Extensive temperature mapping with many sensors reflecting complexity of the room design

Figure 5: Example risk grid and outcomes for warehouse temperature distribution testing effort

Defining calibration intervals

The last example is a decision model for defining calibration interval for a specific measurement system.

The regulations describe that calibration intervals should be based on risk. But how would you do that? What we realized was, first of all, it is not just about the calibration interval. A calibration interval is one of more controls, and it needs to be seen in combination with the other controls i.e., adjustment limits and frequency of checks.

An understanding of the science behind measurement errors, calibration intervals, adjustment limits and frequency of checks, gave us the possibility to identify some parameters that could tell us about the severity or the importance of making the right decision? What is the impact of a bad measurement?’

We identified readily available information like: acceptable rework window, Risk ratings from previously performed assessments, Impact of a wrong measurement. The last one is the measurement range compared to the maximum permissible error (MPE).

Similarly, parameters on the probability of occurrence of a bad measurement were identified. And we were also looking into what we could actually do about it. And, this is the interesting bit, because really, we wanted to find the right calibration interval, or rather the right combination of calibration interval, adjustment limits, and frequency checks for this particular measurement equipment. See Figure 6.

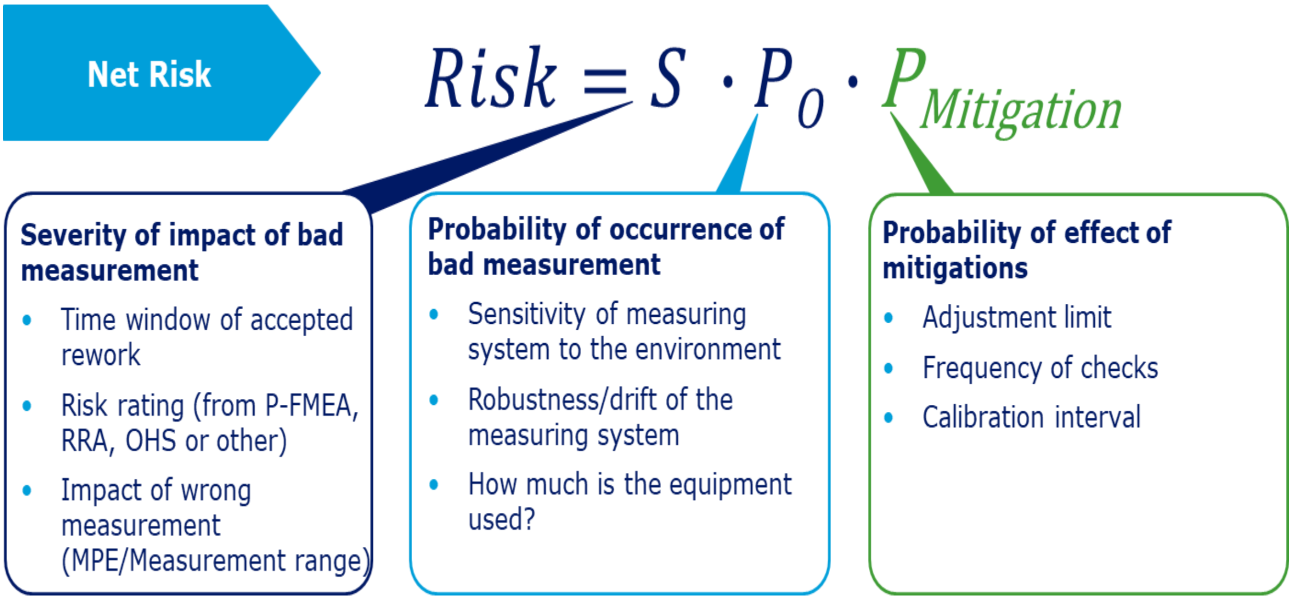


Figure 6: The deduction of parameters for a risk-based model for defining the combination of calibration interval, adjustment limit, and frequency of checks.

We wanted to establish a model where users could write their input, and then they could play around, balancing the three risk control outputs in order to find a combination that is acceptable.

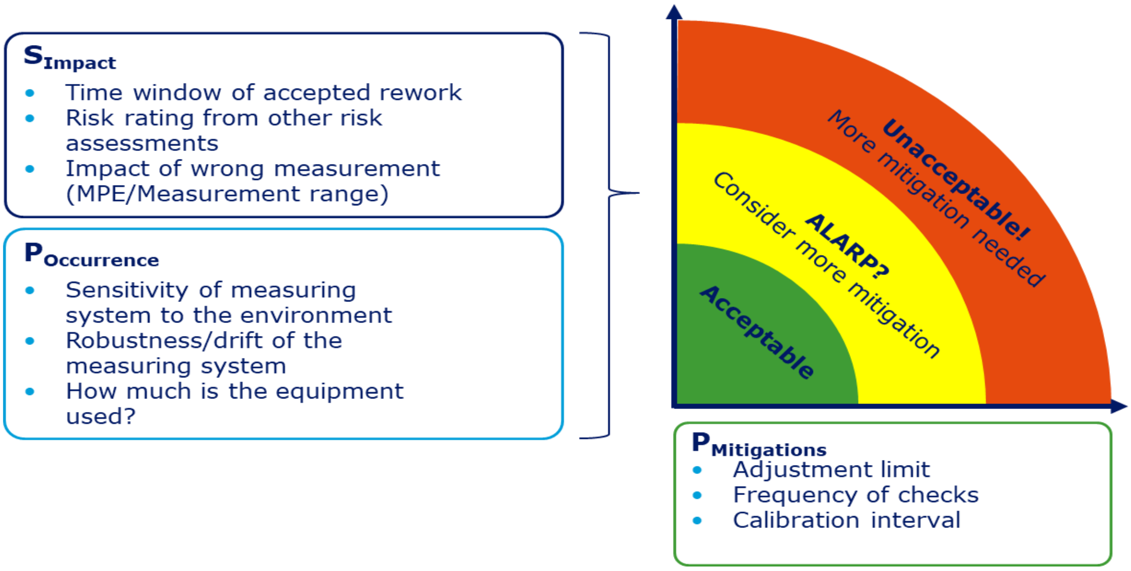


Figure 7: Illustration of how parameters were used to create an acceptability grid for defining calibration interval, adjustment limits and frequency of checks.

Based on the science and understanding an acceptability grid was created to support an excel template, where user cut provide their input and get predefined outputs see Figure 7 and Figure 8.

Chose the scenario that best fit your measuring equipment.

		Question	Low	Medium	High	Score
Impact	1	How long time can you risk to have an equipment which exceeds MPE (how long time are you willing to go back in your documentation if calibration fails)?	14-36 months	8-13 months	0-7 months	
			○ Low	○ Medium	◉ High	3
	2	What is the risk rating of the measurement or parameter in the related risk assessment (p-FMEA, RRA, FMECA or similar)?	Low Risk: No consequences or unlikely impact on product quality	Medium Risk: Potential impact on product quality	High Risk: Impact on product quality	
			○ Low	○ Medium	◉ High	3
		What is the environmental, health and safety rating?	Minor/Moderate	Major	Critical	
			○ Low	○ Medium	◉ High	3
	3	How much does MPE or uncertainty make of the range between lower and upper limit of the measurand ((MPE or U)/((Upper limit-Lower limit)))?	Less than 10%	10-30%	More than 30%	
			○ Low	○ Medium	◉ High	3
	4	Does the environment impact the	No	Yes, but mitigating activities are	Yes	

Figure 8: Cut out of Excel template for risk-based definition of calibration interval, adjustment limit and frequency of checks.

Learnings regarding setting up decision processes

Based on the experience from setting up the decision processes exemplified above and many others, here are some main learnings.

Have a clear scope

When starting on setting up a risk-based decision process it very important to ask yourself: “What do I actually need?” in order both to get the kind of result you need, but also to not overcomplicate the process.

What is the scope that you are trying to focus on? What is the purpose you are trying to address, but also what is the resolution, or the outcome that you want? Because not everything needs to be dealt with to the nth degree.

Teamwork

It is really important to have a good mix of people in the team – someone representing all the pieces of knowledge you might need. People knowledgeable about QRM will not make it on their own.

In all the three examples presented above the successful creation of the model was due to the right people in the team. For example, in the calibration intervals model, the mix of people knowledgeable about measurement systems and the science behind measurements were the ones providing insights into what parameters should be considered, and then the QRM experts could help structure this into a risk model and plan out the decision process.

Variables

You need to look at what you already know, and what variables you have, that can tell you about the different parts of the relevant risk scenarios. Then based on what you need in terms of the decision – for example specific outputs or a need for resolution, you can explore the variation space for each variable.

Business logic

Look at what variables you have available, and the uncertainty and complexity related to the data associated with these variables, and then create a business logic that fulfils that focus based on all of that knowledge. As can be seen by the examples above fitting the different variables into the risk equation will give you a good start at how the logic should work. And from there you can build the sequence or process of how users should work with the decision process.