This article presents a new type of risk tool. Risk Analysis and Mitigation Matrix (RAMM) was developed to be incorporated into a modern risk management system and align with latest FDA guidances.

Risk analysis and management is the cornerstone of any science- and risk-based approach for modern drug development and manufacturing. In order to understand and document processes and products, standard risk analysis tools have been adapted from other industries and academia. These tools include Ishikawa Diagrams, P-Diagrams, Preliminary Hazard Analysis (PHA), Failure Modes and Effect Analysis (FMEA), Failure Modes and Effect Criticality Analysis (FMECA), Hazard Analysis of Critical Control Points (HACCP), and several more.

The Risk Analysis and Mitigation Matrix (RAMM) was created to provide a pragmatic compromise where other risk tools such as Preliminary Hazard Analysis (PHA) or Failure Mode Effects and Criticality Analysis (FMECA) are maybe either too simple and lacking in detail, or they are maybe too complicated, making it difficult to work consistently with limited resource across all products.

The goal of the RAMM was also to align with ICH and FDA guidances (Q8 to Q10 series and Process Validation); especially around tracking Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) in a pragmatic manner. The tool was designed to be at the heart of any modern quality system with regular review in meetings and as a way of tracking risks and any mitigation actions. The tool had to be simple enough that everyone could use it and provide enough detail that critical risks could be tracked, mitigated, and be time savvy. If it were to take days to go through the risk analysis every time a process review occurred, it would never be as useable as it should be.

This article will discuss how the tool works, provide a practical example as applied to a monoclonal antibody (Mab) process, and show how to incorporate the tool into a quality management system.

Use of Risk for Development and Manufacturing

When developing a new process and product or attempting to understand an existing process and product, knowing how materials, processes, and controls affect the final product is essential. If one can identify the critical process input factors, the variation in the process responses should be able to be understood and controlled. Without this knowledge, the developer or manufacturer is simply guessing how good products are made and most likely relying heavily on a quality control unit to reject any bad products manufactured.

From a development or manufacturing perspective, one of the key parts of this pathway is understanding which raw materials and process parameters impact the Critical Quality Attributes (CQAs). Furthermore, in what direction and quantity these parameters affect the CQAs are critical for manufacturing excellence. This is because this understanding can be used to develop more robust processes or add appropriate control measures to adjust processes to make on target product.

Risk Hierarchy

Risk tools are traditionally categorized as simple or detailed. Simple tools are often used as a precursor to using the detailed tools or early in development where little is known about processes, materials, and products. These simple tools include:

- Ishikawa Diagrams
- P-Diagrams
- Preliminary Hazard Analysis (PHA)
- Failure Modes and Effect Analysis (FMEA)
- Failure Modes and Effect Criticality Analysis (FMECA)
- Hazard Analysis of Critical Control Points (HACCP)
Quality Risk Management

- Ishikawa Diagrams
- Preliminary Hazard Analysis (PHA)
- Simple Prioritization Matrices
- P-Diagrams

The list above is not exhaustive and the output of simple risk tools are not particularly quantitative and are typically for identification or hazards and/or risks only. These tools are extremely simple to use and yield results quickly.

More detailed tools are used for comprehensive risk analysis (and mitigation steps) and include a quantitative element. Examples of these tools include:

- Failure Modes and Effects Analysis (FMEA)
- Failure Modes, Effects and Criticality Analysis (FMECA)
- Hazard Analysis and Critical Control Points (HACCP)

The use of these tools typically leads to a comprehensive analysis of risk. All of these risk tools, either simple or detailed, could be complimented by a middle level risk tool as demonstrated in Figure 1. The Risk Analysis and Mitigation Matrix (RAMM) was developed to be quantitative yet simple to use.

The RAMM tool is potentially a useful compliment to the other risk tools and can be used solely or in combination with other risk tools. The potential to use something quantitative, but not as complex as the detailed risk tools can potentially serve as the useful keystone of a risk management system as it is quantitative yet manageable. Each user should of course make their own choice as to which tools serve them best, but it is proposed that the RAMM is a useful addition to that tool set.

Use of RAMM Tool for Monoclonal Antibody Process

The RAMM tool was applied to an example monoclonal antibody process. The tool was applied in six stages as part of a risk management system.

Stage 1 – Team Formation

The first step was selecting the right team to be involved with the RAMM workshop sessions. This situation dealt with an example of a product in late stage development; therefore, the following functions were selected to be involved in the workshops:

- Process Development
- Product Development

It was felt that this team would give the best input to developing the process understanding and risk analysis, although each organization and project is different and may include different functions to those selected here. Though it was not the case in this example, the “right team” may include people who have not seen the actual process before, but who have other experiences. It is important that these individuals get an opportunity to “walk the process” so they get an understanding of what they are dealing with in terms of how the process is run on a daily basis.

Stage 2 – Identifying the CQAs

The strict regulatory definition would be related to CQAs related to strength, purity, and efficacy. The interpretation of CQAs can mean different things to different organizations. In this example, Quality and Regulatory had already defined what this should be as the team was well into preparation for submission documentation. These CQA definitions were developed as an interpretation of pragmatic representation of desired CQAs and what was practically measurable and easily understood with no risk of confusion. The CQAs were defined as the following:

- Mycoplasma
- Viral Contamination
- Identity
- Acidic Variable Levels
- Yield
- Concentration Assay
- Purity Assay
- Visual Appearance
- Osmolality
- pH
- Residual Host Cell Protein
- Residual Host Cell DNA
- Bioburden
- Endotoxin
- Viral Clearance

These CQAs would make up the header row of the RAMM analysis.

Stage 3 – Define the Process Steps

The process steps are considered the major contributors that cause the starting material to be converted to final product. Although this seems complex at first, a great many processes use very similar process steps.

The next piece of pre-work involved process development and manufacturing to prepare the actual process, which would be the center point of the RAMM. This process was defined
in its current state, it was understood the development is an iterative process, and the process tomorrow may be different from that of today. For this example, the process is a fairly straightforward Mab process utilizing single use technology for several of the process steps (in addition to media production).

Production of the monoclonal antibodies was in a fed-batch culture using a single-use bioreactor. The harvest was then clarified by depth filtration using single-use pods. Cation-chromatography was used for a capture-hold step with a reusable column. The product was then transferred to a single-use bag in a mixing tank at which point low pH was used to deactivate the virus for 40 minutes. The product was then polished by membrane filtration (anion-exchange). The product yielded from the anion-exchange chromatography, and the yield was calculated by assay. The product was then sent to single-use ultra-filtration apparatus for buffer exchange. Using the ultra-filtration apparatus, the product was initially concentrated. The concentrated volume was then exchanged by diafiltration into a volume of formulation buffer, determined by the yield calculated by assay following the anion-exchange chromatography. These steps are shown in Figure 2.

Stage 4 – Define Process and Material

Once the overall process is defined, each process step should be broken down into process parameters (some of which would become critical process parameters) and other important parameters.

A P-Diagram was used to capture process parameters in this example; an example can be seen in Figure 3. Each process block is analyzed to determine which inputs, or factors, to that process step are present. These are depicted with an arrow pointing toward the box identifying the process step. Process responses or outputs are depicted with an arrow pointing away from the process step.

Outputs contributing to the next interim step in the process can be shown with the arrow pointing to the next step, but as all outputs do not contribute directly to the next process step, this may be confusing. In practice, the process outputs are generally shown simply pointing away from each process step.

In this example, the P-Diagram was felt to be the most useful, but other simple identification risk tools could have been appropriate such as an Ishikawa Diagram. In this instance, the team felt that systemic issues where well documented around materials and human effects and wanted to concentrate on process parameters.

In addition to the P-Diagram, material attributes also where identified and listed along with systemic issues such as staff training and equipment setup.

Stage 5 – Create RAMM and Score It

The RAMM uses a matrix of process input factors and quality attributes to assess risk and impact. Now that the critical quality attributes and process (or material or other) parameters have been defined, the matrix of these two axes forms the basis of the RAMM. The top row of the RAMM is used to document important responses or quality attributes, and the left most columns are used to describe process steps and process inputs (including material and other parameters).

Once each process step is depicted, the inputs for process parameters can be transferred from Stage 4 (the P-Diagram or other similar tool) to the input column on the RAMM document. It is recommended that the process step be identified as well, in a separate column to the left, as multiple process steps may have similar inputs (consider temperatures, speeds, pressures, etc.).

Assigning stratified scores (one for factors having low impact or risk, three for factors having moderate impact or risk, and nine for factors perceived as having high impact or risk) also facilitates identification of the important factors, and greatly speeds the process. Experience shows that if a group has ten choices to choose from (one to ten), they will become increasingly concerned with the small difference between the scores; for example, “Is it a five or a six?” The stratified (and limited) choices make the decision easier and faster: the important risks or parameters really are important and deserve a high score. The unimportant risks or parameters can receive a low score. The items in between can be assigned a moderate score.

Why are moderate items not scored a middle value, like five? One of the objectives of the RAMM is to force the user to consider the really important items. By weighting the important items, they are elevated to the top and demand
To quantitatively assign the relevant importance of the CQAs, a relative priority score of one, three, or nine (one being relatively important and nine being critical) was assigned. This was greatly assisted by a medical professional (called into the workshops by telemeet on this occasion) to accurately score the CQAs by relating them back to importance to the patient.

With the CQAs defined and ranked (as highlighted in Table A), the process and material piece was analyzed in depth to break down each process unit into individual process parameters. The cross-functional team scored the risk or impact of each parameter or other parameter with relation to each CQA. Scores are limited to stratified levels of one (minor), three (moderate), and nine (high). Stratifying the scores reduces the time required to complete the analysis, while still assessing the relative importance of each factor.

Additionally, parameters which affected the product outcome, but were not necessarily process step specific, also were analyzed. This included items such as raw material properties and their subsequent scoring to critical material attributes.

The example shown in Figure 4 includes only a fraction of the process steps analyzed (this shows details for just one process step) in order to logically fit this report into this article.

In this example, a parameter was defined as critical if it had a direct impact on a CQA. The team discussed what would require action and follow-up work to improve the criticality. The end definition was any process parameter that flagged red (or critical) for a CQA that was also ranked as critical. In addition, the total risk score (similar to a risk priority number) was also used as a flag for anything with a total score of 200 and above, and would require immediate action plans. This definition of 200 and above was a team decision about what was the justified total risk score at which action should be taken based on their knowledge of the product, science, patients, processes, and materials.

At this stage the RAMM could be sorted and filtered so that process inputs can be assessed by their impact on a specific response, by the interim process step, or for their overall impact on the entire process. Likewise, the matrix could be filtered to determine which process step or input factor(s) had the greatest impact on a particular attribute. The order of cross products for both the rows and columns were “gut-checked” with the cross-functional team to ensure the scoring agrees with their perceptions of the process. The parameters receiving the highest cross product scores were checked that they aligned with the cross functional team’s consensus of most important or highest risk parameters.

It can be seen above that for the process step highlighted and the defined criticality flagging criteria that there were several criticality points requiring further action. These included:

- N-1 stage cell expansion – equipment setup
- N-1 stage cell expansion – temperature control
- N-1 stage cell expansion – agitation
- N-1 stage cell expansion – dissolved oxygen
- N-1 stage cell expansion – post inoculation temperature

**Step 6 – Mitigation**

The final point of discussion of the workshop was to assist in defining which action would help mitigate risk for these process parameters. The key action defined was around gaining improved process robustness. In order to improve this, experiments were defined. Additionally, it was indicated that some changes to the equipment would improve the equipment setup weaknesses.

At this point, the team was adjourned, any documents...
signed and workshop team members documented. The RAMM was incorporated into the quality system and a meeting set up for two months later to follow up on how the suggested improvement projects had mitigated risk.

The suggested action steps worked convincingly, greatly improving process understanding and reducing risk for this process step. No further action were deemed necessary at this stage for this process step to lower risk, as it was considered under control and well understood. The RAMM was updated accordingly to demonstrate that risk has been reduced changing the risk scores and providing a simple signal that risk had changed from reds and yellows to greens. This can be seen in Figure 5. It should be noted that other process steps were more complex to understand and required several rounds of mitigation actions to mitigate risk to an acceptable level.

Figure 6 shows that good overview can be gotten at the macro level showing overall risk for a product. This can be especially useful in trying to gain overview at a glance of the risk and how mitigation is working.

A RAMM typically takes one to two days to perform the first time with a team that has some knowledge of the process. This time can be significantly reduced for subsequent products especially if process steps and products are somewhat similar.
Incorporation of the RAMM into the Quality System

The RAMM can be an integral part of an effective quality management system, facilitating implementation of the enabling concepts, knowledge management and quality risk management. This has been elucidated in the Guidance for Industry, ICH Q10 Pharmaceutical Quality System. Inclusion of such a tool in corporate policies/procedures documents the approach to quality risk management, formalizing the systems for assessing, controlling, communicating, and reviewing risk to product quality. Additionally, use of such a tool offers a logical method for continually acquiring, analyzing, storing, and communicating information related to a specific product and its manufacturing processes.

One approach to integrating the RAMM into a quality management system would be to include the RAMM as a tool to be used in a process validation program. The example in Figure 7 demonstrates a quality system hierarchy with the Process Validation Guidance fully incorporated through Process Design (stage 1), Process Qualification (Stage 2), and Continued Process Verification (Stage 3). Policies and/or procedures for the process development may describe the RAMM as a deliverable of Stage 1 of Process Validation. As knowledge is gained throughout the product/process lifecycle (i.e., through Stages 2 and 3 of Process Validation), the RAMM would be reviewed and updated accordingly in order to document the understanding (or lack thereof) and justification for reducing (or increasing) the risk attributed to each step of the manufacturing process. Such a practice would not only track the history of the process development and maintenance, but also document the development of the control strategy and any associated process improvements.

As previously described, the RAMM conveniently maps quality attributes against process parameters (the risk to product quality associated with each step of the manufacturing process). This practice then provides a proactive means to identify and control risks to product quality throughout the product lifecycle from development to routine commercial manufacture and product discontinuation. Effective and consistent risk-based decisions regarding product quality are thus enabled (by both regulators and the regulated industry), allowing an objective means to allocate appropriate resources to address unacceptable risks.

The RAMM offers a systematic approach to quality risk management, providing a sound, risk-based foundation to a corporate QMS. Although relatively simple in structure, the RAMM is a comprehensive tool that complements existing quality practices, standards, regulatory requirements, and recommendations. Furthermore, as an effective mechanism for quality risk management, the RAMM facilitates better and more informed decisions, which may provide regulators with greater assurance of a company’s ability to identify and address potential risks to product quality.

Conclusion

The RAMM offers a risk analysis tool that may prove useful to some as the cornerstone of a quality management system. The authors have found RAMM extremely useful for risk management for various reasons and these include:

- The RAMM neatly handles CQA and CPP (including material attributes and others) parameters in one document and is easily aligned with latest guidances.
- The RAMM is fast; by presenting in a matrix that overlays CQAs against CPPs (including material attributes and others), it is relatively straightforward to set up and rank.
- The RAMM has speed, but is also relatively detailed allowing risk quantification or other risk flags to be identified in detail.
- The RAMM gives excellent overview – an entire process can be printed on just one to two sheets, allowing the overall process to be very easily explained with detail.
- The RAMM is very easy to incorporate into a quality system, follow up on, and make documented changes with.

The authors also have noted some disadvantages to the RAMM:

- The team using RAMM needs to be aligned and have some knowledge of risk analysis; this is especially true of scoring numbers as the individual risks are a combination probability and impact.
- If the process is not well understood, the team needs the experience to realize that some pre-work identifying parameters (such as p-diagrams) are required.

All in all, all risk tools have their value in a risk management system. It is expected that tools like RAMM will be especially
useful for organizations with large numbers of products where the application of detailed analysis tools to every single process and product would not be feasible. Here the RAMM could be used as a total replacement for detailed risk tools or act as a middle risk layer to prioritize which products and processes should have detailed risk analysis applied.

Notes
The RAMM template is available as free templates and downloadable examples. Please contact the creators Alex Brindle and David Tiffany for details. The development and testing of RAMM was greatly helped by the following individuals: Line Lundsberg-Nielsen, Lene Bjerregaard, and George Kizhakethil.

Acronyms

- CMA: Critical Material Attribute
- CPP: Critical Process Parameter
- CQA: Critical Quality Attribute
- FDA: Food and Drug Administration
- FMEA: Failure Modes Effect Analysis
- FMECA: Failure Mode and Effect Criticality Analysis
- ICH: International Conference on Harmonization
- PHA: Preliminary Hazard Analysis
- RAMM: Risk Analysis and Mitigation Matrix

References


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