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Data-driven risk management – a practical approach to minimize subjectivity

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Data-driven risk management – a practical approach to minimize subjectivity

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Abstract

ICH Q9(R1) introduced the necessity to effectively control and minimize subjectivity in risk management to enhance the scientific robustness of risk-based decision-making. This article delineates a practical approach to address this need in the context of managing risks within a production process. Employing a set of digital state-of-the-art integrated tools, the management of risk assessment activities is facilitated. Following the establishment of a risk baseline grounded in existing tacit and explicit knowledge (when accessible), a systematic process of iterative risk refinement is defined. This iterative approach involves recalculating risks as data and knowledge become available. In addition to revising the Risk Priority Number (RPN), the integration with data enables the identification of new risks, contributing to an ongoing enhancement of the control strategy.

Introduction

Quality Risk Management (QRM) is a vital component in safeguarding the quality, safety, and effectiveness of pharmaceutical products. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) recognizes the significance of QRM and has incorporated it into multiple guidelines addressing various stages of the pharmaceutical lifecycle. Notably, the ICH Q8 (Pharmaceutical Development), ICH Q9 (Quality Risk Management), and ICH Q10 (Pharmaceutical Quality System) underscore the pivotal role of QRM as a supportive framework.

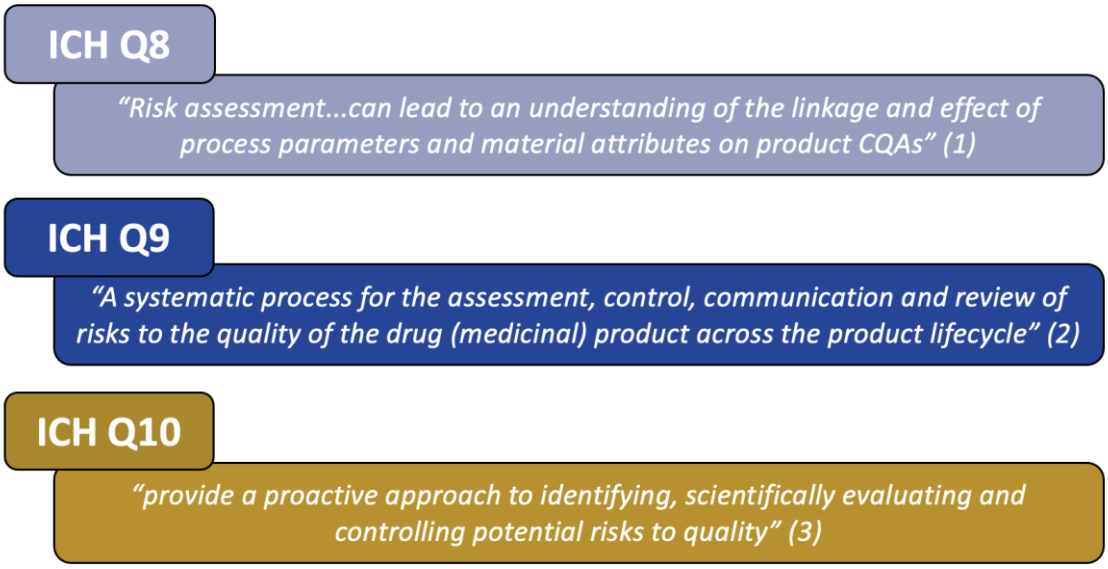

Figure 1 - QRM regulatory framework

Even though this regulatory framework is a well-established concept and organizations are in fact applying QRM principles into their product's lifecycle management, there are still gaps within the pharmaceutical industry, revolving around its requirements in terms of formality, frequency and methodologies to perform the risk revision, and how to minimize subjectivity.

Answering this will only be possible by supporting the decision-making process with science and knowledge coupled with technology and data. This will allow organizations to be better equipped to face manufacturing process lifecycle challenges as well as regulatory challenges.

The revision of ICH Q9 took a step towards closing these gaps by introducing the need to manage and minimize subjectivity in risk management to enhance scientific sound risk-based decision-making. It includes new content focused on "Formality in QRM", "Risk-based decision-making process", "Managing and minimizing Subjectivity", and "The role of QRM in Addressing Product Availability Risks Arising from Quality/Manufacturing Issues".

The new chapters include content that should be considered as a support and justification for the usage of new approaches focused on data and technology.

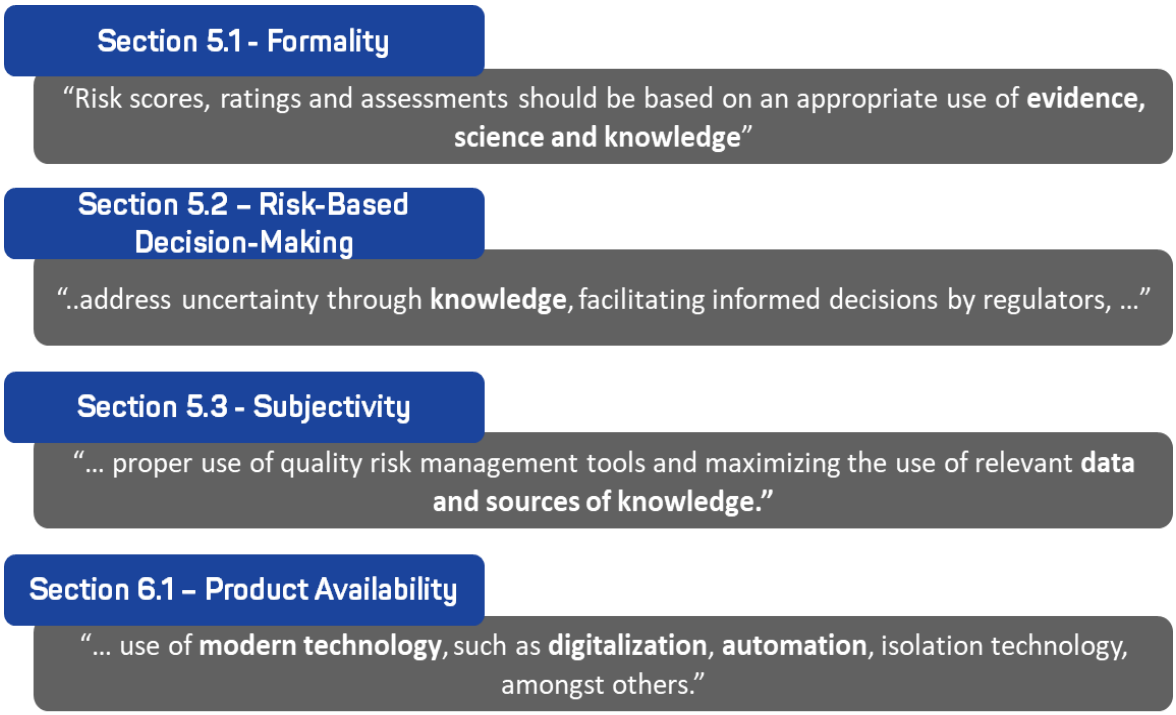

Figure 2 - ICHQ9(R1) new sections as drivers for a data-driven risk management approach

A practical approach to respond to this need is herein outlined, with a set of digital state-of-the-art integrated tools being used to manage risk assessment activities in the context of a production process, based on an existing set of tacit and explicit knowledge (if available), and an iterative process of risk refinement triggered by new evidence and knowledge.

Evidence & Risk

Although the current guidelines and general instructions do tend to mention a holistic approach to the lifecycle management of a pharmaceutical product, we are still faced with strong silos where data and knowledge are being generated but not easily accessible and re-usable.

Knowledge is being generated at the initial stages of product development and risks are being identified. At this point, the designed process has not yet been submitted to the routine manufacturing process, so there is not enough evidence being generated. The proposed control strategy is not supported by solid evidence and the knowledge base around the product is not robust, consistent nor scalable.

On the other hand, when a product reaches the commercial manufacturing stage, the process is generating evidence and in turn increasing the robustness, consistency, and scalability of the knowledge base.

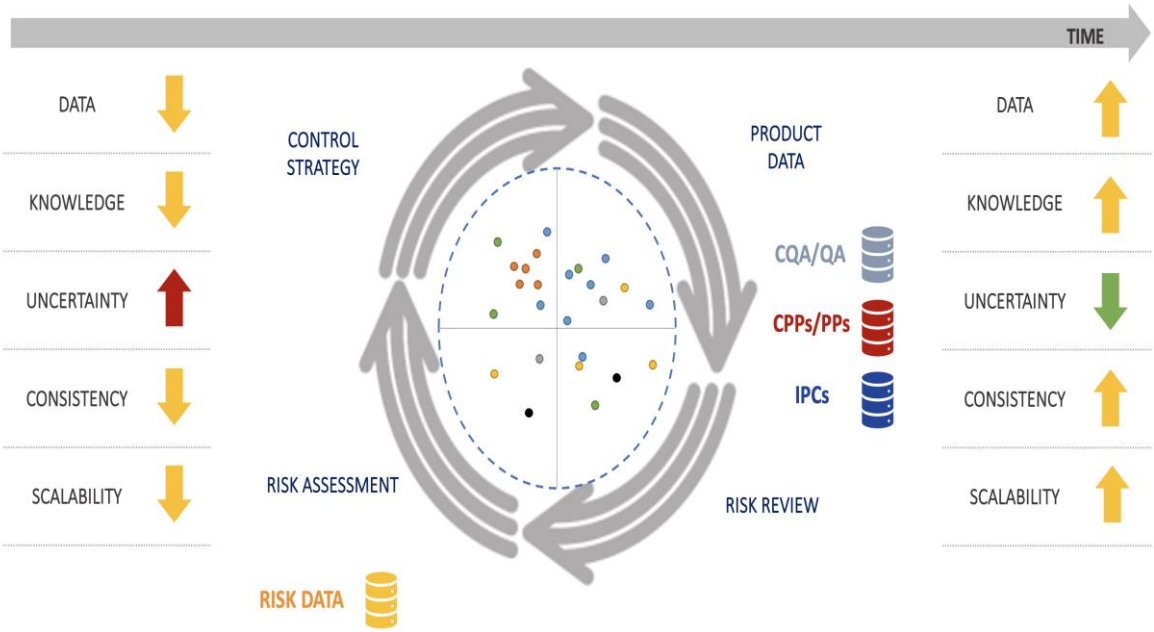

Figure 3 - Risk & Evidence loop

Having digital platforms managing the product lifecycle will enable organizations to break the data and knowledge silos and to close the loop between the initial stage's risk assessment and the ability to refine it *via* late stage's manufacturing process evidence.

With this loop between risk and evidence, organizations will reduce the uncertainty of its QRM activities since they will be using evidence and data as a support for their considerations and decisions.

Being a loop, the more the process is used and matured, the more data are acquired, and the knowledge base gets increasingly more complete. This should be the trigger for the Risk Review action, where the initial risk assessment is refined with new data, resulting in a more robust control strategy.

When implementing this approach, organizations should be aware that the tools and methods of generating knowledge might be by themselves sources of subjectivity if not properly designed. Depending on the nature of the decision to be made, the selection of a risk assessment tool should be flexible enough to accommodate different goals, quantitative vs qualitative

exercises, different levels of formality, different levels of existing knowledge and different risk assessment stages.

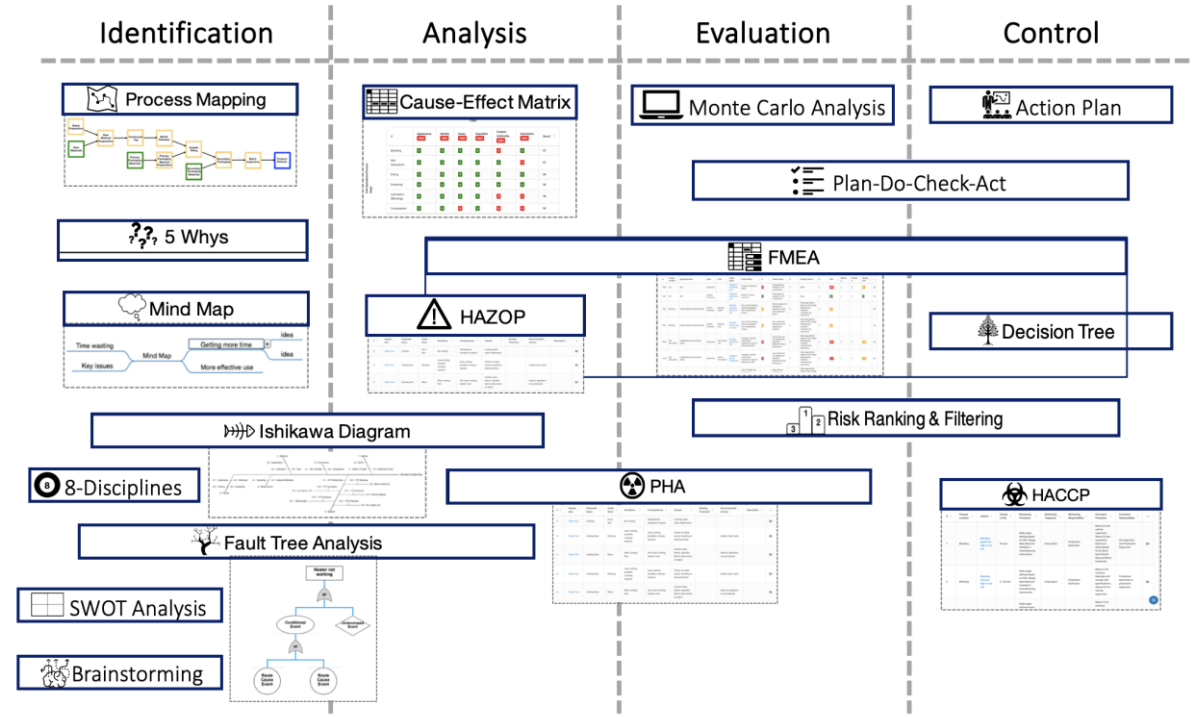

Figure 4 - QRM tools

Having a digital QRM system will offer features such as pre-defined templates, standard workflows, interlinked tools and a digital knowledge base that will minimize the subjectivity. On the other hand, with a digital platform managing manufacturing process intelligence will allow the organization to collect, interpret and to offer evidence and data from multiple sources.

The benefits of such systems will be most noticeable during the later stages of product development, specifically in Stage 3 of process validation known as Continued Process Verification (CPV), as described in the FDA's Guidance for Industry for Process Validation: General Principles and Practices (4) where it will be possible to systematically collect data, trends, detect process variations or deviations, out of specifications (OOS), out of trend (OOT) or any configured alarm.

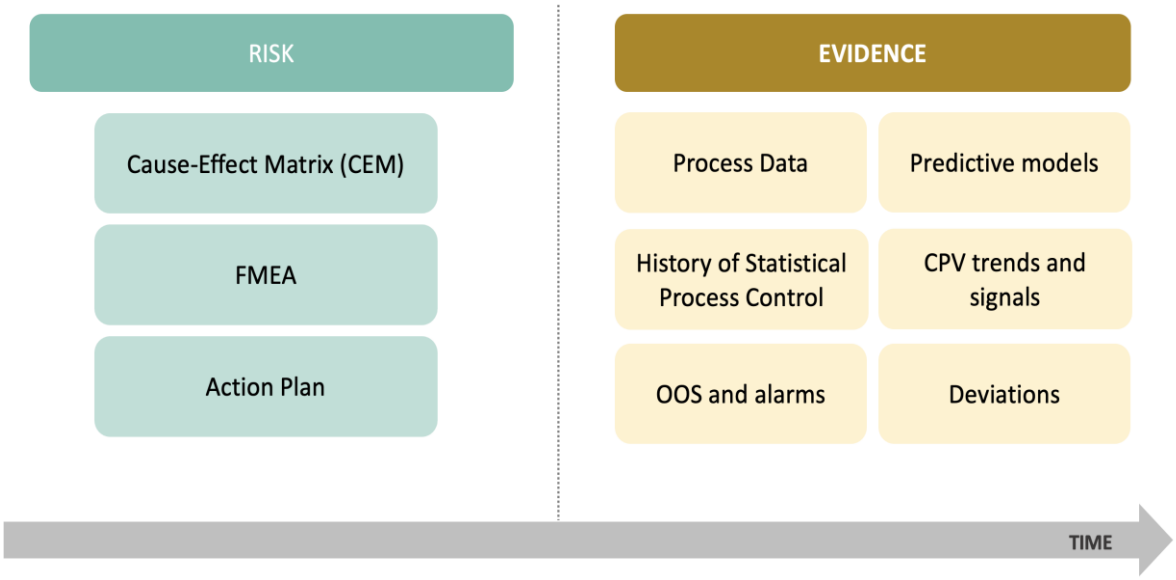

Figure 5 – Sources of Risk and Evidence

With both sources of risk and evidence identified, mapped, and properly designed and implemented, the door is now open for organizations to retrieve the full potential of data and increase the robustness of its risk management process. It will for example, be able to:

- Validate previously identified risks and review risk assessment based on data.
- Determine occurrence.
- Obtain correlation matrices and corroborate cause-effect matrix scores with process evidence.

A Practical Approach to Minimize Subjectivity

Having a digitized CPV is a powerful tool to implement the risk & evidence loop, since a well-planned CPV plan will be continuously generating data to be used as feedback for the initial assumptions while doing initial stages risk assessment.

The following are some “quick win” approaches and proposals for the implementation of this loop between a digital risk and a digital CPV platform.

1) Generation of the CPV program

CPV will be the source of evidence for the risk review, but QRM will also be the source for an efficient CPV plan design. The selection of the variables to be measured during manufacturing

should be the first action when designing the CPV plan. This selection will be done through a criticality assessment of the process parameters, material attributes and quality attributes.

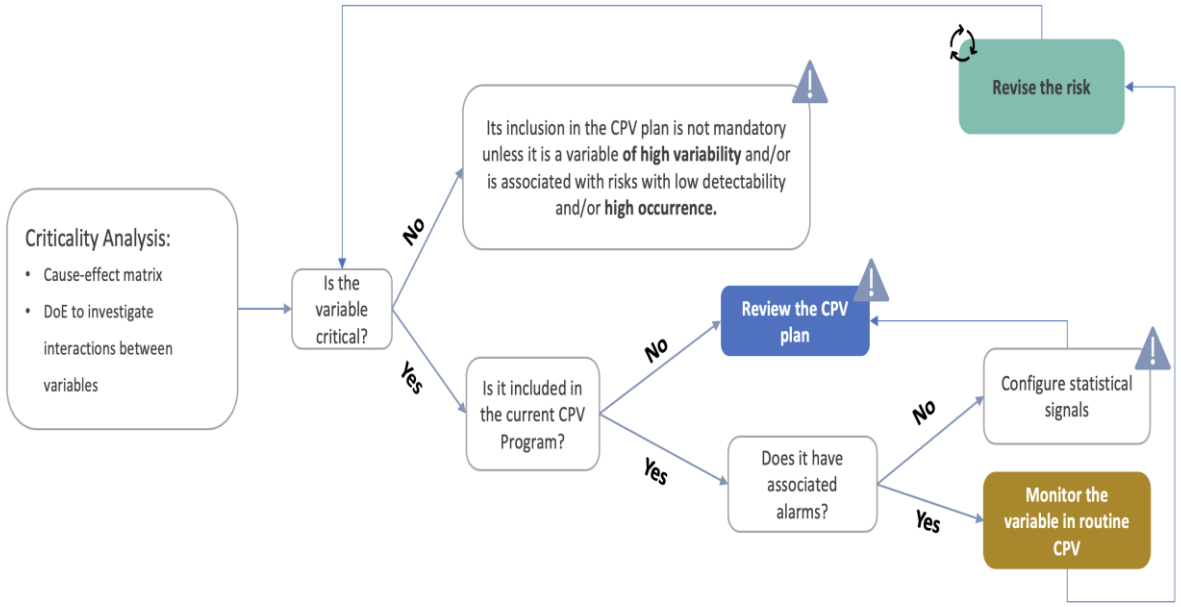

Figure 6 – Risk-based CPV plan definition

Using QRM tools such as cause-effect matrices, FMEA and action plan will not only guide the organization through the process of building knowledge and assess a particular parameter in terms of its criticality, but also, as a direct impact, it will identify which parameters should be included in the CPV plan, and thus for which parameters will data be collected when the process reaches the manufacturing stages.

#	Output Name	Acceptance Criteria	Target Value	Description	Category	Biological Activity		PK/PD		Immunogenicity		Safety		Maximum Risk Score	Criticality	References	Group Type	
						Impact	Uncertainty	Impact	Uncertainty	Impact	Uncertainty	Impact	Uncertainty					
9501	Aggregation	0-5%	N/A	Identity, Purity, Stability categories of ICH Q6B.	PCQA	12	2	12	3	12	5	12	2	60	CQA	• A-Mab DS CQAs • A-mab DS QAs ranges	N/A	
9502	Oxidation	Controled	N/A	Product Related Attribute	PCQA	16	3	4	3	4	2	4	2	48	CQA	N/A	N/A	

Figure 7 - CQA Assessment Tool

2) CPV Plan Management

After the design and implementation of a digital CPV plan, the organization is now able to acquire and process data, transform it into knowledge and make the link with the initial risk assessment information.

This link will empower specific actions such as the risk review as advocated by ICH Q9. One example would be the corroboration of the estimated Occurrence values for a potential failure mode. With a digital platform capturing data from a specific process parameter previously associated with a potential failure mode, it will be possible to compare the actual frequency of deviations or OOT/OOS for the process parameter with the initially estimated occurrence of the potential failure mode and act upon any discrepancy in two ways:

1. By proposing the review and increase of an initially low occurrence estimated value based on the actual frequency of the failure mode.

Unit Operation	Critical Outputs from iRISK FMEA	Inputs from iRISK FMEA	Failure Mode	S	Failure Causes	O	Revised O	D	Revised D	RPN	Revised RPN	Number of Associated Issues	Batches with High OOT (%)	Batches with Medium OOT (%)	Batches with High Historic Alarms (%)	Batches with Medium Historic Alarms (%)	Batches with Input OOS (%)	CPV - CpK
UO_1	QA5	PP4	pump is not working.	3	Technical defect	5	N/A	5	N/A	75	0	0	46.7	6.7	53.3	6.7	6.7	N/A

Figure 8 – Risk review of the underestimated Occurrence

2. By proposing the review and decrease of an initially high occurrence estimated value based on the nonexistence of any issue associated with the failure mode.

Unit Operation	Critical Outputs from iRISK FMEA	Inputs from iRISK FMEA	Failure Mode	S	Failure Causes	O	Revised O	D	Revised D	RPN	Revised RPN	Number of Associated Issues	Batches with High OOT (%)	Batches with Medium OOT (%)	Batches with High Historic Alarms (%)	Batches with Medium Historic Alarms (%)	Batches with Input OOS (%)	CPV - CpK
UO_1	QA3	PP6	Valve is not working	5	Lack of operator training	9	N/A	5	N/A	225	0	1	N/A	N/A	N/A	N/A	N/A	N/A

Figure 9 – Risk review of the overestimated Occurrence

In both cases, we have an example of a data-driven risk review acting as the trigger to continuously improve the defined control strategy.

3) Process Deviation Management

This digital approach will not only be capable of proposing a risk review of the estimated Occurrence for already identified potential deviations (failure modes) but also to propose the definition of new failure modes based on any issue or deviation that was not initially identified.

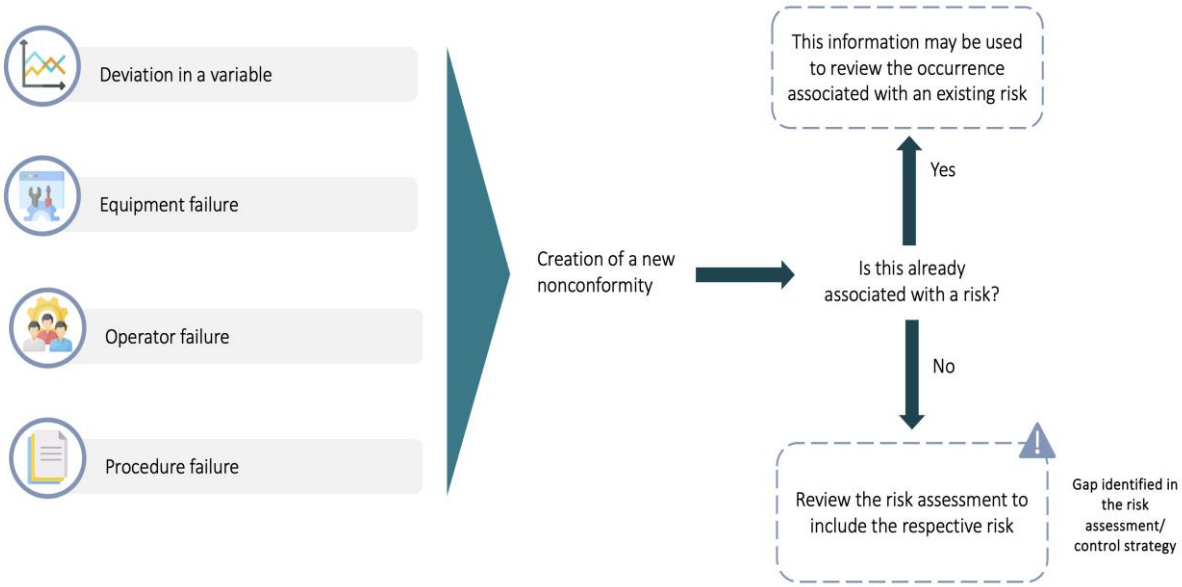

Figure 10 – Risk review of the failure modes

Any deviation in a variable being measured, or any equipment, operator or procedure failure will be identified and tracked as an issue and will in turn be available to be compared with the initially defined risks. If there is a match with an existing failure mode, this issue will be used as a trigger to review its Occurrence value. If there is no match with any existing failure mode, this issue will be the trigger for the review of the FMEA, where a new failure mode should be defined, and consequently new controls should be implemented. This is just another example of a data-driven risk review supporting the continuous improvement of the control strategy and the overall QRM practices.

4) Regulatory Support in Post-Approval Changes

Another use-case for a data-driven risk management approach is the usage of QRM as a support for regulatory interactions, namely in the post-approval changes process.

At this point, with a product in its commercial manufacturing stage, and assuming a CPV plan is in place, the ability to use real evidence as justifications for proposed changes is of utmost importance. The established conditions will be well characterized, the understanding of every parameter criticality will be achieved, and a robust control strategy will be in place.

This will guarantee an efficient first step of analyzing the criticality of the current process and the risk assessment of the impact if the change is implemented.

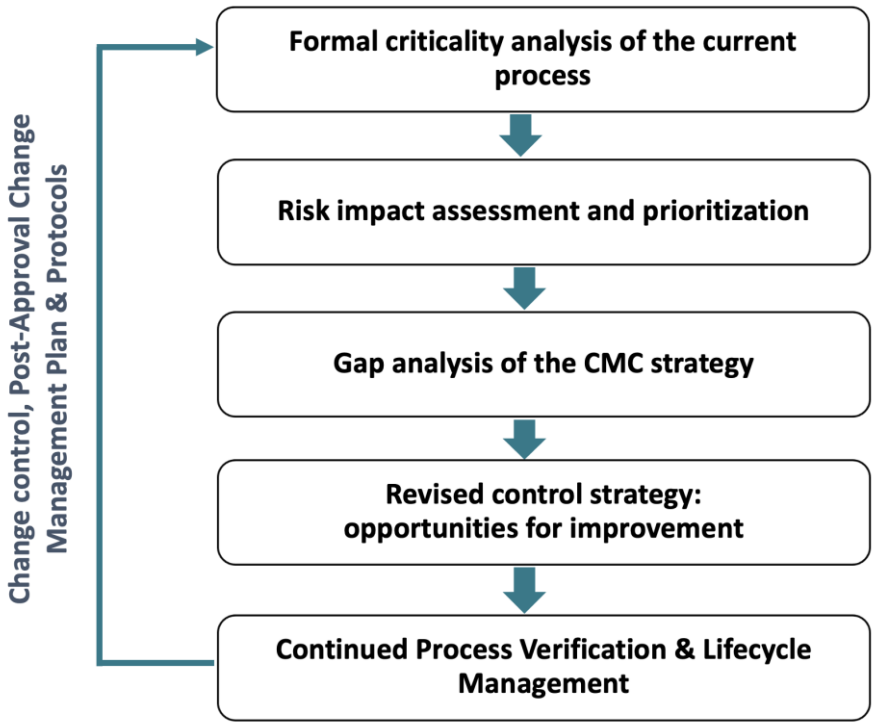

Figure 11 – QRM role in post-approval changes

Using captured data will be a powerful support for this impact assessment and an evidence-based justification for the revision and continued monitoring of the control strategy that must be proposed to accommodate the process change.

Final Remarks

Technology innovation is usually several steps ahead of regulations and working practices. When talking about QRM and having in mind the recently published ICH Q9(R1), we could say that there is no excuse for not using technology, data, and digital tools to help streamline and improve QRM practices.

Implementing a data-driven risk management approach should be seen as a change management trigger, allowing the organization to realize the full potential of QRM as a continuous improvement enabler instead of just a mandatory regulatory exercise.

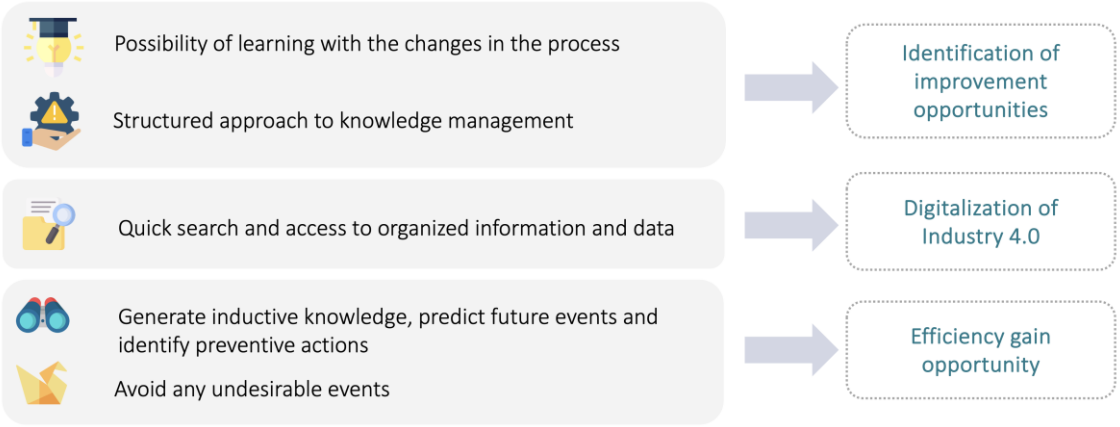

Figure 12 – Advantages of a data-driven risk management approach

To achieve this, the organizations should be able to design and implement an integrated approach based on risk and data, with the proper support of digital platforms capable of providing a more complete view of the product over its entire lifecycle, allowing a structured means for generating, storing, analysing, and managing knowledge over time.

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