



## An Overview of Risk Management and Risk-based Cleaning Validation

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### ABSTRACT

Risk in general means exposure to harm or a factor that can contribute towards bringing harm to a system. Almost every operation in the pharmaceutical industry is susceptible to risks. There is a need to overcome risks and minimise them to prevent unwanted changes in product quality and safety. This prevention can be done by carrying out quality risk management (QRM) that facilitates the proper characterisation of risks, risk analysis, risk assessment to control and reduce risks. ICH Q9 guidelines explain quality risk management and its applications in the pharmaceutical industry. Cleaning validation is performed to verify and evaluate the efficacy of cleaning procedures used to clean the equipment after production and to prevent cross-contamination between products that are manufactured in the production facility. The current study focusses on reviews of quality risk management and cleaning validation policies. By incorporating QRM in the quality policy, companies can look to improve the modern Approach towards facing risks related to the issues that affect the product quality, safety and compliance concerning the cleaning of equipment used in manufacturing and supporting operations in the industries.



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As risks to existing processes and systems can pose a danger by harming the integrity of the operations, it is important to avoid these risks to maintain and improve quality and safety of the products that are produced.

Complete minimisation of risk is not practical as the various risks in any process cannot be accounted for by any given method and also can't be predicted every time. However, managing risks are not new in the present scenario as there are established practices and also approved guidelines from regulatory bodies about risk management and incorporation of risk management in the quality systems of the companies in general.

### INTRODUCTION

Risk in general terms can be defined as an exposure to danger or something that has the potential to cause harm in an existing system or process. In the pharmaceutical terms, the risk is linked to almost all processes being carried out and products being manufactured in any given pharmaceutical industry.

Experts recommend pharmaceutical manufacturing companies to inculcate Quality Risk Management (QRM) process in their quality systems. The introduction of QRM principles is likely to reduce the associated risks and maintain the quality of the end product in toto to enhance its use and stabilise the

risks. QRM focusses on the identification, analysis and evaluation of risk along with measures to control, communicate and review the risks incurred by the end product related to the quality .

The US Food and Drug Administration and other regulatory committees, ICH Q9 guidelines recommend Quality Risk Management. They indicate that QRM tools make it possible for manufacturers and regulators alike, to understand the true extent of risks and the degree of response to be taken to mitigate them. As discussed, a single method cannot be useful at all times to evaluate risk, so, utilising preferable tools for the same is recommended.

### **General ideas that will help in the management of risks and optimisation of taking risks**

The pharma industry doesn't have robust, data-driven risk analysis capabilities. It is not aligned to take actions rapidly, thus making a point that it is difficult to make decisions quickly in terms of risk management. The complexities of the nature of the work and being in a highly regulated sector doesn't help either. So, linking the pharmaceutical industry with similar sectors, we can get general ideas about the models that this sector can reproduce to assist in managing risks and optimising decision making in a better way ([Expanding Horizons for Risk Management, 2018](#)).

#### **Risk Ranking Model**

Risk Ranking Model can be done by developing a powerful method to determine and quantify risks and ranking them based on their severity. Also, the likelihood of the occurrence along with potential effects can be predicted, which will help in planning and management.

#### **Lines of Defence Model**

Lines of Defence Model is a tested method across other sectors where there are fictional lines of defences based on the operations with separate responsibilities.

The first line – constitutes the target personnel or people directly involved in risk management.

Second-line – monitors the risk profile, creates policies and sets standards and supervises the actions to be taken.

The third line – assesses the actions taken and audits the corporate activity along with external help if necessary.

#### **Establishment of a risk limit and prioritising the focus points**

Having a pre-established structure for risk limits can enable a company to have a better understanding

about the situation and about what to expect out of a risk. This will help in taking appropriate actions against the risk, better allocation of resources, better monitoring and effective control of risk.

The risk framework should be designed, keeping in mind the information obtained from customers, external specialists & consultants and company personnel involved in operations and finances. By knowing where to focus on overcoming risks, the company can also boost its business profile and optimise its returns based on risk.

#### **Incorporating Recent Advancements in Data Analytics**

Making use of artificial intelligence, machine learning, significant data handling and advance analytics can simulate models and enhance the capabilities of a company to face and handle risks and also for further planning. This Approach can also aid in planning and arranging quality and regulatory audits.

Also, by incorporating analytics with risk management and quality practices in the company, the identified risks can be monitored appropriately and mitigated.

#### **Establishing Robust Crisis-Management Readiness**

As risks may be unpredictable and if the threats posed by these risks escalate, every organisation should be prepared for a crisis event. This scenario will need necessary action and preparedness and improvement in managing risks. During these times, suitable decisions must be taken only after serious discussions with senior management.

The readiness in facing the risks in crucial times like these, need to include the type of responses for particular classes of risks, classifying critical activities and decisions on investigations on risk analysis. Lastly, it should also think about issues with regulations, vendors, suppliers and the preparedness of the company, as a whole, to face the unprecedented degree of risk.

#### **Regulatory Information about Risk Management**

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) presents the guidelines – Q9 regarding Quality Risk Management. This document is essential to the targeted manufacturing firms, as it offers an approach to deal with the management of risks in a systematic and adaptable manner to the quality culture of the firms. It is independent of other ICH documents but supports and supplements the ICH other documents in enhancing the consistency and efficiency of the processes which are used

in the company. As discussed above, the text serves as a source guide concerning risk management to industry personnel and regulators alike ([Viornerly and Quality Risk Management – PIC/S, 2010](#)).

The Q9 guidelines are meant to be employed in phases of the drug lifecycle like the early stages of development, pilot-scale production, mass production, finishing, packaging, quality checks and distribution of the desired products to circumvent any risks in the process.

### Quality Risk Management Approaches

Generally, the industry follows two approaches to risk management ([Prasad, 2014](#)). They are

1. Proactive Approach: Here, the possible areas which are vulnerable to risks are identified, and actions are taken to reduce the effects of the risk, before the occurrence of loss.
2. Reactive Approach: Here, the main reason for the occurrence of the risk is investigated, to find the appropriate way to overcome the effects, after the incident of loss.

### Integration of QRM in Pharmaceutical Manufacturing

Quality Risk Management in the pharmaceutical field concerns all types of pharmaceutical products and also includes medical devices. Good Manufacturing Practices (GMP) are practices followed in pharmaceutical companies to enhance the product quality, consistency and safety and also to serve as a means to achieve compliance in a simple manner. It was consequently adopted by the European Union in Annex 20 and PIC/S GMP guide to be applied in a step by step manner by pharmaceutical manufacturers ([Das, 2014](#)).

### Risk management focusses mainly on two essential principles. The principles indicate that

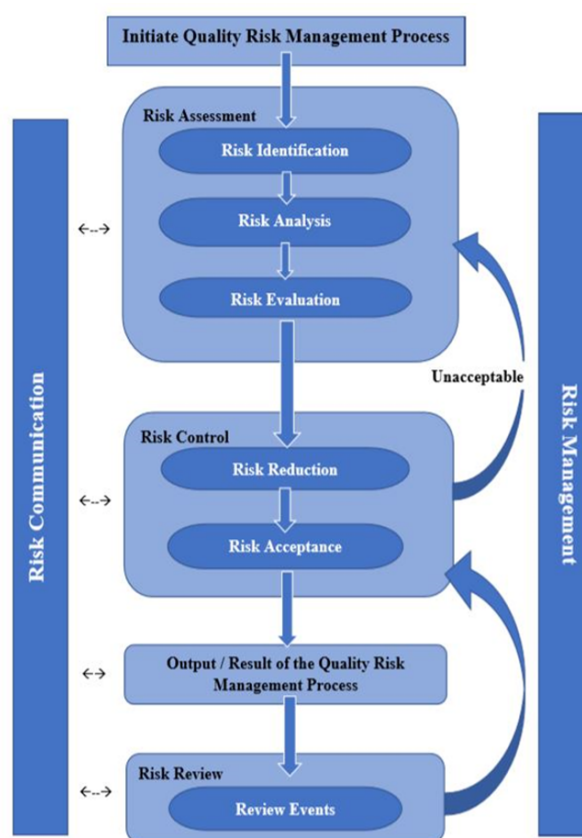
1. The patient's health is of primary importance. Therefore the risk which is related to the quality of the product should be assessed against a robust scientific rationale to get accurate results.
2. The response for a particular risk event, action and documentation process of the QRM should be corresponding to the extent of risk ([Reddy et al., 2014](#)).

However, the methods that are designed to detect and measure risks are not consistent and to implement a single method to determine risk in every process is not practical and difficult to rely on. Therefore, care must be taken to not depend on one method to assess risks and considerations for selection of method must be taken on thorough analysis and suitability in the particular scenario [Figure 1](#).

As a recommendation, the Quality Assurance team in the production facility should develop a transparent methodology of QRM based on the main principles of risk management. That way, it'll be comfortable and practical to implement risk management at a given time and will be easy for the manufacturer to comply with the regulations and the regulatory inspectors to check compliance [Figure 2](#).

### Quality Risk Management Process

Quality Risk Management is a process involving assessment of risks based on the effects it can have over a process, means to control of the identified risks, appropriate communication of the risk to properly understand the effects of the risk and review of actions taken against the risks. The most common model of the quality risk management process is as shown below ([Lotlikar, 2013](#)).



**Figure 1: Overview of Quality Risk Management**

### Explanation

#### Initiation of the Process

For the initiation of QRM, the steps that are to be taken to overcome the risks should be based on a strong scientific rationale. By ensuring this, it will be possible to make the appropriate decisions towards minimisation of the risks. This can be done systematically by

1. Estimating the potential of the risk by understanding the problem and relevant suppositions.
2. Accumulating data which provides a better perception of the risk and its effects
3. To make decisions based on the above points and planning resources to be utilised to overcome the risk.

### **Risk Assessment**

Risk assessment involves analysing and evaluating the risks after referring to the information that is collected during the initiation phase of the process. From the results of the analysis and evaluation, the extent of the problem caused by the risk can be adequately comprehended, thereby, helping in choosing an appropriate risk management tool to tackle the risk.

### **Risk Identification**

Risk identification involves the use of the collected information to point out the hazards in a given system on which the risk assessment is being carried out. It is instrumental in providing a well-defined picture of the consequences that might occur due to the failure in addressing the risk appropriately.

### **Risk Analysis**

Risk analysis links the hazards identified in the previous step with the approximation of potential of risk. It also deals with the qualitative and/or quantitative aspects of the intensity of the harm.

### **Risk Evaluation**

Risk evaluation chiefly contrasts the risk identification and risk analysis. It covers the fundamental queries about the probability of the risk occurrence and the consequences in the process if a risk is left unchecked, and provide the relevant evidence for these queries.

### **Risk Control**

Risk control focusses on taking decisions to mitigate the risks or accepting risks based on information collected priorly. It works on the rationale the proportionality between the effort of taking action towards risk reduction should match the importance of the risk. It also focusses on queries regarding:

1. Potential of the identified risk to cause harm
2. Methods to reduce risks
3. Possibilities of new risks due to the control of an identified risk

### **Risk Reduction**

Risk reduction, as the name suggests, focused on the decline of the risk from a certain level and bringing it

down below the accepted standards. It should also be noted that new risks may emerge in the system or emphasise existing risks. Therefore, it is important to perform risk assessment properly to avoid unprecedented effects after selecting a risk reduction process.

### **Risk Acceptance**

Risk acceptance talks about accepting risks. This is usually seen when even the most suitable risk management method used might not give an appropriate result towards eliminating the risk. So, there will be a recommended acceptance criterion set up in these types of cases to minimise risk to a certain level as the risks cannot be reduced entirely (Sivadasu *et al.*, 2017).

### **Risk Communication**

Risk communication is the exchange of instructions and information about risk and managing risk. Usually, this communication happens between the team that takes decisions about the risk and the personnel concerned with the process. However, it is not just related to the personnel, as the communication can also happen between the industry and regulators, industry and customer, industry and vendor, industry and another industry, etc.

### **Risk Review**

Risk review is a process for examining the results obtained by the implementation of quality risk management in a particular system. The risk management adopted should be checked whether it influences the quality of the event, and trends must be charted for further study.

It is also recommended that the reviews must be conducted as frequently as the degree of risk demands.

### **Risk Management Methodology and Tools**

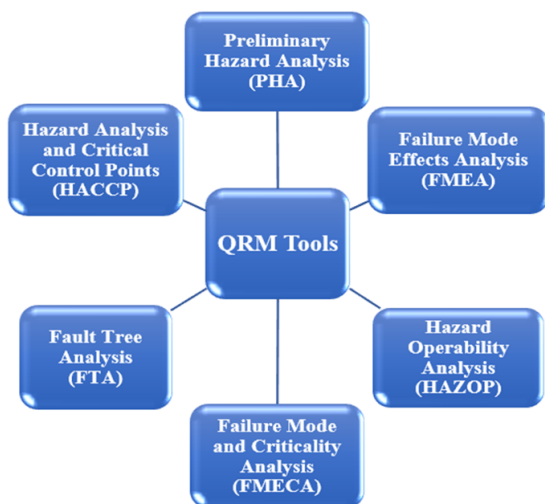
Decisions in any quality risk management process are made under a scientific rationale. To accomplish the stages of QRM, a practical approach based on robust scientific reasoning, tend the methods required transparency, documentation and reproducibility.

Assessment and management of risks related to quality are made based on information, observations and relevant experience.

They prove instrumental in handling deviations, changes, complaints and management of resources.

Also, there are quality risk management tools that the pharmaceutical industry employs practically. These tools are also adopted by regulators to assess the risks. Some tools are:





**Figure 2: Quality Risk Management Tools**

### Cleaning Validation

Cleaning validation can be explained as the process which deals with furnishing evidence, in the form of documentation. It is that the specific cleaning program which is used to clean the equipment in an industry can consistently control the possible carryover of products into subsequent batches of other products, to a degree which is below predetermined levels.

Cleaning validation is much more critical in a multiproduct facility than in a single production facility as the vulnerability for the occurrence of cross-contamination is more pronounced here.

For cleaning validation to be successful, it is crucial to set

1. Acceptance criteria based on the potency of the substance,
2. Exposure limits of the substances,
3. Carryover information, company policy, product study data, etc.

to make sure that the carryover remnants are well under the set acceptance limits.

Guidelines from regulatory bodies dictate that companies should comply with current good manufacturing practices (cGMP) and have a risk-based approach to improve the ability to identify and deal with risks and control critical attributes which influence the process efficiency and quality of the product.

### Importance of Cleaning Validation

It is vital to validate cleaning procedures (Lodhi, 2014; Prabu and Suriyaprakash, 2010).

1. Comply with regulatory requirements; 2. Prove the consistency and effectiveness of the cleaning

- method; 3. Ensure product quality, purity and safety; 4. Ensure avoidance of risks related to contamination and cross-contamination

### Regulatory Perspective of Cleaning Validation

#### Cleaning validation as per the United States Food and Drug Administration (USFDA)

The agency maintains that the cleaning methods employed should be validated. It is emphasised in the Bulk Pharmaceutical Chemicals Inspection Guide and the Inspection Guide for Biotechnology (Validation of Cleaning Processes (7/93), 2014).

#### Cleaning Validation as per Active Pharmaceutical Ingredients Committee (APIC)

The guidelines by APIC provide instructions and information related to specific topics which are relevant in validation of cleaning methods performed in industries which produce active pharmaceutical ingredients. The topics of discussion include determination of acceptance criteria, cleaning levels, selection of worst-case product/procedure and so on (Guidance on Aspects of Cleaning Validation by APIC, 2016).

#### Cleaning validation according to the World Health Organization (WHO)

It highlights the importance and criticality of analytical methods and procedures used for cleaning of equipment (Guidelines on Validation by World Health Organization, 2016).

#### Cleaning Validation as per the European Medicine Agency (EMA)

It emphasises on deciding limits for exposure of substances by considering the safety and threat levels during production processes. By ranking according to the threat levels, appropriate cleaning procedures can be designed to suit the expected standards (EMA, 2014).

#### Cleaning validation according to Parenteral Drug Association (PDA)

It talks about a lifecycle approach for cleaning validation along with risk analysis and its effects on the safety and quality of the drug products. It also gives suggestions and points for considerations for designing cleaning validation programs for process and equipment to achieve compliance with set requirements (PDA and Parenteral Drug Association, 2012).

#### Production of Pharmaceuticals and its Significance in Generation of Remnants

Production of pharmaceuticals require raw materials, excipients, reagents, buffers and may involve steps like condensation, concentration, purification,

etc. During these processes, there may be a generation of undesirable and unwanted remnants. These remnants, along with product residues, might get deposited on the surface of the equipment. Hence, it is very important that, when the equipment is subjected to cleaning, the cleaning method should fulfil the acceptance criteria and remove the remnants, thereby keeping the residual quantity below the limits Figure 3.

It is advisable to adopt a worst-case scenario to reduce the number of validation studies for cleaning processes. Guaranteeing that the cleaning procedures are yielding consistent results and proving its efficiency then it is deemed suitable to be used for most of the cleaning processes barring exceptional cases (Edward, 2005).

### Cleaning Validation – Conventional Approach

Generally, the acceptance criteria would be set up by the industry after considering various supporting factors. Then the cleaning validation program is developed for the worst-case scenario and analysed. If the acceptance criteria are met, then the process is validated to check for consistency. After the method is validated, and the values are found within limits, i.e., below the acceptance criteria, it is summarised, documented and approved, thereby validating the process.

However, in case there is a failure in the validation tests, then, it is expected to determine the reason for the failure. There is a chance that the acceptance criteria set may not have a strong scientific base to it, and it may have caused the failure. This failure might be problematic as it will be too late to change the acceptance criteria at the development stage, consequently, sending the process back into the developmental stage.

### Cleaning Validation – Risk-based Approach

A risk-based approach to a cleaning validation program will ensure that critical decisions aren't taken without prior understanding of the concepts that are put to use here. Here, the acceptance criteria are set up keeping in mind the nature and characteristics of the substances that are meant to be manufactured in the facility with special emphasis on the potential of harm that it can cause. Separate tests will be performed to evaluate the effect of the levels of remnants of Product A (first product) on the manufacturing of Product B (second product), where both the products are manufactured in the same equipment and the same order Figure 4.

The residual limits are reviewed to establish Maximum Allowable Carryover (MACO) value. From the product study reports, a safety factor based on reli-

ability and toxicological data is taken, which is used to divide the MACO value to obtain the acceptance criteria.

In the development of a cleaning program, the worst case is selected. The cleaning agent is also rightfully selected with special emphasis on the ability to remove the cleaning chemicals, product impact on the environment and disposal of waste.

The cleaning procedures will be tested on assessing cleaning parameters, interactions between the cleaning agent and the substance and the nature of the cleaning agent in general. Also, the cleaning process developed must display that it can assure that the remnants are reduced below the set criteria.

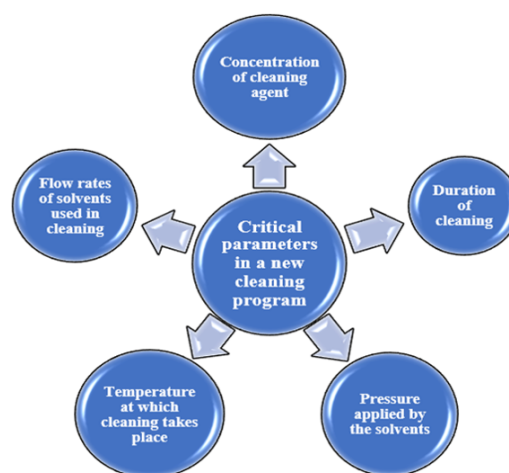
If the acceptance criteria are met, then the process is validated to check for consistency. After the method is validated, and the values are found within limits, i.e., below the acceptance criteria, it is summarised, documented and approved, thereby validating the process.

However, in case there is a failure in the validation tests, an investigation is carried out to find the causative reason for the deviation in results. Here, instead of focusing on the acceptance criteria, the company will look into the shortcomings in the main process and the cycles of cleaning.

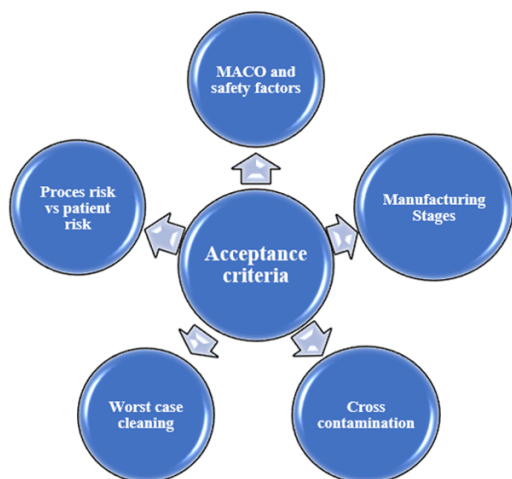
Nevertheless, in case of a failure in the validation run and if it is concluded that the procedure is not up to the expected mark, the acceptance criteria won't be modified. Still, then, it is presumed that the cycle will be tweaked to give a better performance.

### Risk-Based Acceptance Criteria

Factors that are instrumental in developing risk-based acceptance criteria in a cleaning validation program



**Figure 3: Overview of critical parameters in a cleaning program**



**Figure 4: Overview of factors affecting acceptance criteria**

### **Incorporation of Risk Management in Cleaning Validation**

Implementing steps to elicit an overall application of risk management in cleaning validation is necessary. These following areas are fundamental and affect the effectiveness of the cleaning processes and cleaning validation as a whole.

1. Grouping and categorisation of process remnants based on nature, solubility and characteristics.
2. Influence of the design of the equipment and degree of cleanability.
3. Assimilation of previous data of results of cleaning validation batches.
4. Selection of solutions for cleaning and cleaning agents.
5. Prepared Standard Operating Procedures concerning cleaning validation.
6. Studies about Cleaning Design Space and the influence of the space in cleaning.
7. Risk analysis between the differences in manual and machine cleaning.
8. Classifying equipment and process based on cleaning variability.
9. Studies related to dirty hold time and clean hold time influence the cleaning processes.
10. Collective accumulation leads to the creation of a cleaning control strategy, that has to be assessed regularly.
11. The categorisation of sampling practices and understanding sampling strategy.
12. Statistical observations for graphical representation and better understanding.
13. Selection of instruments for analysis.

### **CONCLUSION**

From the above review, we can deduce that risk management in pharmaceutical processes is vital as it helps in checking the threats posed by risks and also provides ways to overcome risks and minimise product non-conformities. Validating cleaning procedures is of paramount significance in the pharmaceutical industry as it provides information about the consistency and efficiency of cleaning methods to control the residual deposition in the manufacturing equipment. A risk-based cleaning validation program, is merely the incorporation of risk management in cleaning validation in a company. We can conclude that it will enhance the quality and safety of the product by validating cleaning methods effectively and also helps in increasing the general preparedness to overcome risks and potential threats.

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### **Conflict of Interest Statement**

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