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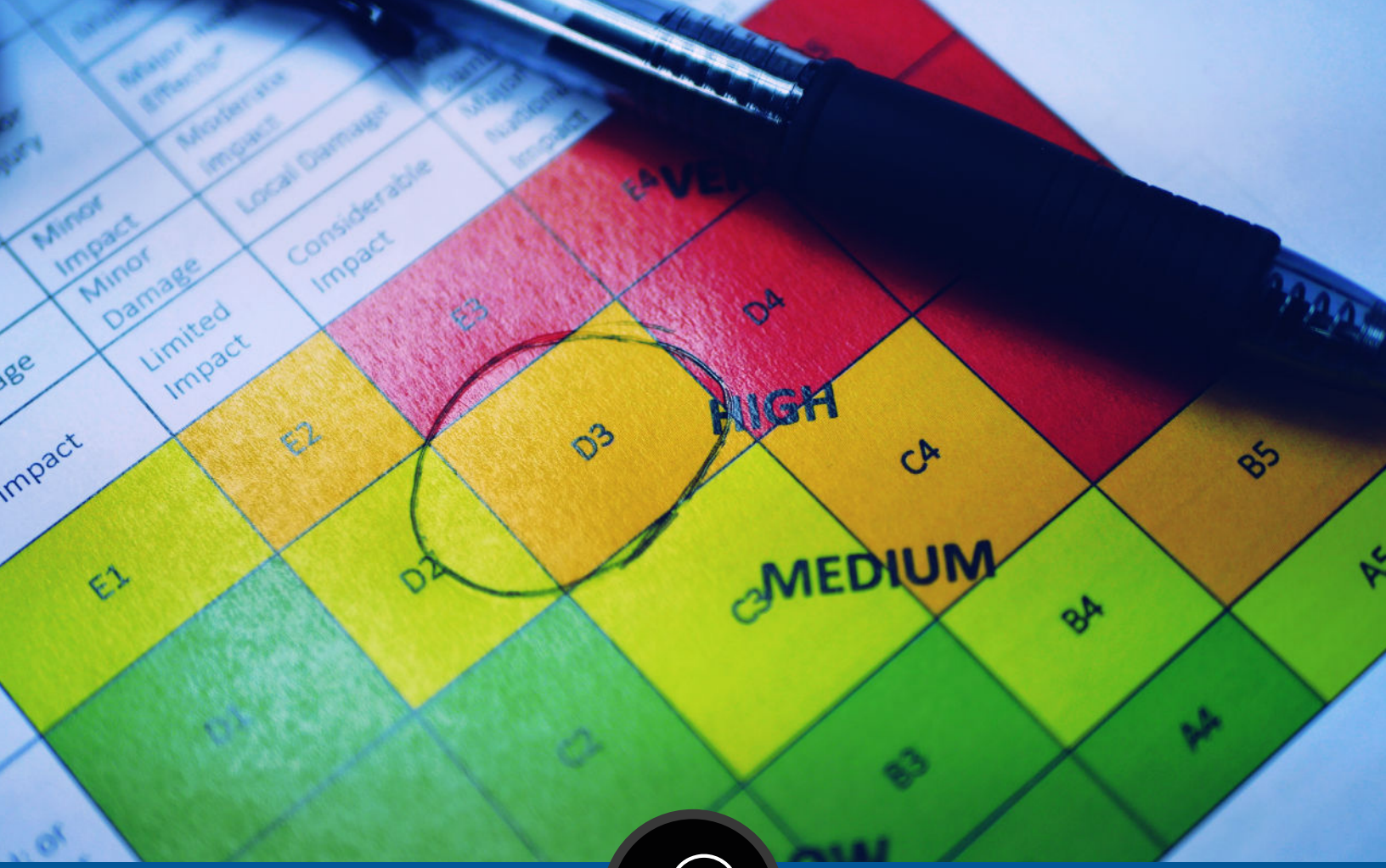
PERFORMING AN ICH-Q9 RISK ASSESSMENT TO IMPLEMENT SAMPLING LOCATIONS FOR A PHARMACEUTICAL FILLING MACHINE

Lighthouse Worldwide Solutions



Overview

A Risk Assessment identifies the Hazards and evaluates the risks associated with exposure to those hazards. The model we will follow today is a systematic approach from ICH Q9 from the European Medicines Agency circulated in 2015.

There are many Risk Management strategies for example the FDA has a great guideline on risk evaluation and mitigation strategies issued in 2015 which is still a draft format but nevertheless good information. The FDA's 2005 Development and Use of Risk Minimization Action Plans is a good guidance document.

Step 1: Initiation of the Risk Assessment

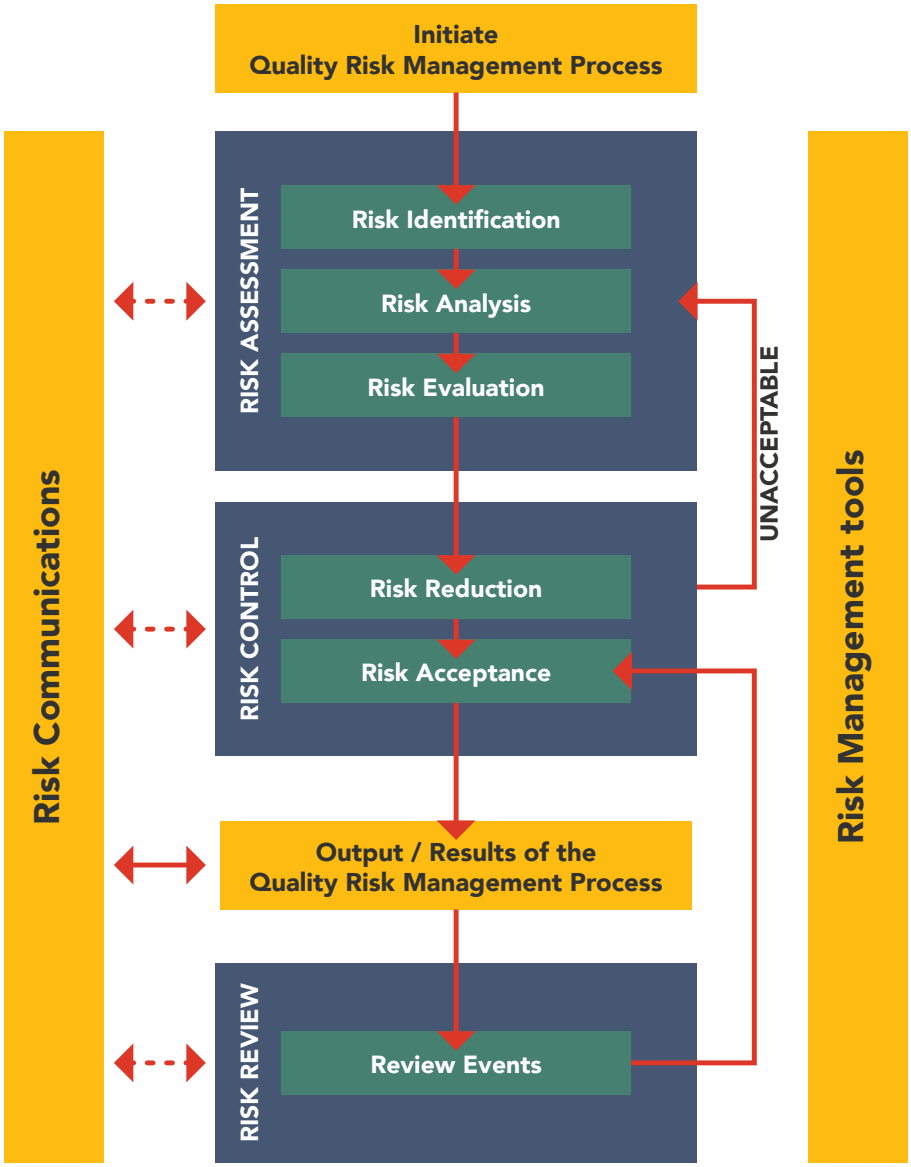
Identify the Risk Assessment Team: Assemble a multidisciplinary team with expertise in quality assurance, microbiology, cleanroom operations, and engineering.

Define the Scope: Clearly outline the objectives, including the specific aspects of the filling line and cleanroom operations to be assessed for contamination risks.

Step 2: Risk Identification

Gather Information: Collect data on the filling line processes, equipment, materials, and cleanroom environment.
This includes SOPs, historical contamination incidents, and workflow diagrams.

Identify Potential Hazards: List all potential sources of contamination, such as personnel, equipment, materials, and environmental conditions. Consider both microbial and particulate contamination.



Risk Assessment ICH-Q9 Model

Step 3: Risk Analysis

Determine the Likelihood of Occurrence: Assess the probability of each identified risk materializing, considering factors like frequency of exposure and past incidents.

Assess the Severity of Impact: Evaluate the potential impact on product quality and patient safety if contamination occurs. Consider the nature of the product and its route of administration.

Prioritize Risks: Use tools like risk ranking and filtering to prioritize risks based on their likelihood and severity.

Step 4: Risk Evaluation

Compare Risks Against Criteria: Use predefined criteria to determine which risks are acceptable and which require further risk control measures.

Decision Making: Decide on the necessity of risk reduction for each identified risk.

Step 5: Risk Control

Select Risk Control Measures: Identify and implement strategies to minimize or eliminate high-priority risks. This may include engineering controls, procedural changes, and enhanced monitoring.

Implement Risk Reduction: Apply the selected control measures in the cleanroom and filling line operations.

Review Effectiveness: Assess the effectiveness of the control measures in reducing or eliminating the risks.

Step 6: Risk Communication

Share Information: Communicate the risk assessment findings, decisions, and actions taken to all relevant stakeholders, including cleanroom personnel, quality assurance teams, and management.

Documentation: Ensure thorough documentation of the risk assessment process, findings, decisions made, and actions taken.

Step 7: Risk Review

Monitor and Review: Regularly review the risk management process and the control measures to ensure they remain effective and consider any changes in the cleanroom environment, processes, or regulations.

Continuous Improvement: Update the risk management plan as necessary to reflect new information, changes in processes, or advancements in technology.

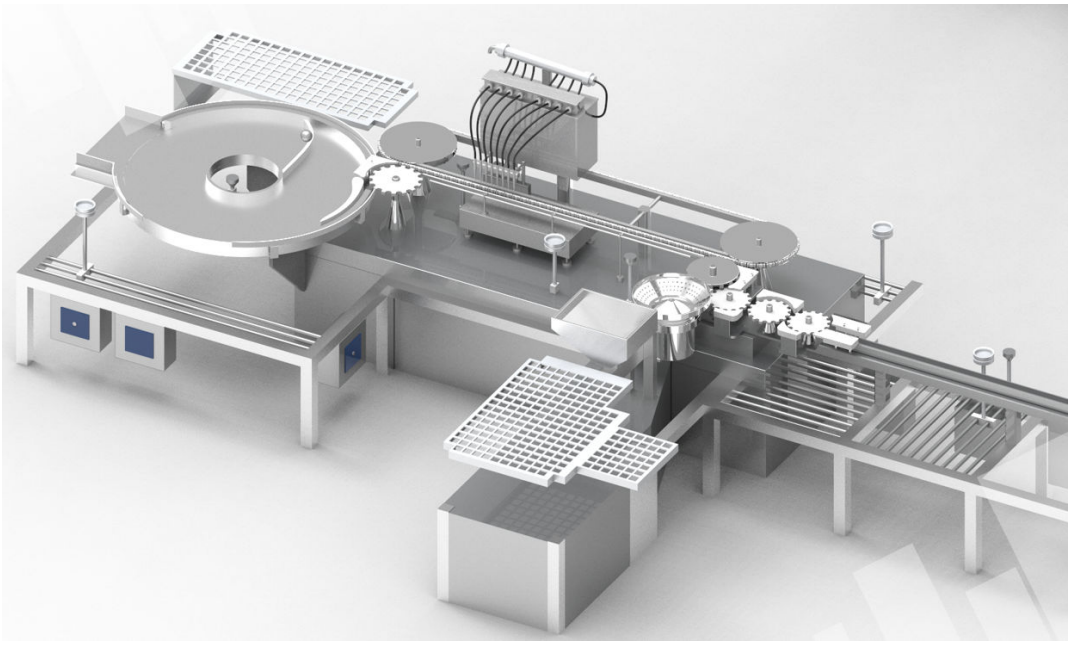
Following the ICH Q9 Quality Risk Management model provides a structured and systematic approach to identifying, analyzing, controlling, and monitoring risks related to contamination in an ISO 5 classified pharmaceutical cleanroom. This ensures not only compliance with regulatory requirements but also the safety and efficacy of pharmaceutical products.

Applying the ICH-Q9 Model to the selection of a Monitoring System for a Pharmaceutical Aseptic manufacturing operation.

Aseptic manufacturing requires an ISO 5 Classified environment, and a monitoring system is used to verify that the ISO 5 conditions are maintained throughout the aseptic operation. In the case of a filling machine, bulk sterile liquids are filled into vials, ampoules or syringes through a filling head which can typically consist of several filling needles which will insert the sterile product into sterile containers.

A Risk Assessment team would consist of specialized individuals, subject matter experts and management who have managerial knowledge on the aseptic filling process, the cleanroom operations and on monitoring systems. If internal knowledge is not available, then external consultants are hired.

The Risks need to be identified and in this case with the filling machine the process needs to be thoroughly studied to identify locations of “risk” where the sterile product may encounter contamination or has the possibility to be contaminated.



A model of a pharmaceutical filling machine

The Risk Analysis process will look at the likelihood of the potential risk and what the impact of that risk would be. The route of the product, vial or ampoule are studied and then during the Risk Evaluation process the necessity of risk reduction is calculated and the reduction tool is implemented. To control the risk in the case of a filling machine a particle and continuous air sampling monitoring system was identified as being the best contingent to averting the risk. This monitoring system will sample the environmental air conditions and alert management and operators if the ISO 5 environment is under threat from contamination.

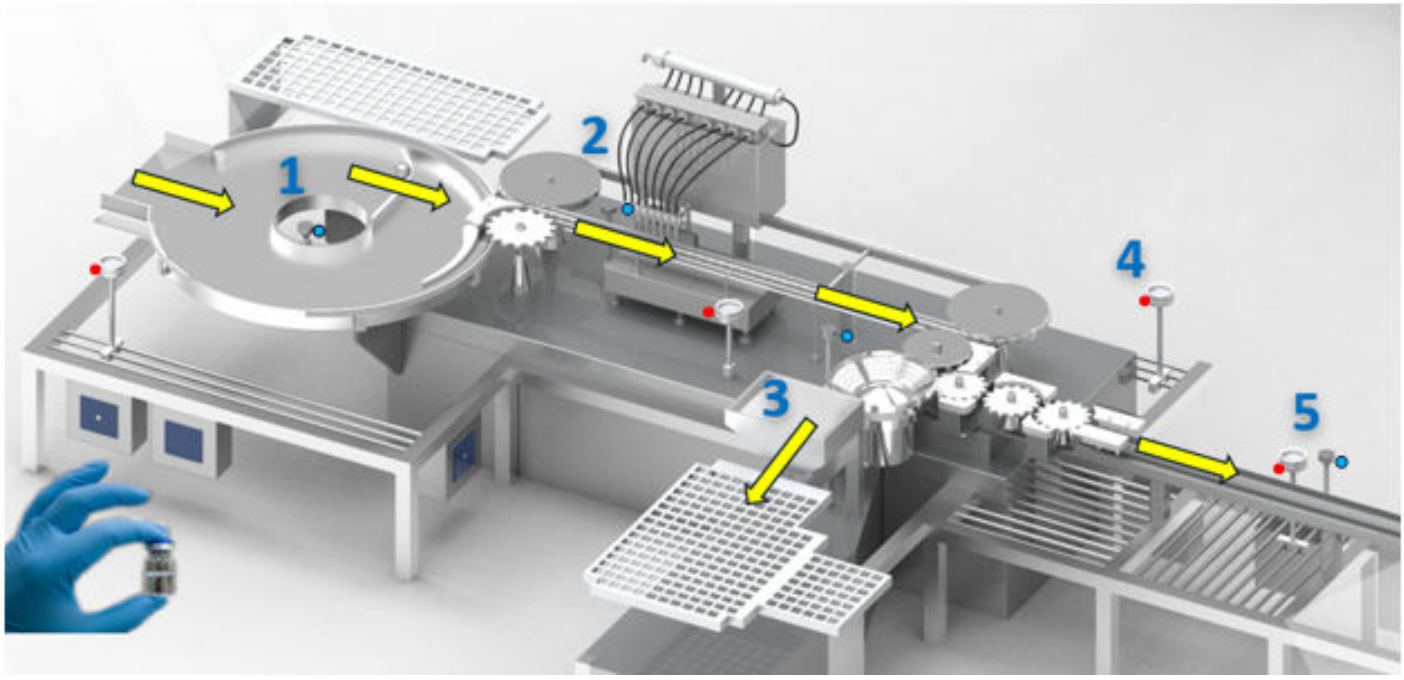
The monitoring system is the Risk Control strategy best identified by management and subject matter experts and this outcome is communicated to all stakeholders. A Risk Assessment table will outline the probability and severity of potential risks to the filling operation and identify where the risks may occur, and the severity of the risks and the risk mitigation used to mitigate the said risks.

Identifying the best locations for the air sampler and particle counters

On the filling machine the highest areas of risk to potential contamination of the sterile product are identified. Typically, subject matter experts will walk the line and see where the risk potential is at its highest potential. Let's walk the filling line and identify the locations where the risks may occur and may have a severity impact that will affect the integrity of the product quality and safety.

		Severity (S)				
		1 - Minor	2 - Marginal	3 - Major	4 - Critical*	5 - Catastrophic*
Probability of Occurence (O)	5- Frequent (1 in 10)	Acceptable Risk	Consider Additional Risk Control	Additional Risk Control Required	Additional Risk Control Required	Additional Risk Control Required
	4- Reasonably Probable (1 in 100)	Acceptable Risk	Consider Additional Risk Control	Consider Additional Risk Control	Additional Risk Control Required	Additional Risk Control Required
	3- Occasional (1 in 500)	Acceptable Risk	Acceptable Risk	Consider Additional Risk Control	Consider Additional Risk Control	Additional Risk Control Required
	2- Remote (1 in 2,500)	Acceptable Risk	Acceptable Risk	Acceptable Risk	Consider Additional Risk Control	Additional Risk Control Required
	1- Extremely Unlikely (1 in 10,000)	Acceptable Risk	Acceptable Risk	Acceptable Risk	Consider Additional Risk Control	Consider Additional Risk Control

Example Risk Assessment Table based on ICH-Q9



Flow path of ampoules along the filling machine with sample locations identified.

In the image above the yellow arrows indicate the flow of movement of the glass ampoules. In area 1 the sterilized "open" glass ampoules are moved from the heat sterilization oven onto the circular accumulation table before being mechanically moved into the filling line slot. In area 2 the open ampoules are passing under the filling head which has several filling needles which align to the ampoules and fill the sterile product into the ampoules. The ampoules then progress to area 3 where the stoppering occurs. In this area the ampoules will either follow the flow to location 3 where they will be transported to a lyophilization machine to be freeze dried or the ampoules will go to aera 4 to be capped and then to aera 5 where the capped ampoules are then transported to controlled storage areas prior to shipping.

From the risk assessment it has been determined the areas of greatest risk among the filling machine are these 5 areas. The vials come out of the sterilization oven, and they are at risk right up to the capping area (4) and GMP even considers aera 5 to be at risk even though the ampoules are capped. The next task is to determine the best locations for the air sampler and particle counters. ISO/TR 14644-21 which was released in November 2023 should be used in order to set up the sampling system for the particle counters. Losses of particles of particles ≥3µm in sampling tubing is a known problem and this ISO technical report helps to address these issues with recommendations based on sample tubing length and reduction of any bends. This helps improve the overall quality of the data and the data integrity. In the image above the blue dots show the locations selected for the particle counter sample probes which are isokinetic probes and face towards the direction of the airflow from HEPA filters above the filling machine. The red dots show the locations of the air sampling heads along the filling machine.

Selection of the right monitoring devices

It is critical to understand the sampling equipment technologies and nuances when implementing a monitoring system. In the example of the pharmaceutical filling machine, we see two types of particle detection technologies deployed along the filling machine.

Remote Particle Counters

These small devices were developed for continuous monitoring. When we say continuous monitoring in the pharmaceutical product manufacturing world these devices are used only when filling operations are running which will include a 15-20 min pre and post operations run as well as during the aseptic process and however long that may last. The data from particle counters is critical GMP data that is used to make critical decisions on the integrity of the filling operations and the surrounding environment during these operations.

Remote particle counters are selected because of their small footprint and the need to get the sample isokinetic probe (ISP) as close to the critical point so meaningful and accurate data can be obtained. These particle counters use an external vacuum source and multiple units are connected to vacuum pumps which are housed in facility areas outside of the cleanrooms. These particle counters connect to real time monitoring software systems which record the 1-minute samples continuously during operations and use alarm systems such as local audio-visual beacons, emails and SMS messages to notify managers and operators if the ISO 5 environment along the filling machine is trending to an alert or action event. Typically, they monitor 0.5 and 5.0 particle sizes based on ISO 14644-1:2015.

Remote Particle Counter

Sample head with 9mm TSA agar plate

Remote Active Air Sampler

These air samplers are also connected to remote vacuum systems and in between the sample heads and the vacuum system is an interface connected to solenoid valve logic controlled remotely or locally by operators. Operators at the filling machine can load the media TSA agar inside the sample head and put the top cover of the sample head into place and start the sample. The monitoring system will automatically end the sample when the cycle completes and notify the operator to take the media plate out and replace it with a new one. Low flow rates are recommended to minimize the operator sequences during the aseptic operation.

Conclusion

ICH-Q9 Quality Risk Management guidelines, specifically tailored for implementing viable and non-viable sampling locations along a pharmaceutical aseptic filling machine. The process begins with the initiation of the risk assessment by assembling a multidisciplinary team and defining the scope. It proceeds through risk identification by gathering information and identifying potential hazards, followed by risk analysis to determine the likelihood and impact of these risks. The evaluation phase helps in deciding which risks need mitigation.

Risk control measures are then selected and implemented, focusing on minimizing high-priority risks through engineering controls, procedural changes, and enhanced monitoring. The effectiveness of these measures is reviewed to ensure they adequately reduce or eliminate risks. Communication and documentation of the risk assessment findings and actions taken are crucial for transparency and compliance. The process concludes with a continuous review and improvement phase, ensuring the risk management process remains effective and up to date with any changes in the cleanroom environment, processes, or regulations.

The application of the ICH-Q9 model to the selection of a monitoring system for a pharmaceutical aseptic manufacturing operation emphasizes the importance of a structured and systematic approach. This approach ensures not only regulatory compliance but also the safety and efficacy of pharmaceutical products. The identification of critical areas along the filling line where contamination risks are highest guides the strategic placement of air samplers and particle counters. The selection of monitoring devices, including remote particle counters and active air samplers, is informed by a thorough understanding of the technologies and their application in maintaining an ISO 5 classified environment.

In conclusion, following the ICH-Q9 Quality Risk Management model provides a robust framework for identifying, analyzing, controlling, and monitoring risks associated with pharmaceutical aseptic filling machine operations. This ensures the production of safe and effective pharmaceutical products while adhering to regulatory standards and best practices. Continuous improvement and adaptation to new information or changes in the operational environment is essential for maintaining the integrity of the risk management process.