sustainability

MDPI

Article

Quality Risk Management in Pharmaceutical Manufacturing Operations: Case Study for Sterile Product Filling and Final Product Handling Stage

Rawidh Alsaidalani [1,*] and Bassam Elmadhoun [2]

[1] Pharmacy Program, Pharmaceutical Sciences Department, Batterjee Medical College, Jeddah 21442, Saudi Arabia
[2] Pharmaceutical Solution Industry Co., Ltd., Jeddah 21485, Saudi Arabia
* Correspondence: pharmacy15.jed@bmc.edu.sa

Abstract: In the highly regulated pharmaceutical industry, significant risks to products/processes must be formally identified, reduced, and controlled to minimize potential negative impacts on patients. Failure Modes and Effects Analysis (FMEA) is one of the well-recognized risk-management tools which is effectively used by the pharmaceutical industry to document and communicate risk control. International Conference on Harmonization (ICH) guideline Q9, Quality Risk Management (QRM), represents the first internationally recognized guideline specifically addressing QRM for the pharmaceutical and biopharmaceutical industries. However, Q9 does not provide details on how to use FMEA in real-world pharmaceutical situations. Authors have previously presented a real case study through which various risks were identified and controlled in an early stage of sterile manufacturing process, including (i) procurement/supply chain, (ii) logistics/warehousing, and (iii) raw materials dispensing. This study represents a modeled risk mitigation approach for professionals or regulators in the industry field associated with sterile pharmaceutical production processes such as (a) glass bottle washing and handling, (b) rubber stopper washing and handling, (c) product filling process, (d) final product receiving and handling. The benefits of this case study include providing a proactive means to identify, control, and communicate risks associated with various vital steps, thereby improving decision making and reducing regulatory non-compliant risk. In this study the outcomes of risk assessments associated with every defined step highlighted all critical hazards with risk priority number (RPN) scores equals to or above 105. These hazards are given the priority to be treated and put under control to reduce the RPN to acceptable levels. Although every manufacturer's product and process are unique, and risk tolerance varies among manufacturers, some processes are generic in nature, and the associated risks are similar. Therefore, our case studies and examples can fit every circumstance in pharmaceutical manufacturing.

Keywords: quality management system; quality risk management; FMEA; GMP; filling process; rubber stopper washing

Citation: Alsaidalani, R.; Elmadhoun, B. Quality Risk Management in Pharmaceutical Manufacturing Operations: Case Study for Sterile Product Filling and Final Product Handling Stage. *Sustainability* **2022**, *14*, 9618. https://doi.org/10.3390/su14159618

Academic Editors: Dorota Klimecka-Tatar and Manuela Ingaldi

Received: 20 June 2022
Accepted: 2 August 2022
Published: 4 August 2022

1. Introduction

Quality risk management (QRM) can be described as a systematic, risk-based approach to quality management. The process is designed to monitor, control, communicate, and review risk quality. It is important in the pharmaceutical industry, where the quality of the product can greatly affect the health and safety of consumers, to incorporate risk assessment into good manufacturing controls [1]. Many industries and government sectors, encompassing financial services, occupational safety and health, pharmacovigilance, and organizations governing these industries, apply risk management principles effectively [2–4]. While there are some good practices of quality risk in several stages of pharmaceutical product manufacturing, they do not cover all of the capabilities that risk

management can genuinely provide [4,5]. Risk assessment, risk control, and risk review comprise three primary components of effective risk management.

The risk assessment process consists of three steps. In the first step, a list of potential risks related to the target process is prepared for risks to be identified, followed by risk analysis to better understand the risks. The possible harms of the risks can be measured, whether qualitatively or quantitatively or simultaneously. Finally, the decision-making step, where the decision to reduce or accept risks is made. Following a risk assessment, an evaluation of risks will be conducted to see if the action taken was successful or negatively affected the overall outcome. Risks should be communicated to all stakeholders, according to ICHQ9, throughout all steps of the risk management process [3,6].

Risk management tools and methods are very important in identifying the risk and minimizing or limiting its corresponding effect. One of the potential tools to evaluate processes failures and their impact on the product is the FMEA, as it helps to shed light on significant failures and the impact they have [3,7,8].

The possible risk may occur at any stage of the drug production and manufacturing process [9], especially when it comes to sterile products manufacturing which can be challenging [10,11]. An example of contamination risk is the particulate contamination of IV fluid which may be caused during the final manufacturing stage [10]. Other examples of implementation of quality risk management in different areas of production were studied in the pharmaceutical supply chain, warehousing, and dispensing [12], In all stages of pharmaceutical production [13], in the pharmaceutical dispensing center [14] and in technological risk from excipients [15]. Yet the literature lacks enough cases of the implementation of QRM in the production stage of sterile products and the associated risks of this step.

In risk assessment, risk identification scenarios can be either utilized prospectively or retrospectively [16]. This paper will work on a prospective scenario to determine what can go wrong in the process/system and its impact on the quality of product and/or patient safety. The main goal is to identify a case study representing a typical manufacturing process and perform the risk assessment. This work is a continuum for a previously published paper in which the first two important stages in producing a sterile drug product which include the supply chain and the warehouse [12]. The case study highlighted in this paper focuses on product filling operation, which is a critical manufacturing operation requiring robust good manufacturing practice (GMP).

Understanding the filling process of terminally sterilized injectable products and the corresponding risks to products can allow producers to continue with more effective controls in such operations. Handling primary packaging components and product bottling in a cleanroom environment imposes a high risk to product quality and patient safety. Pharmaceutical manufacturers face considerable challenges during these two processes such as mix-up, contamination, and cross-contamination. For this reason, it is highly needed to present real-life case scenarios for critical manufacturing processes such as (a) glass bottle washing and handling, (b) rubber stopper washing and handling, (c) product filling process, (d) final (sealed) product receiving and handling.

2. Materials and Methods

A group of researchers, consisting of a pharmaceutical industry consultant and an academic instructor, have chosen a sterile infusion in the form of a 100 mL glass bottle product and decided to conduct a comprehensive review of the whole manufacturing process of the product life cycle as detailed in Figure 1. The production operation of a pharmaceutical product has a few distinct processing stages. Every stage is comprised of a number of smaller process steps. In general, all pharmaceutical manufacturing operations begin with procurement and supply chain management, then move on to storing and controlling of the raw ingredients and the packaging materials, then processes of production as raw materials related operations such as dispensing, formulation, filling, inspection, labeling, packing, palletizing and ending with storing and distributing of the finished product. The focus of this study was on stage 4 of terminally sterilized drug product

manufacturing operation. This study will focus on the following three significant steps: 1-Entry and exit procedure to cleanroom; 2-Glass bottle washing machine and tunnel operation and 3-Glass filling operation and process checks. For every selected step, a thorough risk assessment was conducted utilizing ICHQ9 guideline [3] and FMEA [15]. In order to simplify the method, a particular scheme of work was used:

A Reading and comprehending the applicable standard operating procedure of the selected procedure.

B Meeting with both the process owners and supervisors to simplify the procedure into specific, well-defined steps.

C Using a brainstorming technique and in cooperation with a risk management specialist, all possible risks connected with every step are identified.

D The risk table for risk analysis is filled out by addressing well-known risk specific questions such as, "What could go wrong?" What is the possibility (likelihood) that something could go wrong? What are the effects (severity)? What is detection capability (detectability)? As presented in Figure 2, this is a straightforward implementation of the FMEA risk assessment tool.

E FMEA risk evaluation can identify severity, probability of occurrence, and likelihood of detection ratings on a scale from 1 to 10. 1 is attributed to the lowest risk and 10 to the worst risk to the safety of the product. Risk priority number (RPN) is determined by multiplying the three specified scores: [Severity of effect] × [Likelihood of occurrence] × [Unlikelihood of detection]. Table 1.

F Risk control can be carried out by putting in place new policies or standards, making physical or design changes, or making changes to how work is performed that can completely remove (when possible) or lessen the risk.

Figure 1. Stages of Manufacturing for a Sterile Drug Product in Glass Bottle (100 mL). Stage four is the focus of this study.

For the use and creation of FMEA tool, a team for risk assessment consists of production, engineering, and quality assurance (QA) members headed by a risk management manager and consultant within the industry were responsible to assess/give the score. Scores are assigned based on the knowledge and experience of the team members and

agreed upon. Internally, there is a reference table that explains the score range vs the three levels of risk (Low, Medium and High). The value ranges used to quantify the individual characteristics, for example, the range of possible numeric values, must be defined by the industry. Risk matrices come in many different shapes and sizes. Choosing the appropriate template for a process occasionally results in debates by different regulators and auditors as well as between risk management professionals. Common value ranges are 1–3, 1–5 or 1–10. There is no one system recommended or imposed by any drug regulators or any international reference. In the end, it is an industry experience issue. The assigned values in Table 1 are only estimates and they are built based on evaluation tools, i.e., definitions of all numeric values in our risk matrix (not shown in the paper). Therefore, 1–4 is considered low, 5 to 7 is considered medium, and 8 to 10 is considered high. Different risk matrices have different benefits and drawbacks. A small-scale matrix, for example 1 to 3, may result in putting potential hazards in the medium range and less investigator focus. Large risk matrix scale, for example 1 to 5, can help professionals conduct risk assessment in a more clear and detailed manner. In our study and through risk assessment process, we do not exclusively depend on RPN to define priorities but also look at the severity of the risk whenever 2 risks have the same RPN.

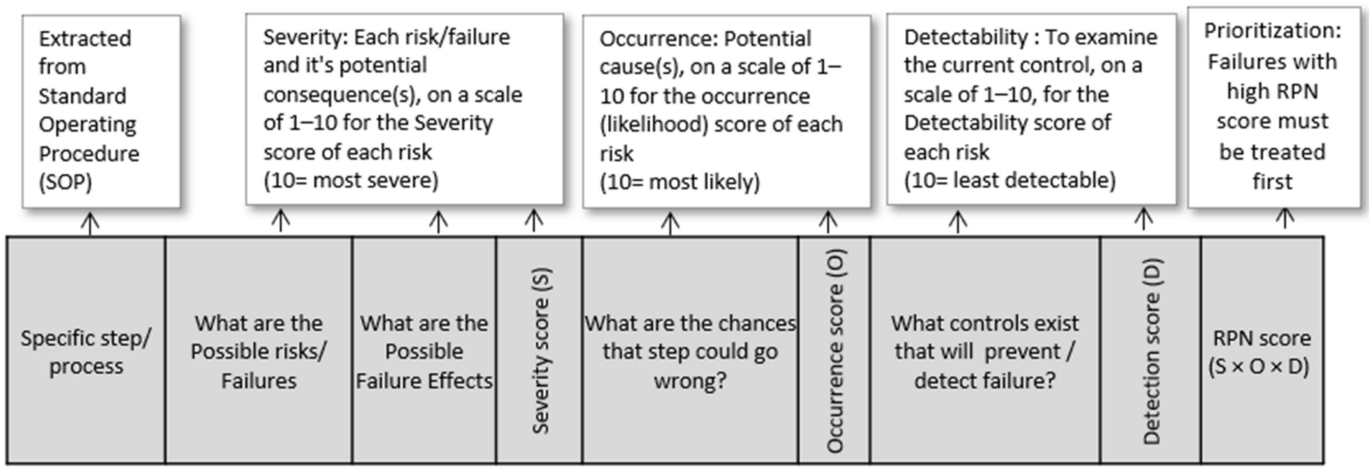

Figure 2. FMEA table questions for risk identification.

Table 1. Matrix of Risk Priority Number (RPN).

Risk Priority Number (Severity × Occurrence × Detection)	Level *	Action
1–34	Low	Risk is acceptable
35–104	Medium	Risk can be acceptable. Reduce risk as much as it is practically possible
105–1000	High	Risk cannot be accepted. Risk reduction and mitigation are required.

* Color coding in "level" column refers to: Low risk level (Green), Medium risk level (Yellow) and High risk level (Red).

Creating a process FMEA Risk assessment is ideally carried out during design phase and afterwards. As this tool is a dynamic process, it depends on the industry's risk management system and how critical the process is. Generally, FMEA is conducted throughout the life cycle of a product or process. The industrial practice is to conduct FMEA annually for every process. However, there are a few factors that necessitate risk assessment such as:

1. Changes are made to the existing process or design.
2. A change is made to the operation conditions.
3. An improvement goal is created for the existing process.
4. New regulations are introduced.
5. Customer feedback.

3. Results and Discussion

As mentioned in the methodology, three standard operating procedures (SOPs) describing three major processes in solution filling operation were covered. Each SOP understudy is converted into specific, detailed, and well-defined steps. The overall number of steps generated per each SOP range from 10 to 15 steps (steps of SOPs are not shown). This simplifies the risk identification process. As a result, each step's risks have been recognized. The FMEA tables were then created with all of the information required for completing the risk assessment as shown in Tables 2–4. In all FMEA tables, the columns were filled with relevant data; in which the process steps are defined (column 2), what might go wrong when carrying out this step (column 3), what effects are possible if this step went wrong (column 4), what are the causes of the step possibly making it go wrong (column 6), any current or existing control on hand to prevent the step from going wrong (column 8). Using this initial data and team discussion, values are allocated to severity (column 5), probability (column 7) as well as detectability (column 9). The calculated risk priority number is displayed in column 10. Depending on the risk score, the associated risk was classified as low, moderate, or high risk (column 11), and what action/decision must be carried out (column 12). Individual who is in charge of carrying out the action (column 13) and actions taken (column 14). Following that, the new RPN was recalculated by the team which was achieved after the action was carried out (column 17). It has been observed, on the basis of the shared experiences of the team as well as the risk severity meaning, that control measures adopted in the process step to mitigate the risk can only be observed in risk probability and risk detectability (column 15 and 16). This provides an explanation as to why the score of risk severity does not change across any of the FMEA tables after the control was implemented.

The risk analysis of the selected three important processes reveals that a large number of risks are within the green limit, indicating that the RPN is less than 34 (not presented in this study); hence, there are no actions or control measures required. This study provides only some examples of risks in the yellow and red limits only, as well as the actions and measures taken to mitigate the risks related to each step. The FMEA tables display risk analysis, followed by interpretation of data.

3.1. Risk Assessment Associated with Entry and Exit Procedure to Cleanrooms

All risks related to the process in question in this section (Table 2) have been evaluated, and RPNs have been determined. Taking into account the severity, occurrence, and detection level of the risk, Table 2 presents an example of a risk that is greater than 104. (red). The team agreed to take the appropriate control measures and precautions to eliminate or mitigate the risk, for instance, the risk associated with taking photographs in the restricted areas and the negative impact of such risk on the company's private property and company confidential information and the misuse of taken photos by any means. The area manager with QA senior staff reviewed the current procedure and found that having a device with a camera or a mobile with a camera increase the probability of taking photographs either with the acknowledgment or not of accompanying staff. Therefore, decision-makers decide to modify/revise the current SOP and add new instructions and control stating that no camera, mobile, or any device has a camera to accompany staff or visitors in the restricted area.

By implementing such control, the risk probability score of 6 and detection score of 4 are changed to 4 and 2, respectively. This control changed RPN from 192 (red) to 64 (yellow). The action's effectiveness is being monitored for six months. All modifications made to GMP documentation, such as SOPs, software, formats, etc., shall be revised, reviewed, and approved. Risk communication then should be addressed with key individuals. A risk review will be conducted annually, or anytime the process undergoes a significant change.

Table 2. Risk assessment associated with Entry and Exit Procedure to Cleanrooms.

Risk Assessment										Risk Control					
Risk Identification				Risk Analysis				Risk Evaluation *		Risk Reduction and Acceptance		Compliance of Action	Risk Re-Evaluation *		
Step No.	Process Step/Input	Potential Failure Mode	Potential Failure Effects	SEVERITY (S) (1–10)	Potential Occurrence	OCCURRENCE (O) (1–10)	Current Controls	DETECTION (D) (1–10)	RPN (S × O × D)	Risk Acceptance	Action Recommended	Resp.	Actions Taken	OCCURRENCE (O)	DETECTION (D)	RPN (S × O × D)
							What Controls Exist That Will Either Prevent or Detect Failure?				What Are the Recommended Actions to Reduce the Occurrence of the Causes or Enhance Detection?	Who is Responsible for Assuring That the Actions Are Carried Out?	What Actions have Been Done Regarding the Rpn?			
1	Photographs are not allowed unless permitted by an authorized person.	Photographs may be intentionally or unintentionally taken in the restricted area.	Company private property is jeopardized. Company confidential information is exposed. Photos may be misused.	8	Absence of site supervision. No or inadequate control on visitors entering cleanrooms. No posters stating photographs are prohibited. Lack of staff awareness	6	Area supervision is available for every shift. Visitors are not allowed in the area without a supervisor. Posters are available stating no photographs.	4	192	No. Risk mitigation is required	Revise SOP and add new instructions and control stating that no camera, mobile, or any device has a camera to accompany staff or visitors in the restricted area.	Production	Action completed	4	2	64

* Color coding in "Risk evaluation" column refers to: Low risk level (Green), Medium risk level (Yellow) and High risk level (Red).

Table 3. Risk assessment associated with Glass Bottle Washing Machine and Tunnel Operation and its Related Activity.

Risk Assessment										Risk Control					
Risk Identification				Risk Analysis				Risk Evaluation *		Risk Reduction and Acceptance		Compliance of Action	Risk Re-Evaluation *		
Step No.	Process Step/Input	Potential Failure Mode	Potential Failure Effects	SEVERITY (S) (1-10)	Potential Occurrence	OCCURRENCE (O) (1 –10)	Current Controls	DETECTION (D) (1 –10)	RPN (S × O × D)	Risk Acceptance	Action Recommended	Resp.	Actions Taken	OCCURRENCE (O)	DETECTION (D)	RPN (S × O × D)
							What Controls Exist That Will Either Prevent or Detect Failure?				What Are the Recommended Actions to Reduce the Occurrence of the Causes or Enhance Detection?	Who Is Responsible for Assuring That the Actions Are Carried Out?	What Actions Have Been Done Regarding the Rpn?			
1	Assure that password level protection is in place and complies with the principles of data integrity.	Loss of protection and possible manipulation and change in setting	Questionable data integrity. GMP and GDocP guideline noncompliance. Regulatory Auditor concern. Negative impact on product quality	8	Improper password level protection. Sharing or delegating password to unauthorized person(s). lack of awareness of data integrity. Inadequate staff training on GDocP and data integrity	4	All authorized machine operators received GDocP and data Integrity training.	6	192	No. Risk mitigation is required	Regular checks of audit trails and report any violation of password level protection. Regular personnel training on the importance of data integrity. Self-inspection should cover the implementation of data integrity principles.	Production/QA and IT	Completed	3	4	96
2	Assure that line clearance activity is conducted, documented, and approved before startup.	No line clearance. Improper line clearance. Line clearance Not documented. Absence of QA check and approval.	Possibility of a mix-up. Product quality is questionable. GMP violation and non-compliance. Regulatory concern, negative impact on patient safety.	9	GMP guidelines not implemented. Absence of proper GxP training. Insufficient quality assurance monitoring and management	6	Clearance procedure is available. Staff training records are documented. Production supervisor review and approve clearance document. Records are available.	5	270	No. Risk mitigation is required	Clearance SOP and associated clearance format should be revised to include involvement of QA inspector. Clearance document should be finally approved by QA before commencing production process.	Production and QA	completed	3	3	81

Table 3. *Cont.*

Risk Assessment										Risk Control					
Risk Identification				Risk Analysis				Risk Evaluation *		Risk Reduction and Acceptance		Compliance of Action	Risk Re-Evaluation *		
Step No.	Process Step/Input	Potential Failure Mode	Potential Failure Effects	SEVERITY (S) (1-10)	Potential Occurrence	OCCURRENCE (O) (1 –10)	Current Controls	DETECTION (D) (1 –10)	RPN (S × O × D)	Risk Acceptance	Action Recommended	Resp.	Actions Taken	OCCURRENCE (O)	DETECTION (D)	RPN (S × O × D)
							What Controls Exist That Will Either Prevent or Detect Failure?				What Are the Recommended Actions to Reduce the Occurrence of the Causes or Enhance Detection?	Who Is Responsible for Assuring That the Actions Are Carried Out?	What Actions Have Been Done Regarding the Rpn?			
3	All primary packaging materials, e.g., rubber stopper, shall be transferred through dynamic pass box by stacking on stainless steel trolleys to filling room.	Primary packaging materials transferred through personal entry. Dynamic pass box is not in function.	Violation of company procedure and GMP guidelines. Disturbances in the cleanroom classification may cause product contamination.	8	Lack of proper production supervision. Ineffective QA inspection. Failure in dynamic pass box due to improper routine maintenance.	4	SOP for handling PPM in glass filling unit is available. Staff is trained, and production supervision exists. QA inspectors are available. The current procedure lacks the provision of checking dynamic pass box operation during checklist before startup of machine or during line clearance	4	128	No. Risk mitigation is required	Process-related SOP should be revised, and provision for checking dynamic pass box should be part of area checking before start and/or during line clearance. Line clearance checklist needs to be changed to cover dynamic pass box status.	Production and QA	completed	3	3	72

Table 3. *Cont.*

Risk Assessment										Risk Control					
Risk Identification				Risk Analysis				Risk Evaluation *		Risk Reduction and Acceptance		Compliance of Action	Risk Re-Evaluation *		
Step No.	Process Step/Input	Potential Failure Mode	Potential Failure Effects	SEVERITY (S) (1-10)	Potential Occurrence	OCCURRENCE (O) (1 –10)	Current Controls	DETECTION (D) (1 –10)	RPN (S × O × D)	Risk Acceptance	Action Recommended	Resp.	Actions Taken	OCCURRENCE (O)	DETECTION (D)	RPN (S × O × D)
							What Controls Exist That Will Either Prevent or Detect Failure?				What Are the Recommended Actions to Reduce the Occurrence of the Causes or Enhance Detection?	Who Is Responsible for Assuring That the Actions Are Carried Out?	What Actions Have Been Done Regarding the Rpn?			
4	No empty washed bottles shall be left inside washing machine during break time or end of shift.	Some empty washed bottles are leftover inside washing machine.	Contaminated bottles may be used in subsequent filling. Lot reconciliation is not accurate. Chance of mix-up. Negative impact on product quality. GMP violation and regulatory concern	7	Unqualified staff handling the process. Lack of monitoring and supervision. No checklist to document the absence of any empty bottles inside glass bottles washing machine. No counter-check.	4	Staff training records on related SOP are available.	4	112	No. Risk mitigation is required	Related SOP should be revised to cover the use of a checklist to assure the absence of any empty glass bottles inside bottle washing machine during breaks and at the end of shift. The checklist should be counter-signed by unit supervisor.	Production department	Completed	2	2	28

* Color coding in "Risk evaluation" column refers to: Low risk level (Green), Medium risk level (Yellow) and High risk level (Red).

Table 4. Risk assessment associated with Glass Filling Operation and Process Checks.

Risk Assessment										Risk Control					
Risk Identification				Risk Analysis				Risk Evaluation *		Risk Reduction and Acceptance		Compliance of Action	Risk Re-Evaluation *		
Step No.	**Process Step/Input**	**Potential Failure Mode**	**Potential Failure Effects**	**SEVERITY (S) (1–10)**	**Potential Occurrence**	**OCCURRENCE (O) (1–10)**	**Current Controls**	**DETECTION (D) (1–10)**	**RPN (S × O × D)**	**Risk Acceptance**	**Action Recommended**	**Resp.**	**Actions Taken**	**OCCURRENCE (O)**	**DETECTION (D)**	**RPN (S × O × D)**
							What Controls Exist That Will Either Prevent or Detect Failure?				**What Are the Recommended Actions to Reduce the Occurrence of the Causes or Enhance Detection?**	**Who Is Responsible for Assuring That the Actions Are Carried Out?**	**What Actions Have Been Done Regarding the Rpn?**			
1	Assure that line clearance activity is conducted, demented, and checked before startup	No line clearance. Line clearance is not double-checked.	Product mix-up. Poor lot reconciliation. Violation of GMP standards. Regulatory authority concern.	8	Line clearance SOP is not available. Line clearance is not propyl conducted. Filling line operators are not trained. No intervention or approval from QA	5	No records are available for filling line clearance. No formal, detailed, and specific SOP for filling line clearance. Line clearance of filling room is conducted by filling line operators without formal documents or double-checking.	5	200	No. Risk mitigation is required	SOP for filling line clearance should be produced, reviewed, and approved. Filling line clearance should be conducted by quailed production personnel, checked, and approved by QA personnel. The filling process should not be started before approved line clearance. Filling line clearance report should be available in BMR	Production and QA	completed	2	3	48

Table 4. *Cont.*

Risk Assessment										Risk Control					
Risk Identification				Risk Analysis				Risk Evaluation *		Risk Reduction and Acceptance		Compliance of Action	Risk Re-Evaluation *		
Step No.	**Process Step/Input**	**Potential Failure Mode**	**Potential Failure Effects**	**SEVERITY (S) (1–10)**	**Potential Occurrence**	**OCCURRENCE (O) (1–10)**	**Current Controls**	**DETECTION (D) (1–10)**	**RPN (S × O × D)**	**Risk Acceptance**	**Action Recommended**	**Resp.**	**Actions Taken**	**OCCURRENCE (O)**	**DETECTION (D)**	**RPN (S × O × D)**
							What Controls Exist That Will Either Prevent or Detect Failure?				**What Are the Recommended Actions to Reduce the Occurrence of the Causes or Enhance Detection?**	**Who Is Responsible for Assuring That the Actions Are Carried Out?**	**What Actions Have Been Done Regarding the Rpn?**			
2	Solution filter shall be wetted with product solution, its integrity is tested, and activity is recorded in BMR.	Filter integrity test is not done or done incorrectly, or failed results are manipulated.	Unqualified solution filter is used. Microbial contamination of product solution. Overall product quality is negatively impacted. GMP non-compliance.	8	Unqualified personnel doing the test. Unavailability of filter integrity test machine. Unqualified testing machine. Manual filter integrity testing	5	Production staff is trained on filter integrity testing procedures. Solution filter integrity test is conducted manually. Testing results are recorded manually in the form. Second operator is double-checking the recorded result.	5	200	No. Risk mitigation is required	Manual filter integrity test shall not be used. Filter test shall be carried out using machine, and testing results should be automatically saved and printed. No manual recording of the result.	Production, engineering, and QA	completed	4	3	96
3	Ensure that the scales in the filling machine are calibrated through IPC station, and such activity shall be done under production condition	Scales of filling machine during adjusting weighing modules are not checked and may be out of calibration.	Inaccurate product volume may be produced. Product volume is out of specification. Non-compliance to GMP guidelines and regulatory concerns.	7	Related procedure is not clear and not understood by line operators. No filling machine checklist. Lack of QA monitoring. Lack of proper training.	3	Activity-related SOP is available and followed. Line operators are well trained on the related SOP. Record is available in BMR and checked by the production supervisor.	4	84	No. Risk mitigation is required	Activity-related SOP shall be revised to implement using a checklist covering scales calibration status and be available in BMR.	Production and QA	Completed	2	3	42

* Color coding in "Risk evaluation" column refers to: Low risk level (Green), Medium risk level (Yellow) and High risk level (Red).

3.2. Risk Assessment Associated with Glass Bottle Washing Machine and Tunnel Operation and Its Related Activity

SOP related to this process was transformed into 22 small and distinct steps. This shall make the identification of risk associated with each step much easier and more precise. All risks in the green zone (RPN less than 34) are considered acceptable, and no further action is necessary. All risks in the red zone (RPN is more than 104) are considered not acceptable, and the level of risk must be reduced. Some risks associated with various steps are in the yellow zone (RPN is between 35 and 104). Here, the team's decision varies between accepting it, and further reduction is required as much as possible. This discussion has selected all risks in the red zone, as shown in (Table 3). The team agreed taking appropriate measures for the elimination or mitigation of the risk.

For the risk related to operator authorization to electronic records and data integrity, the impact of such risk, if it happens, is high. This high-risk level increases when the detection level is low (assigned high score). The total RPN is calculated to be 192 (red). Here the team decided to reduce this unacceptable risk in this step through the implementation of 3 additional control measures such as regular review of audit trails, regular personnel training on the importance of data integrity principles, and self-inspection covering data integrity compliance. This adjustment reduces the residual risk, and the calculated RPN is 96 (Yellow).

For the risk associated with filling line clearance, the impact of not having proper line clearance or not being documented or carried out without QA approval will be very high. This high-risk level is increased when the detection score is high. The total RPN is calculated to be 270 (red). Here the team decided to reduce this unacceptable risk by implementing revising line clearance SOP to cover QA inspector review and approval, and no production can be started before the final approval by QA. With this control, the increase in the detection level (low detection score), the residual risk is reduced, and the calculated RPN becomes 81 (Yellow).

For the risk associated with transferring primary packaging materials to the filling room through a dynamic pass box, the impact of bypassing this device and supplying primary packaging materials through personal entry is considered a significant violation of GMP guidelines. The effect of such risk is the introduction of viable and non-viable particulate matters into the cleanroom and subsequent disturbance in cleanroom cleanness. The total RPN is calculated to be 128 (red). Here the team decided to reduce this unacceptable risk by revising the applicable SOP and introducing the provision of checking the dynamic pass box before start or during line clearance. Line clearance checklist must show this inspection part, reviewed by QA and documented. With this control, the increase in the detection level (low detection score) led to a reduction in residual risk to RPN equal to 72 (Yellow). Considering the risk associated with checking bottle washing machine for the absence of empty washed glass bottles left over during break time or at the end of shift. The impact of having wetted glass bottles inside the bottle washing machine may lead to the use of contaminated bottles and inaccurate primary packaging materials reconciliation. Product contamination is an intolerable defect and should be avoided all time. The negative impact of this failure is high, and therefore the severity score is 7. Since there is no checklist to cover the inspection of bottle washing machine during break time and at the end of shift, the detection level is low (high detection score). The total RPN is calculated to be 112 (red). Here the team decided to reduce this unacceptable risk by revising the applicable SOP and introducing the provision or using a checklist in the process of checking the glass bottle washing machine during break time and at the end of shift to be sure that no wetted empty glass bottles are left. With such control, the increase in the detection level (low detection score) caused residual risk to be reduced to RPN equal to 28 (Green).

3.3. Risk Assessment Associated with Glass Filling Operation and Process Checks

Team members have transformed the SOP related to this process into 28 small and distinct steps. This shall make the identification of risk associated with each step much

easier and more precise. All risks in the green zone (RPN less than 34) are considered acceptable, and no further action is necessary. All risks in the red zone (RPN is more than 104) are considered not acceptable, and the level of risk must be reduced. Some risks associated with various steps are in the yellow zone (RPN is between 35 and 104), and here the team decision varies between accepting it, and further reduction is required. In our discussion here, team members have selected two risks in the red zone and one risk in the yellow zone, as shown in (Table 4). The team agreed taking the appropriate measures for the elimination or mitigation of the risk.

For the risk associated with conducting line clearance before starting operation, the impact of not having proper line clearance or the absence of an independent line clearance check by QA is a serious violation of GMP guidelines (product mix-up and incorrect lot reconciliation). The total RPN is calculated to be 200 (red). Here the team decided to reduce this unacceptable risk by revising the applicable SOP and introducing the provision of conducting line clearance in the presence and approval of the QA inspector. This control must be added to the Batch Manufacturing Record (BMR). This control increased the detection level (low detection score) caused residual risk to be reduced to RPN equal to 48 (Yellow).

For the risk related to conducting a solution filter integrity test before starting filling operation, the impact of not doing the filter test or the unreliable testing result is a a serious violation of GMP guidelines (product contamination). The total RPN is calculated to be 200 (red). Here the team decided to check and investigate the main reason and found that the production staff relies on using manual air bubble integrity tests. The results are observed and recorded manually. This testing process is unreliable and lacks proper control of critical production data. The team decided to revise the current filter integrity test and introduce the provision of using an advanced automatic filter integrity test instrument with testing results generated through validated software. Having this control, the current control has been improved on critical data integrity, and any expected filter failure will be detected with high assurance. The new detection score and occurrence score lead to a new RPN equal to 96 (Yellow).

For the risk associated with checking the calibration status of filling machine scales before the start, the impact of missing such checks with no reliable records has negative consequences on overall product quality, such as product filled volume. Product volume is one of the critical quality parameters which should be under proper control. The total RPN is calculated to be 84 (yellow). Here the team found that not using a checklist to record findings and to be added to the BMR may lead to loss of control on such important manufacturing step. The team decided to revise the SOP and implement the use of a well-designed checklist to be used by the line operator and reviewed by the unit supervisor before starting filling. By implementing such change, the current control has been improved on critical data, and any issues related to scales calibration status will be detected with high assurance. The new detection score and occurrence score lead to a new RPN equal to 42 (Yellow).

In all cases mentioned above (risks associated with all 3 major processes in stage 4 of injectable product manufacturing), all changes made in any GMP documentations, e.g., standard procedure, formats, software, logbook, etc., associated with the discussed risks will be revised, reviewed, and approved. Risk communication then should be addressed with key individuals. A risk review is conducted annually, and anytime the process undergoes a significant change.

4. Conclusions

In the pharmaceutical sector, quality risk management is increasingly becoming a necessity. Multiple, if not all, regulatory agencies recognize QRM as a component of the quality system that enables the reduction, monitoring, and controlling of the probability and/or impact of risk. Risk management in the pharmaceutical industry includes restricting

failures from occurring, detecting possible failures early in the process, minimizing their effects, making them less likely to happen, and accepting some failures.

Effective risk assessment helps management make better, more objective decisions and gives regulators and other stakeholders' confidence in the company's ability to handle potential risks.

Three distinct processes from the drug production operation were selected, which are deemed crucial and require ongoing adherence to good manufacturing practices. The aim is to address the following question: what steps/events create an unacceptable risk to the quality of the product and/or the safety of the patient during injectable product filling operations (1. entry and exit procedure to cleanroom, 2. glass bottle washing machine operation and 3. glass filling process). The three case studies covered emphasize the principles of ICH Q9 guidelines—QRM and how they can be adequately implemented in practice. They are not meant to implement new rules and regulations, or alter regulatory expectations but rather to present the industry with examples of how risk management can be implemented in regular duties and through the product's life cycle.

Risk analysis can be conducted in various means, none of which are inherently correct or wrong. It is acceptable to use different methods, techniques, risk score rankings, and criteria. Every pharmaceutical industry is required to implement an effective risk management program within its quality management system. If the program is ineffective, risk analysis and prioritization may be incorrect. If this occurred, it would be a waste of time, effort, and money.

Resources must be saved and allocated to the most significant risks, so it would be necessary to prioritize risks. As a result of risk management, requirements are met, and the organization's goals are supported by prompt actions and measurements carried out to limit risk that might be fatal to consumers or lead to a product recall. Using the FMEA technique, all risks were reduced to acceptable or fairly practical levels by outlining significant modes of failure, the reasons for these failures, and their likely impacts.

Even though this study effectively implemented QRM, it had some limitations. The first is the extensive workload required to analyze risk at every step of the process. The second limitation is the process owner's lack of experience, which can have an impact on risk assessment. Implementation of QRM on other stages of sterile manufacturing are suggested to be conducted in the future to fill the gap in the literature on this topic, as there is currently a lack of research in this area.

Author Contributions: Conceptualization, writing, methodology, and discussion B.E.; resources, writing—original draft preparation, review and editing, R.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: The assistance provided by all process owners and supervisors is greatly appreciated for the valuable feedback and brainstorming sessions provided by in defining risks in the cleanroom entry and exit procedures, glass bottle washing machine operation, and glass filling process.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Kumar, N.; Jha, A. Quality risk management during pharmaceutical 'good distribution practices'—A plausible solution. *Bull. Fac. Pharm. Cairo Univ.* **2018**, *56*, 18–25. [CrossRef]
2. Chavda, V.P.; Maru, S.; Patel, B. How Quality Risk Management is Useful for Pharmaceuticals. *Glob. Res. J. Sci. Nat.* **2015**, *1*, 10–13.

3. ICH. Committee Report, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, Quality Risk Management. Available online: https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-3.pdf (accessed on 20 April 2022).
4. Nauman, M.; Bano, R. Implementation of Quality Risk (QRM) in Pharmaceutical Manufacturing. *J. Pharm. Biol. Sci.* **2014**, *9*, 95–101.
5. Sivadasu, S.; Gangadharappa, H.; Kiran, H.; Jose, A. Quality Risk Management: A Review. *Int. J. Pharm. Sci. Rev. Res.* **2017**, *44*, 142–148.
6. Das, A.; Kadwey, P.; Mishra, J.K.; Moorkoth, S. Quality Risk Management (QRM) in Pharmaceutical Industry: Tools and Methodology. *Int. J. Pharm. Qual. Assur.* **2014**, *5*, 13–21.
7. Krishna, V.; Srivastava, P. Risk management in pharmaceuticals. *Mintage J. Pharm. Med. Sci.* **2014**, *3*, 32–39.
8. Snee, R.; Rodebaugh, W.F. Failure Modes and Effects Analysis. In *Encycelopedia of Statistics in Quality and Reliability*, 1st ed.; Ruggeri, F., Kenett, R., Faltin, F., Eds.; Wiley: Hoboken, NJ, USA, 2007; Volume 3, pp. 154–196.
9. Vartak, R.; Bhagure, G. Quality Risk Management in Pharmaceutical Industry—A Overview. *Asian J. Chem.* **2012**, *24*, 5576–5578.
10. Perez, M.; Foinar, A.; Barthélémy, C.; Décaudin, B.; Odou, P. Particulate Matter in Injectable Drugs: Evaluation of Risks to Patients. *Pharm. Technol. Hosp. Pharm.* **2016**, *1*, 91–103. [CrossRef]
11. Sandle, T. Sterile Ophthalmic Preparations and Contamination Control. *J. GXP Compliance* **2014**, *18*, 1–5.
12. Alsaidalani, R.; Elmadhoun, B. Quality Risk Management in Pharmaceutical Supply Chain Warehousing and Dispensing. *Int. J. Pharm. Sci. Rev. Res.* **2021**, *68*, 155–164.
13. Ismael, O.A.; Ahmed, M.I. Using Quality Risk Management in Pharmaceutical Industries. *Qual.-Access Success* **2020**, *21*, 106–113.
14. Chitmetha, M.; Prombanpong, S.; Somboonwiwat, T. Quality Risk Management in Pharmaceutical Dispensing. *Int. J. Chem. Eng. Appl.* **2013**, *4*, 241–248. [CrossRef]
15. Carlin, B. Quality Risk Management of Compliant Excipients. *J. Excip. Food Chem.* **2012**, *3*, 143–153.
16. Sandle, T. Aseptic Transfer Risk Assessment: A Case Study. *J. Valid. Technol.* **2015**, *21*, 1–10.