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Investigating The Risk of Glove Punctures in Aseptic Processing Barrier Technology Systems: A Case Study

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Abstract: Aseptic processing is a method of production that is free of microbiological, pyrogen, and particulates and thus it is perceived as one of the most complex manufacturing processes in the pharmaceutical industry. Due to the significant risks associated with aseptic processing a quality risk management (QRM) program is necessary to protect the patient from injury. This study aims to investigate the process followed when glove punctures are detected on glove sleeves of barrier technology systems in a sterile manufacturing facility. Further, this paper utilizes an example of a risk assessment method to illustrate how a risk assessment can be useful in aseptic processing operations. The specific activity being investigated involves glove punctures during aseptic filling operations. The risk assessment approach adopted is in the form of a Fishbone diagram. The findings of the study will provide insights that will aid developing organizations to overcome challenges associated with aseptic processing.

Keywords: Aseptic processing, Quality Risk Management, Barrier Technology Systems

1. Introduction

In today's environment, aseptic processing technology has advanced to a point where personnel is being removed from the aseptic environment almost entirely [1]. However, despite these technological advancements, products and processes that are produced aseptically remain associated with risks [2]. Aseptic processing is a modus operandi of the production process that is free of microbiological, pyrogen, and particulates. Hence, authorities anticipate aseptic processing to be so successful that the removal of microorganisms renders the completed product "sterile." It is for this reason that aseptic processing is perceived as one of the most complex manufacturing processes in the pharmaceutical industry [3].

The significance of aseptic processing in sterile medicinal that are terminally sterilized is because sterility is a critical quality attribute for sterile medicines, meaning that, if the sterility of a product is lost, a poor-quality product is likely to cause disability or death of patients. Sandle [4] , states that the extent of the injury is determined by the type and quantity of microorganisms present, the mode of product administration, immunological and health status of the. Aseptic processing necessitates individual sterilization of objects such as product containers and closures, contact components, and consumables to maintain a sterile environment and preserve product sterility [5]. These items are assembled under ISO Class 5, otherwise referred to as grade A conditions. The central problem in aseptic processing is the necessity to always maintain a high degree of microbial contamination reduction across the aseptic environment [1] . The accepted industry solution to ensuring that aseptic filling operations maintain sterility is using barrier technology systems namely the isolator and restricted area barrier system (RABS).

Barrier technology systems generally feature a product container washer, depyrogenation tunnel, an isolator, a filling line, glove sleeves, and a capping system. During aseptic filling, the sterile product is filled into depyrogenated vials and fitted with a sterile stopper, and then over-sealed. The most vulnerable step in the dispensing of the product, via filling needles, into the vial. Regulatory requirements require that the dispensing of the product into the vial through the filling needle be done under Grade A conditions. The benefit of using barrier technology systems is that it separates the external cleanroom environment from the aseptic processing line and minimizes exposure to personnel. All the while providing a positive pressure that provides unidirectional ISO 5 cleanroom air quality thus meeting the regulatory requirements for particulate and microbiological concentrations [6].

Despite these technological advancements, barrier technology systems present a risk of loss of sterility. Drinkwater & Maier [7] augment that glove sleeves mounted and sealed to barrier technology systems are the weakest link in the barrier integrity since they are prone to punctures and therefore present a risk of microbial and particulate contamination. Since aseptic processing is so risky. White [3] suggests that aseptic processing establishments have an effective quality risk management (QRM) program to protect the patient from harm.

Sandle [4] agrees by stating that products and processes in the pharmaceutical industry are associated with risks, therefore all areas and functions in the pharmaceutical manufacturing plant need to assess the level of risk to a process and then take steps to eliminate that risk [4]. This implies that a lot of time and resources should be allocated to maintain product quality throughout the product life cycle [2].

While the evolution of barrier technology systems within the pharmaceutical industry has advanced over time with aseptic processing technology currently being at a point where personnel is being removed from the aseptic environment almost entirely [1] , these systems are still a risk. Therefore, gloves sleeves in barrier technology can be seen as a point of weakness since they extend into the grade A, such as sterile zone of the systems during process operations.

During process operations, personnel is meant to comply with first air principles with good aseptic technique meaning not positioning gloved hands over critical surfaces or process points so that the first air that leaves the unidirectional airflow is not obstructed or disturbed [7] . Regulatory bodies further maintain that barrier system technologies cannot prevent contamination caused by poor aseptic techniques during process operations. Although gloves appear to be mandatory due to their use during process operations, they are prone to punctures thus presenting a contamination risk to the aseptic environment. Thus, each gloved intervention presents different risk levels. Therefore, to maintain product quality throughout the product life cycle and to better risks associated with the aseptic manufacturing process, a risk assessment is then necessary to assess the process, product, or environmental risk and to aid in formulating better decisions making to prevent the incidents from re-occurring [4].

The primary objective of the study is to investigate the process followed when a risk assessment is performed and provide insights that will aid developing organizations to overcome challenges associated with aseptic processing. The study further investigated the process followed when glove punctures are detected on glove sleeves of barrier technology systems in a sterile manufacturing facility. To achieve this, a case study of LOL Pharmaceutical Company (LOL Pharma) is employed to present and examine the risk assessment approach. The outcome of this study is to provide insight that will aid developing organizations to overcome challenges associated with aseptic processing. The risk assessment approach adopted is a form of FEMA.

1.1 Organization Background

For confidentiality reasons, the pharmaceutical company understudy will be referred to as LOL Pharmaceutical Company (LOL Pharma). LOL Pharma is a pharmaceutical organization that supplies a wide range of medicine to more than 150 countries. This organization manufactures a variety of drug forms as well as active pharmaceutical ingredients. This study was conducted in the small volume parentals manufacturing site where only injectable dosage forms are being manufactured. The company uses the ALF 5080 Bosch Filling and Closing Machine – (refer to Figures 1 and 2 below) - which is designed to fill and close pharmaceutical products under sterile conditions. Interventions in the filling machines are done through the glove sleeves. The isolator is equipped with light barriers that automatically stop the line for each intervention done through the glove sleeves. The critical filling zone is monitored as ISO 5 air quality for particles and microbial contamination.

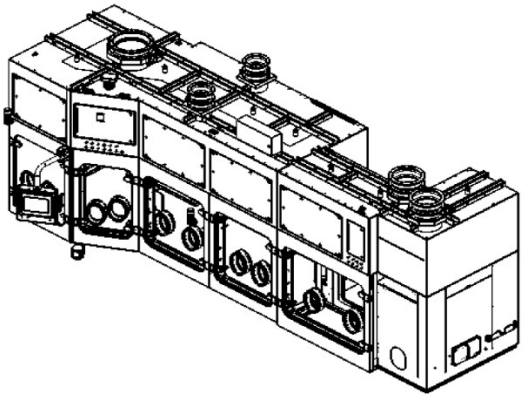

Figure 1. Schematic image of ALF 5080 Barrier Technology

Figure 2. ALF 5080 barrier technology

2. Literature Review

This paper aims to provide insight to organizations looking for ways to overcome challenges associated with aseptic processing. In addition, Aveyard (2014) encourages this objective by stating that the literature review may offer a perception as to why the research is necessary. Therefore, the contribution of this literature overview will outline cutting-edge knowledge concerning the risk-based approach useful in aseptic processing operations.

2.1. History and Evolution of QRM

Although QRM is a relatively new concept to the pharmaceutical industry, it has been a foundational element of regulation of healthcare products since the inception of related regulatory bodies [3]. According to Omar and Moyassar [8], in the early 21st century, a change in regulations led to a shift in the concept of product quality evoked technological development in the pharmaceutical industry. Consequently, a new vision emerged seeking to ensure product quality and focused on an integrated approach to quality risk management. In November 2005, the International Conference on Harmonization published QRM Guidelines [9] and implemented them in the United States, the European Union, and Japan [2]. Quality risk management has since become a critical issue in quality management manufacturing and enhanced the risk-based approach to pharmaceutical manufacturing [3].

2.2. Quality Risk Management

Quality risk management is defined by ICH Q9 as "a systematic process for the assessment, control, communication, and review of risks to the quality of the drug product throughout the product lifecycle" [3]. Thus, QRM, in the authors opinion, can be also interpreted as a methodical approach to assessing, controlling, communicating, and reviewing risks to the quality of sterile products. So, while the quality risk in QRM refers to the organization's failure to comply with good manufacturing practices, risk management refers to a tool that assists the organization in understanding and assessing potential risks (refer to Figure 3 for risks associated with aseptic processing operations), as well as commercializing on lessons learned from them. To organize managing quality risk a set of successive and scientifically designed steps must be followed [2].

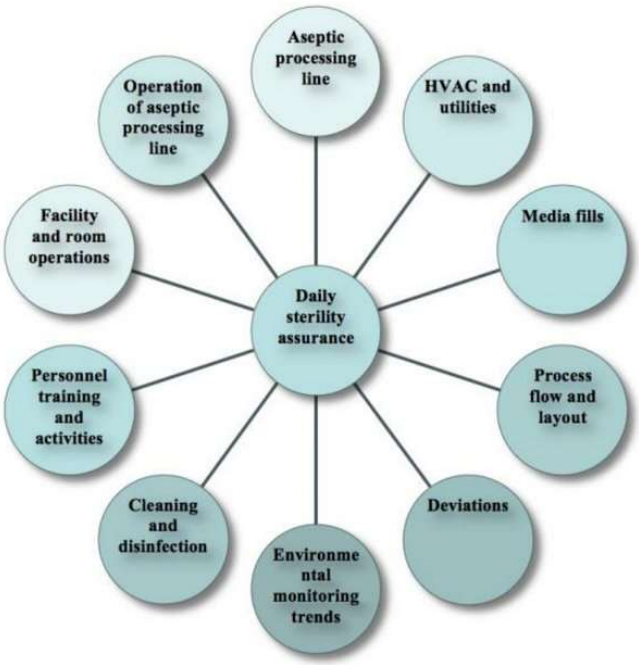

Figure 3. Aseptic processing risks Source [10]

2.3. QRM Principles

Before proceeding with the description of the QRM process (see Figure 3) it is necessary to consider the philosophical principles of QRM. QRM is an approach that promotes fact-based quality management decisions [2] . Hence the assessment of the risk to quality should be based on scientific knowledge and tied to patient protection. Furthermore, the level of effort, formality, and documentation of the quality risk management process should be proportionate to the level of risk. Therefore, to protect the patient, these principles necessitate the development of a formal risk management program for manufacturers of sterile medicine [3].

2.4. QRM Process

The quality risk management process consists of four different phases which attempt to establish the severity to which these risks affect the production process and where the efforts for improvement should be concentrated [2]. The steps of the quality risk management process include the following phases:

2.4.1. Risk assessment

A quality risk assessment is a systematic process of organizing information to support a risk decision made as part of a risk management process. It entails identifying hazards as well as analyzing and evaluating the risks associated with their exposure. The process of quality risk assessment also seeks to identify opportunities for process improvement and ensure documentation and action implementation of the managed risk [11] . White (2009) recommends that a team of qualified experts from multidisciplinary departments is assembled to answer the fundamental questions of a risk assessment.

2.4.2. Risk Control

Risk control entails developing a risk-reduction strategy. The purpose of this phase is to identify the activities necessary to keep risk at a manageable level. The requirement and effort of risk control should be balanced to the level of risk [3]. The documented outcomes of the QRM process must be communicated to the appropriate stakeholders [11]

2.4.3. Risk Communication

Risk communication refers to the information sharing of risks between stakeholders and other relevant individuals within the organization [2]. Lotllikar (2013) adds that information sharing can be done formally or informally, depending on the product and process's risk level.

2.4.4. Risk Review

According to White [3], the risk review phase is simply the periodic examination of risks as part of an ongoing quality management system. Therefore, reviewing the outcomes of the quality risk management process ensures that nothing has changed to affect the QRM assumptions, outputs, and conclusions necessary for a product review [11]. Figure 4 below is an image of the Quality risk assessment management process as described by ICH Q9.

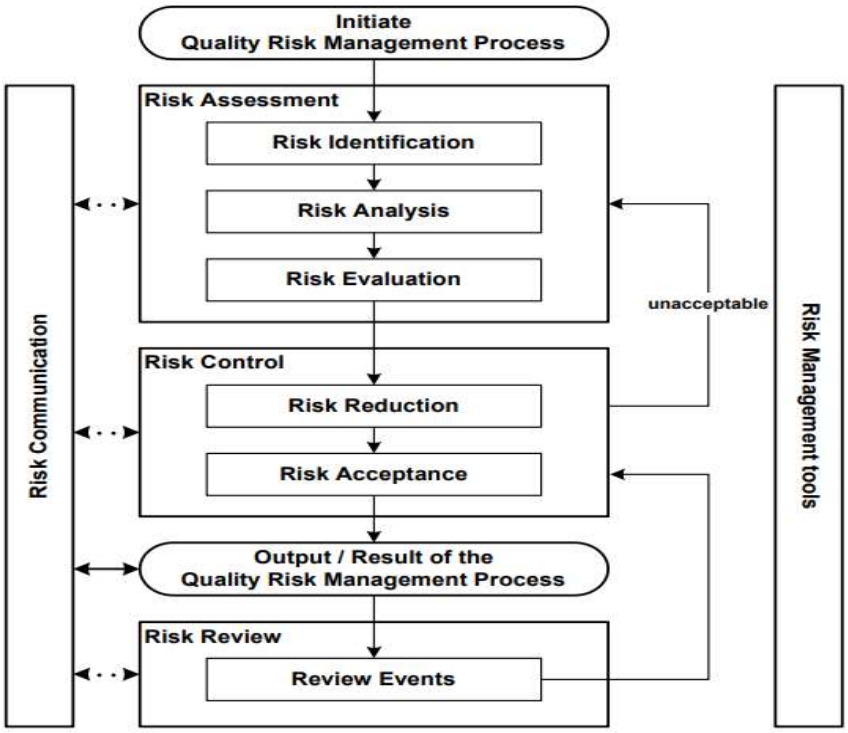

Figure 4. Quality risk assessment management process as described by ICH Q9

2.5. QRM Methods

When analyzing aseptic processing, there are numerous risk factors to consider (see Figure 3), and many methods for mitigating these risks are available. Lotllikar [11] maintains that the selection of appropriate risk-assessment methods is a starting point in conducting a risk analysis. The method must be chosen based on the level of analysis required, the complexity of the risk under consideration, and familiarity with the assessment tool [11]. A list of risk-management tools that are commonly used will be is summarized in the table below [12]

Table 1. Common Risk Management Tools

Risk Management Tool[1]	Description / Attributes	Potential Applications[2]
Basic Tools		
Diagram Analysis • Flowcharts • Check Sheets • Process Mapping • Cause/Effect Diagrams	▪ Simple techniques that are commonly used to gather/organize data, structure risk management processes, and facilitate decision making.	✓ Compilation of observations, trends, or other empirical information to support a variety of less complex deviations, complaints, defects, or other circumstances.
Risk Ranking and Filtering	▪ Method to compare and rank risks ▪ Typically involves evaluation of multiple diverse quantitative and qualitative factors for each risk, and weighting factors and risk scores.	✓ Prioritize operating areas / sites for audit/assessment. ✓ Useful for situations when the risks and underlying consequences are diverse and difficult to compare using a single tool.
Advanced Tools		
Fault Tree Analysis (FTA)	▪ Method used to identify all root causes of an assumed failure or problem. ▪ Used to evaluate system/sub-system failures one at a time, but can combine multiple causes of failure by identifying causal chains. ▪ Relies heavily on full process understanding to identify causal factors.	✓ Investigate product complaints ✓ Evaluate deviations.
Hazard Operability Analysis (HAZOP)	▪ Tool assumes that risk events are caused by deviations from the design and operating intentions ▪ Uses a systematic technique to help identify potential deviations from normal use or design intentions.	✓ Access manufacturing processes, facilities, and equipment ✓ Commonly used to evaluate process safety hazards.
Hazards Analysis and Critical Control Points (HACCP)	▪ Identify and implement process controls that consistently and effectively prevent hazard conditions from occurring ▪ Bottom-up approach that considers how to prevent hazards from occurring and/or propagating ▪ Emphasizes strength of preventive controls rather than ability to detect ▪ Assumes comprehensive understanding of the process and that critical process parameters (CPPs) have been defined prior to initiating the assessment. Tool ensures that critical process parameters will be met.	✓ Better for preventive applications rather than reactive ✓ Great precursor or complement to process validation ✓ Assessment of the efficacy of CPPs and the ability to consistently execute them for any process
Failure Mode Effects Analysis (FMEA)	▪ Assesses potential failure modes for processes, and the probable effect on outcomes and/or product performance. ▪ Once failure modes are known, risk reduction actions can be applied to eliminate, reduce, or control potential failures. ▪ Highly dependent upon strong understanding of product, process and/or facility under evaluation. ▪ Output is a relative "risk score" for each failure mode.	✓ Evaluate equipment and facilities; analyze a manufacturing process to identify high risk steps/critical parameters.

It can be concluded from the literature that when a quality problem arises, QRM plays an important role in the decision-making process. Further, this method improves knowledge and accelerates the identification of potential issues by analyzing and comparing existing data from a quality standpoint through managing product quality, manufacturing processes, validation, and compliance within a risk-based Quality Management System.

3. Methods

The present study aims to provide insights into risk assessment methods that might be useful in assisting developing organizations to resolve challenges associated with aseptic processing. A descriptive study, as Kumar [13] defines it, is intended to systematically summarize, and explain a particular situation. Saunders [14] concurs on this point stating that the purpose of descriptive research is to describe a specific situation. However, he warns that descriptive, explanatory, and exploratory studies may all be undertaken within the same project. Descriptive research was therefore chosen.

The research method used in this paper is qualitative and descriptive, and it will be applied to a case study of investigating glove punctures detected on an aseptic barrier technology system of an aseptic processing plant of a pharmaceutical organization under competitive and market conditions. A case study emerged as the preferred strategy for explaining why glove punctures in aseptic filling lines a quality issue is and how this challenge is addressed to ensure that product quality is not reduced. In addition, the case study method is used to evaluate the usefulness of the risk management approach in sterile manufacturing. The risk-based approach can help companies make better, more informed decisions, give regulators more confidence in a company's ability to deal with potential risks, and influence the scope and level of direct regulatory oversight.

3.1.Research Population and Sample

The unit of analysis for this study was the processes used to assess the risk of glove punctures in barrier technology systems. This study was conducted at a new pharmaceutical manufacturing plant, and the entire population was used to collect glove replacement change history over two years. The case study was identified using a purposive sampling technique. The aseptic filling line was chosen in this case due to its accessibility and because it represents a critical case.

3.2.Data collection

Document Analysis was selected as the method of data collection. Bowen [15] defines document analysis as a qualitative research method where the researcher analyses a set of documents on a specific topic to gather data associated with the study. He further adds that documents analyzed by the document analysis method are accurate and contain exact information of events and references needed.

4. Result and Discussion

4.1.Results from the Case Study

This case study describes a specific activity within the sterile area of a pharmaceutical manufacturing facility. During the post-filling environmental monitoring of 3 batch campaign run of a drug ABC, it is routine to conduct sampling of gloves followed by sanitization and glove testing. During the post-filling environmental monitoring of isolator glove 23 (ITP1-F02-F081), the operator observed it to have a pinhole in the thumb hence, isolator glove 23 (ITP1-F02-F081) failed visual inspections. Putting aside any doubts about the suitability of this process, a team was assembled and asked to risk assess the above case.

4.1.1. Investigation

To accomplish the risk assessment, the team must investigate to identify the root cause of the possible root causes of pinhole in the thumb of the isolator glove. The cause analysis tool used was the fishbone diagram illustrated in Figure 5 below

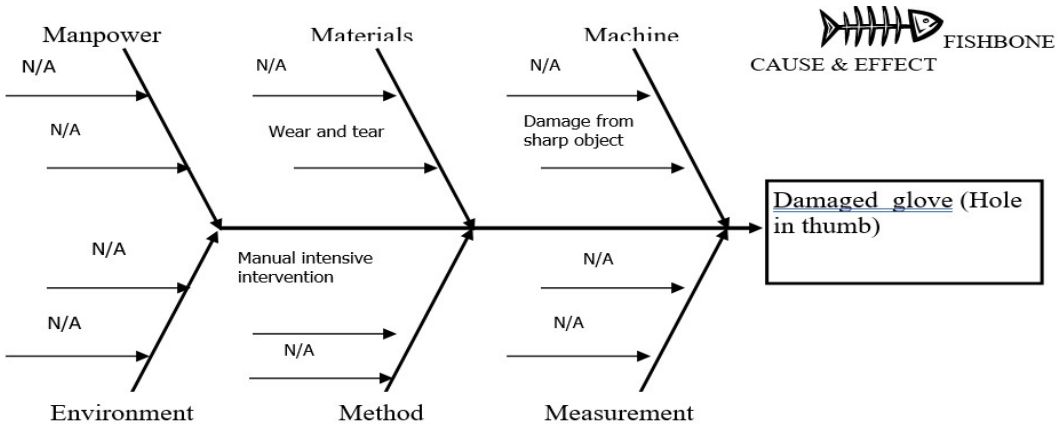

Figure 5. Fish bone diagram illustrating the root cause of damaged glove

4.1.2. Job Card Initiation

A Job card was initiated for the replacement of the glove which is as per Standard operating procedure. A replacement glove was then ordered and replaced on the same day before the next production campaign. Post filling activities continued including EM plates reconciliation, line disassembly, cleaning, and assembly, and Engineering run as per the standard operating procedure. The isolator glove was replaced by the production artisan and visual checks and mechanical tests were performed as per stand operating procedure which is required upon replacement of a new glove.

	Visual Check 1	**Visual check 2**	**Visual Check 3**
Status of the door	Open	Closed	Closed
Performed:	**Prior to Production: Cleaning and Sanitization**	**During Production**	**Before and after Critical Intervention and Post Filling**
Cuff Sets	✓	✓	✓
Glove Hands	✓	✓	✓
Complete Surface of Gloves	✓	N/A	✓
Routine holes	✓	✓	✓
Micro holes	✓	N/A	N/A
Glove Replacement (if required)	Yes	No	No

Figure 6. Visual Checks as per Standard Operating Procedure

4.1.3. Review of Glove Replacement History

The glove location is critical relative to where product contact components are located and should be changed every three (3) months as outlined in Figure 7 extracted from the organization's standard operating procedure.

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Glove Number	Isolator Location	Glove Change Frequency
Glove 11	ITP1.F02.F032	3 monthly
Glove 12	ITP1.F02.F031	3 monthly
Glove 23	ITP1.F02.F081	3 monthly
Glove 09	ITP1.F02.F042	3 monthly
Glove 10	ITP1.F02.F041	3 monthly
Glove 07	ITP1.F02.F052	Annually
Glove 08	ITP1.F02.F051	Annually
Glove 24	ITP1.F02.F071	Annually
Glove 15	ITP1.F02.F012	Annually
Glove 16	ITP1.F02.F011	Annually
Glove 13	ITP1.F02.F022	3 monthly

Figure 7. Glove Change Frequency as per standard operating procedure

The glove change history is outlined below in Table 2 which details all the approved interventions glove ITP1-F02-F081 is used for, the number of times the intervention is likely performed in a single batch, and the recent dates the glove has been replaced. Based on the maintenance program, the glove was due for 3 monthly a change on 14 Aug 21 as per replacement frequency rationale, however, the glove was changed on 06 Aug 2021 at the end of a campaign run

Table 2. Glove change history

Glove used for: refer Intervention SOP009175 P - Process; R - Routine; NR - Non-routine	Frequency Used	Frequency of Intervention	Glove Replacement History
R - Empty vial waste chute on the turntable	Infrequent	2	02 Oct 2020 30 Mar 2021 29 Apr 2021 14 May 2021 06 Aug 2021 10 Aug 2021 19 Sep 2021 11 Oct 2021 01 Nov 2021 10 Nov 2021 03 Jan 2022
R - Waste removal through the chute	Infrequent	2	
P - Placing of reject chute	Before the start of filling	2	
NR - Sensor Insertion	Infrequent	1	

Glove ITP1-F02-F081 is used to perform the following interventions

- Placing of reject chute: The reject chute/Rail is hung on the isolator rail during the decontamination cycle. Thereafter it needs to be placed in its designated area, to contain rejected vials in the filling machine. Aseptic line building activity.
- Waste Removal Inside Isolator: The reject rail/chute is cleared of vials, into the beta bag attached to the RTP port. The rail format part is removed and the RTP is closed to facilitate the removal of the beta bag. The rail is assembled back when an empty beta bag is attached to the isolator.

- Empty vial waste chute on the turntable: material passing of the waste chute is undertaken to transfer the chute to the ITP1.F02.Q081 door and the chute is emptied into a waste beta bag.

In conclusion, possible wear and tear developed over time which resulted in the pinhole is the least likely since the glove was changed on 06 Aug 2021 before the campaign run. During BMR review and CCTV footage review, it was found that there were manual intensive interventions of removal and placement of the waste chute after removal of the beta bag which could result in potential pinch points in the glove. It also indicated the removal of waste from the isolator (including broken glass on the waste chute) which could cause potential damage to the glove during manual handling. Therefore, the possible root cause for the pinhole damage can be attributed to interventions performed during aseptic filling due to possible method errors.

4.2. Interpretation And Discussion

4.2.1. Glove failure Visual Check at end of the production run

In the event that there is a glove failure the following actions are required by LOL Pharma's standard operating procedure: a complete surface sampling of the gloves, an additional sample on the tear or pinhole, the size of the defect measured as precisely as possible, and the location note The glove is then removed after a job card is raised, and the replacement glove is installed, sanitized, visually inspected, and finally checked for leaks.

Glove integrity is important for product quality because it serves as an effective microbial barrier between the product and the operator. The illustration below is used to support risk-based decisions to minimize the risk of glove punctures.

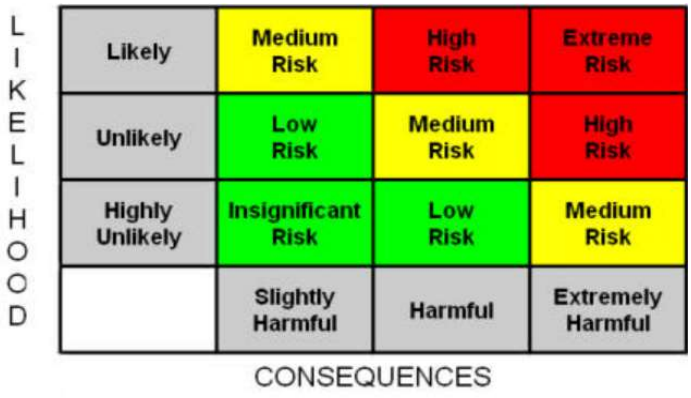

Figure 8. Risk Assessment rating 3x3 Matrix

4.2.2. Severity of risk

All the inspection tests at the beginning of the campaign passed as well as the surface monitoring results of the glove and all the isolator environmental monitoring results passed for this campaign run this includes the QC Results post the filling activity. It can also be observed that Isolator Glove ITP1-F02-F081 is not situated near the filling needles and is approximately 2m from the filling needles and therefore poses a minimum risk. Finally, this specific glove is used for interventions involving the reject waste chute and waste removal which do not have product contact. Therefore, the risk to the product quality is considered low.

4.2.3. Detectability

Based on the quality risk assessment, each glove will have a unique replacement frequency. The replacement of gloves is on the maintenance plan therefore detection of failures is high as gloves are mechanically assessed and visual inspection checked at the start and end of each campaign batch and visually inspected between batches within a campaign. Visual inspection of gloves is also performed after an intervention that could have affected the integrity of the glove. Therefore, due to the various and frequent glove tests, the detectability of a damaged glove is considered a high

4.2.4. Rationale for decision

The mechanical and visual inspection tests at the beginning of the campaign passed. For this campaign run, all environmental monitoring tests, including those conducted by quality control departments, passed. Even though this glove is used for interventions involving the reject waste chute and waste removal, it was determined that the risk is low due to the location of the glove (ITP1-F02-F081) and its proximity to the filling needles being approximately 2m. As a result, the risk to product quality is regarded as low, and the product disposition is regarded as set to release.

5. Conclusion

Aseptic processing is a manufacturing process with numerous risks that must be evaluated in order to protect the patient. The aim of the study was to look into investigate the process when glove punctures are detected on the glove sleeves of barrier technology systems in a sterile manufacturing facility. The findings defined the possible root cause for the glove puncture can be attributed to interventions performed during aseptic filling due to possible method errors. Further, they indicate that the risk-based approach has a strong benefit in identifying the critical risks and ensuring control over them. The results also revealed that, despite the fact that the glove puncture was detected after filling activities, the risk of puncture was low because the glove is far away from the filling needles. This indicates that the aseptic environment was not adversely affected. Although the frequency of glove changes, as specified in the standard operating procedure related to the glove in question corresponds to the planned preventative maintenance schedule, historical data show frequent change/damage/replacement at least monthly. It is suggested that the organization review the results of a risk assessment in order to determine the new frequencies of glove replacements.

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