BSR/PDA Standard 03-202x, Standard Practice for Quality Risk Management of Aseptic Processes

Committee Draft

BSR/PDA Standard 03-202x, Standard Practice for Quality Risk Management of Aseptic Processes

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1. Introduction

This standard describes a Quality Risk Management (QRM) risk assessment method to identify and ensure control of the contamination risks associated with aseptic processing. The standard meets the needs of both industry and regulators for risk-based contamination control strategies that assess the effectiveness of all the controls and measures employed to manage microbiological risks to product quality and patient safety

Aseptic processing incorporates numerous processes, conditions, and factors concomitantly offering opportunity for contamination from many sources and varying means of introduction. Therefore, an effective risk assessment method must evaluate the combination (or suite) of controls and their aggregate effectiveness to mitigate risks associated with all sources of contamination, rather than discretely assessing individual controls and contamination sources. This standard provides an effective evaluation of aseptic processing risk through consideration of the sum combination of interrelated controls purposed to prevent all sources of contamination.

In detailing the QRM risk assessment method this standard contains information on the relevant fundamental principles, and concepts, a description of the risk assessment method, steps to perform the risk assessment, an example to assist the reader with performing the method, key terms, definitions, accompanied with suggested reading.

This method explicitly does not use occurrence of contamination as a factor for assessment. Instead, the method relies on the totality of the strength of the prevention controls with the timing of the associated detection controls. For this tool, ‘occurrence’ of prior events is ineffective in preventing future recurrence.

The intent is to proactively manage contamination risk by preventing the hazard that would allow contamination to occur.

The method incorporates fundamental QRM principles as they apply to aseptic processing. The method aids in identification and assessment of the totality of contamination sources, the combination (or suite) of process controls designed to prevent contamination, and the hazards associated with failure of those contamination controls. The method evaluates the hazards of the failure of those contamination controls, based on the strength of objective evidence of the prevention controls and the timing of the detection controls for those identified hazards.

The effectiveness and utility of the QRM method presented in this standard is based on the following key aspects:

- It is a standardized method which enables a consistent mechanism to assess contamination risks.
- It is designed to assess contamination risks associated with an aseptic process.
- It can be applied to low bioburden manufacturing processes.
- It focuses on assessment of the strength and effectiveness of the totality of controls rather than on individual controls.
- It provides a framework of risk ranking criteria which emphasizes the use of evidence from historical data and scientific knowledge aimed at minimizing the bias that contributes to underestimating and/or over-estimating risk levels.
- It focuses on contamination prevention and detection of control failures before contamination could occur.
- It addresses detection control limitations associated with contamination risk in aseptic processing.
- It is designed to drive organizations toward developing a contamination control system which anticipates and mitigates risks before they are realized.
- It identifies opportunities for process improvement by enhancing controls and ways to prioritize mitigation actions.

- It provides a means to meet Contamination Control Strategy (CCS) development and maintenance requirements as noted in EMA/PIC/S Annex 1 [1].

2. Scope

Quality risk management is an iterative process. This standard provides a lifecycle approach using a holistic evaluation of contamination control systems designed to minimize and/or prevent contamination during aseptic processing and ultimately ensure the safety of the products when delivered to the patient. The standard is also applicable to aseptic processes used to manufacture sterile products, terminally sterilized products as well as low bioburden processes in the manufacture of regulated health care products. It is applicable to pharmaceutical, biological, and ATMP (Advanced Therapeutic Medicinal Products). This standard does not supersede or replace regulatory requirements, such as Current Good Manufacturing Practices (CGMPs) and/or compendial requirements that pertain to a particular national or regional jurisdiction.

3. Terms and Definitions

- Aseptic Process - A process in which sterile materials are handled in an environment in which the air supply, materials, equipment, and personnel are controlled to prevent microbial and particulate contamination [1].

- Aseptic preparation/processing – The handling of sterile product, containers and/or devices in a controlled environment in which the air supply, materials and personnel are regulated to prevent microbial, endotoxin/pyrogen and particle contamination.[2]

- Contamination Control Strategy – A planned set of controls for microorganisms, endotoxin/pyrogen and particles, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to active substance, excipient and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control [1].

- Contamination Control System – a system that considers all the integral elements of a pharmaceutical product manufacturing such as facility design, personnel training, cleaning, etc. to confer sterility assurance and the production of a sterile product [4,21].

- Critical Quality Attribute - A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality [5].

- Control - A function which helps prevent the occurrence of harm due to a hazard or to detect the hazard or harm if it does occur. Controls are intended to ensure process performance and product quality.

- Detection (detectability) - The ability to discover or determine the existence, presence, or fact of a hazard [6].

- Failure - The condition or fact of not achieving expected results; a cessation of proper functioning or performance [7].

- Gemba Walk - A Gemba Walk is a workplace walkthrough which aims to observe employees, ask about their tasks, and identify productivity gains. Gemba Walk is derived from the Japanese word “Gemba” or “Gembutsu” which means “the real place”, so it is often literally defined as the act of seeing where the actual work happens [8]

- Harm - Damage to health, or to the desired outcome of the aseptic process. It is the impact that a realized hazard may have on the process, the patient, or product quality including damage occurring from loss of product quality or availability [6].

- Hazard - The potential source of harm [6].

- Hazard Identification – Hazard identification is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders [6]

- Intervention - An aseptic manipulation or activity that occurs in a critical area [9].

- Low Bioburden (Process) – Manufactured within a controlled and monitored environment in which the final drug product or process intermediate, as applicable, requires bioburden control, but is not required to be sterile (e.g., biological drug substance produced by mammalian cell culture) [1].

- Occurrence - The likelihood or probability that a hazard will result in the harm [7].

- Predictive Maintenance - a technique that uses condition-monitoring tools and techniques to monitor the performance of a structure, a piece of equipment, or procedural process during operation [11].

- Quality - The degree to which a set of inherent properties of a product, system or process fulfils requirements (see definition specifically for “quality” of drug substance and drug (medicinal) products)[6].

- Quality Risk Management (QRM) – A systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle [6].

- Quality System - Formalized business practices that define management responsibilities for organizational structure, processes, procedures, and resources needed to fulfil product/service requirement, customer satisfaction and continual improvement [7].

- Residual Risk – The risk remaining after control measures have been taken [22].

- Risk - The combination of the probability of occurrence of harm and the severity of that harm [6, 7, 12].

- Risk Analysis - The estimation of the risk associated with the identified hazards [6].

- Risk Assessment - A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of identification of hazards and the analysis and evaluation of risk associated with exposure to those hazards [6].

- Risk Communication - The sharing of information about risk and risk management between the decision maker and other stakeholders [6].
- Risk Control – Actions implementing risk management decisions [6].
- Risk Evaluation - The comparison of the estimated risk to the given risk criteria using a quantitative or qualitative scale to determine the significance of the risk [6].
- Risk Management - The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating, and reviewing risk [6].
- Risk Reduction - Actions taken to lessen the probability of occurrence of harm and the severity of that harm [6].
- Risk Review - Review or monitoring of output/results of the risk management process considering (if appropriate) new knowledge and experience about the risk [6].
- Severity - A measure of the possible consequences of a hazard [6].
- Subject Matter Expert -Someone who has the appropriate expertise in a particular area or topic.
- Stakeholder: Any individual, group or organization that can affect, be affected by, or perceive itself to be affected by a risk. Decision makers might also be stakeholders. For the purposes of this guideline, the primary stakeholders are the patient, healthcare professional, regulatory authority, and industry [6].
- Sterile - The absence of viable microorganisms [7].

4. Acronyms /Abbreviations

AMC	Analytical Method Comparability
ANS	American National Standard
BSR	Board of Standards Review
CGMP	Current Good Manufacturing Practice
CQA	Critical Quality Attribute
EMA	European Medicines Agency
HACCP	Hazard Analysis and Critical Control Points
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use

198	PDA	Parenteral Drug Association
199	PEMMMM	People, Environment, Method, Measurement, Machines/Equipment, Materials
200 201	PIC/S	Pharmaceutical Inspection Convention (PIC) / Pharmaceutical Inspection Co-operation Scheme
202	QRM	Quality Risk Management
203	RABS	Restricted Access Barrier System
204	RCA	Root Cause Analysis
205	RCAI	Responsible, Accountable, Consulted, and Informed
206	RTU	Ready To Use
207	SME	Subject Matter Expert

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5. Fundamental Principles of Quality Risk Management

The following section provides the principles, concepts, and caveats on which this standard aseptic processing QRM method is based. Additional information and detail on these and other QRM principles may be found in PDA Technical Report No. 44 [7], Quality Risk Management for Aseptic Processes, Technical Report No. 54 - Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations [12], Technical Report No. 90 Contamination Control Strategy Development [18], ICH Q9(R1) [6], and other suggested readings as described in the Bibliography/References section.

5.1 Basic Concepts

Evaluation of risk is foundational to decision making and the knowledge management process. Risk management planned and executed early in a product or process lifecycle allows for the implementation of robust controls that ensure the drug product meets the critical quality attributes. The objective of QRM is to ensure that safe medicines are delivered to patients. The objective of aseptic processing QRM is the prevention of contamination of sterile products.

At the core of all risk assessments is the identification of hazards. Hazards are the potential sources of harm. Harm is the impact that a realized hazard may have on the process, the patient, or product quality. The combination of harm and hazard are used to describe a set of circumstances broadly considered as "risks". Hazards as defined in QRM can be described as those events that can result in harm to the patient, as damage to health, including the damage that can occur from loss of product quality or availability. As such, hazards can refer to control failures, which are how product quality is protected. The risk assessment tool described in this standard presents hazards as control failures which could result in contamination.

5.2 Risk Perception and Pre-determined Risks

The use of risk management should provide valuable information needed to make transparent, objective, science-based and data driven decisions. An effective QRM approach is one where the method is performed with curiosity about and a sense of ownership of the system or process. Risk assessments should be performed in an environment where the discussion of risks is engaged freely, without judgement, or fear of blame.

Properly applied QRM is beneficial but can be ineffective when used or applied incorrectly. The misuse and misapplication of aseptic processing QRM are often the result of bringing pre-determined risks and outcomes to risk assessments.

Additional instances of misapplication, include using QRM to justify not following regulatory requirements or established specifications and basing assessment results on subjectivity and bias in lieu of scientific evidence, relevant knowledge, and data.

Care should be taken to ensure that QRM is not used to justify a decision that was already made or justify poor aseptic practices or the outcome of such practices. A risk assessment which has a pre-determined outcome will neither enable process improvement nor prevent failures.

5.3 Critical View of Selecting Risk Assessment Tools

The risk assessments methods should be objective, not biased or based on unfounded opinions. It should be selected to be applicable for the process being assessed; it should also be commensurate with the complexity of the process to be assessed. Formality in quality risk management is not a binary concept (i.e., formal /

informal) [6]. The approach taken considers the overall structure, the composition of the tool, and the relationship of the risk inputs. Factors such as complexity, importance, and uncertainty allow organizations to identify the tool formality best suited for the scope and objective of an assessment. The more complex a process or subject is, the higher the formality or formal structure of the approach. The importance of the risk-based decision to product quality also informs formality. The element of uncertainty is a reflection upon the system, product or process that is under assessment.

5.4 Selection of Risk Assessment Team

The multidisciplinary aspect of the team conducting a risk assessment is a key enabler for successful execution of the process from both a process understanding of a process system and QRM perspective. Where novel and or complex technologies are in scope of the review, input from vendors and developers, as subject matter experts (SMEs), should be identified, consulted, and documented as necessary.

The risk assessment team provides input to the QRM process which includes explicit knowledge that comes from historical performance documents, logs, batch records, validation studies, or scientific rationale. It also includes tacit knowledge representing know-how, experience, expertise, context, decision rationale, and related knowledge that is not written down. The SMEs from a cross-functional team or anyone from the risk assessment team should reflect these knowledge sources. SMEs shall include experts with experience from the quality unit, product development, microbiologists, engineering, regulatory affairs, production operations, validation, and supply chain in addition to individuals who are knowledgeable about quality risk management processes.

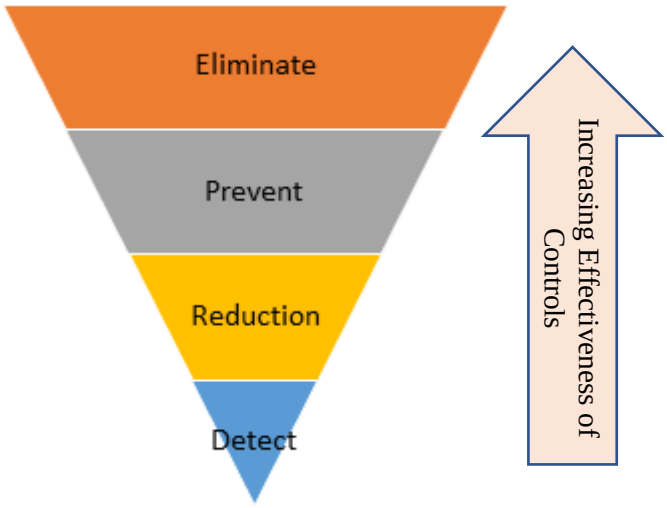
The risk assessment team shall include enough people to provide the required technical input and process knowledge. The team should not be so large as to complicate the flow of opinions and individual team member participation. A core team including system or risk owners and a risk facilitator will define the risk question, the process boundaries, assumptions, and identify the need for additional SMEs. The use of an experienced QRM facilitator will ensure that the risk management process is performed with as much objectivity as possible and to prevent the introduction of bias into the process.

All participants involved with QRM activities must acknowledge, anticipate, and address the potential for subjectivity and bias [6]. Once the risk assessment team composition has been identified, the team shall be trained on the risk method to ensure collective understanding of the objective of the risk assessment.

5.5 Risk Control

Assessment of the effectiveness of contamination controls should be performed during the process development phase, and during the development of changes to an existing process or in response to failures, excursions, deviations, and investigations. Defining controls is critical to ensure that the appropriate layers of protection are in place. Controls that eliminate hazards are the most effective, followed by controls that prevent hazards from occurring (preventive controls), followed by controls that prevent hazards from leading to harm (reduction controls), and finally controls that enable a hazard or harm to be detected (detection controls) **Figure 1**.

Figure 1: Types of Contamination Controls



Elimination is the most robust control because it removes the source of contamination, as might be the case with the use of automation to eliminate risks posed by manual operations. If elimination is not possible, then preventing the source from contaminating product is important, as might be the case with use of an isolator to separate the operator from sterile product. If aspects of prevention are not feasible, then reducing the likelihood of contamination impacting the sterile product is important, as might be the case with utilizing proper aseptic technique using gowned operators during an open-door intervention on a barrier filling line.

Detection controls are valuable because they can detect failures before they harm the patient, and they are indicators of the effectiveness of contamination controls. However, unless they are predictive indicators, detection measures will not necessarily prevent the harm to product quality as the damage may already be done with the only available measure is to discard the product. Therefore, the effectiveness or benefit of detection can be reflected by ranking detection controls according to whether they **predict** contamination, **prevent** contamination, or make one aware of contamination. To do so, detection is determined according to the impact of their timeliness.

a) **Leading indicators** are the most effective types of detection. They are those that provide information that can be used to help predict a failure or hazard before it happens. Therefore, the product is not lost or adulterated. Examples of predictive detection might include such measures as sub-excursion (e.g., alert) level environmental monitoring trend analysis, monitoring of clean room area adjacent to the critical space, predictive maintenance, differential pressure trends, analysis of near misses.
b) **Lagging indicators** are the most common process related detection measures. Depending on timing, they can indicate a process failure that has occurred before patient safety is compromised. Examples include such measures as environmental monitoring, in-process product testing, isolator glove integrity testing, post-use filter integrity testing, visual inspection of filled vials. Lagging indicators also include includes measures that detect failures that have occurred to the extent that product is compromised, and patients may be harmed or at risk. Example indicators include deviations, adverse events, batch rejection, and recall events.

Section 6 presents examples of controls for elimination, prevention, reduction, and detection. It is also, important to be aware that while the implementation of a given control may be effective at mitigating a risk, those controls may also have an unintended consequence that adversely effects the performance of the process or result in additional risk to the product.

Once the risk assessment is completed and the need for additional risk controls is identified, a set of activities best suited for the conditions under assessment is developed with the aim of reducing the unacceptable risks identified. The new control or set of controls should be evaluated prior to implementation via change control to ensure that it is sufficiently targeting the part of the process that has been identified as vulnerable and to ensure that implementation of these new control measures do not introduce new risks to the process.

5.6 Risk Review

Risk review is a fundamental component of the Quality Risk Management lifecycle because it ensures that risk management is a living process and reflects current situations and conditions. The intent of risk review is to consider new knowledge of the product, process and industry innovations and experience obtained in addition to verifying that the current controls and processes are performing as expected. A robust risk review process (i.e., incidence and time based) integrated into the quality system and included in the QRM policy is important to ensure the benefits of QRM are realized and maintained.

Risk review helps ensure that decisions and actions related to the controls in place to prevent contamination are properly communicated (i.e., risk communication), implemented, evaluated for the effectiveness, and remain effective. Additionally, risk review should be designed to capture process variables not present or identified initially. Risk review should also be designed to identify and address residual risk.

Details related to risk review are outlined in PDA TR54, *Implementation for Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations [12]*, ICH Q9(R1) *Quality Risk Management* [6], ISO 31000 *Risk Management Guideline[13]* and other industry publications.

6 Quality Risk Management Method for Aseptic Processes

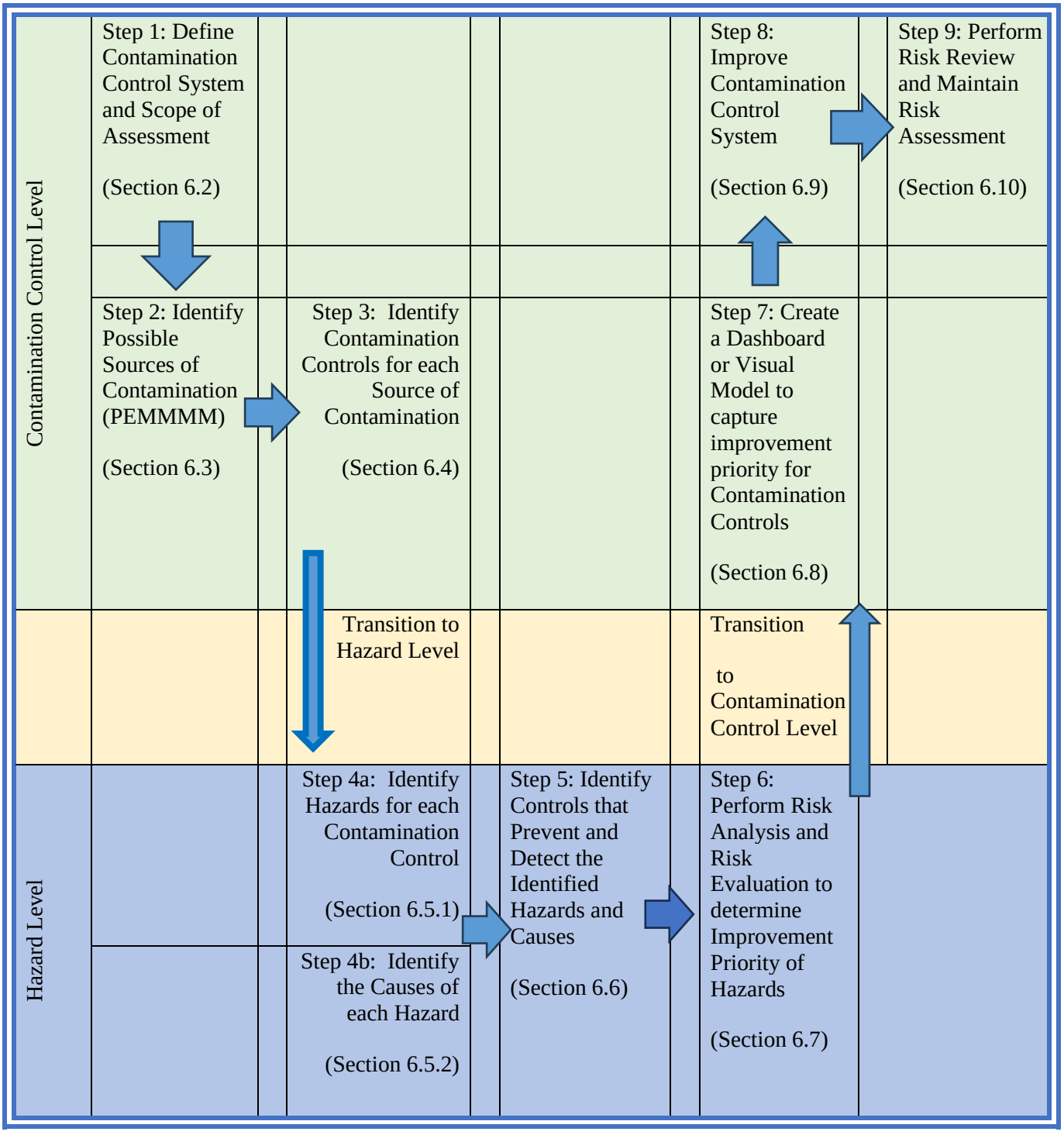
6.1 Background

Unlike a terminal sterilization process, the process of aseptic manufacturing cannot be validated to provide a sterility assurance level (SAL). The absence of contamination in an aseptic product cannot be proven unless every individual unit is destructively tested. Even then, there are limitations in microbial methods that have yet to be addressed. Sometimes microbial recovery and enumeration are not consistently reliable and reproducible, sterility tests are limited in their ability to detect contamination because of the small sample size typically used [23], and media fills occur infrequently and may not be fully representative of all production batches. A few areas that the industry is still learning about and continuing discovery in includes environmental isolates, viable but non-culturable (VBNC) organisms, biofilm growth and detection and mold identification and control.

To provide the assurance of sterility, aseptic processes should be designed to include layers of protection that in some cases are redundant and other cases additive. This could be two or more controls that address the same contamination source. For example, donning sterile gloves when entering a glove port on an isolator system or RABS. The complexity of human factors and human error during the design and control of aseptic processes needs to be incorporated into the evaluation of contamination risks. The intent is to build resilience in the aseptic manufacturing system which can eliminate, prevent, reduce, and predict failures (hazards) of the contamination control systems in place. The method in this standard evaluates the multiple systems of contamination controls of an aseptic processing system, and incorporates James Reason's concept of the 'Swiss Cheese Model' [14]. This QRM method is a stepwise process which integrates the fundamentals of QRM principles as outlined in ICH Q9(R1) across the product lifecycle to enable continuous process improvement. It is an evidence-based approach to risk management that delivers data to support meaningful risk-based decision making while minimizing subjectivity and accounting for uncertainty, where limited data for operations with little to no operational history exists. This works well both as a predictive method and as a reactive method.

The steps involved in this method are outlined the **Figure 2** below.

Figure 2: QRM Method for Aseptic Processing



As illustrated, there are two iterations of identifying a hazard and then identifying controls of the hazard. At first the risk assessment team will identify the contamination sources of a process and the possible controls that

address contamination (i.e., contamination controls). Once the contamination controls are established, the team then performs a further assessment by identifying hazards of those contamination controls and the next level of controls that prevent and detect those hazards (i.e., risk controls). An example of a contamination control is the use of a barrier glove (used to prevent human contamination) that is monitored and inspected at the end of the process (contamination detection). The team will then list and evaluate hazards of that glove (e.g., such as a tear) and evaluate the preventive and detection controls for that hazard (tear) and causes of that hazard (e.g., equipment design to minimize tears and integrity testing). By performing this next level of hazard analysis, the team focuses on the controls that can be put in place and monitored before the contamination hazard could occur.

Primarily the risk tool used for aseptic processing has been Failure Modes and Effects Analysis (FMEA). While the FMEA method has the ability to effectively assess the risks across a number of unit operations, it is not as effective in providing the risk assessment team with a holistic view of the process, product, or system under review. Existing FMEAs can be used as an input to this method.

The representatives of the risk assessment team are responsible for providing process information, making assessment decisions, and delivering a level of awareness needed to implement those decisions. As noted earlier, the method shall be performed by a diverse, cross-functional team that includes representatives from groups that can provide useful knowledge and process information. For aseptic processing, these groups may include manufacturing, the quality units, microbiology, engineering, process development, technical operations and support, and validation. Experts with knowledge of new technologies / innovation are important team members when using the method for new processes/facilities. Because the objective is to assess the ability of the aseptic process to prevent microbiological contamination of product, the inclusion of microbiologists or representatives with applied microbiology knowledge is essential.

6.2 Initiate the QRM Method for the Aseptic Processes

6.2.1 Define the aseptic process: Create a visual map of the process.

To ensure alignment with the intent of the risk assessment and to align the participants on the process under assessment, the risk assessment team must develop an understanding of the current process. This can be achieved by creating Process Flow Diagrams/Process Maps or Visual Maps to identify the current boundaries and elements of the Aseptic Process. Visual mapping is a technique used for displaying complex information as a visual aid. It is a graphical organization and presentation of information. Types of visual maps include Mind maps, Concept maps, Conceptual diagrams, and Visual metaphors, etc.

A visual map(s) of the manufacturing process or a process flow diagram will offer the team a perspective on the process pathways, aid in identifying the potential for contamination and its current control mechanisms and generate a common understanding of the flow of operations. At the end of this step, the visual map(s) shall be reviewed, and the accuracy confirmed, by SMEs who have an in-depth knowledge of the process.

A team facilitator is strongly recommended throughout the risk assessment process, for example to aid in the identification of contamination sources, and to assess and determine the relative strength and value of control and detection measures.

The risk assessment team must be familiar with the process framework and have an opportunity to physically walk down (Gemba walk) the facility and witness the process. For a new process/facility, this can be a virtual Gemba where the process is captured, and the contamination control systems are included. The use of previous experience, vendor information (drawings, pictures, risk assessments), equipment user requirement specifications (URS's), industry examples can be sources of information that can support the virtual Gemba. This will help to strengthen the connection between the intent of the activities with the actual layout/flow of processes. A process walkdown will also enable the team to be aligned on the current design and/or implementation state and, as a result, develop a list of assumptions that are relevant for the assessment. The

intent of the walkdown is to observe the activities while they are occurring and to have a reference of the current state.

6.2.2 Define risk assessment scope, objective, boundaries, and assumptions.

One objective of aseptic processing is to prevent microbiological contamination that adversely affects product quality and patient safety; therefore, the objective of the associated risk assessment is to identify the risks and assess (or establish) the associated controls in preventing and detecting microbiological contamination and conditions or vulnerabilities that may lead to microbiological contamination. The risk assessment team may elect to assess only a portion of a complete aseptic process at a time, or may wish to assess the entire aseptic process, inclusive of cleaning, disinfection, sterilization, and component preparation. The scope can be used to identify boundaries of the aseptic process, whether steps in the visual map, equipment boundaries on a piping and instrumentation diagram, or physical spaces on a facility map. The scope and boundaries of the risk assessment shall be agreed to by the risk assessment team and documented.

The objective, scope, and boundaries of the risk assessment will be included in a risk question that will guide the assessment performance. For example, the risk question may be framed as "what are the risks associated with the sterilizing filtration process of [product], from the end of bulk Formulated Drug Substance (FDS) through collection of sterilized FDS in preparation for filling, that could result in microbial contamination or the failure of contamination controls?" For more guidance and details on establishing the risk question, consult PDA Technical Report 54 [12].

For prospective assessment, such as equipment and process design and facility construction, the method can be used to find areas of potential contamination and can evolve to adopt changes during the design phase including the physical construction of the manufacturing facility and/or aseptic process. During this phase of the process lifecycle, the assessment may undergo refinement, based upon gathered data, to determine if process modifications are required to mitigate contamination risks. It is important to note that the degree of quality risk management formality and extent of contamination controls are influenced by various factors including but not limited to the design of the facility and the nature of the product. Early in the process lifecycle, high levels of uncertainty may exist, which may limit the precision with which the risk assessment can be executed due to the challenge of decision making under uncertainty. As knowledge is gained and data is gathered, the risk assessment can be refined to deliver a more thorough understanding of risk.

For existing, well-established processes this assessment can be performed at various times such as: to help improve an existing contamination control system, in reaction to previously unknown hazards (e.g., deviations), and to support change management, process improvements, and process additions. Retrospective or reactive execution of this assessment requires collection and evaluation of current and readily available data related to the process being evaluated.

Assessments (both prospective and retrospective) may include collection and evaluation of current and readily available data related to the proposed or existing process being evaluated. This may include publicly available information as well as SME knowledge and experience.

The risk assessment team shall discuss, clarify, accept, and document any assumptions that will be made to conduct the risk assessment. This will ensure the team members have a grounded sense of connection to the facts of the risk assessment. These well-defined assumptions, in conjunction with a clearly defined risk question, will provide the team with a common understanding, which will prove invaluable when the risk assessment sessions become complex.

6.3 Identify the Possible Sources of Contamination

Using the visual map, the risk assessment team will identify the potential sources of contamination and highlight where sources of contamination may impact stages of the process under review. This step will occur through knowledge gathering, an evaluation of available information, and via brainstorming exercises or sessions. The

amount of time invested in exploring sources of contamination provides a comprehensive foundation for the risk assessment.

Sources of contamination will be categorized as one or more of the following:

- **P**eople
- **E**nvironment
- **M**ethod (i.e., manufacturing process)
- **M**easurement (e.g., sampling activities)
- **M**achines / Equipment
- **M**aterials (e.g., raw/starting materials, components, consumables, etc.)

Throughout this standard, the acronym PEMMMM will be used when contamination sources are discussed.

The risk assessment team will document a list of credible sources of contamination as are applicable to the scope of the assessment. A variety of information should be considered when developing the list, including but not limited to:

- Historical data associated with the process, such as deviation reports, investigation reports, process performance analytics (may not be available for new processes), and EM data (viable and non-viable) for utilities, clean rooms and personnel.
- Personnel interviews, such as manufacturing operators, process designers and engineers, microbiologists, and vendors
- Review of vendor-supplied documentation
- Review of literature, such as PDA Technical Report 69 Bioburden and Biofilm Management in Pharmaceutical Manufacturing Operations [17] and PDA Technical Report 90 Contamination Control Strategy Development in Pharmaceutical Manufacturing [18].
- Historical experience of SMEs for similar processes, including explicit and tacit knowledge
- Stakeholder feedback.

Brainstorming sessions may also be used to assist the team with identifying sources of contamination. Using an experienced facilitator for this evidence gathering activity can provide the opportunity for a free flow of information. A structured approach such as fishbone diagram or fault tree analysis may be employed [19].

It is important to recognize that identification of a source of contamination does not necessarily mean that it has or will result in failure. Using this risk management method, the documented source of contamination enables the team to identify opportunities for putting appropriate controls as is outlined in the next step of the identifying contamination controls.

6.4 Identifying Contamination Controls

For each identified potential contamination source, the risk assessment team will identify all possible contamination controls that could eliminate, prevent, reduce /minimize, or detect contamination. This is best performed with all relevant stakeholders as a brainstorming session. All possible contamination controls should be identified, regardless of those currently in place.

The risk assessment team shall list controls which are designed to eliminate, prevent, reduce/minimize, and detect contamination from the sources noted in the previous step. A control, measure, or set of controls should be identified for each contamination source.

The risk assessment team might focus on the following questions to help identify contamination controls and measures:

a) What can be done to eliminate, prevent, or reduce the source of contamination or risk of contamination?
b) Can those actions be or are they reflected by a control measure(s)?

c) If so, then what are those measures?
d) Are the control measures feasible and practical?

6.4.1 Contamination elimination controls.

Elimination of contamination sources is the most effective way to control the risk. For an action or control to result in elimination of risk, it should be a complete removal or change of the source, for example:

a) If **People** are identified as a source of contamination, then using automation or robotics, instead of operators or changing the process to eliminate the activity or intervention performed by people, could eliminate that source.
b) If **Environmen**t is identified as a source of contamination, then replacing an open process with a closed process or transfer systems that eliminates the exchange of air between that area of work and the external area/environment could eliminate the source.
c) If **Method** or process activity is identified as a source of contamination, then changing the process to eliminate that step or performing that step outside of the critical aseptic space could eliminate the source.
d) If **Measurement** (e.g., sampling activity) is identified as a source of contamination, then redesigning an open sampling method to a sampling method using a sterile closed system could eliminate that source.
e) If **Machine** or equipment is identified as a source of contamination, then purchasing different equipment or relocating certain equipment or sections of equipment outside of the critical aseptic processing space could eliminate that source.
f) If **Materials** are identified as a source of contamination, then replacing those materials with presterilized materials or removing the use of those materials could eliminate the source.

6.4.2 Contamination prevention controls.

Where the source of contamination cannot be eliminated, steps should be taken to prevent contamination from that source from entering the process stream. Controls to prevent contamination from PEMMMM involve reducing the likelihood of contamination from the source, for example:

a) If **People** are identified as a source of contamination, then the use of barrier gloves, first air principles and barrier systems could prevent contamination from that source.
b) If the **Environment** is identified as a source of contamination, then controls such as closed material transfer systems, and barrier systems could prevent the contamination from that source.
c) If the **Method** or the process itself is identified as a source of contamination, then controls such as a method redesign or segregating operations could prevent contamination from that source.
d) If **Measurement** (or sampling activity) is identified as a source of contamination, then then controls such as a sampling redesign or segregating sampling and operations could prevent contamination from that source.
e) If the presence or use of **Machines** or equipment are identified as sources of contamination, then controls such as enclosing machines or equipment, and preventive maintenance could prevent contamination from this source.
f) If **Materials** are identified as a source of contamination, then controls such as decontamination, or sterilization, could prevent contamination from that source.

6.4.3 Contamination reduction and minimization controls.

Where elimination or prevention of contamination from a source cannot be achieved, then reduction of contamination from that source should be pursued. Controls to reduce contamination are those that minimize contamination from that source, for example:

a) If **People** are identified as a source of contamination, then gowning, reducing the number of people, or minimizing their activities could reduce contamination from that source.

b) If the **Environment** is identified as a source of contamination, then disinfection, HEPA filtered air flow, double or triple wrapping of sterile materials or segregation of sterile surfaces or localized air devices could reduce the contamination from that source.
c) If the **Method** or the process is identified as a source of contamination, then controls such as employing aseptic technique, or reducing the duration of the process activities could reduce contamination from that source.
d) If the **Measurement** (or sampling activity) is identified as a source of contamination, then controls such as employing aseptic technique or relocating a sampling device that disrupts first air could reduce contamination from that source.
e) If the presence or use of **Machines** or equipment are identified as sources of contamination, then controls such as cleaning of and sanitization of surfaces could reduce contamination from this source.
f) If **Materials** are identified as a source of contamination, then controls such as disinfection, controlled storage conditions, and minimizing hold times for materials can help reduce contamination from that source.

6.4.4 Contamination detection controls.

Controls to detect contamination from PEMMMM involve monitoring contamination as a result of that source, for example:

a) If contamination from **People** is identified as a source of contamination, then detection controls such as in-process oversight of aseptic technique, viable and non-viable air sampling performed during aseptic interventions, personnel gowning qualification, personnel gown and glove sampling might detect contamination.
b) If the **Environment** is identified as a source of contamination, then detection controls (e.g., differential pressure, velocity) and environmental monitoring might detect contamination.
c) If the **Method** or the process is identified as a source of contamination, then detection controls such as in-process sampling, aseptic process simulation (media fills), sterility testing, might detect contamination.
d) If the **Measurement** (or sampling activity) is identified as a source of contamination, then detection controls such as bioburden testing of sampling materials or aseptic process simulation (media fills) might detect contamination.
e) If the presence or use of **Machines** or equipment are identified as sources of contamination, then detection controls such as surface sampling or positioning of a particle counter nearby, may prove useful.
f) If **Materials** are identified as a source of contamination, then detection controls such as bioburden testing, endotoxin testing, filter integrity testing, and supplier testing might detect contamination.

6.4.5 Identify implemented controls.

Using the list of potential contamination controls, the risk assessment team shall select those to be employed for the aseptic process. Consultation with relevant stakeholders may be necessary to assist with the design of this preliminary contamination control system or identification of the existing contamination controls.

6.5 Identify Hazards and Causes Associated with Each Contamination Control

In this step, the risk assessment team shall identify hazards that can adversely affect the use or effectiveness of the contamination controls, as well as the causes for each hazard. Hazards and causes will serve as the basis for risk analysis and evaluation in the steps that follow.

6.5.1 Identify hazards associated with each contamination control.

For each contamination control, the risk assessment team shall identify all possible hazards that may render the control ineffective or result in control failure. Recall that a hazard is defined as a potential source of harm; in this case, harm is the lack of effectiveness of the contamination control. Each control will likely have multiple hazards.

Similar to the way sources of contamination were identified, hazard identification should be performed as a brainstorming exercise and should consider available knowledge and data, including but not limited to:

- Historical data associated with the process (may not be available for new processes).
- Existing risk assessments
- Personnel interviews.
- Review of vendor-supplied documentation.
- Review of literature.
- Historical experience of SMEs for similar processes.
- Stakeholder concerns.

The risk assessment team may use a variety of techniques and ask a series of questions to ensure all plausible hazards are identified for each contamination control. For example:

a) Understand how the controls are intended to work in the process.

Identify how the controls might fail to meet the objective of the step. Consider breaking down each control into parts and evaluating the parts of the control and how those parts could fail.

The team shall review what the control entails, how the control works and then document how it could fail/not work. This entails understanding of the engineering/design of the control, including materials of construction, physical construct, intended use of the control, etc.

b) Ask a series of structured questions to help identify hazards, such as:

- In what way can the control fail?
- How can we make the control fail?
- What might go wrong?
- What are the variables associated with the control?
- What are the weaknesses associated with the control?
- What conditions can contribute to control failure?
- What has our experience been?
- Has the control failed in the past?

c) Check for supporting information.

Look for control specific data like emergency work orders, PM/calibration results, vendor-supplied literature, and the like as source of control failure. Vendor recommended maintenance and spare parts lists are often help in identifying materials or parts that have a limited use-life. Refer to the ISPE Good Practice Guide: Equipment Reliability [20] for additional insight on equipment hazards and sources of information to identify equipment related hazards.

6.5.2 Identify causes of hazards associated with each contamination control.

The risk assessment team should identify the possible causes of each hazard in a brainstorming session. Where applicable, use historical data and source literature to assist with the identification of causes. To aid in the identification of the causes of a hazard, the team will consider the events that may lead to the occurrence of a hazard. For example, an equipment failure (hazard) could occur when the functional performance of a particular component is lost or reduced, and the component does not work as it was intended. Some potential causes of this failure could be due to improper design, improper operation (exposed to temperatures outside of the recommended temperature limits), failure to perform preventive maintenance (accumulated material stress due to multiple sterilization cycles), etc.

The risk facilitator may use a variety of techniques to ensure all plausible causes are identified for each hazard. For example:

a) Ask a series of structured questions to help identify the hazard and cause of hazards, such as:

- Why would this hazard occur?

- If this hazard were to occur, where might be the areas to investigate the cause?
- What conditions can contribute to this hazard?
- What has our experience been?
- What caused this hazard to occur in the past?

b) Brainstorming.

When brainstorming the causes of an equipment hazard, the team should consider the events that may lead to the occurrence of a hazard. For example, equipment failure could occur because of such causes as:

- Equipment not suitable for purpose
- Improper equipment design
- Inappropriate equipment usage
- Out of specification components
- Maintenance issues
- Wearing of parts
- Operator training issues
- Support utility issues
- Environmental issues
- Operating equipment beyond its recommended usage
- Insufficient details or unclear details in the procedure

When brainstorming the causes of a process hazard consider situations that may lead to a hazard at the different steps of the process, For example process hazards could occur during:

- Transfer of equipment and materials.
- Cleaning and sanitization or disinfection of materials
- Wrapping and unwrapping of sterilized materials
- Reading environmental monitoring media

c) Root cause analysis (RCA).

Tools such as fishbone diagrams, five whys or fault tree analysis may be used to develop a comprehensive list of potential causes. While most RCA tools eliminate causes where there is an actual failure, this risk assessment will include all potential causes of the hazard, even if they have not actually occurred [19].

6.6 Identify Possible Preventive Controls and Detection Controls for Each Hazard

This is the second iteration of identifying controls within this method, The risk assessment team has already determined the controls for the prevention and detection of contamination. Now the team focuses on the next level of controls at a granular/component level. In this step the team focuses on prevention and detection of the hazards/causes rather than the contamination controls.

6.6.1 Identify all possible preventive controls.

The risk assessment team will identify potential preventive controls that may eliminate, prevent, and/or reduce or minimize the hazard and/or its possible causes. A combination of preventive controls may be identified for a given hazard. All possible preventive controls should be listed. Examples of prevention controls are listed below:

- Eliminate the hazard by redesigning the process or item in question, perhaps by replacing a component in the process with a component that does not present the same hazard. Here, it is

important that any risks presented by the new component are assessed and managed.

- Add design or engineering controls to reduce the likelihood or frequency at which the hazard or cause might occur, such as the addition of fool-proof controls that cannot be by-passed via human error or by accidental or deliberate noncompliance with procedures.
- For equipment-related hazards, improve preventative maintenance activities or frequency of part replacement so that the probability of occurrence of the hazard may be reduced.
- For process-related hazards such as sanitization and transfer of equipment, the preventive controls could be a VHP transfer room, eliminating the transfer of equipment to a lower classified area, redesigning equipment for easier cleaning and sanitization, and visual inspection of incoming equipment.
- Ensure that effective procedures and checking activities are in place to ensure that unwanted steps and actions are avoided.
- Train operators on appropriate aseptic behaviors and specific aseptic technique and other staff to comply with procedures and policies.

Using the list of potential preventive controls, select those to be employed for the aseptic process. Consultation with relevant stakeholders may be necessary to assist with the design of this preliminary preventive control strategy or identification of the existing preventive controls.

6.6.2 Identify all possible detection controls.

The risk assessment team will identify potential detection controls that detect the hazard and/or its possible causes or consequences. Multiple detection controls may be identified for a given hazard. All possible detection controls should be listed, and may include one or more of the following:

- Detect or monitor the hazard.
- Detect or monitor the cause of the hazard.
- Detect or monitor the preventive controls.
- Detect or monitor the impact/consequence of the hazard.

Using the list of potential detection controls, the risk assessment team shall select those to be employed for the aseptic process. Consultation with relevant stakeholders may be necessary to assist with the design of this preliminary detection control strategy or identification of the existing detection controls.

Repeat this process until all preventive and detection controls are identified for all listed hazards. This is an iterative process and shall be repeated until all the controls have been identified for all the identified hazards.

6.7 Perform Risk Analysis and Risk Evaluation

6.7.1 Risk Analysis

The risk assessment team will collect and analyse all available data and evidence to determine the effectiveness of the preventive and detection controls to prevent/detect the hazard and its possible causes. Because this step requires an evaluation of the strength of evidence in support of risk ratings for each hazard, it is important to collect as much data as possible to perform the analysis.

Using the list of preventive and detection controls identified for each hazard and the collected evidence, the risk assessment team will evaluate the cumulative effectiveness of the controls to prevent and detect each hazard (and/or its causes), respectively. Each hazard will receive one rating for preventive controls and one rating for detection controls (See **section 5.5**). Risk ratings for preventive controls will be assigned as either Strong, Moderate, or Limited using the ratings and criteria listed in **Appendix A**. Risk ratings for detection controls will be assigned as either Predictive, Informative, or Delayed/Inconsistent using the ratings and criteria listed in **Appendix B**.

For each of the risk ratings outlined, the risk assessment team must come to an agreement on the risk ranking selection and document the rationale for the level selected. It is critical that all team members are aligned on the definitions of each risk rating. Each set of risk ranking criteria have definitions that apply to the respective ranking. For example, Moderate prevention control ranking is defined as "there is some evidence that the (suite of) preventive control(s) prevent the hazard, however the evidence is limited and/or the hazard may intermittently occur". Each definition is expanded to meet one of the two conditions: for initial design of the control strategy, and once the control strategy has been applied. When selecting the risk rating, the team should consider the data and evidence available and select the category that applied.

The risk assessment team will repeat this process for all identified hazards until each hazard has a specified preventive control rating and detection control rating.

6.7.2 Risk Evaluation

The risk assessment matrix for this method is used to provide a qualitative output of the risk analysis for each identified hazard. For this method the risk evaluation matrix assumes a low ('zero') risk tolerance for contamination and a quality culture that promotes continuous improvement. The matrix is weighted to encourage better preventive controls of the hazard. This evaluation enables the holistic review of the identified hazards and then supports the roll-up of the evaluation output to the contamination control level.

Using the risk matrix in Appendix C, the risk assessment team will determine the improvement for each hazard by finding the intersection of the applicable preventive control rating and detection control rating**.** The risk matrix includes details regarding potential improvement strategies to reduce the risk, based on the assigned improvement priority and the relative strength of various risk control techniques.

Improvement priority is predicated on the team using the matrices which consider the strength of the prevention and detection at predicting and / or eliminating the hazard, preventing, reducing, or minimizing the hazard or at least the ability to detect the hazard which is, by definition, upstream to the harm.

Repeat this process for all identified hazards until each hazard has a defined improvement priority.

6.8 Create a Contamination Control Risk Dashboard to Illustrate the Effectiveness of Contamination Controls

In this step the risk assessment team interprets the details of the hazard level analysis/evaluation and creates high, medium, and low improvement categories for the associated contamination control.

6.8.1 Create a Contamination Control Dashboard/Visual Model.

For each potential contamination source, and associated step in the process, prepare a visual model of the selected contamination control system from most to least effective. See **Figure 3.**

Contamination controls should be represented by positioning those that eliminate contamination nearest the contamination source, followed by those that prevent, followed by those that reduce or minimize contamination, and finally the detection mechanisms. By positioning contamination controls in order of relative effectiveness, there is an easy way to determine the purpose of the controls and the intended function (eliminate, prevent, minimize, or detect contamination).

Figure 3 shows an example of the visual model of contamination sources and controls. In the example, people are noted as the source of contamination during a manual aseptic filling process and the successive control effectiveness are shown as:

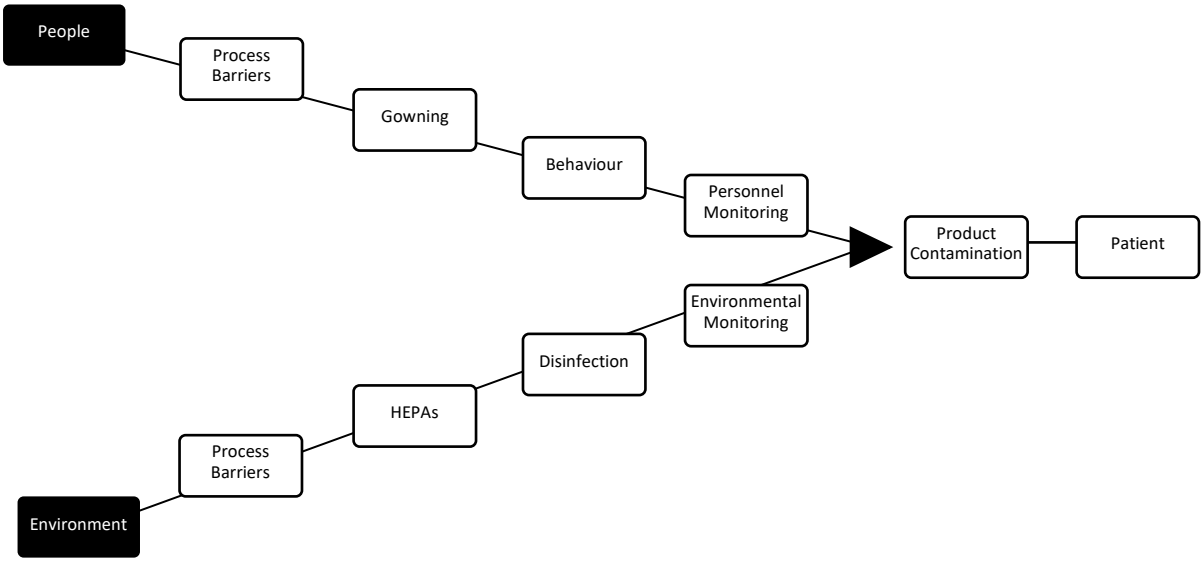
- The separation of people from the process using barrier technologies: **Prevent.**
- Gowning of personnel during set-up and operation, wearing sterile gloves when using isolator glove: **Reduce**.

- Personnel behavior appropriate for aseptic control in all their interfaces with the system during set-up and operations: **Reduce**.
- Personnel sampling: **Detect**.

Note – Because People are still part of the process in this example, there are no controls that eliminate people as a source of contamination.

This example visual model shows controls from the most to the least effective that are in place to reduce the risk of product contamination.

Figure 3: Visual Model of Contamination Controls



The contamination controls, in combination with the preventive and detection risk controls identified for associated hazards, are all part of the overall contamination control system. These controls should be communicated to the applicable stakeholders for inclusion in the contamination control system and to ensure associated vulnerabilities are broadly understood.

A Contamination Control Risk dashboard serves as a visual means of risk communication. For each contamination control, the risk assessment team may determine the overall risk by evaluating the individual improvement priorities for each hazard associated with the contamination control, as follows:

- If ***all*** hazards for a given contamination control are **green or blue,** then the contamination control is **green (low Improvement Priority/Risk of Failure)**.
- If ***all*** hazards for a given contamination control are **red**, then the contamination control is **red (high Improvement Priority/Risk of Failure)**.
- If the hazards for a given contamination control are a **combination of colors** (i.e., the hazards are not all red or green/blue, but rather have multiple separate Improvement Priorities), then the contamination control is **yellow (medium Improvement Priority/Risk of Failure) or red (high Improvement Priority/Risk of Failure),** as determined by the SME input. This determination and the associated rationale must be documented.

In general:

- Contamination controls that are low **improvement priority** (green) means that the contamination control is effective at meeting its objective (prevention, reduction/minimization, or detection). Note however that these objectives carry an "intrinsic" effectiveness from elimination being the most

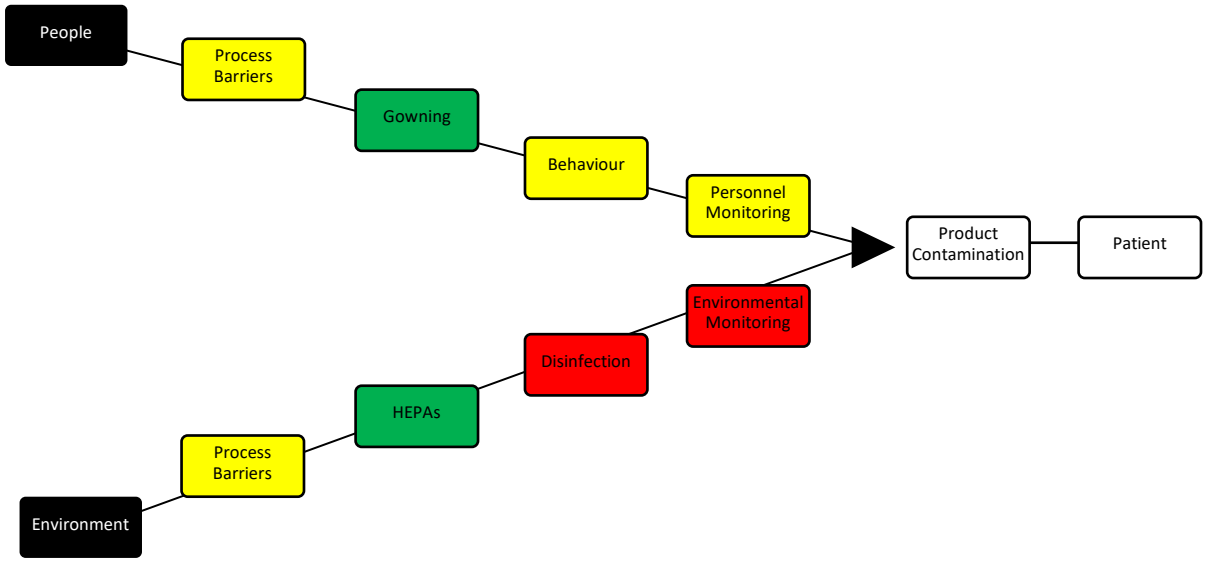
effective to detection being the least. For example, green detection-related contamination control may still only be marginally effective at controlling contamination.

- Contamination controls that are not effective(red) at meeting its objective (prevention, reduction/minimization, or detection). This control does not work. Either it requires improvement, or it is superfluous and can be eliminated and, if needed, replaced.
- Contamination controls that are medium (yellow) means that the contamination control may achieve its objective, but not reliably so.

6.8.2 Repeat this process for all contamination controls.

Update the dashboard (from "Identify contamination controls") to color code each contamination control according to its improvement priority level. This color-coded model will serve as a living means to communicate risk relative to the contamination control system. See **Figure 4** below for an example dashboard.

Figure 4: Example Dashboard



Stakeholders may elect to include additional or alternate dashboards based on risk communication needs. For example:

- The risk matrix (heat map) may be updated to include the number of risks in each box, based on the relative likelihood and detectability ratings. This can be used to prioritize capital investments and other mitigation actions.
- A Pareto chart or word cloud, which increases the size of a given word or phrase based on the frequency it is used in a sample set, may be used to demonstrate the most common causes identified for hazards stemming from contamination control failure. This can be used to assist with CAPA identification for frequent root causes, and associated risk reduction.

6.8.3 Interpret contamination control dashboard, considering both individual contamination controls and the suite of contamination controls.

The interpretation of the dashboard depends largely upon the organization's risk tolerance. The risk status of individual contamination controls as well as the cumulative effectiveness of all controls, together, should be analysed. Generally, contamination controls colored red are largely ineffective and should be targeted for reduction or-- where other, more effective controls are in place for a given source of contamination such that the source has a negligible impact-- removal from the process/control strategy. In the event multiple contamination controls are demonstrated to be marginally effective or ineffective, significant efforts are

warranted to improve the overall state of control. This is particularly true where multiple contamination controls associated with a specific source of contamination are weak—this renders the product and process vulnerable to contamination ingress via that source and deserves special attention.

For example, using the Environment source of contamination above, process barriers are demonstrated to be only marginally effective while disinfection and environmental monitoring are ineffective. HEPA filtration serves as an effective control for environmental-based contamination but is unlikely to be adequate on its own. Stakeholders should examine and communicate the importance of those controls that are effective (in this case, HEPA filters), while working to increase the effectiveness (reduce the risk) of process barriers and the disinfection process and materials used on site.

6.9 Improve Contamination and Risk Control

Using the contamination control dashboard created in the previous step, an improvement plan can be developed to include using information from the color-coded contamination control dashboard and suggested improvement strategies from the risk matrix. The risk assessment team, along with applicable stakeholders and decision makers, will develop an improvement plan that considers the combination and interaction of 'suites of controls' (i.e., groups of multiple controls that function as a unit to control risk, such as multiple preventive controls for a specific hazard and multiple contamination controls for a specific source of contamination) that are in place.

1) Each suite of controls is part of a larger, complex, and holistic system designed to prevent contamination of product.
2) Decision makers must understand the criticality of the suite of controls, identify if there are further upstream or downstream controls, and develop a strategy to prioritize continuous improvement actions.

The evaluation and implementation of improvements across systems and controls must be designed to ensure that the risk of a non-sterile unit of an aseptic process is sufficiently low. This risk assessment method enables the risk reduction strategy to be based on the strength, effectiveness, timing, and associated risk of the controls. The benefit of this method is it encourages organizations to focus on strategic improvement.

The improvement steps to consider at this step could include such options as:

1) Revisiting options to strengthen the contamination control.
2) Revisiting options to eliminate control hazards.
3) Implementing additional or different preventive hazard controls.
4) Gathering more evidence.
5) Improving detection mechanisms.

To assist with the identification of possible improvements, the risk assessment team should review the work that was performed during this method for improvements that are available but not implemented (i.e., those contamination controls and risk controls that were identified as possible solutions but not selected or in place). If there are known better preventive and detection options for the contamination control system, then the team should implement those improvements. New controls may themselves have new hazards that need to be evaluated. The team should consider this and perform the necessary risk analysis and evaluation, as needed, when making improvement recommendations.

The improvement plan should inform existing CAPA, effectiveness check, and change control procedures and contain the following information at a minimum:

- Actions to be taken.
- Rationale for this plan of action.
- Responsible personnel using a RACI approach.
- Target completion date.
- Means to check for control effectiveness.

Once the improvement has been implemented, the suite of controls will be re-evaluated, and the risk analysis is performed based on the improved controls. The risk assessment team will update the dashboard as progress is made, at the completion of actions, and/or after effectiveness checks. Effectiveness checks should be demonstrated and focus on the improved suite of controls rather than the effectiveness of any individual improvement.

It is important to keep management and other stakeholders aware and supportive of the improvement plan. Improvements can have consequences that affect other areas of concern (e.g., financial, safety, production times), and the team will need to map out and identify stakeholders and identify risks to the implementation of identified improvements. The quality organization should also track delayed and overdue improvements plans and communicate any lagging contamination control improvement activities to management.

6.10 Risk Review to Maintain the Risk Assessment

The risk assessment and contamination control risk dashboard are living documents and are intended to be maintained over the product and process lifecycle. Organizations should have internal policies and procedures to periodically review and ensure that the risk assessment remains current and control strategies continue to be effective. Those procedures should define both a time-based and event-driven risk review processes. Time-based review should be scheduled based on the overall risk of the process. As such, higher risk processes will be reviewed more frequently than lower risk processes. The full scope of the risk assessment should be reviewed based on time(periodic) or based on occurrence of events. A gap assessment of the current state of the contamination control system against all changes that have occurred since the last revision will help the organization to keep this process current and relevant.

Organizations with a mature Quality Risk Management program, as supported by significant historical evidence, may opt to forgo time-based risk reviews, and use only the event-driven risk review process. Organizations with less mature Quality Risk Management programs should employ both time-based and event-driven risk reviews. As opposed to time-based reviews, event-driven reviews should occur whenever trends indicate that an update is warranted. Additional triggers that may be considered include facility or equipment updates; failures within a facility or equipment; Investigations such as OOT, OOS, or Complaints; or changes to the process, critical equipment, or components. It is also important to update the risk assessment whenever new information or knowledge becomes available.

Implemented improvements to the contamination control system, changes to the contamination control system, evidence of control effectiveness or ineffectiveness, or newly identified hazards should also be considered as relevant triggers. The organization’s change control system will benefit from defining in advance a change scope and criticality that should trigger a review and revision of the risk assessment. Such criteria may define a partial scope of revision to the strategy, focused on the portion of the system that is known to have changed in the associated change control. The risk assessment may be repeated in full or in part based on these changes and knowledge gained.

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Appendix A: Preventive Controls Ratings and Criteria

Rating	Meaning	Criteria	
		For initial design of control strategy	**Once control strategy has been applied**
Strong	There is sound scientific evidence that the (suite of) preventive control(s) reliably prevent the hazard.	Body of evidence to support the effectiveness of the suite of controls at preventing the hazard in a comparable situation consists of a combination of the following: • Peer reviewed literature. • Ppublished case studies. • Vendor studies. • Internal studies. • Standards. • Technical reports. • Other similar references. Effectiveness of the claim is supported by the number and quality of references. These are: • data-driven; • grounded in the scientific method (e.g., sound experimental design), **and** • scientifically valid & contemporaneous.	Claim of effectiveness is supported by: • Direct qualification/validation study results; • Statistically significant evidence of current and historical performance (instances of the hazard are rare or absent), **and** • Evidence that the suite of controls is maintained in the validated state.
Moderate	There is some evidence that the (suite of) preventive control(s) prevent the hazard, however the evidence is	• Manual, procedural, or personnel-reliant preventive controls with supporting evidence of effectiveness.	• Current and historical performance of controls exhibits some variability. • Intermittent instances of the hazard. • Unreliable performance. • Statistical analysis is available.

	limited and/or the hazard may intermittently occur.	• Effectiveness claim based on precedence ("industry standard" or "best practice") in the absence of multiple, high quality, peer reviewed supporting evidence. • Suite of controls can be qualified but may have inherent potential for variability. • Control effectiveness may vary in response to changing conditions. • Suite of controls are effective but lack redundancy.	• Some instability noted. • Outliers present.
Limited	There is minimal or no evidence that the (suite of) preventive control(s) reliably prevent the hazard, or the evidence suggests the controls are variable in performance, incomplete, and/or unreliable. If predictive detection controls are in place, this rating does not apply.	Minimal to no evidence that the suite of controls is effective at preventing the hazard. Evidence that the suite of controls is effective is of poor quality, and may be: • Not data driven. • Grounded in poorly designed experiments. • Not scientifically valid. • Out-dated. • Anecdotal evidence; could be effective, unable to directly verify. Claims of effectiveness are based on opinion without supporting evidence. • "Best we can do at this time."	• Current and historical performance varies with no assignable cause. • Recurring instances of the risk scenario. • Limited data set available; data set is not statistically significant, data/samples may not represent actual conditions (e.g., time-based, geographic, personnel, or other meaningful differences in conditions exist between data collection conditions and use conditions) • Data set is unstable. Significant outliers. • "This is how we've always done it."

Appendix B: Detection Mechanisms Ratings and Criteria

Rating	Meaning	Criteria		Examples include but are not limited to
		For initial design of control strategy	Once control strategy has been applied	
Predictive	Suite of detection mechanisms detect precursor(s)/ leading indicator(s) to enable preventive or defensive action to avoid the hazard	Mechanism capable of detecting a leading indicator or precursor of the hazard with enough time to intervene before the hazard occurs, and Controls are reliable by design (e.g., automated controls that can be qualified to detect a leading indicator of the hazard), and Must be actionable, enabling action to be taken to keep the hazard from occurring	Mechanisms are qualified to detect a leading indicator or precursor of the hazard with enough time to intervene before hazard can be realized, and Suite of detection controls includes a defined action plan that will be invoked to prevent the risk from occurring in the event the detection control demonstrates a potential loss of control	Automated, predictive detection systems that have been qualified/ validated (e.g. vibration) Predictive trend analysis (i.e. seeking and acting upon indicators of drift) Monitoring isolator glove use frequency and intervention types as a predictor of wear and eventual damage Differential pressure across filter membrane (as opposed to PUPSIT or post use integrity testing) Sterilization/sanitization cycle times could indicate potential leaks
Informative	Suite of detection mechanisms provide information to detect the hazard with enough time to avoid the impact	Mechanisms capable of detecting the hazard with enough time to intervene before the impact occurs, and Mechanisms are reliable by design (e.g., controls that can be qualified to detect the hazard), and Must be actionable, enabling action to be taken to keep the impact from occurring	Mechanisms are qualified to detect the hazard with enough time to intervene before impact is realized, and Suite of detection mechanisms includes a defined action plan that will be invoked in the event the detection mechanism demonstrates the hazard has occurred	Pre-use glove integrity testing and visual inspection to identify a glove breach prior to initiating production, along with a requirement to replace and test the glove before production begins. Testing filter integrity prior to initiating sterilizing filtration, along with a requirement to discard non-integral filters and use a different, integral filter in the sterilizing filtration process. Detection of a leak in the isolator prior to initiating production, along with a requirement to remediate the leak and re-

				sanitize the isolator interior prior to initiating production.
Delayed / Inconsistent	Suite of detection controls provides information with insufficient time to avoid the impact, AND/OR are not confirmed to be effective	Risk control capable of detecting the hazard without enough time to intervene before the impact occurs, or Risk control detecting impact, or Variable detection controls, or Detection may happen by chance alone, or Detection depends solely upon human factors, such as personnel competence or diligence.		Training/procedural controls Product run-specific environmental monitoring results Post-production personnel monitoring End of use integrity tests Sterility testing Visual inspection of finished product

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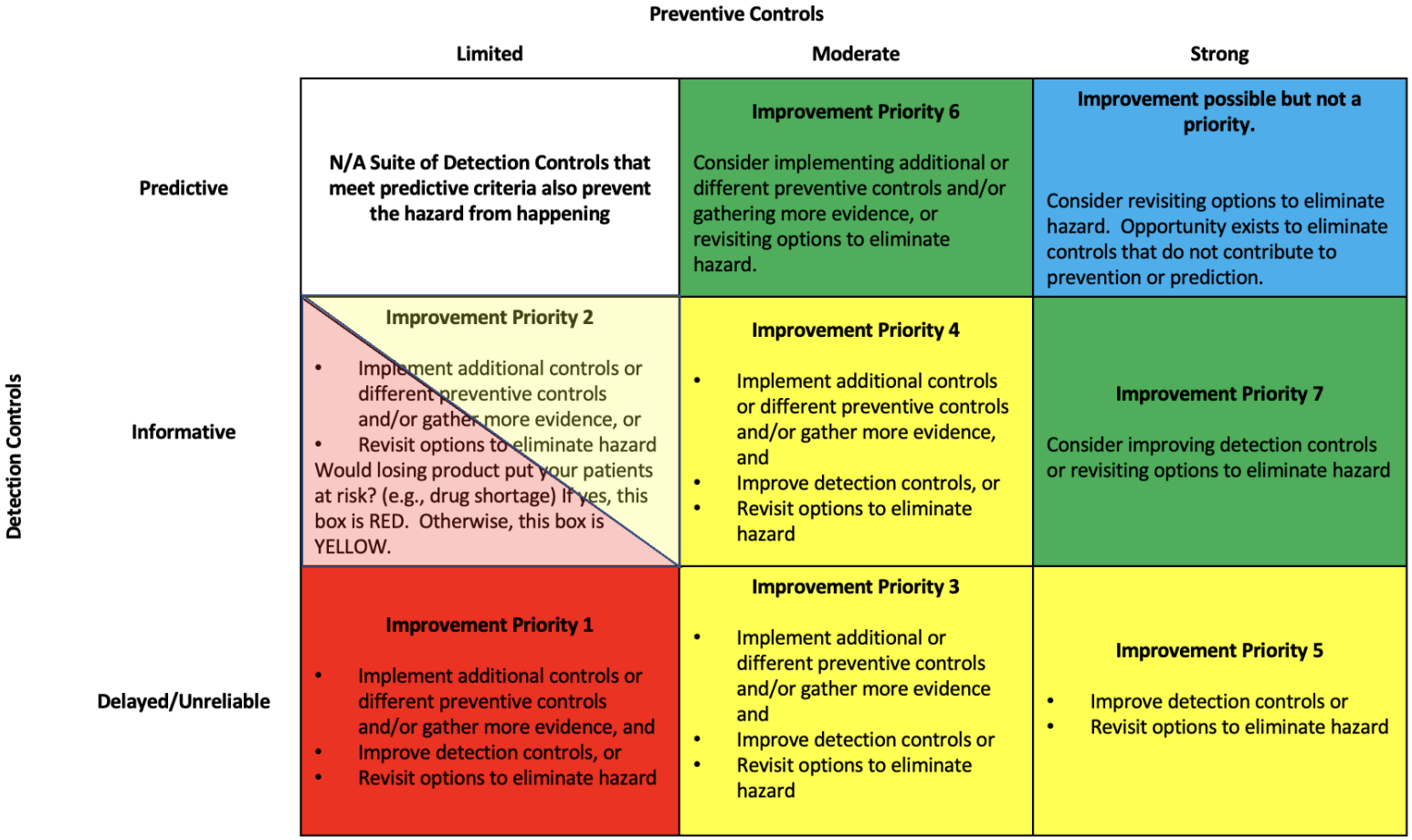
Appendix C: Dashboard



Detection Controls	Preventive Controls: Limited	Preventive Controls: Moderate	Preventive Controls: Strong
Predictive	**N/A Suite of Detection Controls that meet predictive criteria also prevent the hazard from happening**	**Improvement Priority 6** Consider implementing additional or different preventive controls and/or gathering more evidence, or revisiting options to eliminate hazard.	**Improvement possible but not a priority.** Consider revisiting options to eliminate hazard. Opportunity exists to eliminate controls that do not contribute to prevention or prediction.
Informative	**Improvement Priority 2** • Implement additional controls or different preventive controls and/or gather more evidence, or • Revisit options to eliminate hazard Would losing product put your patients at risk? (e.g., drug shortage) If yes, this box is RED. Otherwise, this box is YELLOW.	**Improvement Priority 4** • Implement additional controls or different preventive controls and/or gather more evidence, and • Improve detection controls, or • Revisit options to eliminate hazard	**Improvement Priority 7** Consider improving detection controls or revisiting options to eliminate hazard
Delayed/Unreliable	**Improvement Priority 1** • Implement additional controls or different preventive controls and/or gather more evidence, and • Improve detection controls, or • Revisit options to eliminate hazard	**Improvement Priority 3** • Implement additional or different preventive controls and/or gather more evidence and • Improve detection controls or • Revisit options to eliminate hazard	**Improvement Priority 5** • Improve detection controls or • Revisit options to eliminate hazard

Appendix D: Case Study

Case Study Background

To provide an example and illustrate the use of the described aseptic processing risk management method, the activity of installing a sterilized stopper hopper into a barrier system with accessible doors, an existing process, was analyzed. This case study assesses the existing contamination prevention and detection controls and can be used to determine if any changes to the current process would improve the contamination control of the stopper hopper installation process. This example is for illustrative purposes only and not exhaustive of the full scope that would be addressed by the risk assessment team.

Each step of the risk assessment process is outlined below.

STEP ONE (see section 6.2): Initiate the QRM Method for the Aseptic Processes

The risk assessment team began by performing a Gemba walk to observe the process in real time. The team then created a process flow diagram to outline the process steps associated with the stopper hopper (**Figure 1a**) and drafted a narrative description of the process (**Table 1a**). For the purposes of this case study, the process step "Operator A installs hopper, inspects and removes bonnet" (Step 8 in Table 1) will serve as the scope of the assessment. **Table 1a** provides a narrative description of the process.

Figure 1a: Visual Map (Process Flow Diagram) of Stopper Hopper Handing, Installation and Addition of Stoppers

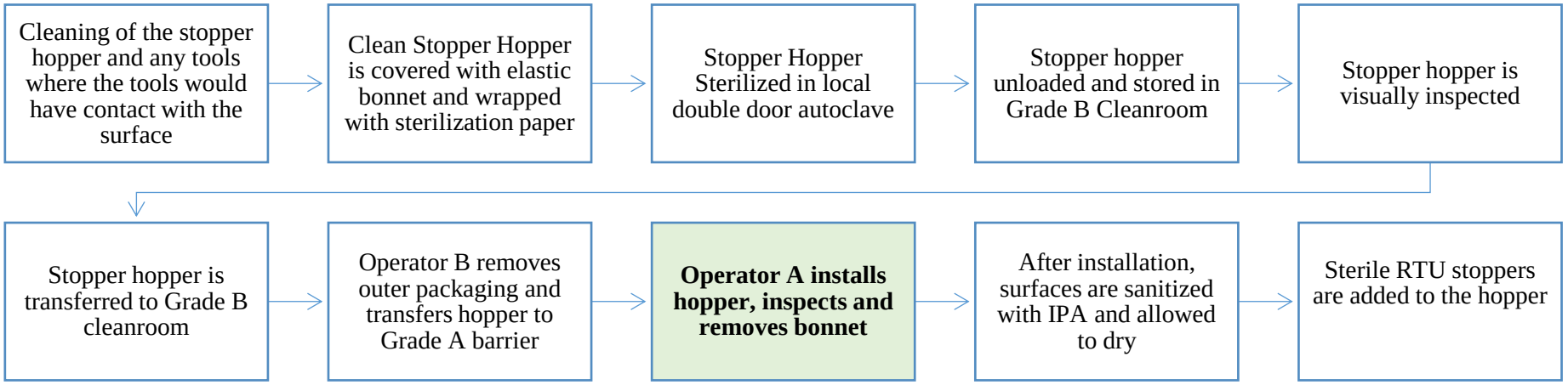


Table 1a: Stopper Hopper Installation Process Flow Narrative

Background information	This process occurs in a pharmaceutical fill and finish facility with Grades of A, B, C & D. Operators follow gowning & gloving procedures while entering the clean zones and while handling the stopper hoppers. The filling line is enclosed in a barrier, and interventions are open-door interventions.

Step	Process and Equipment description
1	Stopper hoppers and required installation tools/parts within the qualified dirty hold time are cleaned and thermally dried in a semi-automated washing unit located in a Grade C "washroom." The following parameters are in place: a) Pharmaceutical grade construction of the stopper hopper. b) WFI final rinse. c) HEPA filtration. d) Validated cycle.
2	Cleaned and dried stopper hoppers and tools are stored covered on the "clean side" of the Grade C washroom before wrapping & preparing the items at a designated workspace in a Grade C environment physically segregated from "dirty" equipment and tools. a) Operator(s) in Grade C garb don sterile gloves for the wrapping & packaging procedure. b) Operators are trained to follow a wrapping & packaging procedure using approved packaging materials. c) Sterile IPA is used to periodically disinfect gloved hands during packaging. d) Wrapping & Packaging consists of a Tyvek® primary elastic bonnet type covering the exposed inner surfaces of stopper hopper, and pouches for tools and/parts; secondary sterilization wrapping paper and autoclave tape. e) Stainless Steel work surface cleaned and disinfected with sterile IPA before wrapping process begins. f) Holding time following cleaning and prior to the qualified and specified autoclaving procedures.  Stopper Bowl Covers | STERIS (sterislifesciences.com)
3	Stopper hoppers and tools are terminally moist heat sterilized (the cycle is qualified and validated per ISO 17665; with an approved loading pattern and cool down stage) in a pass-thru autoclave.

Step	Process and Equipment description
4	After autoclaving and appropriate cool down, the stopper hopper is transferred and stored in a Grade B cleanroom environment. a) Operator(s) places packaged hopper and tools/parts onto a dedicated cart. b) Transfer from pass-thru autoclave into Grade B cleanroom by AP Operator(s) in Grade B garb. c) Stopper hoppers and tools/parts are stored in Grade B cleanroom (Adjacent to aseptic processing cleanroom). d) Sterile hold time following autoclave process is qualified.  DuPont™ Tyvek® Autoclavable Stopper Bowl Covers, Keystone Cleanroom Products | VWR
5	AP Operator visually inspects secondary packaging for any package integrity issues, defects, damage (based on training, written inspection procedure). This includes photographs of types of damage and defects.
6	Items are moved into the aseptic processing Barrier System Filling Unit within a specified time limit. a) Following storage, immediately prior to aseptic processing set up of the Barrier System Unit, AP Operator(s) visually inspect secondary packaging for any package integrity issues (based on training and written inspection procedure). b) The stopper hopper and required tools/parts are placed on disinfected cart and transferred to Grade B aseptic processing cleanroom.
7	Two operators participate in the transfer of the stopper hopper assembly and tools/parts into the Grade A stopper station within the filling barrier ("A" and "B" Operators), "A" person performs all interventions within the Barrier System Unit (BSU), according to detailed written procedures. a) Operators will don gloves, and the "A" Operator will don sterile sleeves. b) Operator "B" opens the door to the Barrier System Unit and sanitizes the area in the barrier dedicated to the stopper hopper. c) Operator "B" lines up a dedicated barrier transfer cart. Operator "A" removes the secondary packaging using sterile forceps and gloved hands and removes the outer secondary packaging at the interface of the Grade B cleanroom and the interior of the Barrier System Unit (Grade A) while pushing the stopper hopper into the barrier. d) Operators visually inspect the inner packaging for package integrity issue(s) and damage according to written procedures.
8	The stopper hopper is installed. a) Operator "A" completes the above interventions in the BSU with only hands and forearms entering the Unit (head and torso remains outside BSU). b) Operator "A" removes the elastic covers from stopper hopper with sterile forceps to avoid the breaking of first air above the hopper or direct contact with exposed surfaces by the aseptic processing operator, using aseptic technique as per written procedures. The elastic cover is placed in a wrapper receiving bin, placed near the door of the barrier. c) The stopper hopper is manually positioned and then secured using sterile tools. d) Immediately after installation, spray the stopper hopper area with sterile IPA spray (or use IPA moistened wipes) to surface disinfect all contacted surfaces. e) Close BSU doors.

Step	Process and Equipment description
9	Before stoppers are added, a specified time is given for the IPA to dry and unidirectional air flow in the BSU to "wash away" potential contaminants that risk being introduced from the disruption of laminar airflow (personnel movement) and/or direct personnel contact with stopper hopper primary package and/or exposed surfaces.
10	Moist heat terminally sterilized (prewashed and siliconized; qualified) stoppers (validated sterilization process) are stored in covered bins and transferred through Grade B cleanroom environments to the Barrier System Unit. a) Operator(s) disinfect hands and sleeves with sterile IPA (RTU- Ready to Use). b) Remove outer layer of packaging (secondary) at the interface of the Grade B cleanroom and the interior of the Barrier System Unit (Grade A) using the sterile scissors (moist heat terminal sterilization – validated, inspection of packaging for damage). c) Open and disinfect surface of mail slot with Sterile IPA. d) Using sterile scissors – cut open top of stopper primary bag at interface with opened mail slot. e) Wearing sterile sleeves Operator "A" pour stoppers down mail slot shoot into the stopper hopper – Operator "A" does not enter the BSU with hands.  https://youtu.be/RWNq_pIwmcc?si=wu75D7Iqfz50hASg www.rnaautomation.com

The risk assessment team then gathered and reviewed data indicative of process performance, which included but was not limited to the following:

A. Aseptic Processing Trends: Contamination Control Performance Record.
   1) Timeframe: most recent 36-month period.
   2) Production Trends: 120-135 batches produced per year (one product formulation, two vial sizes); no aborted runs.

B. Media Fill Trends: 6 Aseptic Process Simulations (media fills) – >10,000 units per media fill.
   1) 1 media fill failure – 5 positive media filled units; isolate ID: Micrococcus luteus; also isolated from AP Operator "A" sleeved forearm.
   2) The result of contamination ingress has included a media fill failure with a most probable root case being operator error.

C. EM data and trends.
   1) Grade B gown room:
      - 2 instances of an exceeded action limit (15 CFU per surface*; Micrococcus luteus*; 21 CFU on surface – mixed culture of Gram (+) cocci.
      - 5 instances where the alert level was exceeded (no identifications were made, as mold colony was found on one surface sampled) in a total of 152 EM sampling events Grade B cleanroom where BSU is located.

- 3 instances where an alert level was exceeded (3, 3 and 8 CFU/surface sampled) – work surface samples only (*Micrococcus luteus, Staphylococcus epidermidis, Bacillus subtilis, Cladosporium allii),* and no instances where the action level was exceeded in a total of 152 EM sampling events.

D. Grade A at stopper hopper location microbial recovery
   1) During Set Up – 2 instances where the viable air sample was positive – 1 CFU, *Micrococcus luteus*, 2 CFU, *Staphylococcus epidermidis* in 152 EM sampling events.
   2) During Filling – 2 contaminated settle plates (1 CFU each, *Micrococcus luteus*) in 152 sampling events.

E. Personnel Monitoring Results
   1) Operator "A" – one instance of a single colony of Micrococcus luteus isolated from AP Operator "A" sleeved forearm (isolated during media fill stopper set up intervention) – investigated, retraining conducted Operator "B" – no exceeded action levels; six instances of exceeded alert levels (isolated *Micrococcus luteus, Staphylococcus epidermidis, Burkholderia cepacian*).

F. Additional Performance Indicators Considered
   1) 0/378 sterility test positive results, 0/378 endotoxin positive results; 0/378 particulate contamination results.
   2) No primary or secondary packaging defects found – packaged and sterilized hoppers and stoppers (500 units per bag).
   3) No autoclave cycle failures or deviations.
   4) No equipment washer/drier failures or deviations.
   5) Two instances of failure to comply with cleaning and disinfection procedures in the Grade B cleanroom where the BSU is located.
   6) Supervisor observations of aseptic processing (from viewing window and camera): several instances of aseptic technique deficiencies during routine interventions by AP Operator "A" and "B"; retraining given.

The team's analysis of the process and related data revealed that personnel and material transfer activities have been sources of contamination recovered inside the Grade A barrier system.

STEP TWO: Identify the Possible Sources of Contamination (see section 6.3)

The risk assessment team then identified and documented potential sources of contamination while installing the stopper hopper (an excerpt of which is provided in **Table 2a**). The PEMMMM model was used to methodically brainstorm all potential sources—the specific PEMMMM category is only meant to assist in comprehensive identification of sources.

Table 2a: Sources of Contamination During Stopper Hopper Installation

PEMMMM Category	Potential Sources of Contamination
People	• Operators in Grade B Gowning. • Aseptic technique during manual operations.
Environment	• Barrier System Aseptic processing cleanroom- air ingress.
Method (Manufacturing process)	• Open door intervention (using sterile tools). • Sleeve donning and sanitization. • IPA wipe down; length of time the door is open. • Unwrapping and wipe down of the surfaces of material being transferred. • Transfer of material into the barrier.
Measurement (Sampling activities)	• EM (during installation) and gloves and sleeved forearms monitoring. • Swab sampling of the Surfaces of the packs, being transferred into the barrier.
Machines/ Equipment	• Barrier system with doors for interventions. • Tools exposed to Grade B.
Materials (raw/starting materials, components, consumables, etc.)	• Sterilized and stored wrapping. • Sterilized and stored IPA and wipes, and spray bottles. • IPA exposed to Grade B.

The risk assessment team agreed that while personnel and material transfer related sources had historically contributed to contamination, as noted during the process and data review from Step One, additional sources of contamination were also present that may not have led to a contamination event in the past. Because there were multiple potential sources of contamination identified for this process step, the team agreed that the process is vulnerable, and the application of risk management and contamination control strategies would be useful to protect product quality and patient safety.

STEP THREE: Identify Contamination Controls (see section 6.4)

The risk assessment team then brainstormed possible contamination controls for the sources of contamination identified in Step Two. In this step, the team sought to identify possible ways that the source of contamination could be eliminated, prevented, minimized, or reduced, and detected. **Table 3a** provides an excerpt of this example and outlines possible contamination controls for installing the stopper hopper.

Table 3a: PEMMMM Contamination Controls for Stopper Hopper Installation

Source of Contamination (PEMMMM) and type of contamination control.	**Contamination Control Description.**
People	
Contamination controls that could **eliminate** the source of contamination.	• Eliminate interventions by a redesign of the filling line eliminating the need for a stopper hopper.
Contamination controls that could **prevent** contamination.	• Use of strategically positioned glove ports to allow personnel to install hopper without any direct contact or open door.
Contamination controls that could **reduce or minimize** contamination.	• Slow movement of personnel (detailed aseptic technique). • Grade B Gowning. • Additional sterile sleeves and gloves. • Limit time of open-door intervention.
Contamination controls that could **detect** contamination.	• EM of Grade A during installation at hopper / stopper station. • Continuous airborne particle monitoring. • Continuous viable air monitoring. • Cameras to observe personnel activities (fixed, limited view). • Personnel monitoring post intervention.

Table 3a: PEMMMM Contamination Controls for Stopper Hopper Installation

Environment	
Contamination controls that could **eliminate** the source of contamination.	• Closed door interventions with transfer carts and glove ports would eliminate people from entering the Grade A space while installing the stopper hopper. • Installation of an Isolator.
Contamination controls that could **prevent** contamination.	• Barrier between stoppering and filling. • Barrier between stoppering and capping. • Barrier HEPA filtration. • Surrounding Clean room HEPA filtration.
Contamination controls that could **reduce or minimize** contamination.	• Barrier with doors in Grade B cleanroom.
Contamination controls that could **detect** contamination.	• EM Trends. • Continuous viable air monitoring.
Method (Manufacturing Process)	
Contamination controls that could **eliminate** the source of contamination.	• Grade A continuity for materials. • Closed door interventions with transfer carts and glove ports would eliminate people from entering the Grade A space while installing the stopper hopper. • Installation of an Isolator System. • Installation of a restricted access barrier system.
Contamination controls that could **prevent** contamination.	• Sanitizing and removing the inner wrapping once the Barrier is closed would prevent surface contamination of the stopper hopper.
Contamination controls that could **reduce or minimize** contamination.	• Inner wrapping remains in place to cover sterilized hopper surface during installation. • Minimize contamination by donning sterile gloves and sleeves prior to entering the -Grade A space during installation. • Minimizing the size of door opening space needed for installation of the stopper hopper. • Using sterile tools to remove the final wrapping once stopper hopper is in place.
Contamination controls that could **detect** contamination.	• Dynamic smoke studies that verify that Grade B air does not enter the Grade A space during the installation. • Continuous viable air monitoring.
Measurement (Sampling activities)	
Contamination controls that could **eliminate** the source of	• Sterilized settle plates.

Table 3a: PEMMMM Contamination Controls for Stopper Hopper Installation

contamination.	• Closed system for active viable air monitoring. • Automated/robotic system for sampling.
Contamination controls that could **prevent** contamination.	• Mail slot for settle plates.
Contamination controls that could **reduce or minimize** contamination.	• Sterile gloves and sleeves. • Aseptic technique to add EM materials.
Contamination controls that could **detect** contamination.	• Trends of EM and pattern assessments. • Optimizing and documenting of aseptic technique with operator training. • Fixed Cameras for monitoring people behavior.
Machines/ Equipment	
Contamination controls that could **eliminate** the source of contamination.	• Closed RABS with glove ports, Isolator. • Tool sterilization with package integrity. • Port transfer of sterile tools to sterile holder.
Contamination controls that could **prevent** contamination.	• HEPA filtered unidirectional Airflow minimizes contamination in opened barrier. • Glove port manipulation of tools. • In closed RABS (no open-door interventions).
Contamination controls that could **reduce or minimize** contamination.	• Barrier cleaning and sanitization. • Sanitization of tools.
Contamination controls that could **detect** contamination.	• Visual inspection of equipment. • EM Trends. • Continuous viable air monitoring. • Differential pressure monitoring across HEPA filters.
Materials (raw/starting materials, components, consumables, etc.)	
Contamination controls that could **eliminate** the source of contamination.	• Installation of an Isolator or RABS glove ports. • IPA validated sterilization. • Materials sterilized in autoclave via validated process.
Contamination controls that could **prevent** contamination.	• Grade A continuity for movement of materials. • Closed door interventions with transfer carts and glove ports would eliminate people from entering the Grade A space while installing the stopper hopper.
Contamination controls that could **reduce or minimize** contamination.	• Grade B Gowning practices. • Proper aseptic technique for intervention.

Table 3a: PEMMMM Contamination Controls for Stopper Hopper Installation

	• Sanitization of surfaces that enter or are an interface between Grade A from Grade B. • Barrier doors in Grade B cleanroom. • Design considerations for the packaging. • Fresh sterilized IPA used. • Sterile gloves and sleeves donned.
Contamination controls that could **detect** contamination.	• Dynamic smoke studies that verify that Grade B air does not enter the Grade A space during installation. • Trends of bioburden monitoring. • Optimizing and documenting of aseptic technique with operator training. • Cameras. • Inspection of operator gloves for leaks and holes.

The risk assessment team then determined which of the possible contamination controls were actually in place. This subset of contamination controls is shown in **Figure 2a**. In some cases, a single control is utilized to control contamination from multiple sources (do we have controls for every source?).

Figure 2a: **Contamination Controls In Place**

	People	Environment	Method	Measurement	Machine	Materials
Eliminate	None.	None.	None.	• Sterilized settle plates. • Closed system for active viable air monitoring.	None.	• Materials sterilized in autoclave via validated process. • IPA validated sterilization.
Prevent	None.	• Barrier between stoppering and filling. • Barrier between stoppering and capping. • Barrier HEPA filtration. • Surrounding cleanroom HEPA filtration.	• Inner wrapping remaining in place to cover sterilized hopper surface during installation.	• Mail slot for settle plates.	• Unidirectional 'first air' airflow that washes over the transfer area and into the Grade B.	None.

	People	Environment	Method	Measurement	Machine	Materials
Minimize/ Reduce	• Slow movement of personnel detailed aseptic technique. • Grade B gowning. • Additional sterile sleeves and gloves. • Limit time of open-door intervention. • Risk-based design of intervention with aseptic technique and associated operator training.	• Barrier with doors in Grade B cleanroom.	• Reduced transfer and exposure times. • Risk-based design of intervention with aseptic technique and associated operator training. • Sterile gloves and sleeves donned at barrier interface. • Fresh IPA used.	• Aseptic technique to add EM materials. • Sterile gloves and sleeves donned at barrier interface.	• Barrier cleaning and sanitization.	• Fresh IPA used.

	People	Environment	Method	Measurement	Machine	Materials
Detect	• EM of Grade A during installation at hopper / stopper station. • Continuous airborne particle monitoring. • Continuous viable air monitoring. • Cameras to observe personnel activities (fixed, limited view). • Personnel monitoring following this intervention. • Optimizing and documenting aseptic technique/ operator training.	None.	• Dynamic smoke studies that verify that Grade B air does not enter the Grade A during the installation.	• Cameras to observe personnel activities (fixed, limited view). • Trends of EM and pattern assessments. • Optimizing and documenting aseptic technique/operator training.	• Continuous airborne particle monitoring. • Continuous airborne particle monitoring. • Trends of EM and pattern assessments. • Visual inspection of equipment.	None.

Following the exercise, the risk assessment team identified gaps in the contamination control system. Specifically, the team noted that there were no contamination controls that eliminated or prevented contamination stemming from personnel—the current design of the process allowed only for minimization of personnel-related contamination. Given that the team had identified historical challenges with personnel-related contamination and have identified a possible contamination control to prevent this source ("Prevent interventions. Use of strategically positioned glove ports to allow personnel to install hopper without any direct contact or open door" as listed in Table 3), the team agreed that escalation of this gap to decision makers was warranted, along with a recommendation to pursue a capital product to upgrade the line. Once this risk communication was complete, the team acknowledged that identification of hazards and establishment of an interim control strategy while the capital project was being pursued was in order, and therefore continued through the remaining steps of the risk assessment process.

STEP FOUR: Identify Hazards and Causes Associated with each contamination control (Section 6.5)

For each of the contamination controls currently in place, the risk assessment team identified hazards and causes. See **Table 4a** for an excerpt of the team's work. In this example, two contamination controls were assessed and a few of the possible hazards and causes were identified:

- P3) Unidirectional airflow that washes over the transfer area and into the Grade B area to reduce contamination (Source of contamination is identified as Machine).
- M5) Inner wrapping remaining in place to cover sterilized hopper surface during installation. (Source of contamination is identified as Method).

Table 4a: Contamination Control Hazards and Causes

Contamination Control	Hazard (i.e., way(s) the contamination control may fail)	Cause (i.e., causes of the hazard)
Unidirectional airflow that washes over the transfer area and into the Grade B area to reduce contamination.	Airflow over transfer area is below the acceptable rate.	Barrier system does not maintain appropriate pressure.
	Air flow/velocity is below the acceptable rate when doors are open resulting in ingress of contaminants from Grade B cleanroom during open door interventions.	Improper balancing, the flow set in the barrier is set fine for the closed barrier, but too low for the door opening.
Inner wrapping remaining in place to cover sterilized hopper surface during installation.	Wrapping: Inner wrapping moves and exposes stopper contact area).	Mishandling the bowl with cover by operator NOTE: manual operation by operator.
	Outer wrapping was removed too early.	Operator removes the wrapping prior to process initiation.

STEP FIVE: Identify Possible Preventive Controls and Detection Controls for Each Hazard (Section 6.6)

The risk assessment team then examined the contamination control hazards and causes of the hazards and documented prevention and detection controls are in place for each. **Table 5a** shows the results of this step for the selected example.

Table 5a: Prevention and Detection Controls

Contamination Control	Hazard (i.e., way(s) the contamination control may fail)	Cause (i.e., causes of the hazard)	Prevention controls in place for hazards/causes	Detection controls in place for hazards/causes
Unidirectional airflow that washes over the transfer area and into the Grade B area to reduce contamination.	Airflow over transfer area is below the acceptable rate when doors are closed.	Barrier system does not maintain appropriate pressure.	Maintenance program of barrier system.	Alarms. Active air monitoring. Air flow detectors. Trended data over time (lagging indicator).
	Air flow/velocity is below the acceptable rate when doors are open resulting in ingress of contaminants from Grade B cleanroom during open door interventions.	Improper balancing, the flow set in the barrier is set fine for the closed barrier, but too low for the door opening.	Velocity in the barrier versus the surrounding room is designed to maintain unidirectional air flow. Smoke studies performed during design phase.	Velocity is measured during manufacturing in real time (leading indicator). Trended data over time (lagging indicator).
Inner wrapping remaining in place to cover sterilized hopper surface during installation.	Wrapping: Inner wrapping moves and exposes stopper contact area.	Mishandling the bowl with cover by operator. NOTE: manual operation by operator.	Wrapper is designed for the bowl under assessment with a fit for purpose wrapper. Operator training.	Visual inspection at beginning and end of stopper installation.
	Outer wrapping was removed too early.	Operator removes the wrapping prior to process initiation.	Operator training.	Visual inspection at beginning and end of stopper installation.

STEP SIX: Perform Risk Analysis and Risk Evaluation (section 6.7)

The risk assessment team then rated the prevention and detection controls using the criteria outlined in **Appendix A** and **Appendix B**, as informed by the data and evidence gathered during Step One. The ratings were then compared to the matrix in Appendix C to determine the improvement priority. **Table 6a** illustrates the results of this step for the selected example.

Table 6a: Contamination Control Risk Analysis and Risk Evaluation

Contamination Control	Hazard (i.e., way(s) the contamination control may fail)	Cause (i.e., causes of the hazard)	Prevention controls in place for hazards/causes	Detection controls in place for hazards/causes	Prevention Controls Ranking and rationale	Detection Control Ranking and rationale	Improvement Priority
P3) Unidirectional airflow that washes over the transfer area and into the Grade B area to reduce contamination.	Airflow over transfer area is below the acceptable rate.	Barrier system does not maintain appropriate pressure.	Maintenance program of barrier HVAC.	Alarms. Active air monitoring. Air flow detectors trended data over time (lagging indicator).	**Limited** Rationale: Maintenance is a manual process. As part of this assessment, a review was performed of the frequency, replacement of parts, change control, training, and qualification of maintenance personnel. There have been gaps (historical deviations) in HVAC maintenance.	**Informative** Rationale: Barrier HVAC - fan velocity with audible and visible alarm when lose velocity.	**Improvement Priority 2**
	Air flow/velocity is below the	Improper balancing, the flow set in the barrier is set fine for	Velocity in the barrier versus the	Velocity is measured during manufacturing	**Strong** Rationale:	**Predictive** Rationale:	**Improvement possible but**

Contamination Control	Hazard (i.e., way(s) the contamination control may fail)	Cause (i.e., causes of the hazard)	Prevention controls in place for hazards/causes	Detection controls in place for hazards/causes	Prevention Controls Ranking and rationale	Detection Control Ranking and rationale	Improvement Priority
	acceptable rate when doors are open resulting in ingress of contaminants from Grade B cleanroom during open door interventions.	the closed barrier, but too low for the door opening.	surrounding room is designed to maintain unidirectional air flow. Smoke study performed (informs the design).	in real time (leading indicator). Trended data over time (lagging indicator).	IQ OQ PQ in place for barrier design is effective.	Automated, predictive detection systems that have been qualified/ validated.	**not a priority.**
M5) Inner wrapping remaining in place to cover sterilized hopper surface during installation.	Wrapping: Inner wrapping moves and exposes stopper contact area).	Mishandling the bowl with cover by operator. NOTE: manual operation by operator.	Wrapper is designed for the bowl under assessment with a fit for purpose wrapper. Operator training.	Visual inspection at beginning and end of stopper installation.	**Moderate** Rationale: Wrapper is fit for purpose but depends on operator technique.	**Informative** Rationale: Hazard would be discovered prior to transfer. During inspection if the cover is not integral, the stopper bowl will be reprocessed.	**Improvement Priority 4.**
	Outer wrapping was removed too early.	Operator removes the wrapping prior to process initiation.	Operator training.	Visual inspection at beginning and end of stopper installation.	**Moderate** Rationale: Procedural, operator dependent.	**Informative** Rationale: Hazard would be discovered prior to transfer.	**Improvement Priority 4.**

Contamination Control	Hazard (i.e., way(s) the contamination control may fail)	Cause (i.e., causes of the hazard)	Prevention controls in place for hazards/causes	Detection controls in place for hazards/causes	Prevention Controls Ranking and rationale	Detection Control Ranking and rationale	Improvement Priority
						During inspection if the cover is not integral, the stopper bowl will be reprocessed.	

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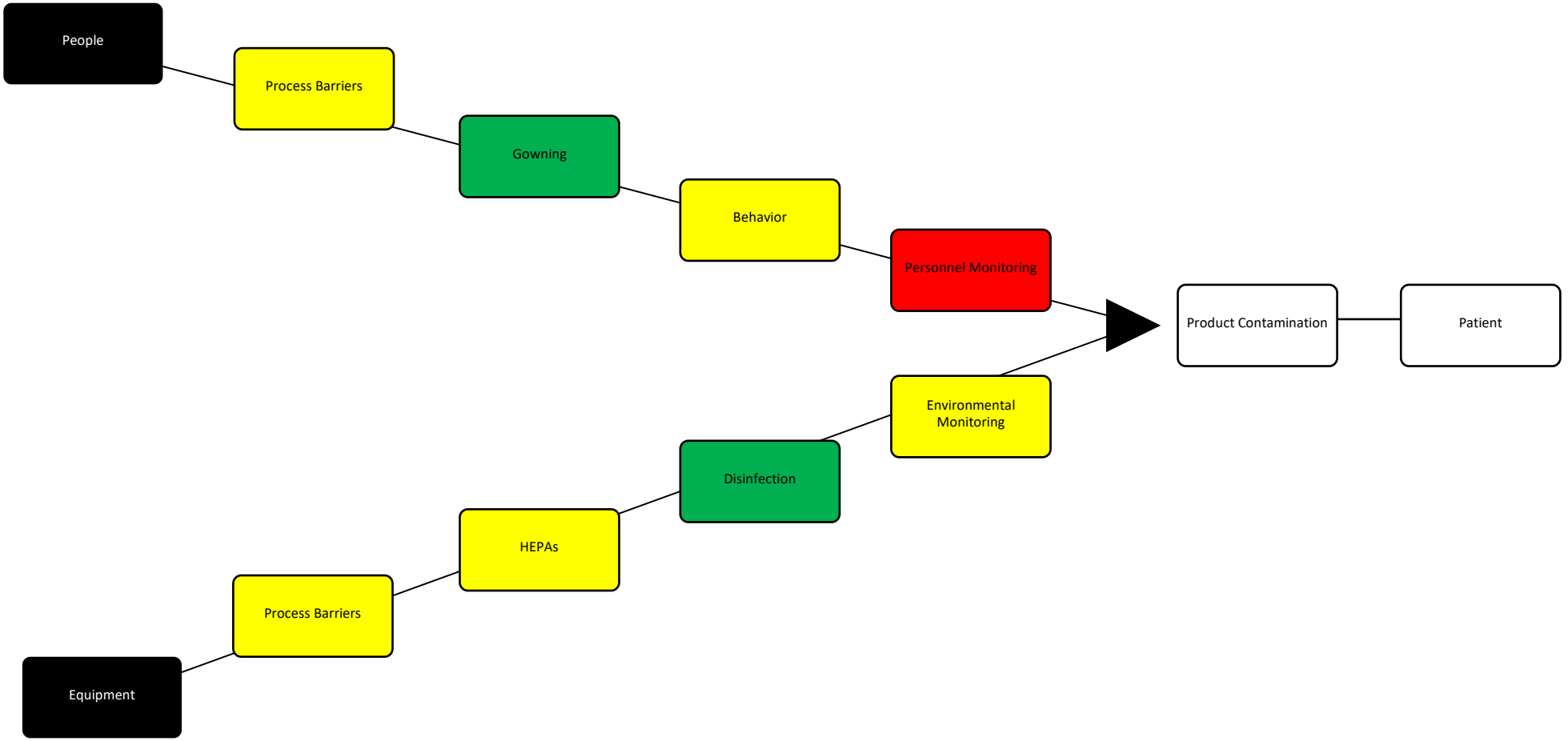
STEP SEVEN Create a Contamination Control Risk Dashboard to Illustrate the Effectiveness of Contamination Controls (Section 6.8)

Once the contamination controls outlined in **Figure 2a** were assessed and improvement priorities assigned, the risk assessment team created a dashboard to provide a visual representation of the strength of controls. To demonstrate an example of a completed dashboard, **Figure 3**a below includes the two controls that were assessed in the above example as well as additional elements not included in the example. The intent of the dashboard is to consolidate the information assessed and provide a high-level illustration of the relative strength of contamination controls.

Figure 3a: Contamination Control Risk Dashboard Resulting from the Case Study



Using the dashboard, the risk assessment team agreed that personnel monitoring (indicated with red color) currently has limited effectiveness and escalated the related information to decision makers to determine next steps. In addition, the team agreed that the elements in yellow will be examined to determine how to increase the level of effectiveness, and the gowning and disinfection programs have a strong level of effectiveness.

STEP EIGHT: Improve Contamination and Risk Control (section 6.9)

For each hazard, the risk assessment team then examined the Improvement Priority and associated risk reduction strategies as noted in **Appendix C.** **Table 7a** shows the output of this step and describes the types of activities that can be considered to improve the effectiveness of the contamination control.

Table 7a: Activities to Improve Effectiveness of the Contamination Controls.

Contamination Control	Hazard (i.e., way(s) the contamination control may fail)	Prevention Controls Ranking and rationale	Detection Control Ranking and rationale	Improvement Priority	Risk Reduction Strategies per Appendix C	Activities to improve effectiveness of the contamination control
Unidirectional airflow that washes over the transfer area and into the Grade B area to reduce contamination.	Airflow over transfer area is below the acceptable rate.	**Limited** Rationale: Maintenance is a manual process. As part of this assessment, a review was performed of the frequency, replacement of parts, change control, training, and qualification of maintenance personnel. There have been gaps (historical deviations) in HVAC maintenance.	**Informative** Rationale: Barrier HVAC - fan speed with audible and visible alarm when lose speed.	**Improvement Priority 2.**	Implement additional controls or different preventive controls and/or gather more evidence, or Revisit options to eliminate hazard.	Prevention controls to be improved. Update the HVAC PM program to increase the frequency of preventative maintenance. The detection controls currently alarm when the velocity is out of specification which is informative but does not give the operators time to respond before a failure of the air velocity is detected. To increase the detection controls, the team will evaluate the current alarm strategy and determine if the alarms can be set below the out of specification level to provide time to recover prior to failure.

Contamination Control	Hazard (i.e., way(s) the contamination control may fail)	Prevention Controls Ranking and rationale	Detection Control Ranking and rationale	Improvement Priority	Risk Reduction Strategies per Appendix C	Activities to improve effectiveness of the contamination control
	Air flow/velocity is below the acceptable rate when doors are open resulting in ingress of contaminants from Grade B cleanroom during open door interventions.	**Strong** Rationale: IQ OQ PQ in place for barrier design is effective.	**Predictive** Rationale: Automated, predictive detection systems that have been qualified/ validated.	**Improvement possible but not a priority.**	Improvement possible but not a priority.	Actions will not be taken; currently the contamination control is strong and predictive.
Inner wrapping remaining in place to cover sterilized hopper surface during installation.	Wrapping: Inner wrapping moves and exposes stopper contact area).	**Moderate** Rationale: Wrapper is fit for purpose but depends on operator technique.	**Informative** Rationale: Hazard would be discovered prior to transfer. During inspection if the cover is not integral, the stopper bowl will be reprocessed.	**Improvement Priority 4.**	Implement additional controls or different preventive controls and/or gather more evidence, and Improve detection controls, or Revisit options to eliminate hazard.	The current prevention controls are moderately effective. Operator handling and technique will be revisited to determine if a HEPA cart can be implemented to avoid contact with the hopper during transfer after autoclaving.
	Outer wrapping was removed too early.	**Moderate** Rationale: Procedural, operator dependent.	**Informative** Rationale: Hazard would be discovered prior to transfer. During inspection if the cover is not integral, the	**Improvement Priority 4.**	Implement additional controls or different preventive controls and/or gather more evidence, and Improve detection controls, or	The current prevention controls are moderately effective. The timing of removal of the outer wrapping will be highlighted at a critical operation in the operator training. Aseptic onboarding and refresher training will be updated to ensure ongoing sustainment of operators aseptic performance.

Contamination Control	Hazard (i.e., way(s) the contamination control may fail)	Prevention Controls Ranking and rationale	Detection Control Ranking and rationale	Improvement Priority	Risk Reduction Strategies per Appendix C	Activities to improve effectiveness of the contamination control
			stopper bowl will be reprocessed.		Revisit options to eliminate hazard.	The batch record will be revised to ensure that the removal step is a stand-alone step and not combined with other processes.