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Quality Risk Management for Aseptic Processes

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The content and views expressed in this technical report are the result of a consensus achieved by the authoring task force and are not necessarily views of the organizations they represent.

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1.0 Introduction

Risk management has been applied to numerous endeavors in a broad range of industries including the development of military strategies, pioneering space discovery and automotive design. A risk management program facilitates the identification of areas of criticality or vulnerability, determines the appropriate application of risk controls and helps to communicate those risks to appropriate organization decision makers. Quality risk management is an important part of science-based decision making which is essential for quality management of pharmaceutical manufacturing.

Pharmaceutical manufacturers have made risk-based decisions for many years. However, a more formal approach to risk management was embraced in 2002 with the FDA's unveiling of "Pharmaceutical cGMP's for the 21st Century: A Risk-Based Approach." This draft report paved the way for a structured, science-based quality risk management approach to ensure industry and regulatory focus on critical operations for patient safety. The final report was issued in September 2004 with additional guidance documents that further outlined FDA's support of quality risk management techniques to ensure product quality and facilitate continuous improvement.

This technical report introduces the basic concepts of quality risk management and includes a model that may be used as a tool for conducting a risk assessment. Aseptic processing has been selected as the focus because it contains inherent risks due to consequences of process failure and challenges in the detection, control and management of product contamination. More detailed information on establishing a quality risk management program for aseptic processing is then provided. This is followed by examples of hypothetical risk assessments designed to illustrate the use of the model. The examples are not designed as a commentary or a guide for aseptic processing practices. The report includes a glossary of terms and concludes with additional examples showing flexibility of the model, references and a bibliography.

Approaches for quality risk management vary according to the needs of the organization, and many models are available for risk analysis (e.g., Failure Mode Effects Analysis (FMEA), Hazard and Operability Analysis (HAZOP), Hazard Analysis and Critical Control Points (HACCP), and fishbone analysis). However, these models are not "one size fits all" and may require modifications to suit their intended uses. The approach chosen for this technical report is a modified FMEA model, although the task force recognizes that other models may be used.

The ICH Q9 guideline, *Quality Risk Management* (QRM) and other literature provide ample guidance on the principles of quality risk management and may be consulted for greater detail about alternative methods or approaches. This report does not attempt to redefine or modify those principles; instead, the purpose of this report is to describe a methodology for implementing those principles, specifically for aseptic processing of sterile drug products.

The task force that drafted this report is comprised of aseptic processing and risk management professionals from the pharmaceutical, biotechnology and medical device industries. During the course of developing this report, the task force conducted a survey of risk management practices in the pharmaceutical industry *(1)*. Survey results revealed current industry practices regarding implementation of QRM. Although there is a growing understanding and appreciation of QRM as a method for science- and risk-based decision making, there also appears to be a need for assistance in the implementation of these approaches. Consequently, the task force included points to consider based on survey results.

This technical report was disseminated in draft for public review and comment prior to publication to ensure its suitability as a valuable guide to industry in aseptic processing.

1.1 Purpose/Scope

The methods used to assess risk should be appropriate for the organization and the process being assessed. The purpose of this technical report is to provide an overview of a quality risk management program and to present a model to facilitate the risk assessment of aseptic processing of sterile products. It provides a tool to assess and evaluate activities, conditions and controls that impact establishing and maintaining aseptic conditions and endotoxin control. Aseptic processing is unique because the severity of the harm is always going to be high and detection of loss of sterility is always going to be low.

The scope of this report is the application of a quality risk management program to aseptic processing. However, the task force recognizes that the quality risk management concepts provided in this report may be used in other areas of pharmaceutical manufacturing.

For purposes of this report, "products" include pharmaceutical, biological and biopharmaceutical products produced by aseptic processing. "Process" refers to the pharmaceutical manufacturing process. Unless otherwise noted, "risk" refers to "quality risk" as it relates to risk to product quality throughout its lifecycle. Applications for quality risk management of aseptic processes include, but are not limited to:

- Personnel – technique, hygiene and activity
- Process and facility design
- Process assessment
- Equipment and system qualification
- Process validation
- Change control and management
- Process/product failure investigation

There are many potential variables that can affect sterility assurance and endotoxin levels. This report provides examples of variables (e.g., personnel, process, equipment, components, sterilization/depyrogenation and facilities/utilities) that directly impact processing of product. Other variables common to pharmaceutical products (e.g., labeling, dosage, functionality or product content) will not be covered in this report. However, the model may be modified to be used as an assessment tool for hazards associated with these activities.

This report neither represents regulatory requirements or guidance, nor does it present the only method for risk assessment of aseptic processes. It does present information that can help the reader understand and use risk management to make science- and risk-based decisions.

2.0 Glossary of Terms

Current FDA, EU, ICH, ISO and other regulatory definitions are used, except when more clarity is added by the task force. In some instances, two definitions used in current guidances are provided where both are considered applicable. Regulatory guidelines offer other definitions that may be considered.

Variations in the usage of some terms may differ from organization to organization, and some may be subject to change in the future. However, the terms used in a quality risk management program must be clearly defined and well understood within the organization and clearly defined in internal standard operating procedures (SOPs), standards and regulatory filings. For the purposes of this technical report, the following terms and definitions are used:

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.

Critical Area:
An area designed to maintain sterility of product, containers, closures and equipment.

Critical Quality Attribute:
A defining characteristic of the product, including purity, strength, identity and safety.

Detection:
The ability to discover or identify a defect or failure.

Endotoxin:
A pyrogenic product (e.g., lipopolysaccharide) present in the bacterial cell wall. Endotoxin can lead to reactions in patients receiving injections, ranging from fever to death *(2)*.

Failure:
The condition or fact of not achieving expected results; a cessation of proper functioning or performance.

FMEA (Failure Mode and Effects Analysis):
A method of assessing and evaluating risk.

Harm:
Damage to health, including damage occurring from loss of product quality or availability *(3)*.

Hazard:
The potential source of harm *(4)*.

Intervention:
An aseptic manipulation or activity that occurs at the critical area.

Occurrence:
The likelihood that the cause of the failure will happen, resulting in harm to the patient.

The likelihood that a unit operation that could potentially cause a failure, happens in such a way that *does* cause the failure.

The FMEA rating scale that defines the frequency of a failure mode *(5)*.

Process Step:
An event that is a necessary part of the manufacturing procedure or unit operation.

Process Validation:
Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes *(6)*.

Quality:
The degree to which a set of inherent properties of a product, system or process fulfills requirements.

The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength and purity *(7)*.

Quality Risk Management (QRM):
A systematic process for the assessment, control, communication and review of risk to the quality of the drug product across the product lifecycle *(3)*.

Quality System:
Formalized business practices that define management responsibilities for organizational structure, processes, procedures and resources needed to fulfill product/service requirements, customer satisfaction and continual improvement.

Reduction:
The act of making changes to reduce risk. (synonym: mitigation)

Residual Risk:
Risk remaining after risk control measures have been taken *(8)*.

Risk:
The combination of the probability of occurrence of *harm* and the *severity* of that harm *(4)*.

Risk Analysis:
The estimation of the risk associated with the identified hazards *(3)*.

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 *(3)*.

Risk Communication:
The sharing of information about risk and risk management between the decision maker and other stakeholders *(3)*.

Risk Control:
Items in place and/or actions to implement risk management decisions.

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 *(3)*.

Risk Identification:
The systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description *(3)*.

Risk Management:
The systematic application of quality management policies, procedures and practices to the tasks of assessing, controlling, communicating and reviewing risk *(3)*.

Risk Prioritization Number (RPN):
A quantitative method for determining the level of risk by multiplying the severity, occurrence and detectability rankings of the failure or event.

Risk Prioritization Ranking (RPR):
A qualitative method for determining the level of risk by combining severity, occurrence and detectability rankings of the failure or event.

Risk Reduction:
The process of decreasing the level of risk.

Risk Review:
An ongoing monitoring of events, output and results of the risk management process that takes into account new knowledge and experience.

[A] step in the risk management process for taking in account of new knowledge and experiences *(3)*.

Severity:
A measure of the possible consequences of a hazard *(3)*.

Sterile:
The absence of viable microorganisms.

Sterility Assurance:
The probability or likelihood that something is sterile.

Terminal Sterilization:
The application of a lethal agent to a sealed, finished drug product for the purpose of achieving a predetermined sterility assurance level of usually less than 10^{-6} (i.e., a probability of a non-sterile unit (PNSU) of greater than one in a million).

Unwanted Event or Condition:
Lack of sterility assurance or an unacceptable level of endotoxin that could result in harm to the patient.

3.0 Aseptic Processing and Quality Risk Management

Sterile drug products differ from other products in that they are required to be free of viable microorganisms and are manufactured to meet allowable endotoxin limits. The result of the loss of sterility assurance or endotoxin levels exceeding allowable limits in product have a high likelihood of causing harm to the patient, while the likelihood of detecting a sterility or endotoxin failure is low. Therefore, risk in sterile product manufacturing, specifically aseptic processing, is relatively high when compared to other pharmaceutical processes, making risk management particularly important.

There are two basic methods for manufacturing sterile pharmaceutical products. One method is terminal sterilization, which involves the assumption of viable microbial contamination and that the process is adequately designed for its removal through post-filling treatment of the final integral container. In this method the critical process parameters (e.g., presterilization bioburden, time, temperature and pressure) that could adversely affect sterility assurance are well characterized, monitored and controlled.

The other method is aseptic processing. Aseptic processing involves protecting the exposed product and product contact surfaces from microbial contamination, usually originating from personnel, surfaces or the processing environment. Conditions that could adversely affect sterility are not as well defined in measurable metrics and are not easily monitored or controlled. If sterility and endotoxin failures do occur, the ability to detect contamination is limited because of the lack of sensitivity of current sampling and testing methodologies. Therefore, the outcome of aseptic processing is less predictable and inherently has more risk. Understanding and managing the conditions and risks associated with aseptic processing are essential for making appropriate decisions and assuring product quality.

Endotoxins are "natural" substances that, when injected in sufficient amounts into a human or animal, will cause a variety of detrimental physiological symptoms, the most quantifiable being an elevation in body temperature. Endotoxins are high molecular weight lipopolysaccharides associated with the outer membrane of Gram-negative bacteria. Endotoxin reduction usually requires validated cleaning procedures or high temperatures that may not be feasible for heat-labile products. Therefore, the use of quality risk management to identify, control and reduce endotoxin contamination is applicable to both aseptic and terminal sterilization processes.

Process failures that can result in elevated endotoxin levels and lack of sterility assurance pose a significant risk to patient safety. The ability to detect a process failure is low given the current methods for sterility testing. The probability of a process failure that could adversely affect the sterility of the product in aseptic processing is higher and less predictable than in terminal sterilization, given the inherent exposure to environmental contaminants. Quality risk management can be an effective method of identifying and reducing aseptic processing risk, thus improving the assurance of sterility, endotoxin control and subsequent patient safety.

3.1 Risk Management Benefits

Successful application of a quality risk management program enhances decision-making capabilities and communication and is an invaluable tool for attaining an effective and efficient aseptic processing operation. This is accomplished by the application of structured approaches to the identification, analysis, control and review of potential risks. Overall benefits of a quality risk management program include:

- Improved planning and preparedness for potential failures
- Increased process understanding
- Improved identification of critical process parameters
- Improved stakeholder relationships through better communication
- Increased quality assurance through documentation of the decision-making process
- Reduced risk to patients by modifying processes to eliminate or reduce high risk process steps
- Identification of fault conditions that need to be monitored
- Optimization and prioritization of validation resources
- Selection of test methods and acceptance criteria that are aligned with critical quality attributes of products
- Compliance with regulatory expectations
- Assistance in maintaining a state of process control

3.2 Risk Management Considerations

Before initiating a quality risk management program, an organization should engage in some thought and deliberation regarding implementation. An evaluation of the current understanding of risk management in the organization should be conducted. A structure should be created in which risk management is accepted, its benefits understood, its tools applied uniformly, and the practitioners properly trained in its concepts.

Managing risk works best in an organization that has the supportive commitment of executive management. Organizations should develop and implement an overall risk management policy to guide procedures written for specific risk processes. These policies and procedures should outline the context in which risk will be managed. This includes who has responsibility and authority, as well as what is in and out of scope for the risk management program. It is also important that the organization identifies and includes internal stakeholders. Once adopted, the risk management program should be integrated into the culture of the organization.

As a part of an organization's continuous improvement plan, the risk management program should be monitored and reviewed periodically for effectiveness.

3.3 Risk Management Program

Quality risk management requires balanced thinking in its treatment. Organizations should be neither too conservative nor too liberal regarding the acceptance of risk. Currently, many organizations test all aspects of the manufacturing process, whether or not these tests add any value. A quality risk management program facilitates identification of critical parameters or conditions that could affect product quality.

Risk management encourages proactive, rather than reactive, management of product processing and is a means to an end, not an end itself. Rigorous thinking is involved with logical, systematic and science-based approaches to improve the effectiveness and efficiency of decision-making. The goals of a quality risk management program should be to better understand the process and improve the process, thereby assuring patient safety.

Structured risk management methods may not always be required. The degree of formality and documentation is a function of both the scale of the risks being addressed and the level of understanding of the manufacturing process being assessed. Risk assessments should be performed during the entire lifecycle of a product. The use of risk management can facilitate communication and compliance with regulatory expectations. It is always advisable to review local regulatory guidance documents when instituting a quality risk management program.

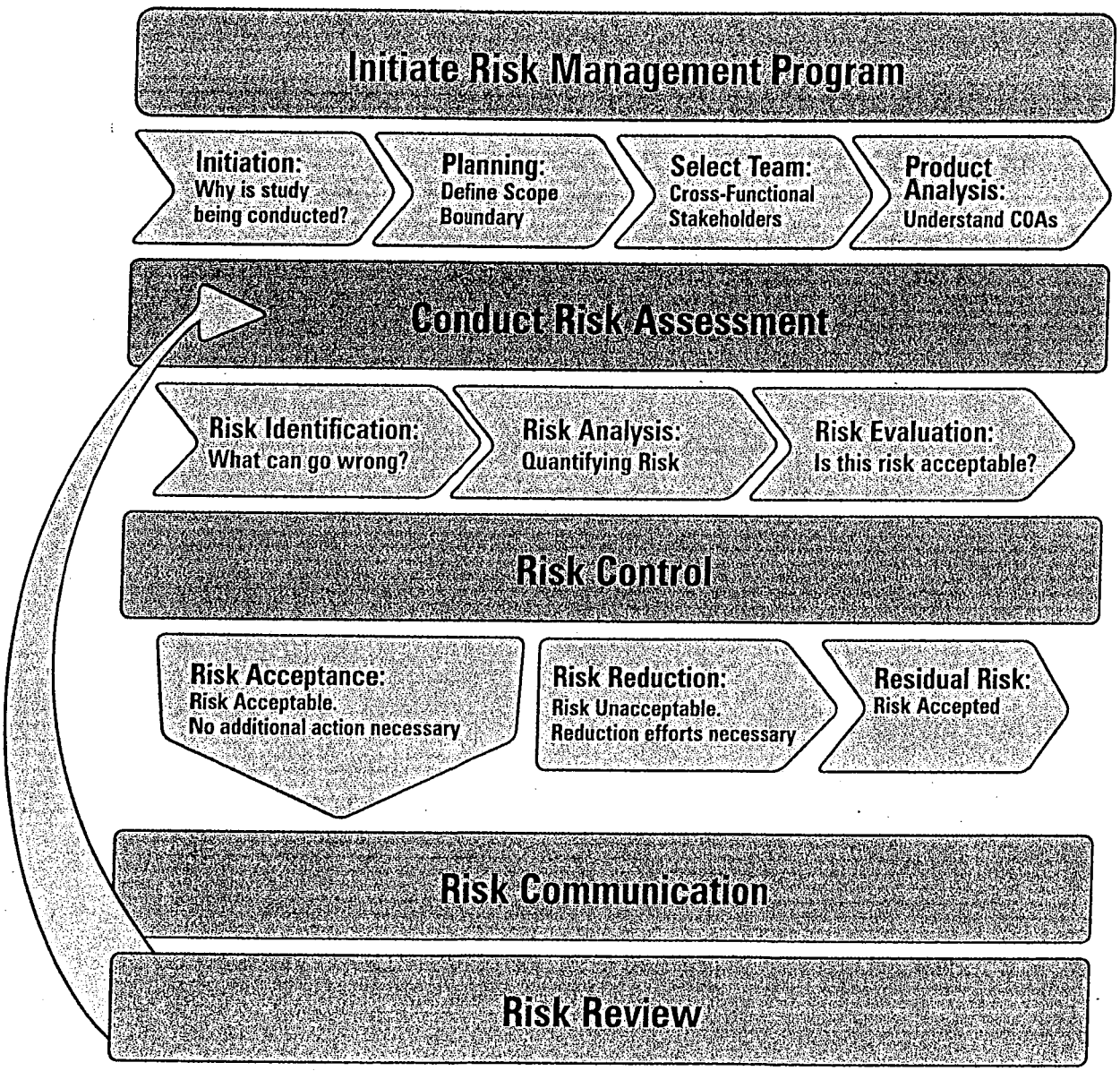
As described in ICH Q9, a quality risk management program embodies the following concepts:

- Risk Initiation
  - Team Selection
  - Product Analysis
- Risk Assessment
  - Risk Identification
  - Risk Analysis
  - Risk Evaluation
- Risk Control
  - Risk Reduction
  - Risk Acceptance
- Risk Communication
- Risk Review

A quality risk management program is an iterative process that involves risk assessment, risk control, risk communication and risk review as depicted in **Figure 3.3-1**. Risk assessment is comprised of risk identification, analysis and evaluation. Risk control includes reduction of "unacceptable" risk and/or acceptance of low risk with proper (science-based) justification. Risk communication includes sharing risk-related information with appropriate individuals and/or groups. Risk review involves periodic evaluation of the effectiveness of the steps employed to reduce risk as a result of the previous assessment. Frequency of this evaluation may be event-, change- or time-based.

It is commonly understood that risk is the combination of the probability of occurrence of harm or an unwanted event and the severity or impact of that harm.

Figure 3.3-1 Risk Management Program Cycle



3.3.1 Risk Initiation

Prior to commencement of a risk assessment, it is important to ask why the study is being initiated. This question should be addressed early on in order to establish an objective and scope within which the study can be maintained.

A risk assessment study does not need to be complicated or time consuming, nor should it be a valueless exercise. Appropriate planning, timelines and preparation will assure that the study has value and that the team accomplishes its goal.

The scope and study boundary should be defined during the planning stage. This can be achieved by creating a map within a defined boundary of the manufacturing process being assessed.

3.3.1.1 Team Selection

It is recommended that a cross-functional team be assembled to use the model. This provides a level of assurance that the qualitative or quantitative evaluation of potential hazards will be as objective as possible. The team should be the appropriate size with the appropriate expertise for the process being evaluated.

Team members should include (but need not be limited to) stakeholders in the areas of: development, engineering, validation, product safety, microbiology, technical services, manufacturing, quality unit, owner, operator and facilitator. Team members should have the appropriate skill, knowledge, authority and expertise necessary to correctly assess and quantify risk in a team environment.

3.3.1.2 Product Analysis

It is important that critical quality attributes of the product (i.e., sterility assurance and the acceptable level of endotoxin) are identified so that risk can be managed and/or reduce risk on steps in the process that can adversely affect the quality of the product and could result in harm to the patient.

3.3.2 Risk Assessment

Risk assessment involves identifying, analyzing and evaluating potential failures in the process. When initiating a risk assessment, the first step is to pose the question, "What can go wrong?" While it is important to list as many potential failures as possible and reasonable, analyzing failures that are highly unlikely to occur may not be value added.

After identifying potential process failures, the second step is to determine the *severity* of the impact of this unwanted event. The model presented in this report is based on the premise that if the unwanted event is the loss of sterility assurance or unacceptable levels of endotoxin, then the severity will always be high because harm to the patient is severe.

In an aseptic process risk assessment, *occurrence* is the likelihood of a process failure happening that causes an unwanted event (e.g., loss of sterility or unacceptable endotoxin levels). If *severity* is always high, as is the case in this model, then *occurrence* is the combination of the likelihood that the failure will occur and that the failure will result in the loss of sterility or an unacceptably high endotoxin level if the failure occurs.

3.3.2.1 Risk Identification

Risk identification addresses the question, "What might go wrong?" Sterility failure is difficult to detect without destructive testing; therefore, process failures that could result in product microbiological contamination should be addressed. Experience, empirical and historical data indicate that the degree of human intervention coupled with environmental and surface contact conditions will affect the likelihood of contamination.

3.3.2.2 Risk Analysis

Risk analysis is a qualitative or quantitative process of linking the likelihood of occurrence to the ability to detect the failure (detectability). A ranking system may be used as a relative scale for determining the severity of the unwanted event and the occurrence and detectability of the process failure.

The purpose is to determine which process steps pose greater or lesser risk, and whether the risk has been reduced or increased with the process change. The ranking system and its defined values are determined by the organization according to their predefined acceptance of level of risk and the process being assessed, and they should be as objective and consistent as possible. The ranking system may be numeric or descriptive and should be described in a procedure in order to better assure consistency of use.

3.3.2.3 Risk Evaluation

Risk evaluations compare the identified and analyzed potential failures to risk acceptance criteria. Uncertainty due to incomplete knowledge of the process and its expected or unexpected variability should be addressed. This includes knowledge gaps in process understanding, sources of failures (e.g., failure modes of a process, sources of variability) and the likelihood of detection of process failures. Where a high level of uncertainty exists, it may be prudent to assume the process step poses greater risk and assign it a value accordingly.

When determining risk acceptability, consideration should be given to regulatory requirements, previous experience and/or technical studies. When risk is quantified either qualitatively (high/medium/low) by assigning a risk prioritization ranking (RPR), or semi-quantitatively by assigning a risk prioritization number (RPN), a decision needs to be made as to whether to accept the risk or pursue additional control and protective steps. This decision is based on an organization's or manufacturing site's acceptance level for risk. (See **Section 4.1.2 (I)** (p. 17) for further discussion of RPR and RPN.)

3.3.3 Risk Control

Once an assessment has been conducted to identify potential process failures, their impact, likelihood of occurrence and detection, a decision on how to address these risks should be made. A process that poses unacceptable risk should be reduced and controlled to an acceptable level. If the risk is acceptable, the process may remain as designed or reasonable steps to further reduce the risk may be considered to improve the process. Risk control should continue throughout the lifecycle of the process.

3.3.3.1 Risk Reduction

Risk reduction is a proactive method of addressing potential process failures through redesign, incorporation of safety features or instructions whose end result is risk reduction to the patient. The amount of reduction effort made should be proportional to the impact of the risk. As stated in ICH Q9, risk reduction might focus on the following questions:

- Is the risk above an acceptable level?
- What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being controlled?

For aseptic processing, reduction of risk involves reducing the likelihood of occurrence and/or increasing the likelihood of detection of the process failure.

Risk may be reduced in a variety of ways in an aseptic process where significant levels of human intervention are used, for example:

- Changing the process to reduce human intervention through engineering solutions (e.g., automation)
- Decreasing the number of interventions, thereby reducing the likelihood they will affect product quality (e.g., increase hopper size to reduce the number of component additions)
- Increasing the level of detection of the identified potential process failure (e.g., door interlocks on filling machines)

A Corrective Action and Preventive Action (CAPA) process may be used to implement risk reduction efforts and to verify their effectiveness.

3.3.3.2 Risk Acceptance

It may not be practical to try to eliminate all risk. After the process has been analyzed, a decision should be made either to accept the risk, or to consider process changes and continue the analysis of the changed process to further reduce the risk. Risks that remain after process changes, including risks introduced as a result of those changes, are considered residual risk.

For some types of failures, even the best controls may not entirely eliminate the cause of the failure resulting in residual risk. In the event residual risk remains, a determination will need to be made to accept this residual risk or the following actions may be considered:

- Modify the process to reduce the risk to an acceptable level. (This usually involves modifications which will decrease the likelihood of occurrence.)
- Enhance the method of detection to reduce the risk to an acceptable level.
- Employ a new process that has an acceptable level of risk.
- Communicate the risk level to the appropriate stakeholders for further consideration.

If modifications to the process are planned, then a risk assessment should be performed on the proposed modifications or new process. A CAPA process may be used to implement risk reduction efforts and to verify their effectiveness.

3.3.4 Risk Communication

Risk communication ensures that appropriate information is reported to stakeholders throughout risk management. Communicating risk may vary from informal (electronic) to more formal (approved documentation), depending on the risk level and the point in the risk assessment process.

3.3.5 Risk Review

Quality risk management should be used throughout the product lifecycle. It can be used to better understand the manufacturing process and to make decisions involved with the design of product, process and facility. Quality risk management may be used, for example, during qualification and validation to prioritize and develop test and acceptance criteria, as well as a component of change control, failure investigations and continuous improvement.

Once appropriate controls are implemented, an evaluation should be conducted to ensure that no new risks have been introduced, and their performance should be reviewed to confirm their effectiveness. The change management program should be linked to the quality risk management program. However, a review of the initial risk assessment may be initiated in the following instances:

- As a part of a failure investigation
- When new risks are identified as a result of increased process knowledge
- As a change control measure that is part of the change control program
- Upon implementation of process changes
- As a part of a periodic review

4.0 Aseptic Processing Quality Risk Management Model

This section provides a practical application of the concepts presented in Section 3. The authors have selected an FMEA approach as the basis for the model in this report, because it is one of the methods that works well with the assessment and decision-making needed for aseptic processing. The authors have taken into account various aspects of aseptic processing, including current levels of control and difficulty in measuring, quantifying and predicting the impact of failure in designing the model.

Quality risk management should be linked to the Critical Quality Attributes (CQAs) of the product that can affect patient safety or harm the patient. Product CQAs include identity, purity, safety and strength. The CQAs addressed in this model—which are unique to sterile products manufactured by aseptic processing—include sterility and acceptable levels of endotoxin. The unwanted events or conditions are lack of sterility assurance and unacceptable levels of endotoxin. Other hazards, such as particulate contamination, foreign matter residue, super- or subpotency or labeling defects are not unique to aseptic processing and are not specifically addressed in this model. However, the principles and elements presented in this model may be modified to assess risk inherent to those hazards.

4.1 FMEA Model Overview

The model may encompass an entire process and provide a high-level assessment or may be narrowed to address a single unit operation that has been experiencing poor performance. It is important that the boundary of the assessment be clearly identified during the planning stage.

Simple flow diagrams and process descriptions are useful to illustrate the process and stimulate discussions on identifying potential failures and reduction controls. In addition, empirical data, brainstorming, experience and failures documented as atypical or manufacturing deviations may be sources for identifying potential process failures. Process controls and actions to reduce risk may be established by compliance to regulatory requirements and by incorporating historical corrective and follow up actions taken to reduce risks.

4.1.1 Preparation for the Model

The key to successful use of the model is the quality of the input. The following are considerations in preparation for the risk assessment to help achieve objectivity and efficiency:

1. Define the problem or risk question, including the scope for the aseptic processing facility, equipment, system or process to be evaluated.

   When defining or stating the problem, the level of detail should be commensurate with the purpose of the decision. The more specific the problem is, the more precise the question should be. If the initial discussion becomes unproductive, then going back to the definition statement may be helpful. Avoid over-analyzing broad questions (i.e., paralysis by analysis).

2. Obtain management support, identify a leader, assemble the team, define responsibilities and allocate resources.

   Select an experienced, objective facilitator who can ensure that the discussion is productive and provide guidance on the risk-assessment process. Members should exhibit good teamwork skills. The team should be diverse and include representatives from as many stakeholder functions as practical.

3. Document all assumptions, scope, boundaries, background and baseline information.

   Assumptions should be stated, such as manual filling process, semiautomated process or isolator technology. Develop or use a process flow diagram and a written description of the aseptic process that includes decision points, a clearly defined scope and risk assessment boundaries. Remain within the scope; avoid scope creep. This is another good opportunity to consider the appropriate level of detail.

4. Collect process knowledge, historical data, industry practices, standards and guidance documents.

   Have up-to-date information available at the start of assessment meetings. For example, filling process information may include line speed, line capacity/fill duration/utilization, number and type of interventions performed, frequency of sterility and endotoxin failures, media fill results, personnel monitoring and environmental monitoring trends.

5. Specify a timeline, the appropriate level of decision-making needed for the risk assessment and how it will be documented.

   Allow sufficient time to complete the assessment. The time commitment may be one meeting or several meetings depending on the complexity of the process.

6. Establish a risk ranking system. This should include severity, occurrence and detection. The system may be quantitative or qualitative; numeric or descriptive.

   A qualitative or quantitative system may be used to establish a risk ranking system. Qualitative system scales may include: high, medium, low or color. The number of choices depends on the organization and process being assessed. A quantitative system involves numeric values, such as 1-10, with 1 being low and 10 being high. Whichever system is chosen, it should be documented and used consistently.

   Choose a ranking system that is appropriate for the level of analysis needed. Be consistent in the type and definitions of the ranking system used. Using more ranking categories or number choices may lead to over-analysis; using fewer choices may result in over-simplification.

   An acceptable level of risk may include a level of subjectivity. Ranking should be challenged in order to confirm its validity.

Table 4.1.1-1 is an example of a qualitative risk-ranking system with accompanying descriptions. An example of a quantitative ranking system is used in **Example 3**. For information on qualitative and quantitative ranking, the reader is referred to current guidance documents *(8, 9)*.

Table 4.1.1-1 Example of Defining Qualitative Risk Component Ranking

Qualitative Ranking	Risk Factors		
	Severity	*Occurrence*	*Detection*
High	Impact of the unwanted event is severe	Occurrence is often	The process failure will almost certainly escape detection.
Medium	Impact of the unwanted event is moderate	Occurrence is periodic	Controls may detect the existence of a process failure.
Low	Impact of the unwanted event is low	Occurrence is seldom	The process failure is obvious and readily detected.

4.1.2 Using the Model

Table 4.1.2-1 is an example of column headings for the FMEA-based model (see 4.2.1.10) used in this technical report. Information may be added below each column heading to identify, assess and evaluate aseptic processing risks in a logical format and may be modified or rearranged as appropriate.

Table 4.1.2-1 Example of Aseptic Processing Risk Assessment Model

REF #	Process Step/Unit Operation	Unwanted Event	SEV	Cause/ Process Failure	OCC	Current Controls	DET	RPR	Risk Accepted?	Recommended Actions	Ranking after actions			
											S E V	O C C	D E T	R P R
(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)	(I)	(J)	(K)	(L)	(L)	(L)	(L)

(A) REF

This is a sequential number or other logical identifier to facilitate referencing at a later date.

(B) Process Step/Unit Operation

List the process step being evaluated. The process map, SOPs or batch records can provide this information. The team should determine how detailed this information needs to be in order to facilitate the assessment.

(C) Failure (Unwanted Event)

The model identifies:

1. sterility assurance and acceptable endotoxin levels as critical quality attributes for injectable products, and
2. sterility as a critical quality attribute for non-injectable sterile products.

Therefore, the failure is not meeting endotoxin and sterility assurance specifications.

(D) SEV – Severity

Assign a severity value by determining the severity of the failure or unwanted event in relation to patient safety. For loss of sterility assurance and unacceptable endotoxin levels, the severity is high. If the model is used for other unwanted events or conditions, the severity of that event or condition may vary. See Section 4.1.1, Consideration 6, for a discussion of ranking systems.

(E) Causes

List potential causes of the failures. A cause is a known or foreseeable failure associated with the aseptic process. There may be multiple causes for each failure type; therefore, they should be listed individually, since they will be evaluated separately.

(F) OCC – Occurrence

Assign an occurrence value by determining the likelihood that the cause of the failure will happen, and if it does happen, whether it will result in loss of sterility and/or unacceptable endotoxin levels. Use historical or empirical data where possible (e.g., process capability data). See Section 4.1.1 (6) for a discussion of ranking system.

(G) Current Controls

List the existing procedural or design controls that detect, reduce or eliminate the cause of failure from occurring. The controls in place should be considered when determining the detection ranking. If there are no controls, the likelihood of detection is low, resulting in a high-risk ranking.

(H) DET – Detectability

Assign a detectability value by determining the detectability of the cause. Detectability is important because it facilitates the identification and correction of failures before they cause harm to the patient.

Evaluate detection by determining the likelihood that the cause will be detected prior to product release. The same type of ranking system should be used for detectability as for severity and occurrence. Be as objective as possible in ranking the likelihood of detection. Use historical or empirical data where possible.

Note: The ranking system for Detectability is the reverse of the Severity and Occurrence ratings. A high detectability has a low ranking. See Section 4.1.1 (6) for a discussion of ranking systems.

(I) RPR – Risk Prioritization Ranking

Risk prioritization ranking is a method of evaluating the overall risk of the process step or item by combining individual risk values. If a quantitative or numeric system is used, this combination can be a matter of multiplying values. In this case, the RPR may be described as an RPN.

However, if a qualitative or descriptive system is used, the RPR becomes a combination of the descriptive values. The RPR may be somewhat intuitive and should be determined prior to starting the assessment. (For example, in the aseptic process model, Severity will, by definition, always be high. Therefore it remains constant.) The RPR then becomes a combination of Occurrence and Detection. The example provided in **Table 4.1.2-2** uses three values: high, medium and low; however, lack of granularity makes the ranking more subjective.

Table 4.1.2-2 Example of Determination of Risk Priority Ranking

		Detection		
		Low	**Medium**	**High**
OCCURRENCE	**HIGH**	This cause is likely to occur, but when it does, it will be detected. If we are certain it will be detected, it is **Low Risk**, but if we are not certain then it should be a **Medium Risk.**	This cause is likely to occur, and the detection is not certain. It is a **High Risk.**	This cause is likely to occur and is not likely to be detected. It has a **High Risk.**
	MEDIUM	This cause could occur, but if it did, it would be detected. Depending on the frequency of occurrence and the confidence in the detection, it is a **Low** or a **Medium Risk.**	This cause could occur, and it could be detected. Depending on our confidence in the detection, its risk would be **Medium** or **High**	The cause may occur, and it will not be detected. The **Risk is High.**
	LOW	This cause is not likely to occur, and if it does it will be detected. This is a **Low Risk.**	The cause is not likely to occur, and if it did, it may be detected. Depending on the frequency of occurrence and the confidence in detection methods, it would be a **Low** or **Medium Risk.**	The cause is not likely to occur, but if it did occur, it probably would not be detected. The **Risk is Medium.**

(J) Risk Accepted?

Risk acceptance is based on several criteria, such as product use, process performance trends, confidence in control systems and training, confidence or robustness of process and controls and regulatory climate. If the level of risk is not acceptable, actions should be taken to reduce the level of risk.

(K) Recommended Actions

If the risk level is accepted or acceptable, the evaluation for that process step is finished. If the risk level is not accepted, any of the following may occur:

- Recommendations are made to modify the process to reduce the risk to an acceptable level.
- The method of detection is enhanced to reduce the risk to an acceptable level.
- A new process is employed that has acceptable risk.

The next step is to determine actions required to reduce risk to an acceptable level. This model and its application to aseptic processing does not allow a reduction of Severity as a way to reduce risk, since loss of sterility assurance or unacceptable endotoxin levels always remains high. Therefore, risk reduction actions involve reducing occurrence or increasing detection. Preference should be given to reducing the occurrence rather than increasing the level of detection.

Note: Changes to the process may introduce new risks that may impact quality attributes that need to be assessed. In a residual risk assessment, consideration should be given to the possibility that new risks may have been introduced that are outside the scope of the original risk assessment.

(L) Ranking After Actions

Once the actions or process changes have been made, another assessment should be performed to determine if the risk has been reduced to an acceptable level. If the risk level is accepted or acceptable, then the evaluation for that process step is finished.

4.2 FMEA Model Examples

The following examples use a modified FMEA model that contains content chosen to illustrate concepts previously introduced. The examples are hypothetical situations and are not intended to represent actual manufacturing conditions or provide commentary or guidance on aseptic processing. Certain assumptions have been made in the development of these examples to better illustrate use of this model as a risk assessment tool.

Risk rankings and classifications are presented as examples only. Risk rankings and classifications should be independently developed based upon the organization's interpretation of risk potential that is most appropriate for their application.

In order to demonstrate the flexibility of this model, two additional examples are provided in the Appendix with a brief overview.

4.2.1 Risk Assessment for Lyophilized Vial Capping – Example One

In anticipation of a proposed regulatory requirement change, an assessment is made to evaluate potential risk of nonsterility associated with performing final capping of a lyophilized vial in a non-Grade A environment. (See **Section 4.2.1.10.**)

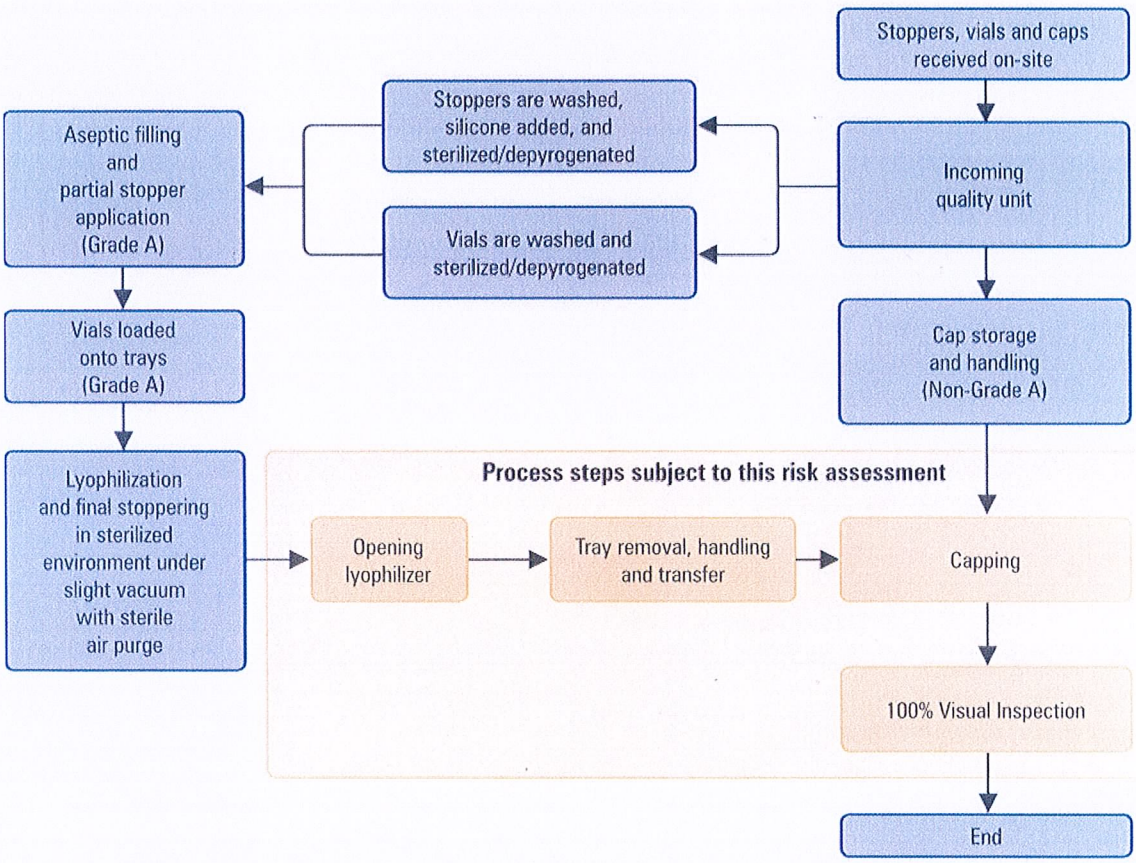
Process Description: A lyophilizer cabinet has been validated with an established leak rate. The lyophilizer is purged with sterile filtered air prior to and at the end of the cycle while still under slight vacuum. Then the final stoppering step takes place.

The lyophilizer chamber trays of vials with fully seated stoppers are manually unloaded and transferred to a capping machine located in a non-Grade A environment. The capping machine does not incorporate a raised-stopper detection device at the in-feed. The capping machine can potentially damage vials (with cracks and/or breaks) during mechanical handling. It also could dislodge and then reseat stoppers during the capping operation. Stoppers are known to dislodge if excess silicone is applied to them, and adequate controls are in place to prevent this from occurring.

Fully stoppered vials, capped and uncapped, have demonstrated satisfactory container-closure integrity. Stopper and vial specification ranges for dimensions are validated for container-closure integrity (with and without cap) and verified upon receipt (incoming Quality Unit). Media fills are monitored, which includes the allowed process hold time between the stoppering and capping steps. The stoppered and capped vials are 100% visually inspected by personnel for visual container defects.

The highlighted areas of **Figure 4.2.1-1** depict the focus of this risk assessment example. The process steps addressed are stoppering and lyophilization operations, including: opening and unloading the lyophilizer chamber, transferring trays of vials to the capper, and capping. It is assumed that the stoppers are all seated in the vials under prescribed partial vacuum during the final stoppering step while inside the aseptic environment of the lyophilizer.

Figure 4.2.1-1 Process Flow Diagram for Lyophilized Vial Capping – Example One Model



4.2.1.1 Risk Assessment

A simplified process description and process flow diagram was first prepared to define the problem, scope and assessment boundary (see **Figure 4.2.1-1**). This was found to be essential to help guide and focus the team discussion. The team found that it needed to frequently update the process description and flow diagram when new information became available throughout the risk assessment process.

4.2.1.2 Risk Identification

The team decided to perform the risk assessment by unit operation. For each unit operation, the team brainstormed to identify potential causes that could lead to non- sterility. The Severity rating of potential failures remained high, which is consistent with the model.

Existing controls were then identified. These controls could be either engineering (mechanical/electronic)- or procedural (training)-type controls to prevent defective product from being released to the market and impacting patient health. (Refer to columns entitled "Process Step," "Causes/Process Failure" and "Current Controls" in **Section 4.2.1.10**.)

4.2.1.3 Risk Analysis

Severity, Occurrence (Likelihood) and Detection were assigned values proportional to the estimation of risk for each cause or process failure. The resulting risk ranking assignments were then entered into spreadsheet columns "OCC" (occurrence) and "DET" (detection). It was found helpful to use a red-yellow-green color scheme in addition to the descriptor to provide a visual aid to better identify risk levels as shown in **Table 4.2.1.3-1.**

Table 4.2.1.3-1 Risk Ranking for Lyophilized Vial Capping Process – Example One Model

Risk Category Ranking/Definition	Low	Medium	High
Severity	N/A	N/A	Direct and severe impact to patient health; life threatening.
Occurrence	The possibility that the cause rarely occurs; unusual event.	The possibility that the cause may occur and may result in loss of sterility.	High possibility that the cause will occur and result in loss of sterility; a common and known event.
Detection	There is a high likelihood that existing controls will detect the cause or the defective product and prevent its release.	The cause, if it occurs, may be detected by existing controls.	If the cause happens, it will probably not be detected by existing controls, and defective product could be released.

4.2.1.4 Risk Evaluation

The three risk rankings were then evaluated to determine the overall RPR according to Table 4.2.1.4-1 (assumes a Severity ranking of High).

The resulting RPR is entered into the spreadsheet column "RPR," and the decision whether to accept this risk (without further reduction) is entered into the column entitled, "Risk Accepted?"

Table 4.2.1.4-1 Example of Risk Evaluation Ranking for Lyophilized Vial Capping Process

		Detection		
		Low (High likelihood failure will be detected)	**Medium**	**High** (It is not likely failure will be detected)
Occurrence	**High**	Medium	High	High
	Medium	Medium	High	High
	Low	Low	Medium	Medium

4.2.1.5 Risk Control

The team decided not to accept risks for process steps two and three and to initiate risk reduction measures.

4.2.1.6 Risk Reduction

The team then discussed means to reduce the risk of the unwanted events with high or medium RPR's. Preference was given to adding additional engineering controls instead of procedural controls whenever possible, because mechanical/electronic controls are more reliable than human-based controls.

4.2.1.7 Risk Acceptance

Risk reduction steps recommended by the team were entered into the spreadsheet column entitled, "Recommended Actions." Based on implementation of these additional controls, the RPR was recalculated using the new Severity, Occurrence and Detection rankings. If the resulting RPR is still high or medium after reduction steps are taken, then a decision would need to be made to accept the residual risk or implement further actions. In this case, the residual risk was due to the continuation of manual operations of loading and unloading the lyophilization cabinet.

The team determined that the potential risk of capping final-stoppered lyophilized vials in a non-Grade A environment can be successfully reduced through the addition of a raised-stopper detection device at the capper in-feed and by implementing a 100% vial head-space analysis leak test after the capping step. Performing the capping step in a Grade A environment without making these other changes might reduce the occurrence of sterility failures; however, it would not impact detection, and the overall risk was medium. If capper controls and design changes were implemented to improve capper operation, then the combination of these remedial actions would reduce the overall risk to low, regardless of the change to a Grade A environment.

4.2.1.8 Risk Communication

A summary report containing a flow chart of unit operations, risk method used, risks identified, areas of high risks, principles of control measures, a list of residual risks and the completed risk assessment report was forwarded by the team to senior management for review.

4.2.1.9 Risk Review

A review will be performed after a defined period of time to ensure that the recommended steps were effective in lowering the risk and have not introduced new risks to the process.

Additional reviews and updates will be performed in response to change control or upon discovery of significant new information or data (e.g., failures, deviations, investigations, CAPAs).

4.2.1.10 Risk Assessment for Lyophilized Vial Capping – Example One Model

Table 4.2.1.10 (opposite page) is an example of the model using the FMEA approach discussed above that reflects the risk assessment made and its outcome.

Table 4.2.1.10 Risk Assessment for Lyophilized Vial Capping – Example One Model

REF #	Process Step	Unwanted Event	SEV	Cause/Process Failure	OCC	Current Controls	DET	RPR	Risk Accepted?	Recommended Actions	Ranking After Actions			
											SEV	OCC	DET	RPR
1	Open lyophilizer chamber	There is no reasonable cause of sterility failure due to opening the lyophilizer chamber	N/A											
2	Remove trays from lyophilizer, transfer trays to capper and load trays into capper	Lack of sterility assurance	H	Stoppers are dislodged or missing	M	Procedural control for in-process visual verification of stopper presence, positioning (Qualification studies indicate this is a potential process failure)	H	H	NO (The cause happens and it is not easily detected)	Add 100% mechanical stopper detection at capper in-feed (This would increase the likelihood of detection and therefore reduce the risk)	H	M	L	M
2a										Redesign handling system to eliminate cause (This modification would decrease the likelihood of the cause from occurring, therefore reducing the risk)	H	L	M	M
2b										Combine Actions from #2 and #2a	H	L	L	L
3	Cap vials using the capping machine.	Lack of sterility assurance	H	Vials are cracked or broken due to overpressure during mechanical handling.	M	100% visual (manual) inspection after capping Equipment and line setup procedures (cause recognition) Equipment PM, calibration and line checks	H	H	NO (Small cracks under cap may not be detected using current controls.)	Upgrade capper controls to improve control over gripping and capping pressure and eliminate the cause.	H	L	H	M
3a			H	Stoppers dislodged and then reseated during capping. (Typically this is caused by high stoppers going into the capping step.)	M	Equipment and line setup procedures (cause recognition)	H	H	NO (Dislodged stopper may be reseated during capping and therefore could go undetected using current controls.)	Improve design of capper to eliminate the possibility of this cause.	H	L	H	M
3b										Implement 100% testing for presence of vacuum. (This increases the likelihood of detecting the cause, thus reducing the risk of the unwanted event.)	H	M	L	M
3c										Perform capping operation in Grade A environment (This would decrease the likelihood that if the cause occurs it will result in an unwanted event, thus decreasing its risk.)	H	L	H	M
3d										Combine actions from #3, 3a and 3b. (This would reduce occurrence and increase the likelihood of detection, therefore further reducing risk.)	H	L	L	L

4.2.2 Risk Assessment for Exceeding Endotoxin Levels – Example Two

This example evaluates the potential risk of exceeding acceptable endotoxin levels in a finished product. There are many potential sources of bioburden and risk of introduction of endotoxin in the manufacturing process. This example focuses on component or raw material endotoxin sources. A cross-functional team was established to proactively audit and assess the risk of incoming raw materials and components. The team consisted of representatives from engineering, manufacturing, technical support, microbiology, validation, quality assurance and quality control to conduct the risk assessment.

Process Description: Dry powder raw materials and components are purchased from an outside approved supplier. They are received in plastic bags and stored in the warehouse upon receipt in their original shipping containers. They remain in the warehouse until needed to manufacture the product.

The quality unit samples the raw material and closures using established procedures and qualified sampling aids. The quality unit tests the materials for endotoxin using qualified methods and instruments. All quality analysts are trained to perform their assigned tasks. The raw materials and closures are released for use only if they meet established test specifications.

According to the batch record instructions, the dry powder raw material is dissolved in Water for Injection (WFI) in a tank prepared with a qualified clean and steam-in-place process. The final solution is sterile filtered for filling into the final containers.

The process steps in this example risk assessment have been highlighted in **Figure 4.2.2.-1** (on opposite page).

Prior to use in processing, the rubber closures are rinsed with WFI to reduce endotoxin to an acceptable level and are sterilized in-house using a validated manual process. The glassware is depyrogenated using a validated dry-heat process. Operating instructions are documented and operators are trained.

There is a vendor audit program in place. Periodically, the vendors are audited to ensure that the materials are manufactured using standards that meet Good Manufacturing Practices (GMP).

4.2.2.1 Risk Assessment

For the purposes of this risk assessment, the only areas being reviewed are component and raw material failure. Potential causes of failures are: dry powder raw material and rubber stopper closures.

4.2.2.2 Risk Identification

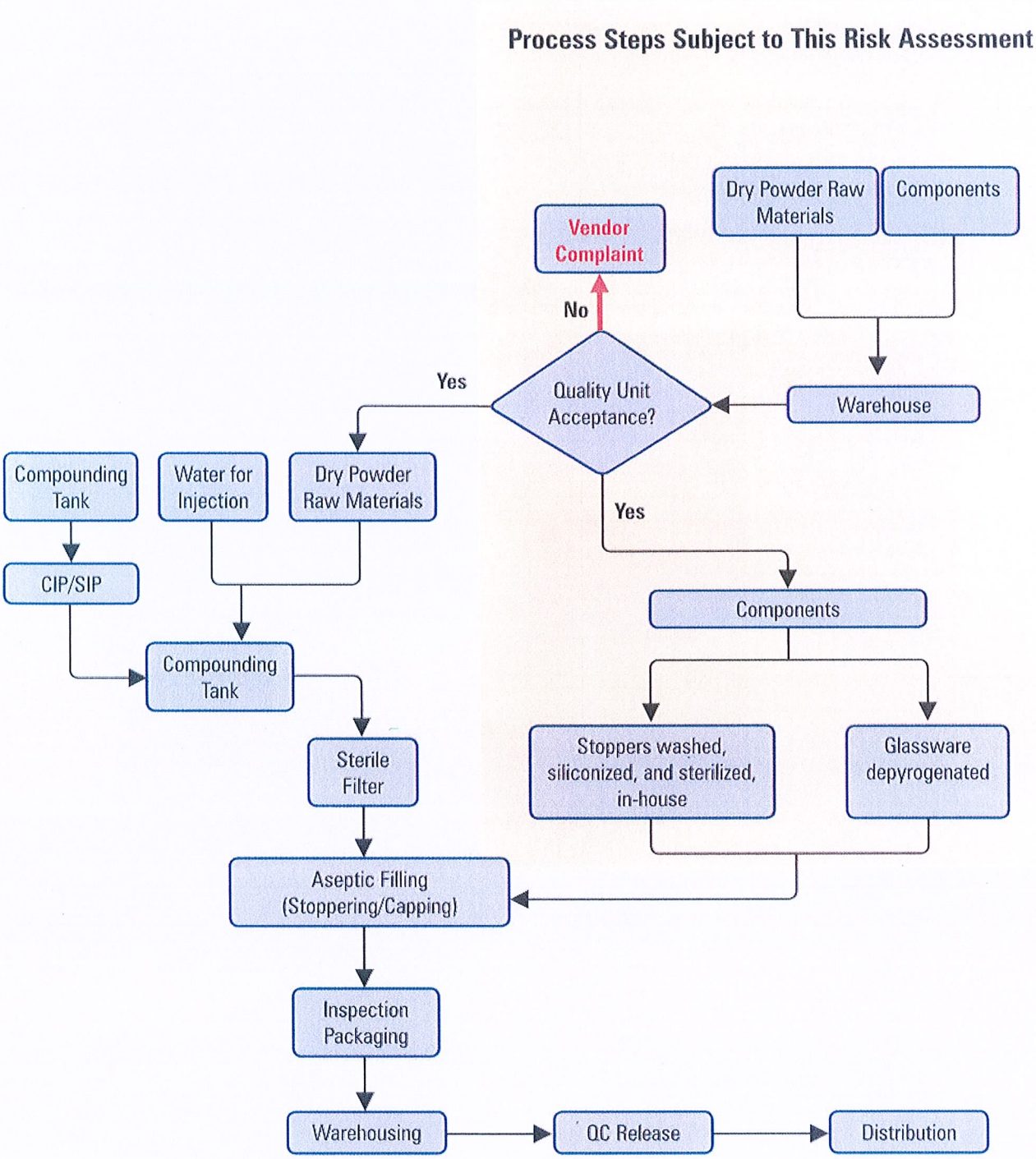
The team brainstormed to identify the potential causes for an endotoxin failure relating to incoming raw material and rubber-stopper closure components. Potential process failures identified were:

- Incoming powder raw material is contaminated with endotoxin.
- Incoming closures are contaminated with endotoxin.
- Closures are not properly depyrogenated.

These are listed individually in the column entitled, "Causes/Process Failure" in the model (see **4.2.2.10**).

Existing controls were then identified. In this example, controls were identified as steps taken to monitor levels of endotoxin on incoming components, reduce endotoxin levels on incoming components or control the conditions that may support endotoxin production. The existing controls for each cause was listed in the column entitled, "Existing Controls."

Figure 4.2.2-1 Process Flow Diagram of Operation – Example Two Model



4.2.2.3 Risk Analysis

For each potential failure cause, the Severity, Occurrence (Likelihood) and Detection were assigned values proportional to the estimation of the risk. Severity (SEV) is always ranked "high," because a component that exceeds acceptable endotoxin levels will always impact patient health and safety.

The resulting risk-ranking values were then entered into spreadsheet columns "OCC" (occurrence) and "DET" (detection). The rationale for the rank assignment was included in the column. As in the first example, it was found to be helpful to use a red-yellow-green color scheme with the descriptor to provide a visual aid to identify risk levels.

The team developed the definitions provided in **Table 4.2.2.3-1** for each area of risk ranking.

Table 4.2.2.3-1 Risk Ranking Assignment for Endotoxin Failure Risk Assessment – Example Two Model

Risk Category Ranking/Definition	High	Medium	Low
Severity	The process failure will result in direct and severe impact to patient health and is life threatening.	Process failure is indirect, moderate or will have a slight impact to patient health; harmful but not life threatening.	Very little or slight impact to patient health.
Occurrence	There is a high probability that process failure will occur and will result in the unwanted event.	Process failure occurs occasionally, but not often; and may result in the unwanted event.	Process failure rarely occurs; not likely to result in an unwanted event.
Detection	If the process failure occurs, it will probably not be detected by existing controls.	If the process failure occurs, it may be detected with existing controls.	There is a high likelihood that existing controls will detect the process failure.

4.2.2.4 Risk Evaluation

The three risk rankings were then evaluated to determine the overall RPR according to **Table 4.2.2.4-1**. Severity ranking is always "high" for endotoxin contamination that exceeds acceptable levels because of the direct and severe impact to patient health.

Table 4.2.2.4-1 Risk Prioritization Ranking for Endotoxin Failure Risk Assessment – Example Two Model

		Detectability		
		Low (high level of detectability)	**Medium**	**High** (low level of detectability)
Occurrence	**High**	Medium	High	High
	Medium	Medium	High	High
	Low	Low	Medium	Medium

The resulting RPR is entered into the spreadsheet column entitled, "RPR," and the decision whether to accept this risk (without further reduction) is entered into column "Risk Accepted (Yes/No)." The team determined that risks with a ranking of "high" were not acceptable and presented the following findings:

- **Incoming powder raw material is contaminated with endotoxin**: The RPR was determined to be "high." The occurrence was ranked as "medium." The incoming endotoxin levels in the raw material varied from lot to lot. The manufacturing process of the raw material may not have been designed to control endotoxin; therefore, the process was not qualified to produce a consistent quality of raw material in terms of endotoxin. The detection was ranked "high," because typically endotoxin is not evenly distributed in a powder material and may be missed by a small sample size or a small number of samples. A risk with an RPR of "high" is not an acceptable risk level.
- **Incoming closures are contaminated with endotoxin**: The RPR was determined to be "high." The occurrence was ranked as "medium," because the vendor's handling and storage of the components may not have been designed to adequately prevent endotoxin contamination. The detection is ranked as "high." Endotoxin may not be easily detected by routine test-sample preparation methods. In addition, the endotoxin may not be evenly dispersed throughout the batch of rubber closures, and random sampling for testing may not capture isolated contamination. A risk with an RPR of "high" is not acceptable.
- **Closures are not properly depyrogenated**: The RPR was determined to be "high." The occurrence was ranked as "medium" because historically, occasional endotoxin failures have occurred with manual processes. The detection was ranked as "medium" because finished product testing is qualified, but testing is performed on a small number of samples.

4.2.2.5 Risk Control

Risk control requires an initial decision whether to reduce or accept the overall risk based on the RPR. The risk in each case was not acceptable.

4.2.2.6 Risk Reduction

The team then discussed means to further reduce risk for each cause of failure.

- **Incoming powder raw material is contaminated with endotoxin**: A vendor audit may be conducted to review the manufacturing process. As needed, engineering and technical support departments would work with the vendor to design an endotoxin reduction step and to qualify the entire manufacturing process. The recommendations were added to the "Risk Controls" column on the model. With these controls in place, the occurrence was reduced to a risk ranking of "low." Detection remained "high," since no effective controls were identified.
- **Incoming closures are contaminated with endotoxin**: The team decided that an audit of the vendor may be conducted to ensure that the components manufacturer has adequate manufacturing, storage and handling controls. Engineering and technical support will work with the vendor to address recommended improvements in the vendor's manufacturing process, as needed. The test sample preparation method will be assessed and requalified (if necessary) to ensure improved detection of endotoxin. The recommendations were added to the "Risk Controls" column on the model. With these controls in place, the occurrence and detection were reduced to a risk ranking of "low."

- **Closures are not properly depyrogenated**: The team decided that engineering and technical support departments would purchase and qualify automated closure-washing equipment to replace the manual rinsing as an endotoxin reduction process. A qualified, automated system will increase the reliability of this step. As a backup measure, quality and technical support would determine and qualify a vendor to supply sterile and depyrogenated closures. The number of finished product samples for endotoxin testing were increased. An increased number of samples increases the likelihood that the endotoxin will be detected. The recommendations were added to the "Risk Controls" column on the model. With these controls in place, the occurrence and detection were reduced to a risk ranking of "low."

4.2.2.7 Risk Acceptance

The RPR was recalculated using the Occurrence and Detection rankings after reduction. (Note that Severity always remains "high.") In the case of Cause 1 (incoming raw material contamination), occurrence was reduced to "low" and detection remained "high," making the resulting RPR "medium." The team decided not to accept this risk and to take actions to increase the level of detection. Therefore, additional process improvements in the form of new technology and continuous monitoring were recommended.

In the case of Cause 2 (incoming closure contamination), the RPR has a risk ranking of "medium," which was accepted because steps were implemented to improve detection. As a result, no additional controls were required.

In the case of Cause 3 (improper closure depyrogenation), the RPR became a risk ranking of "low." The team decided that a risk ranking of "low" was acceptable, and no further controls were required.

4.2.2.8 Risk Communication

A summary of the identified high risks, recommendations, actions implemented and residual risk was forwarded to management for review and approval. Risk assessment documentation will be maintained and is subject to change control.

4.2.2.9 Risk Review

A review will be performed after a defined period of time to ensure that the recommended actions were effective in lowering the risk and have not introduced new risk to the process.

Reviews and updates will be performed based on events and in response to change control or discovery of significant new information or data (for example, failures, deviations, investigations and other CAPAs).

4.2.2.10 Risk Assessment for Exceeding Endotoxin Levels – Example Two Model

Table 4.2.2.10 (opposite page) is an example of the model using the FMEA approach that reflects the risk assessment made and its outcome.

Table 4.2.2.10 Risk Assessment for Exceeding Endotoxin Levels – Example Two Model

REF #	Process Steps (Personnel) (Process) (Equipment Failure) (Primary Packaging Failure) (Component Failure) (Facility/ utilities)	Unwanted Event	Severity (SEV) Impact of the Hazard	Cause/Process Failure	OCCURANCE (OCC) The Chance that the Process Step Will Fail	Existing Controls	DETECTION (DET) The Chance that We Will NOT Detect the Process Failure	RPR *Includes Severity, *Occurrence *Detection	Risk Accepted (Yes/No)	Risk Controls	Rankings after Risk Control Actions				
											SEV	OCC	DET	RPR	Risk Accepted
1	Component Failures	Endotoxin Contamination	High	Incoming powder raw material is endotoxin contaminated.	**Medium** (Endotoxin is not controlled during manufacturing. Incoming endotoxin levels are not consistent from lot to lot.)	Incoming sampling and testing program for endotoxin with accept/reject specifications.	**High** (Difficult to detect in small sample size from individual areas of the holding container. Typically endotoxin is not evenly distributed throughout a powder material.	High	NO	Conduct vendor audit. Have vendor add an in-process endotoxin reduction step and validate process to ensure consistent quality from lot to lot.	High	**Low** (The validated in-process depyrogenation step reduces the likelihood that the powder will contain levels of endotoxin that exceed specifications.)	**High** (Increased sample size and number of samples will not increase the likelihood of high endotoxin because powder is not evenly distributed.)	Medium	NO
2	Component Failures	Endotoxin Contamination	High	Incoming closures are contaminated with endotoxin.	**Medium** (The rubber components are manufactured under high heat, but handling and storage conditions after the heat-processing step are not known.)	Incoming sampling and testing program for endotoxin with accept/reject specifications.	**High** (Endotoxin is not easily detected and not evenly distributed.)	High	NO	Supplier audit ensures manufacturer has adequate manufacturing, storage and handling controls in place to reduce the likelihood of endotoxin contamination on incoming closures. Requalify incoming test to improve endotoxin detection and increase sample size.	High	**Low** (Measures to control endotoxin contamination at the closure manufacturer will reduce the likelihood that the incoming closures will be contaminated.)	**Medium** (Requalification of sample preparation in test method to improve endotoxin detection.)	Medium	YES
3	Component Failures	Endotoxin Contamination	High	Closures are not properly depyrogenated because the process is manual.	**Medium** (Historically, occasional endotoxin failures have occurred with manual processes.)	Validated procedures and hold times are in place. Operators are trained. WFI is tested and must meet specifications. Incoming closures are tested for endotoxin. Endotoxin is detected during product release testing.	**Medium** (Endotoxin in the finished product is more evenly distributed in liquid form, but testing is conducted on a small number of samples.)	High	NO	Automate and validate depyrogenation of closures to replace the manual process. Purchase sterile and depyrogenated closures from a qualified vendor. Increase number of samples to be tested for product release.	High	**Low** (A validated automated depyrogenation process will decrease the likelihood of closure contamination.)	**Low** (An increased number of samples increases the likelihood that the endotoxin will be detected.)	Low	YES

5.0 Conclusion

Relative to other pharmaceutical processes, the manufacture of sterile products using aseptic processing is inherently high risk. This is due to the impact on the patient because of potential sterility failures and unacceptable endotoxin levels. Control of sterility assurance and endotoxin levels presents a challenge to the pharmaceutical industry and to regulators reviewing risk studies. Managing risk of failures and knowledge of residual risk is essential to an effective aseptic processing quality program.

Quality risk management is a useful process for decision-making during process development, facility design, equipment selection, change control and failure investigation, as well as validation activity planning and prioritization. As demonstrated in the model presented by this task force, this process is an effective means of assessing, controlling and reviewing risk in aseptic processing.

The models and examples provide practical suggestions on risk assessment and are not meant to be all inclusive or exclusive.

The approach used for quality risk management should be practical, useful, not overly burdensome and commensurate to the task at hand. It is important to remain objective when evaluating process steps in order to avoid preconceived notions and conclusions and to resist using the risk assessment process to justify opinions and desired results.

It is important to understand the purpose of the risk assessment. Risk assessments should not be performed solely to satisfy a procedural requirement. Instead, the outcome of the risk assessment should be used as one piece of the information guiding quality-related decisions.

The sole purpose of quality risk management should not be simply to assess and communicate risk. Recognizing, yet ignoring risk is not productive. Organizations should facilitate methods to use the concepts and principles presented in this report and other publications to make better decisions and improve the efficiency and effectiveness of their operations. The ultimate goal of quality risk management should be to reduce risk, understand residual risk, improve the effectiveness of the process, preserve the quality of the product, and maintain patient safety.

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6.0 Appendix

The following two examples illustrate the flexibility of the risk assessment model described in **Section 4.1** of this report by using a modified version of the spreadsheet. In addition, the third example uses an RPN "scoring" method for determining risk.

6.1 Risk Assessment of Aseptic Filling – Example Three

This example uses an alternate method of risk scoring known as an RPN. RPN scoring may be a more appropriate scoring technique when the team wishes to quantitatively rank risks that have been identified. The RPN scoring used in this example is for illustrative purposes only and should be independently developed based upon the organization's interpretation of risk potential for their application.

Process Description: This case study focuses on a high-speed, conventional aseptic filling line. In the initial design of the line, operations had to be performed manually, resulting in numerous manual interventions per shift. For example, vial stoppers were added manually, requiring frequent intrusions into the Grade A environment. For every human intervention, there is an increased risk of contamination. The larger the number of interventions, the greater the risk of potential sources of contamination that could lead to a sterility failure.

To help assess the risks and improve the filling-line design, environmental monitoring was used to detect and quantify particulates. The intent was to focus resources on the operations with the greatest risk, and then identify specific redesigns or procedural controls to reduce the risk.

6.1.1 Risk Priority Number Determination

The model will be used to assess and reduce the risks for specific process steps that may contribute to a contamination failure. An RPN would be calculated for each of the operations in this filling line, as depicted in **Figure 6.1.1-1**. With this level of specificity, a semi-quantitative approach has been chosen using numerical values, and an RPN is calculated. The RPN is calculated using Severity × Occurrence × Detection. In this example, the unwanted event is the loss of sterility assurance.

Figure 6.1.1-1 – RPN Ranges

Scale 1–10	RPN
Severity × Occurrence × Detection	<70
	71–99
	≥100

6.1.1.1 Severity

Severity has been assigned a value of 10. Events contributing to the loss of sterility assurance will always be considered very high (10) because of the direct and severe impact to the patient.

6.1.1.2 Occurrence

It is difficult to quantify the correlation between the impact of personnel intervention and sterility failure. However, in an effort to demonstrate the use of the model, the number of interventions in critical areas was assessed. In this example, incursions into the Grade A area to refill a stopper bowl was one of the operations evaluated. Occurrence in this model was determined as follows:

(8–10) The number of inventions is frequent (more than one per hour) in critical areas.
(4–7) The number of interventions is less frequent (less than one per hour) in critical areas.
(1–3) The number of interventions is infrequent (less than one per shift) in critical areas.

6.1.1.3 Detection

Environmental monitoring of particulates was used for detection to help quantify risk. The assumption is that the greater the number of particulates generated for a particular operation, the greater the risk to sterility. Better or more frequent testing of these particulates would improve detection and lower the risk. Detection in this model was determined as follows:

(8–10) Intermittent manual testing of critical areas
(4–7) Intermittent automated testing with probes in critical areas (close proximity)
(1–3) Continuous automated testing with independent probes placed in critical areas (close proximity)

6.1.2 Risk Assessment

The initial assessment (model row #1) indicates that the use of a manual stopper-feed system requires many interventions and poses an inherently high risk. Intermittent manual testing for particulates in critical areas is not a robust method, therefore detection is low, and an RPN of 560 is calculated.

6.1.3 Risk Acceptance

For the purposes of this assessment, an initial risk acceptance RPN of 100 has been established as the target risk acceptance value. This acceptance value will be reassessed periodically to further reduce risk in this aseptic process. Therefore, the RPN of 560 for this process step is not accepted.

6.1.4 Risk Reduction

The assessment team then identified three possible means to reduce the risk. These included: better aseptic technique training, enhanced environmental monitoring, and a larger, automated hopper placed outside the enclosure. Note that other steps to reduce risk may be identified by the reader; however, these steps were chosen to illustrate use of the model for simplicity.

An assessment of these risk reduction steps are presented in the model. Only the use of the automated hopper (which reduced the number of interventions) and improved environmental monitoring resulted in an acceptable RPN. However, the use of the hopper may pose additional risks.

In process Step #2, the team assessed the impact of installing a larger, semi-automated stopper bowl and determined that the residual risk was found to be acceptable. Note that the use of the larger hopper may increase the duration of the intervention. The assessment team would be encouraged to also consider this factor in its assessment of the process step change.

6.1.5 Ongoing Risk Evaluation and Acceptance

The decision of this team was to put the automated hopper into permanent use. The team will continue to evaluate other manual interventions that are performed frequently during the filling operation. In this example, intermittent automated sampling for detection was sufficient to assess risk. Improved detection by installing continuous automated testing may be necessary to further assess and differentiate risks with other manual interventions in the filling process.

Once implemented, a periodic review of process performance is conducted to determine if the recommendations made by the assessment team are effective, and if they are not, what steps may be necessary to further reduce residual risk.

6.1.6 Risk Assessment of Aseptic Filling – Example Three Model

Table 6.1.6 (opposite page) is an example of the model using the FMEA approach that reflects the risk assessment made and its outcome.

Table 6.1.6 Risk Assessment of Aseptic Filling – Example Three Model

REF #	Unwanted Event	Process Step (Personnel) (Process) (Equipment Failure) (Primary Packaging Failure) (Component Failure) (Facility/ Utilities)	Causes/ Process Failure	Existing Controls	SEVERITY	OCCURRENCE The chance that the process step will fail and cause a loss of sterility assurance	DETECTION The chance that we will not detect the process failure	Risk Includes Significance, Occurrence, Detection	Risk Accepted (Yes/No)	Reduction (New controls, new design, procedures)	SEVERITY	OCCURRENCE The chance that the process step will fail and cause a loss of sterility assurance	DETECTION The chance that we will not detect the process failure	Risk Includes Significance, Occurrence, Detection	Risk Accepted (Yes/No)
1	Loss of Sterility Assurance	Personnel	Manual addition of stoppers to filling line bowl could result in microbial contamination of product contact components or product	Aseptic technique training, environmental monitoring, and simulation studies	10	7 (The number of interventions or times stoppers that must be added is high.)	8 (The likelihood of detecting particulates contamination is low.)	560	NO	Better aseptic technique training	10 (Severity remains unchanged.)	5 (While it is possible that better training will decrease the likelihood of a process failure, the number of interventions do not change.)	8 (Detection remains unchanged.)	400	NO
1a										Enhanced environmental monitoring (intermittent automated testing)	10 (Severity remains unchanged.)	7 (Occurrence remains unchanged.)	4 (The level of monitoring has increased.)	280	NO
1b										Add a larger fully automated hopper that reduces the number of stopper additions to less than one per shift.	10 (Severity remains unchanged.)	1 (The use of the larger hopper decreases the number of interventions.)	4 (Monitoring level has increased has well.)	40	YES*
2		Equipment *Use of the larger, fully automated hopper presented in Step #1b (risk reduction step) may introduce new risk. Process Step #2 assesses this residual risk.	Placement and use of larger, fully automated hopper for stopper handling could result in microbial contamination from inadequate equipment sterilization.	Equipment sterilization procedures and environmental monitoring	10	1 (The hopper will be sterilized using a validated sterilization process.)	4 (The likelihood of detecting particulates as a result of this change remains the same.)	40	YES						

6.2 Risk Assessment of Autoclave Failure – Example Four

This autoclave failure example depicts a comprehensive evaluation of various process failures. In addition, the model includes a column to identify the quality systems associated with the process failures. The risk assessment model used for this example is comparable to the exceeding of endotoxin levels (Example 2), in which process steps are categorized as a guide in performing the risk assessment.

Process Description

In this example, the unwanted event is a sterility failure that has occurred. The autoclave sterilization process used to support the filling operation has been identified as one step of the aseptic process, which, if it failed, could be the cause of the sterility failure. Process step failures associated with the autoclave use were considered for each category (personnel, process, equipment, primary packaging, component and facility/utility) listed in the model.

For the "personnel" category, the causes were those identified with the use of the autoclave and personnel's performance impact on the sterilization process. For example, if an item is wrapped with the wrong material or loaded in a way that has not been validated to allow steam penetration, there is the likelihood that the items will not be successfully sterilized, regardless of the proper functioning of the autoclave.

For the "process" category, the causes were those identified with the autoclave cycle and the factors that support a successful sterilization cycle. For example, if the cycle deviates from the validated parameters of time, temperature and pressure, product quality may be impacted. It was noted that changing the process related to sterility assurance (i.e., resetting sterilization dwell time based on low temperature) may result in additional risk to other product quality attributes. Therefore, it is recommended that a risk assessment be performed on the revised process with regard to the potential impact to product quality.

For the "equipment" category, the causes were those directly related to the functioning of the autoclave. For "facilities/utilities," the causes identified were those related to the steam supply, which is required to support the sterilization process. "Primary packaging" failure and "component" failure do not apply in this example.

The risk rankings were determined based on **Table 4.2.2.4-1** in Example 2. Severity ranking is always "high" for a sterility failure. The resulting RPR was entered into the "Risk" column and the decision whether to accept the risk was entered in the "Risk Accepted (Yes/No)" column of the model. The risk assessment team determined that risks with a ranking of "high" or "medium" were not acceptable and further action to reduce the risk would be taken.

6.2.1 Risk Assessment for Autoclave Failure – Example Four Model

The following table is an example of the model using the FMEA approach that reflects the risk assessment made and its outcome.

Table 6.2.1 Risk Assessment for Autoclave Failure – Example Four Model

Item	Unwanted Event	Process Categories (Personnel) (Process) (Equipment Failure) (Primary Packaging Failure) (Component Failure) (Facility/ Utilities)	Causes / Process Failure	Existing Controls	SEVERITY	OCCURRENCE The likelihood that the process step will fail	DETECTION The likelihood that we will NOT detect the process failure.	Risk Includes Severity, Occurrence, Detection	Risk Accepted (Yes/No)	Reduction (new controls, new design, procedures)	SEVERITY	OCCURRENCE The likelihood that the process step will fail.	DETECTION The likelihood that we will NOT detect the process failure.	Risk Includes Significance, Occurrence, Detection	Risk Accepted (Yes/No)	Quality System (Facilities and Equipment) (Laboratory Control) (Packaging and Labeling) (Production) (Quality) (Materials)
1	Sterility Failure (boundary final product)	Personnel	Autoclave parameters are not set up correctly.	SOP's and training, review of chart recording	HIGH	**Medium** (Autoclave parameter settings are entirely operator-dependent and directly impact the sterilization process. This failure occurs with some frequency.)	**Low** (Review of chart recording from process monitor will show if proper parameters were set.)	MEDIUM	NO	Use new digital control system with predefined recipe parameters with security access to prevent unauthorized changes; new autoclave	HIGH	**Low** (Operator selects only one of two recipes; settings are pre-programmed and automatic.)	**Low** (Auto fault detection, review of printout)	LOW	YES	Quality systems (training, supplier quality, auditing)
2			Load items wrapped incorrectly	SOP's, training of Operators, visual check for proper wrapping prior to loading the autoclave	HIGH	**Low** (Wrapping is a manual procedure that is operator-dependent. Improper wrapping rarely occurs.)	**Low** (Visual inspection is highly effective.)	LOW	YES	**None** (no further reduction possible)	N/A	N/A	N/A			Quality systems (training, auditing); facilities and equipment; laboratory controls
3			Load items placed in wrong (non-validated) location	SOP's, training of operators, visual check for proper load configuration prior to starting the autoclave sterilization	HIGH	**Low** (Loading the autoclave is operator-dependent. Improper load configuration inside the autoclave rarely occurs.)	**Low** (Visual inspection of the proper load configuration is very effective.)	LOW	YES	**None** (No further reduction possible.)	N/A	N/A	N/A			Quality systems (training, management responsibilities), production controls

4	Sterility Failure (boundary final product)	Process	Excess exposure to heat (liquid cycle) due to sterilization timer being reset when T <121°C during cycle	Preventive maintenance of autoclave; review of chart recording from process monitor.	HIGH	**Low** (There was no adverse impact to sterility due to longer sterilization times.)	**Low** (Review of chart recording from the process monitor shows sterilization time.)	LOW	Yes (Product temperature sensitivity/ loss of product potency should be evaluated.							Production facilities and equipment, laboratory control
5			Steam quality not sufficient for sterilization (excess air is left in autoclave)	SOPs and training, validated sterilization cycles	HIGH	**Medium** (Gravity of steam is the driving force to remove air. No data to support occurrence but there is a known potential issue due to the inherent limitations of steam-gravity-air displacement autoclave.)	**High** (There is no way to know if pockets of air were not removed)	HIGH	No	Utilize multiple pre-steam vacuum pulses to assure the removal of all air prior to sterilization.		**Low** (Use of multiple vacuum cycles reduces the likelihood that pockets of air adversely impacting the sterilization process would be entrapped.)	**Low** (Auto fault detection if inadequate vacuum)	LOW	YES	Production, facilities and equipment
6			Inadequate sterilization of media due to low/variable starting liquid temperature	SOPs and training, review of chart recording, validation of sterilization cycles	HIGH	**High** (Low/variable starting fluid temperature is known to occur on a frequent basis.)	**Medium** (Review of chart recording from process monitor does not show starting temperature of media.)	HIGH	No	Upgrade sterilization cycle control to allow sterilization time based on actual temperature of media; new autoclave with auto jacket preheat	HIGH	**Low** (Cycle time is based on actual media temperature.)	**Low** (Auto fault detection, process information would be monitored and recorded directly from the media temperature driving the sterilization cycle.)	LOW	YES	Production, facilities and equipment

7	Sterility Failure (boundary final product)	Equipment Failure	Failure of analog cycle timers to turn on or shut off correctly (mechanical failure)	Manual observation of cycle chart recording, equipment preventive maintenance program.	HIGH	**Medium** (This event is known to occur occasionally.)	**Low** (Review of cycle chart recording from process monitor shows time, temperature and pressure during each phase of cycle.)	MEDIUM	No	Replace analog timers and control system with digital systems. Add auto fault detection.	HIGH	**Low** (Based on better mechanical reliability)	**Low** (Auto fault detection)	LOW	YES	Quality system, facilities and equipment, production controls
8			Failure of steam control valve to adequately control steam pressure	Manual observation of cycle chart recording, equipment preventive maintenance program.	HIGH	**Low** (This event rarely occurs.)	**Low** (Review of cycle chart recording from process monitor shows steam pressure for each phase of cycle.)	LOW	Yes	None	N/A	N/A	N/A	N/A	N/A	Quality systems, facilities and equipment; production controls
9			Autoclave door seals leaks allowing ingress of non-sterile air during cool down phase of cycle.	Periodic leak test	HIGH	**Low** (This event rarely occurs.)	**Medium** (Leak test is effective, but only performed periodically. There is no means to determine leaks between test periods.)	MEDIUM	No	Install new control system that automatically checks for leaks pre- and post-sterilization cycle (pressure hold test)	HIGH	**Low**	**Low**	LOW	YES	Quality systems: facilities and equipment, production controls
10			Vent filter integrity failure allows ingress of unclean air into the autoclave after the sterilization cycle.	Monthly filter integrity check	HIGH	**Low** (This event rarely occurs.)	**Low** (Vent filter integrity test is completed monthly. Integrity test is very effective.)	LOW	Yes	None	N/A	N/A	N/A			Quality system: facilities and equipment, production controls
11		Primary Packaging Failure	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Packaging, labeling facilities and equipment materials
12		Component Failure	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Packaging, labeling facilities and equipment materials
13		Facility / Utilities	Excessive Steam Condensate	Steam trap in place. Monitor Temperature and pressure data.	HIGH	**Medium** (This event is known to occur occasionally)	**Low**	MEDIUM	No	Improve preventive maintenance and trap design. Maintain steam jacket pressure.	HIGH	**Low**	**Low**	LOW	YES	Facilities and equipment

Fold open for Table 6.2.1
Risk Assessment for Autoclave Failure – Example Four Model

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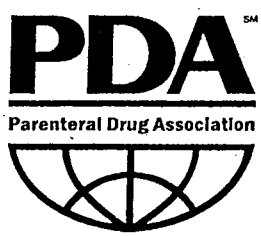

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