

# Technical Report No. 44

## Quality Risk Management for Aseptic Processes

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## **PDA Quality Risk Management Task Force Members**

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**Ruhi Ahmed**, PhD, BioMarin Pharmaceutical Inc

**Harold Baseman**, ValSource LLC

**Kristen D. Evans**, Amgen

**Jorge Ferreira**, Jacobs Engineering Group, Inc.

**Thomas Genova**, PhD, Johnson & Johnson Global Biological Supply Chain LLC

**William Harclerode**, Forest Laboratories, Inc.

**Jeffrey L. Hartman**, Merck & Co., Inc.

**Samuel Kim**, Biogen Idec, Inc.

**Nanette Londeree**, Consultant, Bayer Healthcare (retired)

**Michael Long**, AstraZeneca

**William H. Miele**, PhD, Pfizer Inc

**Timothy Ramjit**, Schering-Plough Corporation

**Marlene Raschiatore**, Wyeth Pharmaceuticals

**Charles Tomonto**, PhD, Cordis, a Johnson & Johnson Company

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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 fish-bone 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.

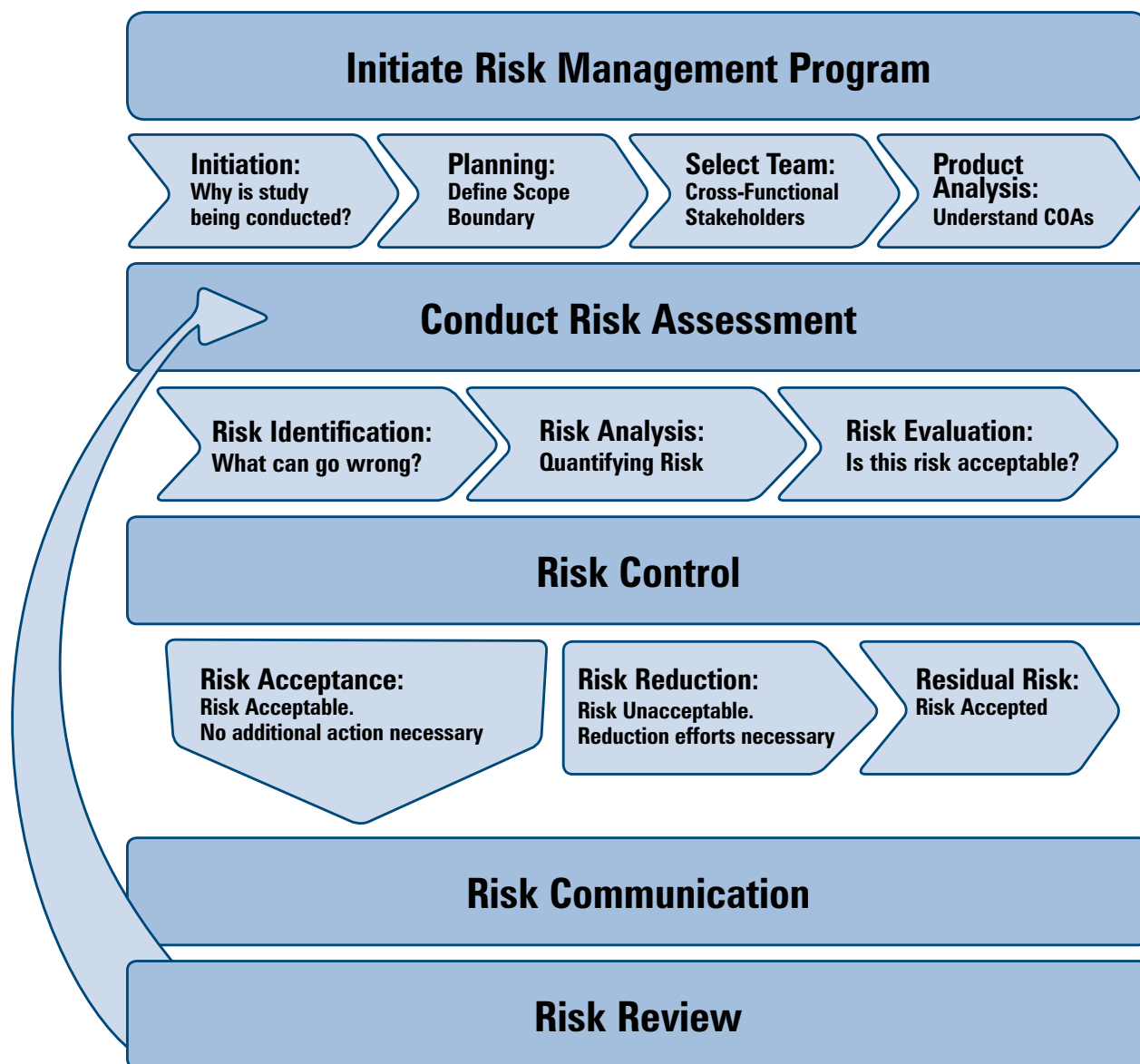
As described in ICH Q9, a quality risk management program embodies the following concepts:

- 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)** 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.