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ASEPTIC PROCESSING RISK MANAGEMENT: A REVIEW

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ABSTRACT

Aseptic processing is a widely used technology in the field of pharmaceutical, biotech, and medical device industries for the preparation of sterile materials. The term aseptic processing as it is applied in the pharmaceutical industry refers to the assembly of sterilized components and product in a specialized clean environment. Aseptic processes are some of the most difficult processes to conduct in the pharmaceutical industry. Because of the nature of aseptic processes, sterile products produced aseptically present a significantly higher risk to the patient than terminally sterilized products. Because of the high level of risk, an effective quality risk management program is necessary to protect the patient. An effective risk-management program aids in the careful control of the process, reducing the risk of contamination as well as wasted effort in controlling insignificant risks.

INTRODUCTION: A sterile product is one that is free from all living organisms, whether in a vegetative or spore state. This is an absolute condition, something cannot be partially or nearly sterile, the presence of a single viable organism represents a failure of the product, and the systems (environment, equipment, and procedures as well as operators) used to produce it. Asepsis, that state in which all aseptically filled sterile products are manufactured, cannot be established as "sterile." Aseptic processing is the most demanding of manufacturing processes. It requires precise attention to operator training and behavior, process validation, production process documentation, plant and equipment maintenance and change control management [1]. Sterile Products may be broadly classified into two main categories, according to the manner in which they are produced: those which are sterilized after the product has been filled and sealed in the final container(s) ("terminally sterilized" products) and those where the sterilization stage (or stages) takes place before the bulk product is filled. In this latter instance, all subsequent processing (typically, the filling and sealing operations) must be conducted aseptically in order to prevent recontamination of the sterilized product.

It is recognized that aseptic processes play an important role in rendering sterile formulations which cannot be terminally sterilized. However, terminal sterilization, in particular using moist heat processes, is considered to be the method of choice in the manufacture of sterile products due to the enhanced sterility assurance which it affords. Manufacturers who choose to manufacture a sterile product without terminal sterilization must be prepared to justify this decision by demonstrating that the product cannot be terminally sterilized, even under less severe autoclave cycles tailored to the bioburden of the batch (Probability of Survival approach). The two most common pharmaceutical applications of aseptic processing methods are (a) the filling of liquid products following sterilization by filtration and (b) the filling of previously sterilized bulk powder products [2].

Aseptic Processing in Pharmaceutical Companies: Aseptic processing is the most demanding of pharmaceutical manufacturing processes. It requires precise attention to operator training and behavior, process validation, production process documentation, plant and equipment maintenance and change control management. Regulators will endeavor to ensure that the safety of the health care consumer is never compromised. Aseptic processing attracts a high level of regulatory scrutiny due to the risks associated with this type of manufacturing and its potential adverse effect on the health care consumer. Contamination of an aseptic process can have a serious impact on a company's financial viability, manufacturing license and industry reputation. Regulatory GMP codes for the aseptic manufacture of human and veterinary products mandate that an incidence involving product sterility failure or media fill contamination is fully investigated and also that the manufacturer establishes an environmental monitoring program that is properly validated to ensure that environmental contaminates are detected.

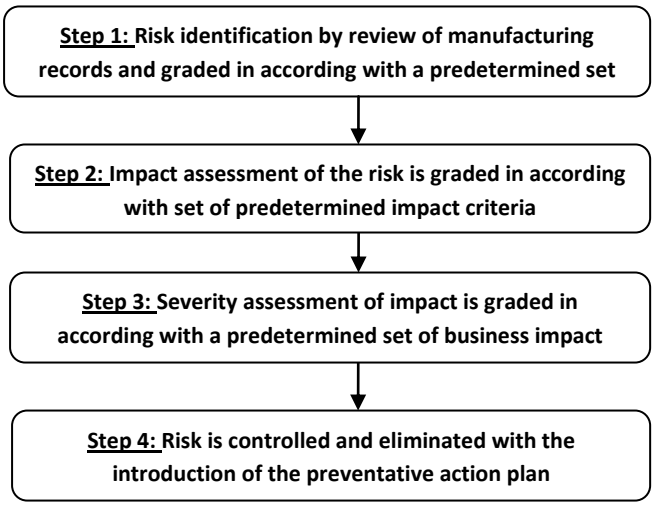

FIGURE 1: STEPS INVOLVED IN RISK MANAGEMENT

TABLE 1: THE MAIN AREAS OF INVESTIGATION IN PHARMACEUTICAL COMPANY

Area of Investigation	Description
Environmental monitoring results and trends	All environmental monitoring results and trends from the process are systematically reviewed to establish the presence of or increasing levels of bioburden.
Environmental cleaning	Environmental cleaning documentation is reviewed to ensure conformance to procedures.
Operator behavior	Operators are observed and appraised for conformance to "correct" clean room behavioral standards.
HVAC operations	The operational data from the HVAC is analyzed to ensure conformance to validated limits.
Sterilization processes	The operational data from autoclaves, hot air sterilizers, ethylene oxide and gamma irradiation etc are reviewed to ensure conformance with validated limits.
Process deviations/observations	The batch/lot manufacturing records are reviewed for the documentation of process deviations/observations.
Process validation	The Process Validation procedures and results are examined to determine whether the process was carried out within validated limits.
Test Methods	Quality Control product sterility and microbial test methods are investigated to ensure they were performed correctly and are appropriately validated.
Change Control	An investigation is carried out to establish whether approved or non approved changes were introduced into the process and if so, what impact the change may have had on the aseptic process [3].

Risk Management for Aseptic Processing: Aseptic processes are some of the most difficult processes to conduct in the pharmaceutical industry. Because of the nature of aseptic processes, sterile products produced aseptically present a significantly higher risk to the patient than terminally sterilized products. Because of the high level of risk, an effective quality-risk-management program is necessary to protect the patient. An effective risk-management program aids in the careful control of the process, reducing the risk of contamination as well as wasted effort in controlling insignificant risks.

Aseptic Process: Aseptic processing involves manipulation of sterile components in a carefully controlled environment using careful techniques to produce a sterile product. While aseptic processing usually involves filling of final drug product, there are other types of aseptic processes, including aseptic assembly of devices or combination products, aseptic crystallization or aseptic precipitation of drug product to produce a sterile bulk-drug substance, and aseptic formulation of final drug product. One thing all aseptic processes have in common is their high level of risk. They require careful control of the aseptic environment, of personnel practices and procedures, sterilization of equipment and components, extensive environmental monitoring, and many other controls. The number of controls required and the severe consequences of control failure make aseptic processing one of the highest-risk pharmaceutical processes. Quality risk management is an essential tool in ensuring product quality.

Quality risk management (QRM): Risk is the combination of the probability of harm and the severity of harm. For the purposes of QRM, it is the risk to the patient that is important, not the risk to other stakeholders such as government, industry, medical practitioners, etc. According to ICH Q9, quality risk management is defined as "a systematic process for the assessment, control, communication, and review of risks to the

quality of the drug product across the product lifecycle" [4.] Some key concepts in this definition are that QRM is a systematic process, and that it is designed to manage the risks to product quality across the product lifecycle. The introduction of a systematic process for managing product quality is crucial to consistently providing a high-quality product to the customer. ICH Q9 defines the two primary principles of quality risk management are;

- The evaluation of risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient.
- The level of effort, formality, and documentation of the quality- risk-management process should be commensurate with the level of risk [4.]

These principles lead to a need for a formal risk-management program for manufacturers of parenteral products. Because these products, which include most biotechnology-derived drugs, bypass many of the body's defense systems, the level of risk to the patient is significantly higher than in oral or topical products. Although quality risk management (QRM) is a relatively new concept to the pharmaceutical industry, it has been used in other industries for many decades, with some risk-assessment tools dating back to the World-War-II era.

The pharmaceutical industry has been slow to adopt many of these tools because of the industry focus on regulatory compliance as the driving force for quality. This traditional compliance based approach had its drawbacks that became more evident as the industry became more diverse and sophisticated. A "one-size-fits-all" approach to quality became increasingly unworkable, leading the US Food and Drug Administration to develop a quality systems approach to regulation. The quality systems approach to the pharmaceutical industry was launched on a large scale with the FDA publication of Pharmaceutical CGMPs for the 21st Century- a Risk Based Approach in August 2002 [5]. There are many potential uses for quality risk management in the pharmaceutical industry, including:

- Determining the scope, complexity, and frequency of internal and external audits,
- Identifying, evaluating, and communicating the potential quality impact of quality defects, complaints, trends, and non-conformances,
- Providing a framework for evaluation of environmental monitoring data,
- Evaluating the impact of changes to the facility, equipment, or process on product quality,
- Establishing appropriate specifications and identifying critical process parameters during product and process development,
- Assisting facility design (e.g., determining appropriate material, equipment, and personnel flows, appropriate level of cleanliness for processing areas),
- Determining the scope and extent of qualification of facilities, buildings, and production equipment and/or laboratory instruments (including proper calibration methods),
- Determining acceptable cleaning validation limits,
- Determining revalidation frequency,
- Determining the extent of computerized system validation,

- Identifying the scope and extent of verification, qualification, and validation activities,

- Determining the critical and noncritical steps in a process to assist in the design of process validation

The uses for quality-risk-management tools are nearly limitless. A few examples of the uses of these tools in aseptic processing include:

- **Equipment and Facility Design:** QRM tools such as 3-D risk assessment can be used to identify high-risk equipment and facilities, as well as low-risk equipment and facilities; this will allow risk-control efforts to focus on eliminating the highest risks [6]. Design of high-risk equipment and facilities can be enhanced using input from tools such as failure mode and effects analysis (FMEA) and fault tree analysis to identify potential failure modes. This input allows the equipment designer to add preventive measures to the equipment design to reduce the occurrence of, or even eliminate, potential failure modes.

- **Equipment and Facility Qualification:** QRM tools can be used to identify the critical aspects of the aseptic processing equipment or facility that need to be intensively qualified, and the low-risk aspects of the equipment or facility. QRM tools can also be used to determine the extent and frequency of requalification efforts.

- **Change Control:** QRM tools can be used to identify high-risk equipment and facilities that need to be maintained under strict change control, as well as the equipment and facilities that can be placed under a simpler engineering change management program.

- **Process Validation:** QRM tools can be used to identify the key inputs, key process parameters, and key outputs that need to be monitored and controlled. This allows for focused process validation that ensures that process parameters that are critical to product quality are appropriately validated.

The Quality Risk-Management Process:

Risk Assessment: Risk assessment is the first portion of the quality risk-management process. It consists of identifying potential hazards, analyzing hazards, and risks associated with exposure to those hazards. A few key points about the risk assessment process include:

- Risk assessments should be performed by a team of qualified experts from disciplines such as engineering, quality assurance, validation, and manufacturing, preferably facilitated by someone familiar with the risk assessment process. This team should clearly define the risk question. A poorly defined risk question can lead to lack of focus in the risk assessment.

- Three fundamental questions should be answered in the risk assessment: What can go wrong, how likely it to go is wrong and how severe are the consequences.

- A few of the more popular methods for risk assessment are given in the "Risk assessment tools" section. These tools share some of the key characteristics of a risk assessment process,

- Systematic identification of hazards referring to the risk question (risk identification),

- Estimation of the risk associated with the identified hazard (risk analysis),

- Comparison of the identified and analyzed risk against pre-determined criteria (risk evaluation).

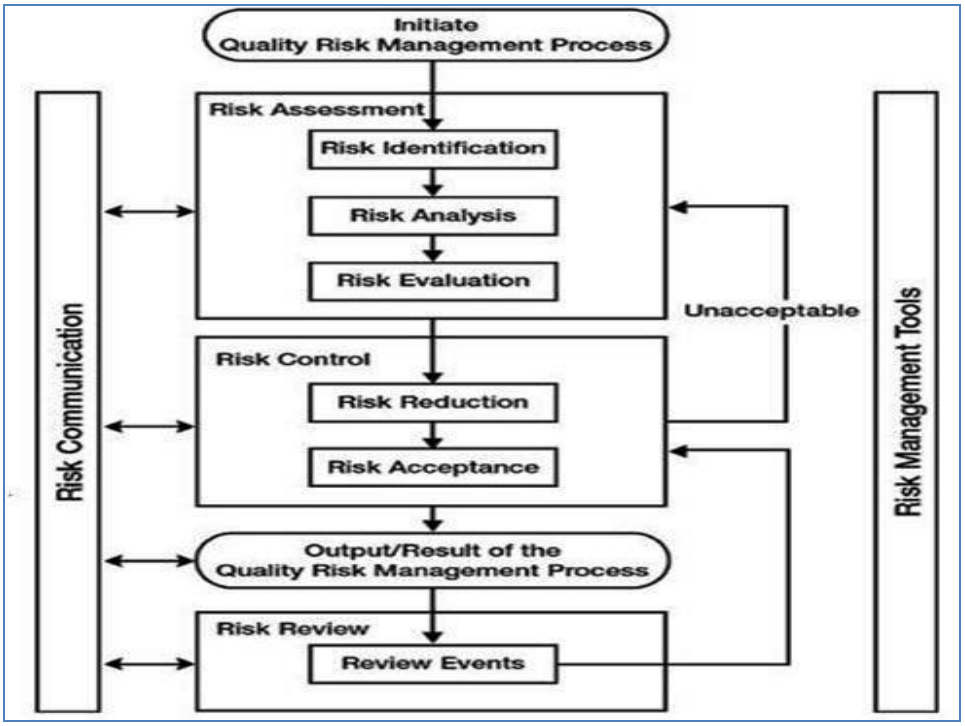

FIGURE 2: RISK-MANAGEMENT PROCESS

The output of the risk-assessment portion of the risk-management process is used in the risk-control portion of the risk-management process

Risk Control: Risk control consists of developing a plan to reduce and/or accept risks. The purpose of risk control is to reduce risk to an acceptable level. The formality and effort of risk control should be appropriate for the level of risk. The following questions should be asked during this phase: a) Is the risk level acceptable? , b) What can we do to reduce or eliminate risks? c) What is the right balance between risks, benefits, and resources?, d)Do the risk control efforts introduce new risks?

A risk control plan may be the output of the risk control process. This plan may be included in a project plan or validation master plan, as part of the risk-communication process.

Risk Communication: Risk communication is simply that the communication of risks between decision makers and other interested parties, either within or outside the company. This may be done formally or informally, as appropriate for the risk level of the product and process.

Risk Review: Risk review is simply periodic review of risks as part of the ongoing quality management process. Examples of where formal or informal risk review might be performed include periodic management review, as part of a change control program or as part of annual product reviews. However it is performed, risk review should be integrated into the quality-management system.

Risk Assessment Tools: The following is a partial list of some of the risk-assessment tools used in the pharmaceutical industry. This is hardly a comprehensive list. There are numerous risk-assessment tools available in different industries and for different functions within the same industry

3-D risk Assessment: Three-dimensional (3-D) risk assessment is a risk assessment tool that takes into account a system's distance from the process stream, its location along the process stream (e.g., active pharmaceutical ingredient [API] synthesis, and purification, bulk product

formulation, sterile filtration, filling and stoppering, etc.), and the system's complexity [6].

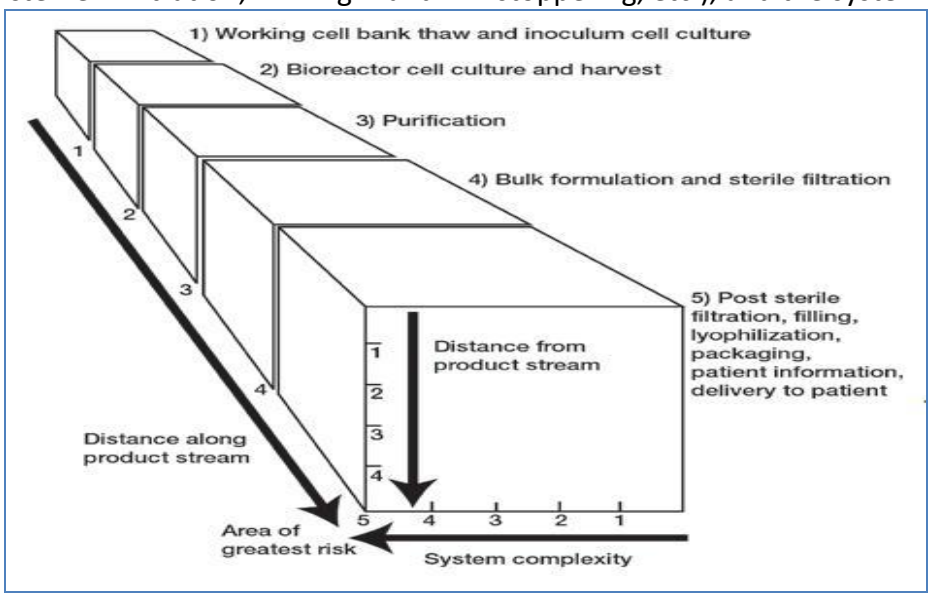

FIGURE 3: 3-D RISK ASSESSMENT MATRIX

This tool is mainly used to assign a risk level to an overall system. Where appropriate, additional risk assessment tools may be used to evaluate risks within a pharmaceutical system.

Failure mode and effects analysis (FMEA): Failure mode and effects analysis (FMEA) is one of the most commonly used methods for pharmaceutical risk assessment. It is a team-based structured risk assessment method that can assign a numerical risk priority number based on relative perceived risk. A FMEA is dependent on the expertise of the team members.

TABLE 2: SAMPLE FMEA FOR FILL LINE CHANGE OVER

System ID usage	Failure mode	Potential effects	S	Potential causes	O	Current controls	D	RPN	Risk mitigation
Gasket and silicone tubing changed between products to prevent cross contamination	Gaskets and tubing not changed out between products	Residual product could remain in tubing or gaskets, contaminating next product	5	Operator error, inadequate instructions	5	None	5	125	Use documented operator check to ensure change over is performed
			5	CIP is not performed	1	Filler interlocked to prevent use without CIP/SIP	1	5	Current controls are adequate
Filler is cleaned in place to ensure removal of residual product	Filler not cleaned properly	Residual product could contaminate next product	5	Excessive temperature on initial rinse causes protein denaturation	1	Over temperature alarm and cycle abort	1	5	Periodic testing and calibration of alarms
			5	Automatic chemical addition fails	3	Conductivity alarm to detect failure to add chemicals	2	30	Periodic testing and calibration of alarms

S-severity, O-probability of occurrence, D-probability of detection, RPN-risk priority number. RPN is calculated by multiplying the severity times the probability of occurrence times the probabilities of detection

Hazard analysis and critical control points (HACCP): Hazard analysis and critical control a point (HACCP) is a tool mandated by FDA's Center for Food Safety and Applied Nutrition for use in the seafood industry and other food processing industries. Its use in the pharmaceutical industry was described in detail by the World Health Organization (WHO) in 2003 [7, 8]. The seven principles of HACCP include:

- Conduct a hazard analysis,
- Determine the critical control points (CCPs),
- Establish critical limits,
- Establish a system to monitor control of the CCP,
- Establish the corrective action to be taken when monitoring indicates that a particular CCP is not under control,
- Establish procedures for verification to confirm that the HACCP system is working effectively,
- Establish documentation concerning all procedures and records appropriate to these principles and their application.

Fault tree analysis (FTA): Fault tree analysis (FTA) is a risk-assessment method that begins with a failure event, and uses logic diagrams to determine the sequence of events required to cause the failure. FTA is frequently used as a design tool for critical systems. FTA can be used with other tools such as FMEA to ensure all failure modes are included and to develop estimates of the frequency of a particular failure mode. This tool is excellent for equipment design and commissioning, for determining procedural controls needed to prevent a failure event, and for determining qualification and control strategies. With modification, it can also be used to assign probabilities to each failure mode. The limitation of this tool is that it requires a large amount of time and effort to construct properly; it can expand rapidly as more detail is added. It is more suitable for large, complex systems than for simple systems because of the time and effort required [4]. FTA involves the following steps:

- Define the failure (undesired event) to study,
- Gain knowledge of the system-gather a team of experts to analyze the system,
- Construct the fault tree,
- Evaluate the fault tree,
- Develop control strategies for the identified hazards.

Implications of Risk Assessment on Processing: When a process step or other activity is determined to be high risk, these determinations should cause initiation of project activities to reduce the risk level. However, if reduction is not possible, there should be additional in-process controls, additional testing, additional training, and so on. In summary, the organization should expend additional effort to mitigate or control the risk situation. At the same time, efforts on processes or activities that are well controlled or do not represent risk can be minimized.

Implications of Risk Determination on Validation: When validating high-risk processes or activities, there should be proportionately increased sampling, testing, or more rigorous acceptance criteria to provide greater assurance of process acceptability. The 2008 FDA process validation draft guidance specifically incorporates the following risk management principles:

- Risk analysis tools can be used to screen potential variables for DOE studies to minimize the total number of experiments conducted while maximizing knowledge gained.
- Qualification of utilities and equipment can be covered under individual plans or as part of an overall project plan.

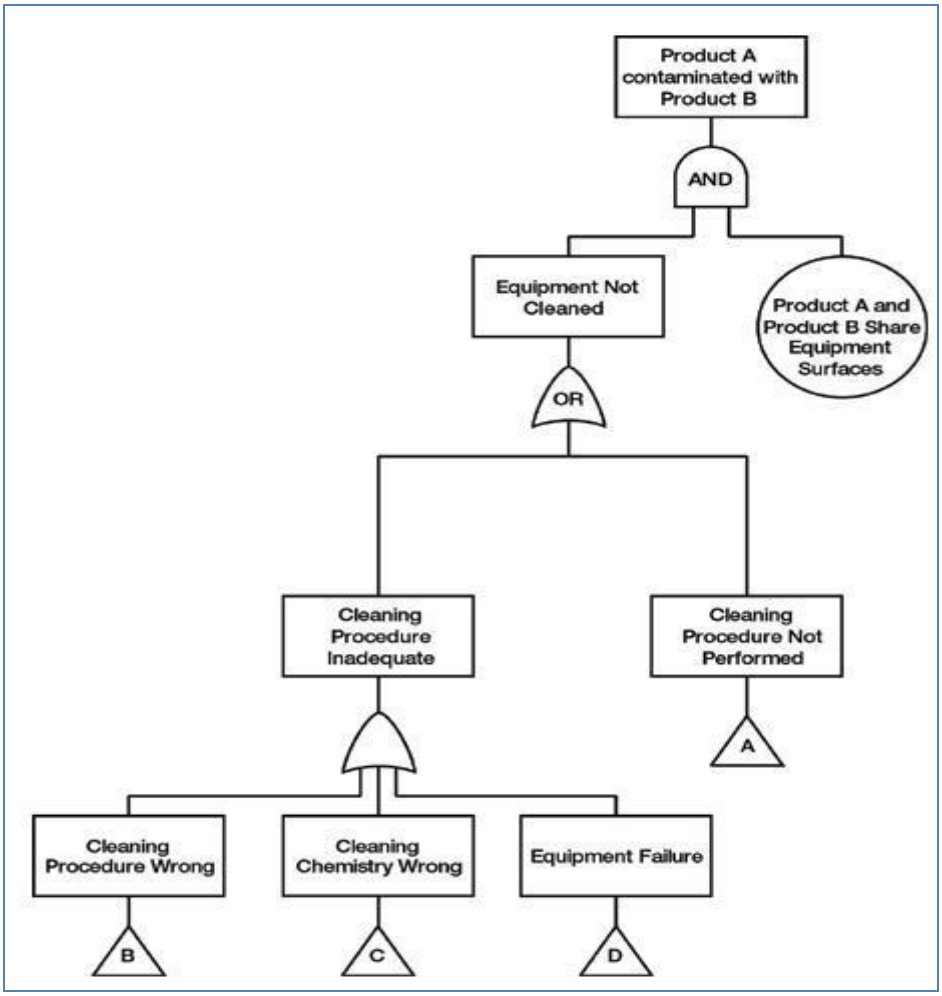

FIGURE 4: FAULT TREE ANALYSIS DIAGRAM

The plan should consider the requirements of use and can incorporate risk management to prioritize certain activities and to identify a level of effort in both the performance and documentation of qualification activities [9]. "Significant changes to the facilities, the equipment, and the processes, which may affect the quality of the product, should be validated. A risk assessment approach should be used to determine the scope and extent of validation" [10].

Risk- Assessment Tools: Risk-assessment tools are used to determine the extent of validation and frequency of validation.

Low Risk System: A chilled water system was used to cool a jacketed tank during formulation of a product prior to sterile filtration. This system contacts the tank jacket only. The chilled water system was controlled by an off-the-shelf temperature control system with a chart recorder.

TABLE 3: LOW RISK SYSTEM CHART

System	Distance along product stream	Distance from product stream	System complexity	Overall score
Chilled water system	4	1	1	4

The chilled water system is low risk system because no qualification was necessary beyond engineering commissioning of the system. Once commissioned, the system was placed under a standard PM program, and the chart recorder and temperature controller were calibrated on an annual basis.

Medium Risk System: A bulk formulation tank was used to compound a parenteral product before sterile filtration. This tank was connected to a distributed control system (DCS) that controls mixing speed and temperature according to set points entered by the operator from a local panel in the compounding area. Ingredients other than WFI were added manually by the operators. WFI was added from a WFI drop at the mixing tank, which was opened by the operator from the DCS local panel. A level transmitter connected to the tank indicates the volume of WFI added to the tank.

TABLE 4: MEDIUM RISK SYSTEM CHART

System	Distance along product stream	Distance from product stream	System complexity	Overall score
Bulk formulation tank	4	5	3	60

Based on the risk score of 60, the system was designated as a medium-risk system. Construction and operation of the formulation tank were verified under installation qualification (IQ) and operational qualification (OQ) protocols. The compounding process itself was verified under a performance qualification (PQ) protocol. After completing IQ, OQ, and PQ, the formulation tank was placed under change control. No periodic requalification was required, but periodic assessment of the system was required to ensure it maintained its validated state of control.

High Risk System: An injectable protein therapeutic was not stable in liquid form and requires lyophilization. The lyophilizer was highly automated, with automated CIP (clean in place) and SIP (sterilization in place), automated moisture content and product temperature monitoring using pressure rise methodology, and a supervisory control and data acquisition system containing the lyophilization recipes for each dosage form of the product. Product was loaded into the lyophilizer by an autoloading system

TABLE 5: HIGH RISK SYSTEM CHART

System	Distance along product stream	Distance from product stream	System complexity	Overall score
Automated lyophilizer	5	5	5	125

Based on the risk score of 125, the lyophilizer was designated a high-risk system. Extensive validation efforts, including computerized system validation (CSV), CIP, and SIP validation, IQ and OQ including shelf mapping, condenser capacity and sublimation rate, and other tests were performed to characterize the performance of the lyophilizer. PQ of the lyophilizer included surrogate lots with site-specific sampling for moisture content, cake appearance and reconstitution, followed by media fills and conformance lots for the protein therapeutic. The lyophilizer was placed under change control with periodic requalification, including shelf mapping and requalification of the CIP and SIP processes. Media fills were performed using the lyophilizer on a quarterly basis.

CONCLUSION: Quality risk management is one of the most important tools for qualification of aseptic processes. It is not just a tool for CGMP compliance; it offers real benefits to the validation process by identifying risks and ensuring that critical risks are controlled. By focusing managing risks to the patient, pharmaceutical manufacturers can ensure that the right resources are applied at the right place at the right time improving patient safety while eliminating unnecessary validation efforts.

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