# REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

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# REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

## REPORT CONTENTS

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# REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

## 1. Report Approval

This is a specific report for Risk assessment and Mitigation of Process Simulation Study which has to be carried out in Sterile Plant.

**Prepared By:**

| Name | Designation | Department | Signature | Date |
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**Checked By:**

| Name | Designation | Department | Signature | Date |
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**Approved By:**

| Name | Designation | Department | Signature | Date |
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# REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

## 2.0 Overview

### 2.1 Objective:

The Objective of this report is to adopt a systematic process for the assessment, control, communication and review of risk associated with the Process Simulation study which is to be carried out in the Sterile Plant.

### 2.2 Purpose and Scope:

The purpose of this report is to outline a scientific and practical approach for decision making process by applying a suitable tool of risk assessment covering all aspects of risk associated with Process Simulation study.

### 2.3 Risk Assessment Team:

- Production Executive/Officer/Manager
- Quality control Executive/Officer/Manager
- Projects Engineer/Sr. Engineer/Manager
- Maintenance Executive/Officer/Manager
- Quality Assurance Executive/Officer/Manager

### 2.4 Responsibility:

| S.No. | Department | Designation | Responsibility |
|---|---|---|---|
| 1. | Production | Executive/Officer/ Manager | Review of Protocol & report<br>To Provide the all relevant information that are required while undergoing Risk assessment process i.e. Quantity, Packaging etc. |
| 2. | Quality control | Executive/Officer/ Manager | Review of Protocol & report<br>To Provide information about the availability of Analytical methods<br>Pharmacopeia reference and finally reviewing the testing procedures |
| 3. | Maintenance | Executive/Officer/ Manager | Review of Protocol & report<br>To assist the risk assessment team about the technical queries of facility & equipments |
| 4. | Projects | Executive/Officer/ Manager | Review of Protocol & report<br>To assist the risk assessment team about the technical queries of facility & equipments & also provide provisions for further reduction of associated risk with facility & operations |
| 5. | Quality Assurance | Executive/Officer/ Manager | Preparation of Protocol & report<br>To review all the Procedural controls both in-house and vendor<br>To conduct audits to assess the quality management system and manufacturing facility<br>Final approval of Protocol & report By head quality Assurance |

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## 3. Introduction:

Risk analysis for Process Simulation study shall be done by considering the below mentioned factors

- The Risk Impact on the Process
- The Risk impact on the Process Equipment
- The Risk impact on the Aseptic Environment of the Plant
- The Risk impact on the Product Quality & Sterility
- The Risk impact on the regulatory compliance
- The Risk impact on customer

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## 4. Quality Risk Management Process

Risk assessment is a systematic process of organizing information to support a risk decision to be made within a risk management process. Its consists Identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards Quality risk assessment begins with a well defined problem description or risk question. For risk assessment process three fundamental questions are considered

- What might go wrong?
- What is likely hood **(Occurrence)** it will go wrong?
- What are the consequences **(Severity)?**

- **Risk Identification**

  Risk Identification is systematic use of information to identify hazards referring to risk questions or problem description. Information may include historical data theoretical analysis, informed opinions and concerns of stakeholders. risk Identification will be conducted by reviewing the types of events that might occur in both normal and unusual situations. This may be done by challenging the normal presumptions, and considering the possibilities of unanticipated situations. For each risk event, the underlying (root) cause should be determined that will create the potential risk occurrence.

  Risk Identification addresses the "what might go wrong" question including identifying the possible consequences. This provides the basis for the further steps in quality risk management process.

- **Risk Analysis**

  Risk analysis is the estimation of risk associated with the identified hazards.
  It is the quantitative or qualitative process of linking the likelihood of occurrence and severity of harm and sometime the detectability of harm is also consider during estimation of risk.

- **Risk Evaluation**

  Risk Evaluation compares the identified and analyzed risk against the given risk criteria. Risk evaluation considers the strength of evidence for all three of fundamental questions.

  Risks are ranked by scoring various criteria with appropriate numerical ratings, adding to scores to determine the overall score of each risk, and sorting the risks into descending order based on each score. A risk scoring threshold is established, over which risks must be mitigated using adequate design and/ or process controls that will protect the system. Those risks that fall below the threshold are either unmitigated or scheduled for later mitigation. An additional threshold or

characteristic of risk can be used to determine the differentiation of non-mitigation versus postponed mitigation.

- **Risk Control**

  Risk control includes decision making to reduce or mitigate risk. The purpose of risk control is to reduce the risk to the acceptance level

  The risk control is done by considering the following question

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

- **Risk Reduction**

  Risk reduction focuses on processes the mitigation or avoidance of quality risk when it exceeds the acceptable level. Risk reduction includes action taken to mitigate the severity, occurrence or probability of harm and the processes that improve the detectability of harm. It is the part of risk control strategy and involves

  - Engineering Control
  - Procedural Control
  - Manual control etc.

## 5. Risk Assessment for Process Simulation Study

### 5.1 Risk Assessment Legend

**A. Severity**

| Ranking | Effect | Criteria |
|---|---|---|
| **10** | Hazardous | Hazardous effect without warning. Safety related. Regulatory non-compliant. |
| **9** | Serious | Potential hazardous effect. Able to stop without mishap. Regulatory compliance in jeopardy. |
| **8** | Extreme | Item inoperable but safe. Customer very dissatisfied. |
| **7** | Major | Performance severely affected but functional and safe. Customer dissatisfied. |
| **6** | Significant | Performance degraded but operable and safe. Non-vital part inoperable. Customer experiences discomfort. |
| **5** | Moderate | Performance moderately affected. Fault on non-vital part requires repair. Customer experiences some dissatisfaction. |
| **4** | Minor | Minor effect on performance. Fault does not require repair. Non-vital fault always noticed. Customer experiences minor nuisance. |
| **3** | Slight | Slight effect on performance. Non-vital fault notice most of the time. Customer is slightly annoyed. |
| **2** | Very Slight | Very slight effect on performance. Non-vital fault may be noticed. Customer is not annoyed. |
| **1** | None | No effect. |

**B. Probability or Occurrence**

| Ranking | Possible Failure Rates | Probability of Failure |
|---|---|---|
| **10** | ≥ 1 in 2 | Almost certain. |
| **9** | 1 in 3 | Very high. |
| **8** | 1 in 8 | High. |
| **7** | 1 in 20 | Moderately high. |
| **6** | 1 in 80 | Medium |
| **5** | 1 in 400 | Low |
| **4** | 1 in 2,000 | Slight |
| **3** | 1 in 15,000 | Very slight. |
| **2** | 1 in 150,000 | Remote. |
| **1** | 1 in 1,500,000 | Almost impossible. |

**C. Detection**

| Ranking | Detection | Likelihood of Detection by design control |
|---|---|---|
| **10** | Absolute Uncertainty | No design control or design control will not detect potential cause |
| **9** | Very Remote | Very remote chance design control will detect potential cause. |
| **8** | Remote | Remote chance design control will detect potential cause. |
| **7** | Very Low | Very low chance design control will detect potential cause. |
| **6** | Low | Low chance design control will detect potential cause. |
| **5** | Moderate | Moderate chance design control will detect potential cause. |
| **4** | Moderately High | Moderately high chance design control will detect potential cause. |
| **3** | High | High chance design control will detect potential cause. |
| **2** | Very High | Very high chance design control will detect potential |
| **1** | Almost Certain | Almost certain that the design control will detect potential cause. |

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## 5.2 Risk Assessment Tool– Failure Mode effect Analysis (FMEA)

### 5.2.1 Risk Identification

| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Justification |
|---|---|---|---|---|
| | **Risk Identification** | | | |
| **1.** | **Lack of Personnel Hygiene & Attitude** | No Formal or Practical training for aseptic Behavior<br><br>Lack of knowledge about the aseptic Manufacturing<br><br>Medically unfit for aseptic manufacturing<br><br>Lack of facility provisions to maintain Personnel Hygiene | The environmental conditions required for the Aseptic manufacturing get disturbed which directly effects product quality<br><br>Adversely effect the working Culture | Personnel Hygiene and healthy attitude for aseptic behavior is vital as it ensures the sterility of product.<br><br>The Good aseptic behavior regulates and boost healthy working environment |
| **2.** | **Inappropriate Man Movement** | No Defined Flow for Man Movement<br><br>No Procedural Control<br><br>In adequate Training for the Person's<br><br>No supervisory Control<br><br>No display for instructions i.e. SOPs or Photographs | The environmental conditions required for the Aseptic manufacturing get disturbed which directly effects product quality | The man movements must be designed and defined so as to establish the load capacity of HVAC system to withstand limited disturbances<br><br>Procedural and supervisory control is required for the maintenance of desired environmental conditions for aseptic processing |

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| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Justification |
|---|---|---|---|---|
| | **Risk Identification** | | | |
| **3.** | **Inappropriate Cleaning, Sanitization or Disinfection of Controlled Rooms (walls, roofs& floor), Outer surfaces of Equipment, instruments, utility lines, other pipe work and Platforms** | -Non Availability of standard procedure for cleaning, Disinfection or sanitization and procedure for cleaning or disinfectant solution Preparation<br>-Personnel not Trained<br>Inappropriate design<br>- Excessive Height of roof<br>- Inaccessible surfaces<br>- No finishing in the roofs Walls & Floor surfaces<br>Ineffective and non validated Cleaning agents, sanitizers or disinfectant | Environment conditions not maintained for Aseptic processing Which leads to Product contamination | Cleaning , Sanitization or disinfection of Walls, floors & roofs by using ineffective and non validated Cleaning agents, sanitizers or disinfectant in of the various rooms of the appropriately designed facility increase Viable & Non viable load in the controlled area<br>Which Leads to product contamination |
| 4. | **Failure in the Raw Material Procurement, Storage, Testing & Approval** | Non availability of Vendor Approval Procedure<br>Non Availability & Inappropriate design of Ware house for good storage<br>Non Availability of Approved testing Methods<br>Non Availability of Procedure for Rejection & Approval of Raw material for use | Regulatory Non compliance<br>Poor Material quality<br>Wrong analysis results in False positive results for the quality of material<br>Use of substandard material in the Batch Processing, Material Packing etc. | The vendor approval procedure confirm the minimum requirement for the consistent manufacturing, testing & supply of Quality Raw Material<br>Availability of suitable ware housing facility prevent Product contamination & sterility<br>Approved testing method ensures exactness in the analysis and reporting results<br>Procedure for rejection & approval of Raw material prevents the Use of substandard material in the Batch Processing, Material Packing etc. |

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| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Justification |
|---|---|---|---|---|
| | **Risk Identification** | | | |
| **5.** | **Inappropriate Raw & Packing material Handling** | No Define Procedure and Provision for<br>- material Flow<br>- good storage conditions<br>- Material Dispensing<br>- Accurate weighing<br>- Material Identification (Labeling) | - Deteriorate Material quality<br>- Deteriorate Environment conditions for storage<br>- Spillage of Material<br>- Poor Material Segregation<br>- Poor Process Performance | Material transfer may hamper the Material quality or may hamper the environment conditions<br>No good storage condition spoil the material quality which ultimately effects the quality of the end product<br>No provision for Segregate Material dispensing may lead to spillage and ultimately unhygienic condition in Raw material room<br>In accurate weighing lead to wrong inputs of material in the process which adversely effect process performance and product quality<br>improper Identification of material may lead to cross contamination |

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| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Justification |
|---|---|---|---|---|
| | **Risk Identification** | | | |
| **6.** | **Drain System Failure** | Non availability of GMP Model of the drains<br><br>Non availability of Standard procedure for the disinfection and sanitization of the available drains<br><br>Operator are not trained for the sanitization procedure of the drain | The aseptic environmental condition may be deteriorated | Non availability of GMP Model of the drains leads to improper water collection which may result into Back- Siphoning of dirty water in the washing area. |
| **7.** | **Inappropriate Handling of sterilized Material during transfer, storage or usage** | Non Availability of standard procedure<br><br>Non Availability of Required Provision<br><br>Operator Not Trained | Sterility destroyed<br><br>ultimately ends into product contamination | The sterilized material if not handled properly during carrying, storage or usage<br><br>Will loose its sterility and get contaminated which further contaminate surfaces, equipment or product if get in contact with it. |

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| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Justification |
|---|---|---|---|---|
| | **Risk Identification** | | | |
| **8.** | **Failure of Processing Equipment** | | | |
| **8.1** | **Operational Error** | Operator Not trained to operate the equipment | Malfunctioning of Equipment, impact Processing of product | Training Ensures Exactness of procedure to be followed for operating an equipment |
| | | Non availability of SOPs for the Operation of Equipment | Inappropriate handling of Equipment, Results in Poor Processing, Product contamination, Accidents, Breakdowns | Standard Operating procedure ensure correct sequence of Steps, safety measures to be taken during operating an equipment |
| **8.2** | **Dissolution Vessel, Vessel Washing Solvents & Crystallizer** | Break Down Electrical Failure | Incomplete Dissolution or Spillage Increase operation time | Breakdown of agitator, Bottom Valve Rectification of breakdown increase operation time |
| | | Lose of filter integrity of Vent filter & Nitrogen filter | Product Contamination | Ruptured filter allow exposure to Product content |
| | | Utility failure | Poor Process Performance | Process Parameters not maintained Like temperature, Pressure etc. |
| | | MOC Not Compatible | Product Contamination | Because of Corrosion & undesired surface reactions with the Processing Material |
| **8.3** | **Sparkler Filter Filter train Product Line Solvent Line Buffer Line** | High Pressure of Solution to be Filtered | Rupture filter, Clamp gaskets Injury | Excessive Pressure from holding capacity result in breakdown |
| | | Lose of Filter Integrity | Product Contamination | Ruptured filter do not filter efficiently |
| | | Loosening of Clamp holdings | Spillage, Injury, Product Lose & Product Contamination | Loose Clamp holdings can not hold pressure during material transfer & Nitrogen purging |
| | | Breakdown | Increase operation time, Product Contamination | Breakdown rectification take time for operation completion & may product |
| | | MOC Not Compatible | Product Contamination | Because of Corrosion & undesired surface reactions with the Processing Material |

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| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Justification |
|---|---|---|---|---|
| | **Risk Identification** | | | |
| **8.** | **Failure of Processing Equipment** | | | |
| **8.4** | **PFE** | Breakdown Electrical Failure | Ineffective Isolation & Drying of product, Increase operation | Agitator working plays important role for proper isolation and drying of Product in PFE |
| | | Lose of filter integrity of Filter mesh | Product Lose & Product Contamination | Ruptured filter allow material to pass through it, result in product loss & product contamination |
| | | Lose of filter integrity of Nitrogen filter | Product Contamination | Ruptured filter allow exposure to Product content during nitrogen purging |
| | | Loosening of Clamp holdings used to fix Material & ML | Spillage, Injury, Product Lose & Product Contamination | Loose Clamp holdings can not hold pressure during material transfer & Nitrogen purging |
| | | Utility failure | Poor Process Performance | Process Parameters not maintained Like temperature, Pressure etc. |
| | | MOC Not Compatible | Product Contamination | Because of Corrosion & undesired surface reactions with the Processing Material |
| **8.5** | **Combi & Conveyer System** | Rotating Motor Failure | Ineffective Homogenization of product, Increase operation time | Motor rotation plays important role for proper Homogenization of Product in Combi |
| | | Lose of integrity of Mesh | Ineffective homogenization | Lumps will not be removed properly |
| | | Inappropriate Mesh Size | inappropriate Particle size | Material will not be of required Particle size if Mesh is not required size |
| | | Breakdown Electrical Failure | Spillage & Increase operation time | Breakdown rectification take time for operation completion & may product contamination during handling the material |
| | | Loosening of Clamp holdings | Spillage of Material | Loose Clamp holdings can not hold pressure during material transfer |
| | | MOC Not Compatible | Product Contamination | Because of Corrosion & undesired surface reactions with the Processing Material |

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| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Justification |
|---|---|---|---|---|
| | **Risk Identification** | | | |
| **8.** | **Failure of Processing Equipment** | | | |
| **8.6** | **Blender** | Breakdown<br>Electrical Failure | Blending not Homogeneous<br>Increase operation time | Rectification of breakdown increase operation time |
| | | Product exposure during Material charging & Unloading | Product Contamination | During charging and unloading Bin is get opened and give direct powder exposure to environment |
| | | Accident during Rotation | Injury | During rotation operator may come under the area of blender movement |
| | | Loosening of Clamp holdings to Powder win | Spillage, Injury, Product Lose & Product Contamination | Loose Clamp holdings can not hold pressure during material transfer to blender |
| | | MOC Not Compatible | Product Contamination | Because of Corrosion & undesired surface reactions with the Processing Material |

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| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Justification |
|---|---|---|---|---|
| | **Risk Identification** | | | |
| **9.** | **Failure of Environment Monitoring Equipments** | | | |
| **9.1** | **HVAC System** | Breakdown<br>Electrical Failure | -Product Contamination<br>-Production Loss<br>-The Aseptic Processing environment get disturbed | Break down and electrical failure make the system Non working under such situation there is greater chance of Viable & Non Viable load due to Air stagnation, Increased temperature & humidity etc. |
| | | Lose of integrity of HEPA filters | Product Contamination | Ruptured HEPA filter of HVAC System allow the particles both viable and Non Viable to pass through them |
| | | Disturbed Differential Pressure | Product Contamination | The disturbed Air balancing can not maintain required differential Pressure for different area ,because of which Aseptic Processing environment get disturbed which leads to product contamination |
| | | Improper Cleaning of Pre & microbe Filters | Product Contamination | The improper cleaning of filters is the source of microbial growth & particle generation in the processing area |
| | | Cleaning of Return Risers | Product Contamination | The improper cleaning of filters lead to stagnation of air & also source of microbial growth in the processing area |

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| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Justification |
|---|---|---|---|---|
| | **Risk Identification** | | | |
| **9.** | **Failure of Environment Monitoring Equipments** | | | |
| **9.2** | **Dynamic Pass Boxes** | Breakdown<br>Electrical Failure | Product Contamination<br>-Production Loss<br>-The Aseptic Processing environment get disturbed | Break down and electrical failure make the system Non working under such situation there is greater chance of microbial load due to Improper segregation of Environmental conditions of different class Area during Material Transfer |
| | | Lose of integrity of HEPA filters | Product Contamination | Ruptured HEPA filter allow the particles to pass through them due to ineffective filtration |
| | | Disturbed Differential Pressure | Product Contamination | The disturbed Air balancing can not maintain required differential Pressure for different area ,because of which air can be flushed in from lower class area to Dynamic Pass Boxes and finally into Aseptic Processing area during material transfer |
| | | Improper Cleaning of Pre Filters | Product Contamination | The improper cleaning of filters is the source of microbial growth in the processing area |
| | | Improper Door Closing or Opening | Product Contamination | Improper working of doors lead to disturbed pressure gradient Leads to microbial contamination<br>In aseptic area |
| | | Interlock for Door opening not activated or working | Product Contamination | Both the doors get opened simultaneously and result in contamination |

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|---|---|---|---|---|
| | **Risk Identification** | | | |
| **9.** | **Failure of Environment Monitoring Equipments** | | | |
| **9.3** | **Laminar Air Flow Units** | Breakdown<br>Electrical Failure | Product Contamination<br>-Production Loss<br>-The Aseptic Processing environment get disturbed | Break down and electrical failure make the system Non working under such situation there is greater chance of microbial load to effect sterility of material or Product |
| | | Lose of integrity of HEPA filters | Product Contamination | Ruptured HEPA filter allow the particles to pass through them without filtration |
| | | Disturbed Differential Pressure | Product Contamination<br>Sterile Material contamination | The disturbed Air balancing can not maintain required differential Pressure for different area ,because of which air can be flushed in from lower class area to Higher class area for working |
| | | Improper Cleaning of Pre Filters | Product Contamination | The improper cleaning of filters is the source of microbial growth & Non viable particles in the processing area |

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| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Justification |
|---|---|---|---|---|
| | **Risk Identification** | | | |
| **10.** | **Failure of Equipment For Sterilization & De pyrogenation** | | | |
| | **Steam Heat Sterilizer & Dry Heat Sterilizer** | Breakdown<br>Electrical Failure | -Production Loss<br>-Increase operation time | Break down and electrical failure make the system Non working under such situation Production will be stopped & rectification increase the operation time |
| | | Non availability of Utility at required parameters Like Nitrogen, Compressed air, Pure Steam etc | Production Loss<br>-Increase operation time | Sterilization cycle cannot be carried out in absence of required utility |
| | | Instrument Malfunctioning | Product Contamination<br>Material destruction | Monitoring instruments for temperature, pressure are not giving the actual value hence cannot be controlled & monitored exactly to requirements |
| | | PLC Malfunctioning | Production Loss<br>Product Contamination<br>Material destruction | Sterilization cannot be achieved without the functioning of designed control i.e. PLC |
| | | Inappropriate Load for sterilization | Inefficient Sterilization | The equipment works efficiently for a specific load. |
| | | Non availability of validated standard Procedure of Sterilization | Inappropriate handling of Equipment, Results in Poor Processing, Product, contamination, Accidents, Breakdowns | Standard Operating procedure ensure correct sequence of Steps, safety measures to be taken during operating an equipment |
| | | Operator Not trained | Malfunctioning of Equipment, Adverse impact on Processing & Safety | Training Ensures Exactness of procedure to be followed for operating an equipment |

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|---|---|---|---|---|
| | **Risk Identification** | | | |
| **10.** | **Failure of Equipment For Sterilization & De pyrogenation** | | | |
| | **Steam Heat Sterilizer & Dry Heat Sterilizer** | Lose of integrity of HEPA filters (DHS) | Material contamination | Allow the passage of unfiltered air in the chamber of DHS |
| | | Alarms & Interlocks Not working | Material contamination &Safety break | Alarms & Interlocks are designed for the safety of Man Material & Machine |
| | | MOC Not Compatible | Product Contamination Deterioration of Components, Garments & other Accessories | Because of Corrosion & undesired surface reactions with the Processing Material |

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|---|---|---|---|---|
| | **Risk Identification** | | | |
| **11.** | **Failure of Simulation Study** | | | |
| **11.1** | **The Wrong Selection of growth supporting media** | Inadequate Knowledge of the person Performing selection for medium nutrient | Failure of Process simulation study | The Media may not support vital microbial growth required for detection in Process simulation study |
| | | Regulatory guidelines not followed | Deterioration of Environment conditions in Aseptic Processing Area | The Process Simulation study involves huge volumes of growth supporting media which may cause the contamination of all the critical area walls / roof / ducts, thereby making these contact surface prone to support microbial growth |
| | | | Poor Performance of Process Equipment | The Viscosity and flow ability of the nutrient media will effect the motor performance and the cleaning and processing parameters |
| | | | The Non compatibility of the Nutrient media with the equipment surface | This may lead to Corrosion and ultimately product contamination |

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| | **Risk Identification** | | | |
| **11.** | **Failure of Simulation Study** | | | |
| **11.2** | **Wrong Process design for Simulation Study** | The Person is not qualified or trained for designing the Process for Simulation study | Wrong designing of Process for simulation study | Unqualified & untrained person do not understand the Process requirement for simulation study |
| | | The Process matrix may not cover all the products | The simulation study do not represent all the products of the plant | The simulation study must be representative of all the products by considering all extremities of process parameters like concentration, holding time, Non sterile load on the filters, process flow etc. |
| | | The Process Parameters are not decided as per Process package Like concentration, time temperature etc. | | |
| | | The Process manipulations are not studied and evaluated | | |
| | | The worst case scenario is not appropriately decided | Irrational base leads to failure of the simulation study & regulatory non compliance | The rational behind the simulation study is to run a representative process at worst case scenario to accomplish the capability of the facility to produce different sterile products |
| | | Incorporation of process step, having inhibitory action on the Microbial growth like use of solvents, acids, alkalis, High/low temperature, High agitation etc | The inappropriate assessment of microbial load<br><br>Objective of simulation study not fulfilled | The microbial growth inhibition minimize the microbial load on the aseptic process which is selected for simulation study and ultimately do not give factual information about the process , equipment and the whole facility for its qualification for sterile manufacturing |

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| | **Risk Identification** | | | |
| **11.** | **Failure of Simulation Study** | | | |
| **11.3** | **Wrong Calculation of Quantity of growth supporting Media for the Process simulation study** | The complete details of total qty. of Non sterile Raw material which will give complete load on the Filter train may not be calculated | The objective of simulation study to ensure capability of filter train to withstand required non sterile load will not be achieved | Exact Quantity of Non sterile is very important to assess the capability of filter train. The filter train helps to reduce the bio burden to the acceptable level for sterilization if qty. is not assessed properly the results will not give factual information's. |
| **11.4** | **Wrong Calculation of Holding Time in the Equipment** | The total time taken for the processing in a particular equipment is not ascertain correctly | The equipment performance to carry out aseptic processing for the highest occupancy time will not be established and confirmed | The challenging of process is required for the highest occupancy time to get the capability of the equipment for aseptic processing for longer duration. |
| **11.5** | **Wrong agitation Time, Temperature & Pressure** | Process is not studied for agitation requirement so as prevent microbial inhibition | The excessive & high agitation may give inhibitory action on the microbial growth | The well studied & appropriate agitation is required to ensure proper growth of microbes in the growth supporting media for challenging the process in its true sense. |
| | | Temperature & Pressure requirements of process not studied or maintained | Poor Performance of Process<br>Hamper Product Quality | Observing Process Parameters are vital for getting the desired output & quality of the Product . |

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| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Justification |
|---|---|---|---|---|
| | **Risk Identification** | | | |
| **11.** | **Failure of Simulation Study** | | | |
| **11.6** | **In process Sampling & Final Sampling** | Untrained & Unqualified person performing sampling | Wrong analytical results | The trained ,qualified person & The same sampling procedure, time and frequency for sampling will provided a uniform pattern for challenge study |
| | | Non Availability of SOPs for cleaning & up keep of sampling tools | Un cleaned tools may increase the bio burden in the sample<br>Result in wrong analytical results for microbial load | |
| | | Standard operating procedure may not be in place | Different procedure will be used for sampling each time | |
| | | Sampling time for in process may not be studied or | Sampling time variation may lead to different duration of product exposure | |
| | | Sampling frequency for in process may not be studied or established | Sampling frequency variation may lead to different duration of product exposure and different pattern for challenge study | |
| **11.7** | **Testing Failure** | -Non Availability of Standard testing method for sterility testing<br>-Non Availability of Validated Analytical Method<br>-Analyst Not trained<br>-Expired Reagents | -Wrong Analysis<br>-False positive results<br>-Regulatory non compliance | -The validated analytical method and standard testing procedure ensure correct sequence of testing<br>-Training Ensures Exactness of procedure to be followed for analysis<br>-Expired reagents gives poor performance of testing method |
| | | Poor membrane filter performance | -Non Representative Sampling<br>-Faulty analytical results | If membrane used for filtration can not filter the solution efficiently then membrane sample to ascertain Microbial load in the solution gives false positive results |

# REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Justification |
|---|---|---|---|---|
| | **Risk Identification** | | | |
| **12.** | **Process Manipulations** | | | |
| **12.1** | **Disturbance of aseptic environment in the crystallizer because of seeding** | Operator error | The Aseptic Processing environment get disturbed | The product exposure must be acceptable under grade A otherwise it may hamper the product quality and sterility |
| **12.2** | **Product exposure during transfer of material from PFE to Combi through Conveyer** | Malfunctioning of Clamp used to fix Bellow<br><br>Operator Error | | |
| **12.3** | **Product exposure during Blending &Packing** | Malfunctioning of Clamp used to fix Bellow<br>Operator Error | | |
| **12.4** | **Cleaning & sanitization after the completion of each batch** | -In appropriate Manual fixation of Hose pipes for cleaning<br>-Spillage during Transfer of spent solution to CIP tank<br>-Mishandling during Dismantling & fixation of components & accessories during cleaning | | The spillage, Drain & mishandling of cleaning medium, spent solution in the controlled area will increase the chance of microbial growth |

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## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Justification |
|---|---|---|---|---|
| | **Risk Identification** | | | |
| **13.** | **Challenge Design for Process simulation study** | | | |
| 13.1 | Failure to simulate Process for 24 hrs | All the shifts may not be considered for Simulation study | Process simulation study will not be represent all the times for aseptic manufacturing | Process is required to simulate in all the three shifts so as to establish its capability for 24 hrs |
| 13.2 | Aseptic Environment deterioration on employment of additional Man power in case of requirement | Inefficiency of HAVC system to withstand the disturbance by employing additional person for aseptic area manufacturing | Product contamination | Addition disturbance because of additional manpower in aseptic manufacturing area increase the load |
| 13.3 | Aseptic Environment deterioration on performing minor maintenance work in the aseptic manufacturing area | Inefficiency of HVAC system to withstand the disturbance by carrying out minor maintenance work in the aseptic manufacturing area | Product contamination | Addition disturbance due to maintenance work in aseptic manufacturing area increase the load |
| 13.4 | Aseptic Environment deterioration on Power failure | Non Working of HVAC System | Product contamination | Stagnant air increase the load of viable & Non Viable counts in aseptic manufacturing area |

# REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

**5.2.2 Risk Analysis**

| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number RPN=S x P x D | Existing Design Control |
|---|---|---|---|---|---|---|---|---|
| | **Risk Analysis** | | | | | | **Risk valuation** | |
| **1.** | **Lack of Personnel Hygiene & Attitude** | No Formal or Practical training for aseptic manufacturing<br>Lack of knowledge about the aseptic Manufacturing<br>Medically unfit for aseptic manufacturing<br>Lack of facility provisions to maintain Personnel Hygiene | The environmental conditions required for the Aseptic manufacturing get disturbed which directly effects product quality<br><br>Adversely effect the working Culture | 9 | 8 | 7 | =9 x 8 x 7=504 | Training for Personnel Hygiene for all persons<br>Personnel Monitoring Once a day<br>Training on Positive attitude for working |
| **2.** | **No Defined Man Movement Procedures** | No Defined Flow for Man Movement<br><br>No Procedural Control<br><br>In adequate Training for the Person's<br>No supervisory Control<br>No display for instructions i.e. SOPs or Photographs | The environmental conditions required for the Aseptic manufacturing get disturbed which directly effects product quality | 9 | 5 | 7 | =9 x 5 x 7=315 | Approved Layouts for Man movement<br><br>Training on SOP for Exit & exit , Do's & Don'ts in sterile plant<br><br>One shift in charge per shift |

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## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Severity | Probability | Detection | Risk Priority Number | Existing Design Control |
|---|---|---|---|---|---|---|---|---|
| | | | | (S) | (P) | (D) | RPN=S x P x D | |
| | Risk Analysis | | | | | | Risk Evaluation | |
| 3. | **Inappropriate Cleaning, Sanitization or Disinfection of Controlled Rooms (walls, roofs& floor), Outer surfaces of Equipment, instruments, utility lines, other pipe work and Platforms** | -Non Availability of standard procedure for cleaning, Disinfection or sanitization and procedure for cleaning or disinfectant solution Preparation<br>-Personnel not Trained<br>Inappropriate design<br>- Excessive Height of roof<br>- Inaccessible surfaces<br>- No finishing in the roofs Walls & Floor surfaces<br>Ineffective and non validated Cleaning agents, sanitizers or disinfectant | Environment conditions not maintained for Aseptic processing<br><br>Which leads to Product contamination | 8 | 8 | 7 | =8 x 8 x 7=448 | Approved SOPs Training for the Persons<br><br>Validated & Effective Cleaning agents, sanitizers or disinfectant<br><br>SOP for Building Management verification is done half yearly |

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## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Severity | Probability | Detection | Risk Priority Number | Existing Design Control |
|---|---|---|---|---|---|---|---|---|
| | | | | (S) | (P) | (D) | RPN=S x P x D | |
| | Risk Analysis | | | | | | Risk Evaluation | |
| 4. | **Failure in the Raw Material Procurement, Storage, Testing & Approval** | Non availability of Vendor Approval Procedure<br><br>Non Availability & Inappropriate design of Ware house for good storage<br><br>Non Availability of Approved testing Methods<br><br>Non Availability of Procedure for Rejection & Approval of Raw material for use | Regulatory Non compliance<br><br>Poor Material quality<br><br>Wrong analysis results in False positive results for the quality of material<br><br>Use of substandard material in the Batch Processing, Material Packing etc. | 9 | 5 | 2 | =9 x 5 x 2=90 | Availability of Vendor Approval Procedure<br><br>Availability & Inappropriate design of Ware house<br><br>Availability of Approved testing Methods<br>Availability Procedure for Rejection & Approval of Raw material for use |

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## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Severity | Probability | Detection | Risk Priority Number | Existing Design Control |
|---|---|---|---|---|---|---|---|---|
| | | | | (S) | (P) | (D) | RPN=S x P x D | |
| | **Risk Analysis** | | | | | | **Risk Evaluation** | |
| **5.** | **Inappropriate Raw & Packing material Handling** | No Define Procedure and Provision for<br>- material Flow<br>- good storage conditions<br>- Material Dispensing<br>- Accurate weighing<br>- Material Identification (Labeling) | - Deteriorate Material quality<br>- Deteriorate Environment conditions for storage<br>- Spillage of Material<br>- Poor Material Segregation<br>- Poor Process Performance | 7 | 7 | 4 | =7 x 7 x 4=196 | Approved Layouts for Material movement<br>SOP for the storage of Raw & Packing Material<br>SOP for the Dispensing of Material<br>SOP for the operation of Weighing Balances |

## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Severity | Probability | Detection | Risk Priority Number | Existing Design Control |
|---|---|---|---|---|---|---|---|---|
| | | | | (S) | (P) | (D) | RPN=S x P x D | |
| | **Risk Analysis** | | | | | | **Risk Evaluation** | |
| **6.** | **Drain System Failure** | Non availability of GMP Model of the drains<br><br>Non availability of Standard procedure for the disinfection and sanitization of the available drains<br><br>Operator are not trained for the sanitization procedure of the drain | The aseptic environmental condition may be deteriorated | 7 | 4 | 2 | =7 x 4 x 2=56 | The GMP Model of drains are provided in the Plant<br><br>Standard procedure for the disinfection and sanitization of the are available for drains<br>Operators are trained for the sanitization procedures |

## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Severity | Probability | Detection | Risk Priority Number | Existing Design Control |
|---|---|---|---|---|---|---|---|---|
| | | | | (S) | (P) | (D) | RPN=S x P x D | |
| | **Risk Analysis** | | | | | | **Risk Evaluation** | |
| **7.** | **Inappropriate Handling of sterilized Material during transfer, storage or usage** | Non Availability of standard procedure<br>Non Availability of Required Provision<br>Operator Not Trained | Sterility destroyed<br>ultimately ends into product contamination | 9 | 5 | 4 | =9 x 5 x 4=180 | Availability of validated standard procedure<br>Mobile LAF for carrying Sterilized material<br>Garment Cubicles for storage of sterilized garments<br>Formal Training to the operator |

# REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Severity | Probability | Detection | Risk Priority Number | Existing Design Control |
|---|---|---|---|---|---|---|---|---|
| | | | | (S) | (P) | (D) | RPN=S x P x D | |
| | Risk Analysis – | | | | | | Risk Evaluation | |
| 8. | **Failure of Processing Equipments** | | | | | | | |
| 8.1 | **Operational Error** | Operator Not trained to operate the equipment<br><br>Non availability of SOPs for the Operation of Equipment | Malfunctioning of Equipment, impact Processing<br><br>Inappropriate handling of Equipment, Results in Poor Processing, Product contamination, Accidents, Breakdowns | 9 | 5 | 4 | =9 x 5 x 4=180 | Availability of validated standard procedure<br><br>Formal training to the operator for the operation of all Processing equipment |
| 8.2 | **Dissolution Vessel, Vessel Washing Solvents**<br><br>**& Crystallizer** | Break Down<br><br>Electrical Failure<br><br>Lose of filter integrity of Vent filter<br><br>Lose of filter integrity of Nitrogen filter<br><br>MOC Not Compatible | Incomplete Dissolution or Spillage<br><br>Increase operation time<br><br>Product Contamination | 7 | 8 | 5 | =7 x 8 x 5=280 | SOP for Equipment Operation<br><br>SOP to check filter before and after the batch<br><br>SS 316 L verified during Qualification through certification |

# REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number RPN=S x P x D | Existing Design Control |
|---|---|---|---|---|---|---|---|---|
| | **Risk Analysis –** | | | | | | **Risk Evaluation** | |
| **8.** | **Failure of Processing Equipments** | | | | | | | |
| **8.3** | **Filter train**<br>-Product Line<br>-Solvent Line<br>-Buffer Line | Breakdown<br><br>High Pressure of Solution to be Filtered<br>Lose of filter integrity of filter<br>Loosening of Clamp holdings<br><br>MOC Not Compatible | Increase operation time, Product Contamination<br><br>Rupture filter, Clamp gaskets Injury<br>Spillage, Injury, Product Lose & Product Contamination<br><br>Product Contamination | 9 | 5 | 4 | =9 x 5 x 4=180 | SOP for Equipment Operation<br>Formal training to the operator for the operation of filtration through different filter trains<br>SS 316 L verified during Qualification through certification |

# REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number RPN=S x P x D | Existing Design Control |
|---|---|---|---|---|---|---|---|---|
| | **Risk Analysis –** | | | | | | **Risk Evaluation** | |
| **8.** | **Failure of Processing Equipments** | | | | | | | |
| **8.4** | **PFE** | Breakdown<br>Electrical Failure<br><br>Lose of filter integrity of Filter Mesh<br><br>Lose of filter integrity of Compressed Air filter<br><br>Loosening of Clamp holdings used to fix Material & ML<br><br>MOC Not Compatible | Ineffective Isolation & Drying of product, Increase operation time<br><br>Product Lose & Product Contamination<br><br>Spillage, Injury, Product Lose & Product Contamination<br><br>Product Contamination | 9 | 5 | 4 | =9 x 5 x 4=180 | SOP for Equipment Operation<br><br>Formal training to the operator for the operation of filtration through different filter trains<br>Supervisory control during Clamp & line assembling<br><br>SS 316 L verified during Qualification through certification |

# REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number RPN=S x P x D / Risk Evaluation | Existing Design Control |
|---|---|---|---|---|---|---|---|---|
| | **Risk Analysis –** | | | | | | | |
| **8.** | **Failure of Processing Equipments** | | | | | | | |
| **8.5** | **Combi & Conveyer System** | Rotating Motor Failure<br>Lose of filter integrity of Mesh<br>Inappropriate Mesh Size<br>Breakdown<br>Electrical Failure<br>Loosening of Clamp holdings<br>MOC Not Compatible | Ineffective Homogenization of product, Increase operation time<br>Ineffective homogenization<br>inappropriate Particle size<br>Spillage & Increase operation time<br>Spillage of Material<br>Product Contamination | 7 | 5 | 4 | =9 x 5 x 4=180 | SOP for Equipment Operation<br>Formal training to the operator for the operation of filtration through different filter trains<br>Supervisory control during Clamp , line assembling & Mesh Fixing<br>SS 316 L verified during Qualification through certification |

# REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number RPN=S x P x D | Existing Design Control |
|---|---|---|---|---|---|---|---|---|
| | **Risk Analysis –** | | | | | | **Risk Evaluation** | |
| **8.** | **Failure of Processing Equipments** | | | | | | | |
| **8.6** | **Blender** | Breakdown<br>Electrical Failure<br><br>Product exposure during Material charging & Unloading<br><br>Accident during Rotation<br><br>Loosening of Clamp holdings to Powder Bin<br><br>MOC Not Compatible | Blending not Homogeneous<br><br>Increase operation time<br><br>Product Contamination<br><br>Injury<br><br>Spillage, Injury, Product Lose & Product Contamination<br><br>Product Contamination | 9 | 5 | 4 | =9 x 5 x 4=180 | SOP for Equipment Operation<br><br>Formal training to the operator for the operation of blender<br><br>Supervisory control during Clamping the Powder Bin<br><br>Railing guard as safety measure<br><br>SS 316 L verified during Qualification through certification |

# REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number RPN=S x P x D | Existing Design Control |
|---|---|---|---|---|---|---|---|---|
| | **Risk Analysis –** | | | | | | **Risk Evaluation** | |
| **9.** | **Failure of Environment Monitoring Equipments** | | | | | | | |
| **9.1** | **HVAC System** | Breakdown<br>Electrical Failure<br><br>Lose of integrity of HEPA filters<br>Accident during Rotation<br><br>Disturbed Differential Pressure<br><br>Improper Cleaning of Pre & microbe Filters<br><br>Cleaning of Return Risers | Product Contamination<br><br>-Production Loss<br><br>-The Aseptic Processing environment get disturbed<br><br>Product Contamination | 9 | 5 | 4 | =9 x 5 x 4=180 | SOP for Equipment Operation<br><br>Formal training to the operator for the operation of HVAC<br><br>SOP for DP Monitoring in each shift<br>SOP for the cleaning of Filters & return riser<br><br>Half yearly Qualification Procedure For HVAC System |

# REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number RPN=S x P x D | Existing Design Control |
|---|---|---|---|---|---|---|---|---|
| | **Risk Analysis –** | | | | | | **Risk Evaluation** | |
| **9.** | **Failure of Environment Monitoring Equipments** | | | | | | | |
| **9.2** | **Dynamic Pass Boxes** | Breakdown<br>Electrical Failure<br><br>Lose of integrity of HEPA filters<br><br>Disturbed Differential Pressure<br><br>Improper Cleaning of Pre Filters<br><br>Improper Door Closing or Opening<br><br>Interlock for Door opening not activated or working | Product Contamination<br><br>-Production Loss<br><br>-The Aseptic Processing environment get disturbed<br><br>Product Contamination | 9 | 5 | 4 | =9 x 5 x 4=180 | SOP for Equipment Operation<br><br>Formal training to the operator for the operation of Dynamic Pass Boxes<br><br>DP Monitoring during Operation is the instructional part of SOP for operation<br><br>SOP for the cleaning of Filters<br>Half yearly Qualification Procedure For Equipment |

# REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number RPN=S x P x D | Existing Design Control |
|---|---|---|---|---|---|---|---|---|
| | **Risk Analysis –** | | | | | | **Risk Evaluation** | |
| **9.** | **Failure of Environment Monitoring Equipments** | | | | | | | |
| **9.3** | **Laminar Air Flow Units** | Breakdown<br>Electrical Failure<br><br>Lose of integrity of HEPA filters<br><br>Disturbed Differential Pressure<br><br>Improper Cleaning of Pre Filters | Product Contamination<br><br>-Production Loss<br><br>-The Aseptic Processing environment get disturbed<br><br>Product Contamination<br><br>Sterile Material contamination | 9 | 5 | 4 | =9 x 5 x 4=180 | SOP for Equipment Operation<br><br>Formal training to the operator for the operation of Dynamic Pass Boxes<br><br>DP Monitoring during Operation is the instructional part of SOP for operation<br><br>SOP for the cleaning of Filters<br><br>Half yearly Qualification Procedure For Equipment |

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## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number RPN=S x P x D | Existing Design Control |
|---|---|---|---|---|---|---|---|---|
| | **Risk Analysis –** | | | | | | **Risk Evaluation** | |
| **10.** | **Failure of Equipment For Sterilization & De pyrogenation** | | | | | | | |
| | **Steam Heat Sterilizer**<br><br>**& Dry Heat Sterilizer** | Breakdown<br>Electrical Failure<br><br>Non availability of Utility at required parameters Like compressed air, Pure Steam etc<br><br>Instrument Malfunctioning<br>PLC Malfunctioning<br><br>Inappropriate Load for sterilization<br><br>Non availability of validated standard Procedure of Sterilization | -Production Loss & Increase operation time<br><br>Product Contamination<br><br>Material destruction<br><br>Inefficient Sterilization<br><br>Inappropriate handling of Equipment, Results in Poor Processing, Product, contamination, Accidents, Breakdowns | 9 | 5 | 4 | =9 x 5 x 4=180 | SOP for Equipment Operation<br><br>Interlocks & alarm configuration for utility requirements<br><br>Instrument Calibration<br>Equipment Qualification<br><br>Validated Load configuration<br><br>SOP for sterilization process for SHS & DHS |

# REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number RPN=S x P x D | Existing Design Control |
|---|---|---|---|---|---|---|---|---|
| | **Risk Analysis –** | | | | | | **Risk Evaluation** | |
| **10.** | **Failure of Equipment For Sterilization & De pyrogenation** | | | | | | | |
| | **Steam Heat Sterilizer**<br><br>**& Dry Heat Sterilizer** | Operator Not trained | Malfunctioning of Equipment, Adverse impact on Processing | | | | | Formal & Practical training to the operator for the operation of SHS & DHS |
| | | Lose of integrity of HEPA filters (DHS) | Material contamination | 9 | 5 | 4 | =9 x 5 x 4=180 | DP Monitoring during Operation is the instructional part of SOP for operation |
| | | Alarms & Interlocks Not working | Material contamination &Safety break | | | | | SOP for the cleaning of Filters<br>Verification of Alarms & Interlocks Is the part of Qualification |
| | | MOC Not Compatible | Product Contamination Deterioration of Components, Garments & other Accessories | | | | | |

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## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number RPN= S x P x D | Existing Design Control |
|---|---|---|---|---|---|---|---|---|
| | **Risk Analysis** | | | | | | **Risk Evaluation** | |
| **11.** | **Failure of Simulation Study** | | | | | | | |
| **11.1** | **The Wrong Selection of growth supporting media** | Inadequate Knowledge of the person Performing selection for medium nutrient<br><br>Regulatory guidelines not followed | - Failure of Media Fill study<br>- Non Compliance to regulatory<br>-Deterioration of Environment conditions in Aseptic Processing Area<br><br>-Poor Performance of Process Equipment<br>-The Non compatibility of the Nutrient media with the equipment surface<br><br>Non Compliance to Regulatory | 7 | 4 | 3 | =7 x 4 x 3=84 | Formal training for media fill selection Criteria<br><br>SS 316 L is the MOC of Different Processing Equipment which is compatible to Lactose<br>The MOC is verified During qualification of Equipments<br><br>Referred Guidance must be mentioned in the protocol<br><br>Approval Procedure from Experience & Qualified Management |

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## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number RPN= S x P x D | Existing Design Control |
|---|---|---|---|---|---|---|---|---|
| | **Risk Analysis** | | | | | | **Risk Evaluation** | |
| **11.** | **Failure of Simulation Study** | | | | | | | |
| **11.2** | **Wrong Process design for Simulation Study** | The Person is not qualified or trained for designing the Process for Simulation study<br><br>The Process Simulation study may not cover all the products<br><br>The Process Parameters are not decided as per Process package<br><br>The Process manipulations are not studied and evaluated<br><br>The worst case scenario is not appropriately decided Incorporation of process step, having inhibitory action on the Microbial growth like use of solvents, acids, alkalis, High/low temperature, High agitation etc | Wrong designing of Process for simulation study<br><br>The simulation study do not represent all the products of the plant<br><br>Irrational base leads to failure of the simulation study & regulatory non compliance<br><br>The inappropriate assessment of microbial load<br><br>Objective of simulation study not fulfilled | 7 | 4 | 3 | =7 x 4 x 3=84 | Formal Training & relevant Experience is Assessed for Process design<br><br>Product List is a the Part of Protocol<br><br>Reference of process Package must be mentioned in the protocol<br><br>The worst case scenario is calculated through Product Matrix Only WFI & Lactose is used, which is a supports microbial growth |

# REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number RPN= S x P x D | Existing Design Control |
|---|---|---|---|---|---|---|---|---|
| | Risk Analysis | | | | | | Risk Evaluation | |
| 11. | Failure of Simulation Study | | | | | | | |
| 11.3 | Wrong Calculation of Quantity of Nutrient Medium for the simulation study | The complete details of total qty. of Non sterile Raw material which will give complete load on the Filter train may not be calculated | The objective of simulation study to ensure capability of filter train to withstand required non sterile load will not be achieved | 7 | 6 | 4 | =7 x 6 x 4 =168 | Total quantity is considered as per batch size |
| 11.4 | Wrong Calculation of Holding Time in the Equipment | The total time taken for the processing in a particular equipment is not ascertain correctly | The equipment performance to carry out aseptic processing for the highest occupancy time will not be established and confirmed | 7 | 6 | 4 | =7 x 6 x 4 =168 | Crystallizer time is considered for crystallizer<br>Drying time for PFE |

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## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number RPN= S x P x D | Existing Design Control |
|---|---|---|---|---|---|---|---|---|
| | **Risk Analysis** | | | | | | **Risk Evaluation** | |
| **11.** | **Failure of Simulation Study** | | | | | | | |
| **11.5** | **Wrong agitation Time, Temperature & Pressure** | Process is not studied for agitation, Temperature & Pressure requirement so as to prevent microbial inhibition | The excessive & high agitation may give inhibitory action on the microbial growth<br><br>Poor Performance of Process<br><br>Hamper Product Quality | 7 | 5 | 4 | =7 x 5 x 4 =140 | Minimum Agitation is Considered in crystallizer & PFE<br><br>Temperature Conditions for the various Processes are considered |

# REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Severity | Probability | Detection | Risk Priority Number | Existing Design Control |
|---|---|---|---|---|---|---|---|---|
| | | | | (S) | (P) | (D) | RPN= S x P x D | |
| | **Risk Analysis** | | | | | | **Risk Evaluation** | |
| **11.6** | **Failure of Simulation Study** | | | | | | | |
| | **Wrong In process Sampling & Final Sampling** | Untrained & Unqualified person performing sampling<br><br>Non Availability of SOPs for cleaning & up keep of sampling tools<br><br>Standard operating procedure may not be in place<br><br>Sampling time for in process may not be studied or established<br><br>Sampling frequency for in process may not be studied or established | Wrong analytical results<br><br>Un cleaned tools may increase the bio burden in the sample<br><br>Result in wrong analytical results for microbial load<br><br>Different procedure will be used for sampling each time<br><br>Sampling time variation may lead to different duration of product exposure<br><br>Sampling frequency variation may lead to different duration of product exposure and different pattern for challenge study | 7 | 5 | 4 | =7 x 5 x 4=140 | Trained & Qualified persons for sampling<br><br>Provision for Cleaning and Up keep of sampling tools and formal training for the same<br><br>SOP for the Sampling procedure and formal training for the same<br><br>Sampling time is fixed<br><br>Protocols define the clear Sampling frequency |

# REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Severity | Probability | Detection | Risk Priority Number | Existing Design Control |
|---|---|---|---|---|---|---|---|---|
| | | | | (S) | (P) | (D) | RPN= S x P x D | |
| | **Risk Analysis** | | | | | | **Risk Evaluation** | |
| **11.7** | **Failure of Simulation Study** | | | | | | | |
| | **Testing Failure** | Non Availability of Standard testing sterility Method<br>-Non Availability of Validated Analytical Method<br>-Analyst Not trained<br>-Expired Reagents<br>Poor membrane filter performance<br>Non Calibrated Analytical Instrument | Wrong Analysis<br>-Faulty results<br>-Regulatory non compliance<br>Non Representative Sampling<br>-Faulty analytical results<br>Poor Performance of Analytical Instrument | 7 | 4 | 3 | =7 x4x3=84 | Procedure for the use of only Approved & validated Testing Procedure<br>Qualified and trained Analyst<br>Procedural check for the expiry date during Media Preparation & other chemical testing<br>Pore size consideration during the selection Filter membrane<br>Instrument Calibration Procedure |

# REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number RPN= S x P x D | Existing Design Control |
|---|---|---|---|---|---|---|---|---|
| | **Risk Analysis** | | | | | | **Risk Evaluation** | |
| **12.** | **Manual Interruptions** | | | | | | | |
| **12.1** | **Disturbance of aseptic environment in the crystallizer because of seeding** | Operator error- | The Aseptic Processing environment get disturbed | 7 | 5 | 4 | =9 x 5 x 4=140 | SOP for Seeding the material in Crystallizer<br>Supervisory Control<br>Separate Seeding Port |
| **12.2** | **Product exposure during transfer of material from PFE to Combi through Conveyer** | Malfunctioning of Clamp used to fix Bellow<br>Operator Error | | 7 | 5 | 4 | =7 x 5 x 4=140 | SOP for the Operation<br>Formal training for the same<br>Supervisory Control<br>Mobile LAF for fixing the Bellow to the conveyer |
| **12.3** | **Product exposure during Blending & Packing** | Malfunctioning of Clamp used to fix Bellow<br>Operator Error | | 7 | 5 | 4 | =7 x 5 x 4=140 | SOP for the Operation<br>Formal training for the same<br>Supervisory Control<br>Mobile LAF & Vertical LAF for fixing the Powder Bin to Blender & performing Packing respectively |

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## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Severity | Probability | Detection | Risk Priority Number | Existing Design Control |
|---|---|---|---|---|---|---|---|---|
| | | | | (S) | (P) | (D) | RPN= S x P x D | |
| | **Risk Analysis** | | | | | | **Risk Evaluation** | |
| **12.** | **Manual Interruptions** | | | | | | | |
| **12.4** | **Cleaning & sanitization after Each batch** | -In appropriate Manual fixation of Hose pipes for cleaning<br>-Spillage during Transfer of spent solution to CIP tank<br>-Mishandling during Dismantling & fixation of components & accessories during cleaning | The Aseptic Processing environment get disturbed | 7 | 5 | 4 | =9 x 5 x 4=140 | SOP for Seeding the material in Crystallizer<br>Supervisory Control<br>Separate Seeding Port |

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# REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Severity | Probability | Detection | Risk Priority Number | Existing Design Control |
|---|---|---|---|---|---|---|---|---|
| | | | | (S) | (P) | (D) | RPN= S x P x D | |
| | **Risk Analysis** | | | | | | **Risk Evaluation** | |
| **13.** | **Challenge Design for Process simulation study** | | | | | | | |
| **13.1** | Failure to simulate Process for 24 hrs | All the shifts may not be considered for Simulation study | Process simulation study will not be represent all the times for aseptic manufacturing | 9 | 5 | 2 | =9 x 5 x 2=90 | All the shifts are considered in the Protocol |
| **13.2** | Aseptic Environment deterioration on employment of additional Man power in case of requirement | Inefficiency of HAVC system to withstand the disturbance by employing additional person for aseptic area manufacturing | Product contamination | 9 | 5 | 7 | =6 x 5 x 7=378 | One additional Person is considered for Simulation study<br>Gowning Procedure During Entry & exit<br>HVAC Performance Study in Trial Batch |
| **13.3** | Aseptic Environment deterioration on performing minor maintenance work in the aseptic manufacturing area | Inefficiency of HAVC system to withstand the disturbance by carrying out minor maintenance work in the aseptic manufacturing area | Product contamination | 9 | 5 | 7 | =9 x 9 x 7=378 | Environmental parameters recording in each shift |

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## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | What are the Consequences | Severity | Probability | Detection | Risk Priority Number | Existing Design Control |
|---|---|---|---|---|---|---|---|---|
| | | | | (S) | (P) | (D) | RPN= S x P x D | |
| | **Risk Analysis** | | | | | | **Risk Evaluation** | |
| **13.3** | **Challenge Design for Process simulation study** | | | | | | | |
| **13.4** | Aseptic Environment deterioration on Power failure | Non Working of HVAC System | Product contamination | 9 | 5 | 7 | =6 x 5 x 7=378 | Power Will be tripped Deliberately during Media Fill study for studying the disturbance during simulation study<br><br>HVAC Recovery Study in Trial Batch |

**REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY**

### 5.2.3 Risk Reduction or Mitigation

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| 1. | **Lack of Personnel Hygiene & Attitude** | No Formal or Practical training for aseptic manufacturing<br><br>Lack of Attitude<br><br>Medically unfit for aseptic manufacturing | Training for Personnel Hygiene for all persons<br><br>Personnel Monitoring Once a day<br><br>Training on Positive attitude for working.<br>Yearly Medical Examination | 9 | 8 | 7 | 504 | Personnel Hygiene Monitoring **in each shift**<br><br>**Half** yearly Medical Examination<br><br>Adoption of Personnel Hygiene verification through Checklist before entering to Sterile Manufacturing area | 9 | 3 | 3 | **81** |

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## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| 2. | **No Defined Man Movement Procedures** | No Defined Flow for Man Movement<br><br>No Procedural Control<br>In adequate Training for the Person's<br>No supervisory Control<br>No display for instructions | Approved Layouts for Man movement<br><br>Training on SOP for Exit & exit , Do's & Don'ts in sterile plant<br><br>One shift in charge per shift<br><br>SOP Display | 9 | 5 | 7 | 315 | Lay out Display in the corridor describing proper flow of material, Man & Waste Movement<br><br>Provision for the Video recording to check the various activity in controlled area<br><br>Exhaustive training for the staff about Man movement Procedure | 9 | 3 | 2 | 54 |

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| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| 3. | **Inappropriate Cleaning, Sanitization or Disinfection of Rooms (walls, roofs& floor), Outer surfaces of Equipment, instruments, utility lines, other pipe work and Platforms** | -Non Availability of standard procedure for cleaning, Disinfection or sanitization and procedure for cleaning or disinfectant solution Preparation<br>-Personnel not Trained<br>Inappropriate design<br>- Excessive Height of roof<br>- Inaccessible surfaces<br>- No finishing in the roofs Walls & Floor surfaces<br>Ineffective and non validated Cleaning agents, sanitizers or disinfectant | Approved SOPs<br>Training for the Persons<br>Validated & Effective Cleaning agents, sanitizers or disinfectant<br>SOP for Building Management verification is done half yearly | 8 | 8 | 7 | 448 | Ladder design with<br>-platform to get stand for cleaning & disinfection<br>-Safety measures to prevent fall from height<br>-Proper height to reach the inaccessible area<br>- SOP for Building Management has to be revised to include special consideration for sterile facility, Monthly verification is done for the finishing of roof, walls & Floor surfaces and other area of sterile manufacturing facility | 8 | 4 | 3 | **96** |

# REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| 4. | **Failure in the Raw Material Procurement, Storage, Testing & Approval** | -Non availability of Vendor Approval Procedure<br>-Non Availability & Inappropriate design of Ware house for good storage<br>-Non Availability of Approved testing Methods<br>-Non Availability Procedure for Rejection & Approval of Raw material for use | Availability of Vendor Approval Procedure<br>Availability & Inappropriate design of Ware house<br>Availability of Approved testing Methods<br>Availability Procedure for Rejection & Approval of Raw material for use | 9 | 5 | 2 | 90 | Since the Existing design control keep the risk at acceptable level so no additional Design control is required | 9 | 5 | 2 | 90 |

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## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| 5. | **Inappropriate Raw & Packing material Handling** | No Define Procedure and Provision for<br>- material Flow<br>- good storage conditions<br>- Material Dispensing<br>- Accurate Weighing<br>- Material Identification | Approved Layouts for Material movement<br>SOP for the storage of Raw & Packing Material<br>SOP for the Dispensing of Material<br>SOP for the operation of Weighing Balances | 7 | 7 | 4 | 196 | Lay out Display in the corridor describing proper flow of material, Man & Waste Movement<br>The SS racks are required for the storage finished good<br>SS pellets are required for keeping the Raw & Packing material intact as per requirement for batch Processing<br>Additional gowning procedure is required for RM & PM Dispensing and also provision to keep gowns<br>Supervisory control at the time of RM& PM Dispensing | 7 | 4 | 3 | **84** |

## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| 6. | **Drain System Failure** | Non availability of GMP Model of the drains<br><br>Non availability of Standard procedure for the disinfection and sanitization of the available drains<br><br>Operator are not trained for the sanitization procedure of the drain | The GMP Model of drains are provided in the Plant<br><br>Standard procedure for the disinfection and sanitization of the are available for drains<br><br>Operators are trained for the sanitization procedures | 7 | 4 | 2 | 56 | Since the Existing design control keep the risk at acceptable level so no additional Design control is required | 7 | 4 | 2 | **56** |

## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| **7.** | **Inappropriate Handling of sterilized Material during carrying, storage or usage** | Non Availability of standard procedure<br><br>Non Availability of Required Provision<br><br>Operator Not Trained | Availability of validated standard procedure<br><br>Mobile LAF for carrying Sterilized material<br><br>Garment Cubicles for storage of sterilized garments<br><br>Formal training to the operator | 9 | 5 | 4 | 180 | Provision for the Video recording to check the various activity in controlled area<br><br>Additional Supervisory Control<br><br>Formal & Practical training to the operator to assess the Capability of Man and machine to maintain the sterility of sterilized material | 9 | 3 | 3 | **81** |

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| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| **8.** | **Failure of Processing Equipments** | | | | | | | | | | | |
| **8.1** | **Operational Failure of Equipment** | Non Availability of standard procedure<br><br>Operator Not Trained | Availability of validated standard procedure<br><br>Formal training to the operator for the operation of all Processing equipment operator | 9 | 5 | 4 | 180 | Provision for Easy Accessibility and Display of the Standard Operating Procedure<br><br>The Practical Training for the operation of All equipments in the sterile Plant<br><br>Additional Supervisory Control | 9 | 3 | 3 | **81** |

# REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| **8.** | **Failure of Processing Equipments** | | | | | | | | | | | |
| **8.2** | **Dissolution Vessel, Vessel Washing Solvents & Crystallizer** | Break Down<br>Electrical Failure<br>Lose of filter integrity of Vent filter<br>MOC Not Compatible | SOP for Equipment Operation<br>SOP to check filter before and after the batch<br>SS 316 L verified during Qualification through certification | 7 | 8 | 5 | 280 | The Process Handling during Breakdown & Electrical failure must be the Part of SOP for the operation of equipment<br>Provision for the Video recording to check the various activity in controlled area | 7 | 4 | 2 | **56** |

# REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| **8.** | **Failure of Processing Equipments** | | | | | | | | | | | |
| **8.3** | **Filter train**<br><br>-Product Line<br><br>-Solvent Line<br><br>-Buffer Line | Breakdown High Pressure of Solution to be Filtered<br><br>Lose of filter integrity of filter<br><br>Loosening of Clamp holdings<br><br>MOC Not Compatible | SOP for Equipment Operation<br><br>Formal training to the operator for the operation of filtration through different filter trains<br><br>SS 316 L verified during Qualification through certification | 9 | 5 | 4 | 180 | The Process Handling during Breakdown & Electrical failure must be the Part of SOP for the operation of Filter Train<br><br>The Practical Training for the operation<br><br>Supervisory control during Clamp & line assembling | 9 | 3 | 3 | **81** |

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## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| **8.** | **Failure of Processing Equipments** | | | | | | | | | | | |
| **8.4** | **PFE** | Breakdown Electrical Failure<br><br>Lose of filter integrity of Filter cloth<br><br>Lose of filter integrity of Nitrogen filter<br><br>Loosening of Clamp holdings used to fix Material & ML<br><br>MOC Not Compatible | SOP for Equipment Operation<br><br>Formal training to the operator for the operation of filtration through different filter trains<br><br>Supervisory control during Clamp & line assembling<br><br>SS 316 L verified during Qualification | 9 | 5 | 4 | 180 | The Process Handling during Breakdown & Electrical failure must be the Part of SOP for the operation of PFE<br><br>Provision for the Video recording to check the various activity in controlled area<br><br>The Practical Training for the operation | 9 | 3 | 2 | **54** |

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## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| **8.** | **Failure of Processing Equipments** | | | | | | | | | | | |
| **8.5** | **Combi & Conveyer System** | Rotating Motor Failure<br><br>Lose of filter integrity of Mesh<br><br>Inappropriate Mesh Size<br><br>Breakdown Electrical Failure<br><br>Loosening of Clamp holdings<br><br>MOC Not Compatible | SOP for Equipment Operation<br><br>Formal training to the operator for the operation of filtration through different filter trains<br><br>Supervisory control during Clamp & line assembling<br><br>SS 316 L verified during Qualification | 9 | 5 | 4 | 180 | The Process Handling during Breakdown & Electrical failure must be the Part of SOP for the operation of Combi & Conveyer System<br><br>Provision for the Video recording to check the various activity in controlled area<br><br>The Practical Training for the operation | 9 | 4 | 2 | **72** |

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## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| **8.** | **Failure of Processing Equipments** | | | | | | | | | | | |
| **8.6** | **Blender** | Breakdown Electrical Failure<br><br>Product exposure during Material charging & Unloading<br><br>Accident during Rotation<br><br>Loosening of Clamp holdings to Powder Bin<br><br>MOC Not Compatible | SOP for Equipment Operation<br><br>Formal training to the operator for the operation of blender<br><br>Railing guard as safety measure<br><br>Supervisory control during Clamping the Powder Bin<br><br>SS 316 L verified during Qualification through certification | 9 | 5 | 4 | 180 | Provision for the Video recording to check the various activity in controlled area<br><br>The Process Handling during Breakdown & Electrical failure must be the Part of SOP for the operation of Blender<br><br>The Practical Training for the operation | 9 | 4 | 2 | **72** |

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| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| **9.** | **Failure of Environment Monitoring Equipments** | | | | | | | | | | | |
| **9.1** | **HVAC System** | Breakdown Electrical Failure<br>Lose of integrity of HEPA filters Accident during Rotation<br><br>Disturbed Differential Pressure<br>Improper Cleaning of Pre & microbe Filters<br><br>Cleaning of Return Risers | SOP for Equipment Operation<br><br>Formal training to the operator for the operation of HVAC<br><br>SOP for DP Monitoring in each shift<br><br>SOP for the cleaning of Filters & return riser<br><br>Half yearly Qualification Procedure For HVAC System | 9 | 5 | 4 | 180 | SOP for The Process Handling during Breakdown & Electrical failure of HVAC System<br><br>The Practical Training for the operation<br><br>On line Particle counter<br><br>Provision for Separate location for the cleaning of supply filters & return riser | 9 | 4 | 2 | **72** |

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| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| **9.** | **Failure of Environment Monitoring Equipments** | | | | | | | | | | | |
| **9.2** | **Dynamic Pass Boxes** | -Breakdown Electrical Failure<br>-Lose of integrity of HEPA filters<br><br>-Disturbed Differential Pressure.<br><br>-Improper Cleaning of Pre Filters<br><br>-Improper Door Closing or Opening<br><br>-Interlock for Door opening not activated or working | SOP for Equipment Operation<br><br>Formal training to the operator for the operation of Dynamic Pass Boxes<br><br>DP Monitoring during Operation is the instructional part of SOP for operation<br>SOP for the cleaning of Filters<br><br>Half yearly Qualification Procedure For Equipment | 9 | 5 | 4 | 180 | SOP for handling the operation during Electrical failure & Breakdown of Dynamic Pass Box<br><br>The Practical Training for the operation<br><br>Additional Supervisory Control<br><br>Provision for the Video recording to check the various activity in controlled area | 9 | 4 | 2 | **72** |

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| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| **9.** | **Failure of Environment Monitoring Equipments** | | | | | | | | | | | |
| **9.3** | **Laminar Air Flow Units** | Breakdown Electrical Failure<br><br>Lose of integrity of HEPA filters<br><br>Disturbed Differential Pressure<br><br>Improper Cleaning of Pre Filters | SOP for Equipment Operation<br><br>Formal training to the operator for the operation of Dynamic Pass Boxes<br><br>DP Monitoring during Operation is the instructional part of SOP for operation<br><br>SOP for the cleaning of Filters<br><br>Half yearly Qualification Procedure For Equipment | 9 | 5 | 4 | 180 | SOP for handling the operation during Electrical failure & Breakdown of Dynamic Pass Box<br><br>The Practical Training for the operation<br><br>Additional Supervisory Control<br><br>Provision for the Video recording to check the various activity in controlled area | 9 | 4 | 2 | **72** |

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| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| **10.** | **Failure of Equipment For Sterilization & De** | | | | | | | | | | | |
| | **Steam Heat Sterilizer**<br><br>**& Dry Heat Sterilizer** | Breakdown Electrical Failure<br><br>Non availability of Utility at required parameters Like Nitrogen, Pneumatic air, Pure Steam etc Instrument Malfunctioning PLC Malfunctioning Inappropriate Load for sterilization<br><br>Non availability of validated standard Procedure of Sterilization | SOP for Equipment Operation<br><br>Interlocks & alarm configuration for utility requirements<br><br>-Instrument Calibration<br><br>-Equipment Qualification<br><br>-Validated Load configuration<br><br>SOP for sterilization process for SHS & DHS | 9 | 5 | 4 | 180 | The Process Handling during Breakdown & Electrical failure must be the Part of SOP for the operation of Dry Heat Sterilizer & Steam Heat Sterilizer<br><br>Qualification of PLC<br><br>Instrument must be calibrated Quarterly<br><br>Additional Supervisory Control | 9 | 3 | 3 | **81** |

## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| **10.** | **Failure of Equipment For Sterilization** | | | | | | | | | | | |
| | **Steam Heat Sterilizer**<br><br>**& Dry Heat Sterilizer** | Operator Not trained<br><br>Lose of integrity of HEPA filters (DHS)<br><br>Improper Cleaning of HEPA Filters<br><br>Alarms & Interlocks Not working<br><br>MOC Not Compatible<br><br>Non availability of validated standard Procedure of Sterilization | Formal training to the operator for the operation of SHS & DHS<br><br>DP Monitoring during Operation is the instructional part of SOP for operation<br><br>SOP for the cleaning of Filters<br><br>Verification of Alarms & Interlocks Is the part of Qualification | 9 | 5 | 4 | 180 | Practical Training to the Operator<br><br>Qualification Procedure For HEPA filters Half Yearly | 9 | 3 | 3 | **81** |

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## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| **11.** | **Failure of Simulation Study** | | | | | | | | | | | |
| **11.1** | **The Wrong Selection of Nutrient Media** | Inadequate Knowledge of the person Performing selection for medium nutrient<br><br>Regulatory guidelines not followed | Formal training for media fill selection Criteria<br><br>SS 316 L is the MOC of Different Processing Equipment which is compatible to Lactose The MOC is verified During qualification of Equipments<br><br>Referred Guidance must be mentioned in the protocol<br><br>Approval Procedure from Experience & Qualified Management | 7 | 4 | 3 | 84 | Since the Existing design control keep the risk at acceptable level so no additional Design control is required | 7 | 4 | 3 | 84 |

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## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| **11.** | **Failure of Simulation Study** | | | | | | | | | | | |
| **11.2** | **Wrong Process design for Simulation Study** | The Person is not qualified or trained for designing the Process for Simulation study<br>The Process Simulation study may not cover all the products<br>The Process Parameters are not decided as per Process package<br>The Process manipulations are not studied and evaluated<br><br>The worst case scenario is not appropriately decided<br>Incorporation of process step, having inhibitory action on the Microbial growth like use of solvents, acids, alkalis, High/low temperature, High agitation etc | Formal Training & relevant Experience is Assessed for Process design<br><br>Product List is a the Part of Protocol<br><br>Reference of process Package must be mentioned in the protocol<br><br>The worst case scenario is calculated through Product Matrix<br><br>Only WFI & Lactose is used, which is a supports microbial growth | 7 | 4 | 3 | 84 | Since the Existing design control keep the risk at acceptable level so no additional Design control is required | 7 | 4 | 3 | 84 |

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## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| **11.** | **Failure of Simulation Study** | | | | | | | | | | | |
| **11.3** | **Wrong Calculation of Quantity of Nutrient Medium for the simulation study** | The complete details of total qty. of Non sterile Raw material which gives complete load on the Filter train may not be calculated | Total quantity is considered as per batch size | 7 | 6 | 4 | 168 | Total Non Sterile Load Calculation for different Products Shall be the Part of Protocol<br><br>Approval Procedure from Experience & Qualified Management | 7 | 4 | 3 | **84** |
| **11.4** | **Wrong Calculation of Holding Time in the Equipment** | The total time taken for the processing in a particular equipment is not ascertain correctly | Crystallizer time is considered for crystallizer<br><br>Drying time for PFE | 7 | 6 | 4 | 168 | Total Holding time Calculation for different Products Shall be the Part of Protocol<br><br>Approval Procedure from Experience & Qualified Management | 7 | 4 | 3 | **84** |

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## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| **11.** | **Failure of Simulation Study** | | | | | | | | | | | |
| **11.5** | **Wrong agitation Time** | Process is not studied for agitation requirement so as to prevent microbial inhibition | Minimum Agitation is Considered in crystallizer & PFE | 7 | 5 | 4 | 140 | Total Agitation time Calculation for different Products Shall be the Part of Protocol<br><br>Approval Procedure from Experience & Qualified | 7 | 4 | 3 | **84** |

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## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| **11.6** | **Failure of Simulation Study** | | | | | | | | | | | |
| **11.6** | **Wrong In process Sampling & Final Sampling** | Untrained & Unqualified person<br>Non Availability of SOPs for cleaning & up keep of sampling tools<br><br>Standard operating procedure may not be in place<br><br>Sampling time for in process may not be studied or established<br><br>Sampling frequency for in process may not be studied or established | Trained & Qualified persons for sampling<br><br>Provision for Cleaning and Up keep of sampling tools and formal training for the same<br><br>SOP for the Sampling procedure and formal training for the same<br><br>Sampling time is fixed<br><br>Protocols define the clear Sampling frequency | 7 | 5 | 4 | 140 | Additional Supervisory Control<br><br>Practical Training | 7 | 4 | 3 | **84** |

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## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| **11.6** | **Failure of Simulation Study** | | | | | | | | | | | |
| **11.7** | **Testing Failure** | Non Availability of Standard testing sterility Method<br>-Non Availability of Validated Analytical Method<br>-Analyst Not trained<br>-Expired Reagents<br>Poor membrane filter performance<br>Non Calibrated Analytical Instrument | Wrong Analysis<br>-Faulty results<br>-Regulatory non compliance<br>Non Representative Sampling<br>-Faulty analytical results<br>Poor Performance of Analytical Instrument | 7 | 4 | 3 | **84** | Since the Existing design control keep the risk at acceptable level so no additional Design control is required | 7 | 4 | 3 | **84** |

## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| **12.** | **Manual Interruptions** | | | | | | | | | | | |
| **12.1** | **Disturbance of aseptic environment in the crystallizer because of seeding** | Operator error- | SOP for Seeding the material in Crystallizer<br><br>Supervisory Control for the same<br>Separate Seeding Port | 7 | 5 | 4 | 140 | Formal &Practical Training<br><br>For seeding | 7 | 3 | 4 | **84** |
| **12.2** | **Product exposure during transfer of material from PFE to Combi through Conveyer** | Malfunctioning of Clamp used to fix Bellow<br>Operator Error | SOP for the Operation<br>Formal training for the same<br>Supervisory Control<br>Mobile LAF for fixing the Bellow to the conveyer | 7 | 5 | 4 | 140 | Formal &Practical Training | 7 | 3 | 4 | **84** |

**REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **12.3** | **Product exposure during Blending & Packing** | Malfunctioning of Clamp used to fix Bellow<br><br>Operator Error | SOP for the Operation<br>Formal training for the same<br>Supervisory Control<br>Mobile LAF & Vertical LAF for fixing the Powder Bin to Blender & performing Packing respectively | 7 | 5 | 4 | 140 | Formal &Practical Training | 7 | 3 | 4 | **84** |

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## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S.No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| **13.** | **Challenge Design for Process simulation study** | | | | | | | | | | | |
| **13.1** | **Failure to simulate Process for 24 hrs** | All the shifts may not be considered for Simulation study | All the shifts are considered in the Protocol | 9 | 5 | 2 | 90 | Risk Is under Acceptance Criteria | 9 | 5 | 2 | 90 |
| **13.2** | **Aseptic Environment deterioration on employment of additional Man power in case of requirement** | Inefficiency of HAVC system to withstand the disturbance by employing additional person for aseptic area manufacturing | One additional Person is considered for Simulation study<br>Gowning Procedure During Entry & exit<br>HVAC Performance Study in Trail Batch | 9 | 5 | 7 | 378 | Personnel Monitoring In Each shift<br>Environmental Monitoring In each Shift<br>Online Particular counter<br>Environmental parameters recording in each shift hourly interval<br>Provision for the Video recording to check the various activity in controlled area | 9 | 4 | 2 | 72 |
| **13.3** | **Aseptic Environment deterioration on performing minor maintenance work in the aseptic manufacturing area** | Inefficiency of HAVC system to withstand the disturbance by carrying out minor maintenance work in the aseptic manufacturing area | | 9 | 5 | 7 | 378 | | 9 | 4 | 2 | 72 |

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## REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

| S. No. | Failure Mode {What can go wrong} | Potential cause of Failure | Existing Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) | Additional Design Control | Severity (S) | Probability (P) | Detection (D) | Risk Priority Number (RPN) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Risk Mitigation** | | | | | | | | | | | |
| **13.** | **Challenge Design for Process simulation study** | | | | | | | | | | | |
| **13.4** | **Aseptic Environment deterioration on Power failure** | Non Working of HVAC System | Power Will be tripped Deliberately during Media Fill study for studying the disturbance level<br><br>HVAC Recovery Study in Trail Batch | 9 | 5 | 7 | 378 | SOP for Process Handling during Power Failure<br><br>Environmental Monitoring In each Shift<br>Online Particular counter Environmental parameters recording in each shift hourly interval | 9 | 4 | 2 | **72** |

# REPORT FOR RISK ASSESSMENT & MITIGATION OF PROCESS SIMULATION STUDY

## 6. Acceptance criteria

The Risk Priority Number shall be within the range 0<RPN<100.

## 7. Risk Control Strategy

| S.No. | Risk Priority Number | Risk Decision | Risk control strategy |
|---|---|---|---|
| 1. | 0<RPN<100 | Risk Acceptable | No control is required |
| 2. | 100<RPN<500 | Risk Reduction | Additional Procedural Control |
| | | | Manual Control |
| | | | Documentary Evidence |
| 3. | 500<RPN<1000 | Risk Reduction | Rugged Procedural control |
| | | | Additional Manual Control |
| | | | Auditing |
| | | | Engineering controls (if Possible) |

## 8. Summary and Conclusion

The risk associated with each Failure mode lies in between the range 0<RPN<100 after going through risk mitigation and reduction process

Hence it meets the acceptance criteria for risk acceptance

On the basis of Risk assessment process using FMEA tool it is concluded that the Process Simulation Study is associated with an acceptable level of risk and there is no any adverse impact of on carrying out the simulation study under the given set up of manufacturing facility and process design strategy.

## 9. References:

**1.** Risk Management Master Plan
**2.** ICH Q9