APPROVAL

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Author** |  |  |  |  |  |  |
| Gearoid Cronin |  | Director, Process Engineering Specialists |  |  |  |  |
| Name |  | Designation |  | Signature |  | Date |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| **Reviewer** |  |  |  |  |  |  |
| Craig Newby |  | Director R&D, Consumer Healthcare |  |  |  |  |
| Name |  | Designation |  | Signature |  | Date |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| **Approver** |  |  |  |  |  |  |
| Belinda Braggs |  | Quality Assurance Consultant |  |  |  |  |
| Name |  | Designation |  | Signature |  | Date |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |

REVISION HISTORY

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# PURPOSE

The purpose of this procedure is to identify the critical parameters for equipment, processes, utilities and facilities (herein collectively referred to as “Systems”) that have been classified as direct impact systems. Critical parameters have an impact on proper operation of the System and may impact Patient Safety and Product Quality. The procedure will define the Risk Assessment Process and provide the required documentation to successfully complete the Risk Assessment Process. The Risk Assessment will be used to determine the quality approach of the documentation, testing and validation.

# SCOPE

This procedure applies to Direct Impact systems. This includes Systems used to support manufacturing, storage, packaging, testing and labeling of commercial products produced at Mundipharma Manufacturing Pte Ltd. The Risk Assessment will be used to determine the quality approach of the documentation, testing, qualification and validation.

The scope of this procedure does not cover the procedure for the System Level Impact Assessment to identify Direct Impact Systems. The SLIA will be covered in another procedure.

# RESPONSIBILITIES

|  |  |
| --- | --- |
| **Function** | **Responsibility** |
| Research and Development | * Provide the Product and Process knowledge document that describes the CQAs and CPPs * Part of the team to develop, execute and review / approve Risk Assessments |
| Operations / Engineering | * Part of the team to develop, execute and review / approve Risk Assessments |
| Risk Assessment Lead | * Enter all required data in the Risk Assessment record as directed by the Risk Assessment team |
| Quality Assurance | * Identify resources to develop, execute and approve Risk Assessments * Manage the Risk Assessment process * Approve all Risk Assessments (final approval) |

# DEFINITIONS

Abbreviations and terms used in this document are listed below.

| **Abbreviation / Term** | **Definition** |
| --- | --- |
| Automation Controls | Expected automation functions that serve to control the identified hazard via the identified pathway. |
| CPP (Critical Process Parameter) | A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. |
| CQA (Critical Quality Attribute) | A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials) and drug product. |
| Design Controls | Equipment or facility design features that serve to control the identified hazard via the identified pathway. |
| Direct Impact Systems | A system that is expected to have a direct impact on product quality, via product contact or direct influence on quality. In some instances, direct impact systems will depend on indirect impact systems for effective operation and therefore, any interfaces need to be carefully assessed |
| DQ | Design Qualification |
| Field Verifiable | Physical items on the system that can be tested objectively, typically include design elements (layout, installation and materials), automation elements (controls, alarms and interlocks) and physical detection elements (instrumentation, field alarms etc.).  This definition is closely related to items that may be qualified in DQ, IQ, OQ, and PQ where the severity is greater than 5.  This definition also closely relates to items that must all be verified under Good Engineering Practice during construction and commissioning. |
| GEP | Good Engineering Practice |
| Hazard | Defined in ICH Q9 as the potential source of harm.  In this context hazards are defined only as credible hazards to patient safety or product quality within the bounds of the process area or system being considered. |
| IQ | Installation Qualification |
| No Impact system | A system that will not have any impact, either directly or indirectly, on product quality, and will not support a direct impact system. |
| OQ | Operational Qualification |
| PQ | Performance Qualification |
| Quality System Controls | Quality system controls that serve to mitigate the identified hazard via the identified pathway |
| Risk Assessment | Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards (as defined below). |
| Risk Priority Number (RPN) | The Risk Priority Number, or RPN, is a numeric assessment of risk assigned to a process, or steps in a process, as part of Failure Modes and Effects Analysis (FMEA), in which a team assigns each failure mode numeric values that quantify likelihood of occurrence, likelihood of detection, and severity of impact. |
| SLIA | System Level Impact Assessment |

# PROCEDURE

## Process Flow



## Overview

To capture the best input for the Risk Assessment the process should include a selected team consisting of a Risk Assessment Lead, effected department management, SME’s (technical expertise) to include Operations, Quality Control, Quality Assurance, Research and Development, Engineering, Maintenance, and Regulatory when required. The Risk Assessment team, at a minimum, consists of Research and Development, Quality Assurance and Operations / Engineering.

The Risk Assessment consists of identification of Hazards and the analysis of their Severity, Probability, and Detectability as well as documenting the solution to abate each Hazard. The process will utilize a quantitative method to numerically assign a priority number. The Risk Assessment program is a tool for establishing critical parameters and associated acceptance criteria for each direct Impact System. This information is directly leveraged when developing the qualification protocols.

## Identify Direct Impact Systems

A System Level Impact Assessment will be performed to identify the Direct Impact systems that will undergo the Risk Assessment process. Refer to SOP-TD-001 System Level Impact Assessment Betadine Greenfield Facility Singapore. The No Impact systems will not undergo the risk assessment process and will not be qualified but will undergo commissioning.

## Risk Assessment Methodology

Failure Modes and Effects Analysis (FMEA) provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce or control the potential failures. FMEA relies on product and process understanding. FMEA methodically breaks down the analysis of complex processes into manageable steps. It is a powerful tool for summarizing the important modes of failure, factors causing these failures and the likely effects of these failures.

FMEA can be extended to incorporate an investigation of the degree of severity of the consequences, their respective probabilities of occurrence, and their detectability, thereby becoming a Failure Mode Effect and Criticality Analysis (FMECA). In order for such an analysis to be performed, the product or process specifications should be established. FMECA can identify places where additional preventive actions might be appropriate to minimize risks.

The methodology in this procedure will use a process Failure Modes Effects and Criticality Analysis (pFMECA). Other tools may also be used.

## Risk Assessment Process

### Documenting the Risk Assessment

A spreadsheet shall be used to capture the risk assessment process.

The Risk assessment Team will create the list of systems to be assessed from the SLIA and perform a risk assessment on each Direct Impact System. The Risk Assessment spreadsheet will include the minimum information:

* + System Number
  + System Name

The Risk Assessment worksheet table will include the following information:

* + Risk Identifier
  + Area of Review
  + General Hazard
  + Severity
  + Pathway for Hazard Impact to Patient Safety and / or Product Quality
  + Related CPP
  + Risk Control Strategy (RCS)
    - Risk Controls (Design Controls, Automation Controls, Quality System Controls)
    - Probability
    - Detection (On-line, At-Line, Off-line)
    - Detectability
    - Risk Priority Number (RPN)
    - Comments (Severity, Probability, Detectability)
    - Action
  + Proposed Rectification
    - Design Actions
    - Owner
    - Severity (same as above)
    - Projected Probability, Detectability and RPN recalculated with Design Actions
  + Qualification Actions
    - Automation
    - Clean Build
    - Detection
  + Traceability Matrix
    - Process Design Reference
    - Automation Design Reference
    - IQ Reference
    - OQ Reference
    - PQ Reference

Template of Headings for a Risk Assessment Spreadsheet are shown in Appendix 1 for documenting findings. If there are columns that are not applicable write N/A.

### Risk Identifier

Assign a unique risk identifier number starting with the System Number to each hazard considered within the area of review.

### Area of Review

Areas of Review will be determined according to the functional aspects of the manufacturing such as Processing, Contamination and Mix ups,

### General Hazard

List individually each of the credible hazards to patient safety or product quality within the bounds of the system being considered. “General Hazards” to consider could include Microbial Contamination, Particulate / Foreign Matter, Cross Product Contamination, Purity Assessment, Potency/Strength, Product Degradation, Product Misbranding and/or Identity.

### Severity

Rate the severity of the hazard were it to occur according to the following rating system and worst case scenario:

|  |  |
| --- | --- |
| 1 | No consequences to product quality/ No impact to patient. |
| 3 | Minimal impact on product quality/ Possible Patient discomfort/ Possible Minor CAPA or deviation. |
| 5 | Product quality may be affected/ Possible Patient Illness/ Possible Major CAPA or deviation. |
| 8 | Product quality likely to be affected/ Possible Serious Patient Illness or Injury/ Possible Product Recall. |
| 10 | Significant risk to product quality/ Possible Patient Death. |

### Pathway for Hazard Impact to Patient Safety and / or Product Quality

Describe the mechanism or pathway by which the hazard could occur.

### Related CPP

Identify the Critical Process Parameter related to the potential hazard. The CPPs are defined in a product and process knowledge document.

### Risk Control Strategy (RCS) – Risk Controls

Design Controls – List all of the equipment or facility design features that serve to control the identified hazard via the identified pathway.

Automation controls – List expected automation functions that serve to control the identified hazard via the identified pathway.

Quality System Controls – List quality system controls that serve to mitigate the identified hazard via the identified pathway

### Risk Control Strategy (RCS) – Probability

Based on the controls above, and the expertise of the risk review team, provide an assessment of the probability the hazard will occur through the specified pathway:

|  |  |  |
| --- | --- | --- |
| **Rating of Probability** | **Probability** | **Defined as frequency / observations over time** |
| 1 | Highly unlikely to occur | Less than once per annum |
| 3 | Minimal chance of occurring | Average once per annum to per month (1 year to 1 month, 1 to 12 per annum) |
| 5 | May occur | Average once per week (1 week to 1 month, 20 to 50 per annum) |
| 8 | Occurs with high frequency | Average greater than once per week (50 to 100 annum) |
| 10 | Always present | Estimate every day - greater than 100 per annum |

### Risk Control Strategy (RCS) – Detection

List all of the means by which the hazard occurrence or pathway failure can be detected, categorized by on-line, at-line, or off-line methods.

### Risk Control Strategy (RCS) – Detectability

Based on the controls above, and the expertise of the risk review team, provide an assessment of the detectability of the hazard by the detection methods above.

|  |  |  |
| --- | --- | --- |
| **Rating of Detectability** | **Detectability** | **Defined as type, place and frequency of detection** |
| 1 | Will be detected | Instrumentation on-line, Assay of finished product (bulk property)  Notes: Instruments must specifically be installed for the purpose, constant monitoring for that Hazard. |
| 3 | Likely to be detected | At-line sampling in which frequency of sampling is higher  Regular and procedure driven in process checks that are specific to the hazard. Expectation is that the frequency will identify intermittent issue and that the detection is enhanced by presence on the line and familiarity. |
| 5 | Will probably be detected | Off - line sampling  Either:  - Sampling of batch taken off line and evaluated by someone not on the line.  - In Process testing that is not specific to the hazard or for a hazard that may not be detected due to intermittent nature. |
| 8 | Minimal chance of detection | Visual  Intermittent detections/ sampling will not pick it up, but might be detected. Might be detected by chance. |
| 10 | Will not be detected | Will not plausibly be detected |

### Risk Priority Number (RPN)

The Risk Priority Number is computed based on Severity x Probability x Detectability.

Where the RPN is <60 the risk may be considered as acceptable, but for any risks with a severity ≥ 5, then all controls (design, automation and quality system) that are field verifiable must undergo appropriate qualification. The qualification actions will be defined in the risk assessment report and in the traceability matrix contained therein. If the RPN < 60, it does not need to be justified in the risk assessment report.

Where the RPN is ≥ 60, then the risk must be additionally evaluated:

* + Proposed Rectifications/ Mitigations are considered, and where a design change is proposed, the following are evaluated:
    - Design Actions/ Owner
    - Severity
    - Projected Probability
    - Projected Detectability
    - Projected RPN if proposed mitigation is implemented.
  + If the design change is accepted then the design is updated and the risk assessment is re-conducted and updated accordingly.

Once the final design is in place:

* + For RPN > 100 the risk is still likely unacceptable and proposed rectifications/ mitigations must be considered until the RPN is lowered below 100.
  + If the RPN is between 60 and 100 then the risk may be accepted with clear justifications identified in the risk assessment report.
  + For any risks with a severity ≥ 5, all controls (design, automation and quality system) that are field verifiable must undergo appropriate qualification. The qualification actions (DQ, IQ, OQ and PQ) will be defined in the risk assessment report and in the traceability matrix contained therein.

All controls (design, automation and quality system) that are field verifiable must be commissioned according to GEP regardless of severity.

# APPLICABLE REFERENCES

List of applicable References are:

|  |  |  |
| --- | --- | --- |
| [1] | SOP-TD-001 | System Level Impact Assessment Betadine Greenfield Facility Singapore |
| [2] | SOP-QA-003 | Qualification and Validation Strategy - Greenfield Project |
| [3] | ICH Q9 | Quality Risk Management |
| [4] | ASTM E2500 | Standard Guide for Specification, Design and Verification of Pharmaceutical and Biopharmaceutical Manufacturing systems and Equipment |

# RECORDS

Not Applicable.

# APPENDICES:

## Appendix 1: Headings for Risk Assessment Spreadsheets

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Risk Identifier** | **Area of Review** | **General Hazard** | **Severity** | **Pathway for Hazard to Impact Patient** | **Related CPP** |
|  |  |  |  |  |  |

Continue headings across

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **RISK CONTROL STRATEGY - [R C S]** | | | | | | | | | | | | |
| **Design Controls** | **Automation Controls** | **Quality System Controls** | **Probability** | **On-line Detection** | **At-line Detection** | **Off-line Detection** | **Detectability** | **RPN** | **Severity Comments** | **Probability Comment** | **Detectability Comment** | **Action** |
|  |  |  |  |  |  |  |  |  |  |  |  |  |

Continue Headings Across

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Proposed Rectification** | | | | | | **Qualification Actions** | | | **Traceability Matrix** | | | | |
| **Design Actions** | **Owner** | **Severity** | **Projected Probability** | **Projected Detectability** | **Projected RPN** | **Qualification Action- Automation** | **Qualification Action- Clean Build** | **Qualification Action- Detection** | **Process Design Reference** | **Automation Design Reference** | **IQ Reference** | **OQ Reference** | **PQ Reference** |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |