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COMM-QA-080
QUALITY RISK MANAGEMENT

1   PURPOSE

1.1   The primary purpose of this standard operating procedure (SOP) is to frame the process for managing risk in the GMP operations of the Marcus Center for Cellular Cures (MC3) using the FDA Q9 Quality Risk Management guidance to help ensure product quality, patient safety, and optimal facility management. This SOP outlines a process for Risk Assessments (RA) and identifies Risk Assessment Tools to enable effective risk assessments.

2   INTRODUCTION

2.1   Risk is defined as the combination of the probability of occurrence of harm and the severity of that harm.

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

2.3   The Risk Management Process is composed of four major parts:

    2.3.1   Risk Assessment consists of the identification of hazards and the analysis and evaluation of risks associated with those hazards.

    2.3.2   Risk Control includes decision making to reduce risks to an acceptable level and/or accept risks.

    2.3.3   Risk Communication is the documentation and sharing of risk information with the appropriate individuals, both internally and externally.

    2.3.4   Risk Review is part of the Quality System management process and is included in periodic Management Reviews.

2.4   For general information, refer to Figure 1 and FDA Q9 Quality Risk Management Guidance for details and risk management tools.

Figure 1: Risk Management Process per FDA Q9 Quality Risk Management Guidance.

3 SCOPE AND RESPONSIBILITIES

3.1 The required scope of this SOP includes the Carolinas Cord Blood Bank (CCBB) and Robertson GMP Laboratory as well as related GMP quality and administrative functions. MC3 risk management encompasses MC3 GMP production operations that include, but are not limited to, materials management, facility management, manufacturing/processing, holding, distribution, as well as inspection and testing of the materials/products processed in MC3.

3.2 Quality is responsible for the development of the Risk Management process including the SOPs, identification of potential tools, methods and manner of documentation, as well as frequency and content of management reviews.

3.3 MC3 Management is responsible for:

3.3.1 Identifying applicable Subject Matter Experts (SMEs) to support the Risk Management process and Risk Assessments.

3.3.2 Governing the Risk Management process by providing the necessary resources, communicating Risk Assessment results to the organization, as applicable, and periodically reviewing Risk Control Plan progress and effectiveness.

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      3.3.3   Providing appropriate FDA Q9 Quality Risk Management principles and process training for all MC3 Production, Quality, SMEs, and staff who participate in the Risk Management Process.

3.4   Management-identified SMEs are responsible for participating in Risk Assessments, identifying significant risks, developing Risk Control Plans, and communicating them to Management.

4   DEFINITIONS/ACRONYMS

4.1   CCBB: Carolinas Cord Blood Bank

4.2   Detectability: The ability to discover or determine the existence, presence, or fact of a hazard.

4.3   DOE: Design of Experiments

4.4   FMEA: Failure Mode Effects Analysis

4.5   Hazard: The potential source of harm (ISO/IEC Guide 51).

4.6   MC3: Marcus Center for Cellular Cures

4.7   Probability: The likelihood of something happening or being the case.

4.8   Quality Risk Management: A systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle.

4.9   Residual Risk: Risk that remains or is still present. In these circumstances, it might be agreed that an appropriate quality risk management strategy has been applied and that quality risk is reduced to a specified (acceptable) level. This (specified) acceptable level will depend on many parameters and should be decided on a case-by-case basis.

4.10   Risk: The combination of the probability of occurrence of harm and the severity of that harm.

4.11   Risk Acceptance: The decision to accept risk (ISO Guide 73).

4.12   Risk Analysis: The estimation of the risk associated with the identified hazards.

4.13   Risk Assessment (RA): A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

4.14   Risk Communication: The sharing of information about risk and risk management between the decision maker and other stakeholders.

4.15   Risk Control: Actions implementing risk management decisions (ISO Guide 73).

4.16   Risk Evaluation: The comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk.

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

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

4.19 Risk Reduction: Actions taken to lessen the probability of occurrence of harm and the severity of that harm.

4.20 Risk Review: Review or monitoring of output/results of the risk management process considering (if appropriate) new knowledge and experience about the risk.

4.21 Severity: A measure of the possible consequences of a hazard.

4.22 SOP: Standard Operating Procedure

5   MATERIALS

5.1 N/A

6   EQUIPMENT

6.1 N/A

7   SAFETY

7.1 N/A

8   PROCEDURE

8.1 Risk Assessment – Identification

8.1.1   The Quality function is responsible for periodically identifying and updating Management on potential areas of risk.

8.1.2   Risks can be identified by any employee and from any source/input. Risks are commonly identified during consideration of changes or during investigations initiated due to deviations, product complaints, and/or adverse events. Risk assessments can be initiated based on any applicable input, including data trend analysis, reject investigations, or information from other internal and external sources.

8.1.2.1   Risks related to information discovered about donors or products undergoing manufacturing may require urgent assessment and management.

8.1.2.2   Risks related to the product and its impact to the patient for whom it is intended may also be identified in real time and without prior warning. These risks will need to be assessed in the context of impact on the patient and impact on the facility and will need to be assessed in a timely fashion.

8.1.3   Recommendations for a formal and separate Risk Assessment, outside of those that are part of MC3 standard processes, are referred to a SME team, with representation from Quality, who have both the technical knowledge, scientific expertise and risk assessment training to assess the situation, to determine the level of the resulting identified risk and to make appropriate remediation recommendations.

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8.1.3.1 A supplemental risk assessment and associated report, separate from the matrix described in *COMM-QA-077 Risk Assessment Procedure*, may be deemed necessary for a number of reasons, including, but not limited to, a situation where a different tool/method is needed to assess risk than what is outlined in the current, applicable quality system, the change requires a more extensive assessment than can be captured in the change control form alone, or to evaluate a system or trend that needs a comprehensive risk assessment consisting of a SME team.

8.2 Risk Assessment – Analysis

8.2.1 As part of various MC3 SOPs, risk is already required to be assessed during standard processes, including, but not limited to, Deviation Investigations (COMM-QA-042 *Deviations and Investigations),* change control (COMM-QA-019 *Change Control*), risk assessment procedure (COMM-QA-077 Risk Assessment *Procedure*), and vendor management (COMM-QA-002 *Supplier Qualifications*).

8.2.2 If risks are identified to require assessment with this cross-functional team and process, MC3 Management and Quality should identify a team leader and appropriate SMEs to participate in Risk Assessments.

8.2.3 The Risk Assessment leader and SMEs determine if there is more information, in addition to the Investigation data, that is needed to conduct the Risk Assessment; the team of SMEs also selects recommended risk assessment tool(s) appropriate to the complexity of the assessment and the potential level of risk. To aid in clearly defining the risk(s) for risk assessment purposes, the following questions can be considered:

8.2.3.1 What might go wrong?

8.2.3.2 What is the likelihood (probability) that it will go wrong?

8.2.3.3 What are the consequences (severity)?

8.2.3.4 Are there controls in place to detect the potential failures (detectability)?

Note: The FDA Q9 Risk Management Guidance states "The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk."

8.2.3.5 Examples of Assessment Tools (see Appendix 1):

8.2.3.5.1 Risk ranking and filtering (ex. Moody's Preference Chart)

8.2.3.5.2 Flowcharts – Process Mapping and Analysis Charts

8.2.3.5.3 Failure Mode Effects Analysis (FMEA)

8.2.3.5.4 Supporting Statistical Tools

Note: Examples of Statistical Tools:

- Control Charts
- Histograms
- Pareto Charts
- Process Capability Analysis
- Design of Experiments (DOE)

8.2.4 The risk assessment team uses the selected Assessment and/or Statistical tools to:

8.2.4.1 Determine the level of risk based on the tool(s) chosen to be used for the assessment. Tables 1-3 below can also be used to summarize the final output or assessment, if applicable to the selected risk assessment tool and the relevant topic.

8.2.4.2 Recommend a Risk Control Plan that includes the appropriate level of Risk Reduction, including Corrective Action (CA), Interim Controls, and Preventive Action (PA), as necessary. See Section 8.3 for additional details on the Risk Control Plan.

Table 1: Severity Risk Matrix

S	Severity	Definition	Anticipated Harm to the Patient	GMP Non-compliance	Impact on Product
1	Negligible	Insignificant	None	None	No perceived impact on product
2	Marginal	At the outer or lower limits, minimal for requirements	Minimal	Minor	Unlikely impact on product, SQIPP not likely to be affected
3	Moderate	Within reasonable limits, transient or persistent	Transient or persistent, not life threatening	Significant	May indirectly impact product quality/SQIPP
4	Serious	Very important	Permanent, life threatening	Major	High likelihood of impacting product quality/SQIPP
5	Critical	Abnormal, unstable, unfavorable	May cause or contribute to death	Serious	Evidence of Product Impact, SQIPP affected

Abbreviation: SQIPP - safety, quality, identity, potency and purity

Table 2: Probability Risk Matrix

P	Probability	Definition (Occurrence)	Definition (Recurrence)
1	Rare	Not likely to happen, nearly impossible	Extremely unlikely to recur
2	Low	Occurrence is hardly likely, but possible	Unlikely to recur
3	Occasional	May occur sometimes	Likely to recur sometimes
4	Probable	Repeated occurrence, high likelihood of occurrence	Recur at moderate rate
5	Frequent	Will happen for certain, a regularly observed event	Likely to recur regularly

Table 3: Detectability Risk Matrix

D	Detectability	Definition	Examples
1	High	Control system in place; automated detectability certain	Automatic detection system that is a direct measure of the failure
2	Good	Control system is in place with a high probability to detect the issue or its effects	SOP driven process that facilitates a direct measure of the failure
3	Moderate	Control system in place could detect the issue or its effects	SOP driven process that is NOT directly measuring or assessing the failure
4	Fair	Control system in place with a low probability to detect the issue or its effects	Non-SOP driven process for detection of direct measure of the failure
5	Low	No control system in place to detect the issue.	No ability to detect the failure or no SOP-driven process to indirectly detect the failure

8.2.5   A report should be written and will minimally include background on the issue/risk, a summary meeting(s) with the SME team, the risk assessment process/output, and the recommended Risk Control Plan. A tracking number for the report will be assigned by Quality per COMM-QA-044 *Approaches to Validation.* Minimally, the report should be signed off and approved by the Facility Director/SME, Medical Director, and Quality (or designees, as appropriate).

8.3   Risk Control – Risk Reduction

8.3.1   A Risk Control Plan is developed commensurate with the level of risk and includes actions taken to mitigate the severity and probability of harm as well as, when possible, improving the detectability of hazards and quality risks.

8.3.2   Risk control can include, but may not be limited to, helping to address the following questions:

8.3.2.1   Is the risk above an acceptable level?

8.3.2.2   What can be done to reduce or eliminate risks?

8.3.2.3   What is the appropriate balance among benefits, risks, and resources?

8.3.2.4   Are new risks introduced as a result of the identified risks being controlled?

8.3.3   The Risk Control Plan contains these elements:

8.3.3.1   Corrective Action(s) – action taken to correct the situation that created the risk, including, as feasible, the cause of the risk. Examples of Corrective Actions are SOP enhancement and/or changes to training and documentation that require a Change Control to assess impact.

8.3.3.2   Interim Control(s) – may be necessary if the Preventive Action is delayed or is a long-term solution with multiple implementation stages. Interim controls may include additional verification that the Corrective Action is effective or expansion of the Corrective Action.

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8.3.3.3 Preventive Action(s) – systematic and/or long-term actions that look across the Quality System for system-wide preventive solutions. Examples of Preventive Actions are changes to processes or individual operations that require a Change Control to assess system-wide impact.

8.3.3.4 Effectiveness Checks – verification assessments that the corrective, interim and preventive actions are effective. Effectiveness checks are included in the Management Reviews as part of the Risk Review agenda item.

8.3.4 If the Risk Control Plan outlines recommended Corrective or Preventive Actions, a CAPA should be launched in MasterControl per COMM-QA-076 *Corrective and Preventive Actions.* The Risk Control Plan is documented in the report from the corresponding risk assessment and/or presented at the Management Reviews.

8.4 Risk Control – Risk Acceptance

8.4.1 Risks, once assessed and mitigated, may be at or reduced to a level of Risk Acceptance by the team of SMEs.

8.4.2 This level of Risk Reduction and Residual Risk is presented to MC3 Management in the report from the risk assessment and/or presented at the Management Review.

8.4.3 This Risk Acceptance decision is documented in the report from the risk assessment and/or presented at the Management Review.

8.5 Risk Communication

8.5.1 The output of the Quality Risk Management process is documented in the report(s) described here for each individual assessment, as well as discussed during Management Reviews.

8.5.2 Management decides how to communicate risk information to the appropriate parties. As applicable, Management communications include the necessary information about the existence, nature, form, probability, severity, acceptability, control, treatment, detectability or other aspects of risks to quality.

8.6 Risk Review

8.6.1 Quality is responsible for scheduling periodic Risk Reviews with Management.

8.6.2 Risk reviews include:

8.6.2.1 Review of the Risk Management Process

8.6.2.2 Discussion of resources necessary to sustain the Risk Management Process

8.6.2.3 Risk Control Plan(s) progress and effectiveness

8.6.2.4 Risk Management Communications

8.6.3 Minutes are generated from any Management Review meetings.

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9   RELATED DOCUMENTS/FORMS

9.1   COMM-QA-002 Supplier Qualifications

9.2   COMM-QA-019 Change Control

9.3   COMM-QA-042 Deviations and Investigations

9.4   COMM-QA-044 Approaches to Validation

9.5   COMM-QA-076 Corrective and Preventive Actions

9.6   COMM-QA-077 Risk Assessment Procedure

10   REFERENCES

10.1 FDA Guidance for Industry, Q9 Quality Risk Management, June 2006.

11   REVISION HISTORY

Revision No.	Author	Description of Change(s)
02	Patrick Killela	• Updated risk matrix tables to align with new changes in COMM-QA-077 and included language to clarify when COMM-QA-080 risk assessment may be needed. • Clarified certain aspects of SOP, including risk control plan, CAPAs determination, and risk assessment analysis. • Clarify that any corrective or preventive actions defined as part of the risk control plan should be tracked in a formal CAPA in MasterControl per COMM-QA-076. • Added Appendix to better describe different tools for risk assessment, such as process mapping and FMEA.

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Appendix 1:

The purpose of this appendix is to provide a general overview of and references for some of the primary tools that might be used in quality risk management. The references are included as an aid to gain more knowledge and detail about the tool. This is not an exhaustive list. It is important to note that no one tool or set of tools is applicable to every situation in which a quality risk management procedure is used.

Risk Ranking and Filtering
Risk ranking and filtering is a tool for comparing and ranking risks. Risk ranking of complex systems typically involves evaluation of multiple diverse quantitative and qualitative factors for each risk. The tool involves breaking down a basic risk question into as many components as needed to capture factors involved in the risk. These factors are combined into a single relative risk score that can then be used for ranking risks. "Filters," in the form of weighting factors or cut-offs for risk scores, can be used to scale or fit the risk ranking to management or policy objectives.

Potential Areas of Use(s):
Risk ranking and filtering can be used to prioritize manufacturing sites for inspection/audit by regulators or industry. Risk ranking methods are particularly helpful in situations in which the portfolio of risks and the underlying consequences to be managed are diverse and difficult to compare using a single tool. Risk ranking is useful for management to evaluate both quantitatively assessed and qualitatively assessed risks within the same organizational framework.

Basic Risk Management Facilitation Methods
Some of the simple techniques that are commonly used to structure risk management by organizing data and facilitating decision making are:
- Flowcharts
- Check Sheets
- Process Mapping
- Cause and Effect Diagrams (also called an Ishikawa diagram or fish bone diagram – see example below)
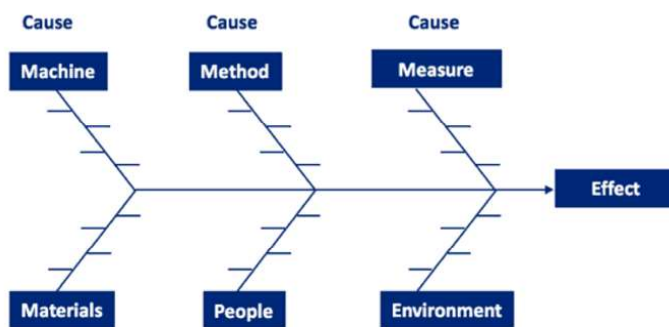
Failure Mode Effects Analysis (FMEA)
FMEA provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce, or control the potential failures. FMEA

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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.

Potential Areas of Use(s):
FMEA can be used to prioritize risks and monitor the effectiveness of risk control activities. FMEA can be applied to equipment and facilities and might be used to analyze a manufacturing operation and its effect on product or process. It identifies elements/operations within the system that render it vulnerable. The output/results of FMEA can be used as a basis for design or further analysis or to guide resource deployment.

Example Basic FMEA Template

Key Input	Failure Mode	Impact	S	Potential Cause(s)	P	Current Controls	D	RPN S*P*D	Action
What failed?	*How did it fail?*	*What is the impact of the failure?*		*Why did it fail?*		*How is it detected?*			*What to do about it.*

Supporting Statistical Tools
Statistical tools can support and facilitate quality risk management. They can enable effective data assessment, aid in determining the significance of the data set(s) and facilitate more reliable decision making.

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