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Risk Assessment Procedure

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COMM-QA-077
RISK ASSESSMENT PROCEDURE

1 PURPOSE

1.1 The purpose of this procedure is to describe the assessment of risk and resulting mitigation activities/control actions for change controls and applicable events, including but not limited to, Deviations/Investigations, CAPA, and Product Complaints.

2 INTRODUCTION

2.1 A risk assessment (RA) system is necessary to adequately assess the potential impact of a change and event as well as what, if any, additional actions may be necessary to effectively address and/or monitor the risk.

3 SCOPE AND RESPONSIBILITIES

3.1 This procedure is referenced when assessing risk for change controls and events associated with the Carolinas Cord Blood Bank (CCBB), Stem Cell Laboratory (STCL), Adult and Pediatric Blood and Marrow Transplant (APBMT) Programs, and the Robertson GMP Laboratory.

3.2 A supplemental risk assessment and associated report, separate from the matrix described here, 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. These would be conducted per COMM-QA-080 *Quality Risk Management*.

3.3 Responsibilities for assessing risk are shared among all staff involved in writing or reviewing Change Controls, CAPAs, Deviations/Investigations, and other events, such as Complaints. Approval of any associated risk assessment is implicit with electronic signatures in MasterControl. Section 3.4 below details specific responsibilities for the different aspects of risk assessment.

3.4 Responsibilities

3.4.1 Operations/Manufacturing

Operations is responsible for:

- Participating in risk management assessments and discussions.
- Identifying subject matter experts (SMEs) and providing expert input on risk assessment.
- Participating in determination if any external reporting is required to outside vendors/sponsors of events that may impact products related to their organization.

3.4.2 Quality Systems Unit (QSU)

Quality Assurance (QA) is responsible for:

- Participating in risk management assessments and discussions.
- Maintaining this risk management procedure.
- Facilitating risk assessment activities.
- Determining if any external reporting is required to outside vendors/sponsors of events that may impact products related to their organization.

3.4.3 Medical Director (MD)

The Medical Director is responsible for:

- Participating in risk management assessments and discussions.

3.4.4 Subject Matter Experts (SME)

Subject Matter Experts are responsible for:

- Participating in risk management assessments and discussions as needed based on their expertise of the product and topic of evaluation.

3.4.5 Executive Management (Operations/Medical Director and Quality Director)

Executive Management is responsible for:

- 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.
- Reviewing and approving additional resources that may be requested.

4 DEFINITIONS/ACRONYMS

4.1 **APBMT**: Adult and Pediatric Blood and Marrow Transplant, also includes cellular therapy

4.2 **CAPA**: Corrective and Preventive Action

4.3 **CBU**: Cord Blood Unit

4.4 **CCBB**: Carolinas Cord Blood Bank

4.5 **Corrective Action**: Action to eliminate the cause of a detected event or deviation. Corrective action is taken to prevent the recurrence of a problem

4.6 **DCO**: Document Control Operations

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

4.8 **Effectiveness Check**: Method or data used to determine effectiveness of a CAPA.

4.9 **Events**: Examples may include planned and unplanned deviations from SOP, customer complaints, out of specification or unexpected results, internal and external audit findings, reoccurring problems/trends.

4.10 **External Reporting**: The dissemination of information to an outside party as required by any applicable regulation, standard, contract or quality agreement. This could include reporting to FDA, an external sponsor, or another entity.

4.11 **Final Quality Approval**: The point in the review process after which an event report is considered to be complete/final and in a form that may be disseminated to an outside party as a complete/final document.

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

4.13 **MasterControl**: An electronic 21 CFR compliant data management system.

4.14 **MD**: Medical Director

4.15 **Preventive Action**: An activity or step implemented to prevent the initial occurrence of a problem, based on an understanding of the product or process.

4.16 **Probability:** the likelihood of something happening or being the case.

4.17 **QA**: Quality Assurance

4.18 **QSU**: Quality Systems Unit

4.19 **Risk**: The combination of the probability of occurrence (Rate of Occurrence and/or Likelihood of Recurrence) of harm, the impact (Risk Severity) of that harm, and the detectability of the associated hazard.

4.20 **Risk Assessment (RA)**: A systematic process comprised of a Risk Analysis and Risk Evaluation.

4.21 **Risk Classification**: The process of categorizing the risk against established criteria.

4.22 **Risk Evaluation**: The process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk.

4.23 **Risk Management**: A systematic application of management policies, procedures and practices to the tasks of analyzing, evaluating, controlling and monitoring the risk.

4.24 **STCL**: Stem Cell Laboratory

4.25 **Severity:** A measure of the possible consequences of a hazard.

4.26 **Subject Matter Expert (SME)**: A person who is an authority in a particular area or topic, based on training and experience.

4.27 **SQIPP**: An acronym referring to Safety, Quality, Identity, Potency, Purity of a product.

5 MATERIALS

5.1 Supporting reports/documents; e.g., product recall notification, email correspondences.

6 EQUIPMENT

6.1 Computer access to MasterControl

7 SAFETY

7.1 N/A

8 PROCEDURE

8.1 Risk Matrix

8.1.1 As part of change controls, deviations/investigations, applicable events, and risk assessments reports per COMM-QA-080 *Quality Risk Management*, as applicable, three parameters, severity, probability, and detectability, are required to be considered in order to assess risk consistently and effectively.

8.1.2 Tables 1-3 describe and define the three parameters in a 5-point scale that should be used to identify a risk score within an applicable change control, CAPA, event, or investigation. The score assigned to each parameter, as well as rationale for the assigned score, are captured on the applicable forms (ex. Change Control Request Form, Deviation and Investigation Report, Complaint).

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

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

Table 4: Overall Risk Scores (Ranges) and Recommended Actions

Risk Score ***(Severity Multiplied by Probability Multiplied by Detectability)***	***Recommended Action***
1-25	Evaluate the current controls and determine whether additional efforts can be made to bring the risk as low as reasonably possible.
	Event: It is likely that events associated with this risk score profile are not significant enough to require CAPAs. Therefore, CAPAs are optional, but one would be strongly recommended if one risk parameter (severity/probability/detectability) is scored a 5 and CAPA is feasible for the root cause identified. If one risk parameter is scored a 5 and no CAPA is launched, justification will be required within the associated event. **Change Control:** It is likely that changes associated with this risk score profile are not significant enough to require effectiveness checks, therefore, no effectiveness check required. However, effectiveness checks are recommended if one risk parameter (severity/probability/detectability) is scored a 5. If one risk parameter is scored a 5 and no effectiveness check is completed, justification will be required within the associated change control.
26-50	Evaluate the current controls and determine whether additional efforts can be made to bring the risk as low as reasonably possible.
	Event: CAPAs are optional but recommended if one risk parameter (severity/probability/detectability) is scored a 5 and CAPA is feasible for the root cause identified. If one risk parameter is scored a 5 and no CAPA is launched, justification will be required within the associated event. **Change Control:** No effectiveness check is required but recommended if one risk parameter (severity/probability/detectability) is scored a 5. If one risk parameter is scored a 5 and no effectiveness check is completed, justification will be required within the associated change control.
51-75	Additional effort should be considered to bring risk as low as reasonably possible and/or to an acceptable level.
	Event: CAPAs are optional but recommended if one risk parameter (severity/probability/detectability) is scored a 5 and CAPA is feasible for the root cause identified. If one risk parameter is scored a 5 and no CAPA is launched, justification will be required within the associated event. **Change Control:** No effectiveness check is required but recommended if one risk parameter (severity/probability/detectability) is scored a 5. If one risk parameter is scored a 5 and no effectiveness check is completed, justification will be required within the associated change control.
76-100	Additional efforts should be made to reduce the risk to as low as reasonably possible and to an acceptable level.
	Event: CAPA Mandatory **Change Control:** Effectiveness Check Mandatory
101-125	Additional efforts are required to reduce the risk to as low as reasonably possible and to an acceptable level.
	Event: CAPA Mandatory **Change Control:** Effectiveness Check Mandatory

Note: Within an event investigation/report, risk assessments should be expanded to include potential, related outcomes that could occur in the future despite not having occurred in this specific event so that any potential preventive actions can be evaluated and captured appropriately as a CAPA. To accomplish this, a systemic view should be taken when looking at the event/issue to help determine if any changes can be made to facilitate reduced risk of a similar event occurring in the future. The risk score and rationale should reflect this "what if"/future assessment to ensure risk has been assessed most completely.

8.2 Risk Evaluation

8.2.1 Trained personnel, when completing and/or reviewing applicable MasterControl documentation, will use the three required parameters, severity, probability, and detectability (Tables 1-3), to evaluate risk and determine any potential requirements for additional actions.

8.2.2 With this risk assessment methodology, each parameter, severity, probability, and detectability will be scored individually 1-5 based on definitions and examples in Tables 1-3 above.

8.2.3 The scores of each parameter will then be multiplied to generate a final risk score for the event or change. Explanations and/or rationale for the determined score will be required for each parameter within a deviation/investigation, complaint, change control, or other document as described. When assessing risk within one parameter, if two scores are determined (such as severity on product vs patient), the more stringent (higher score) assessment will be used when calculating the final risk score. Rationale for the lower score should also be provided in the associated Deviation/Investigation, Complaint, or Change Control.

8.2.3.1 Within an event investigation/report, risk assessments should be expanded to include potential, related outcomes that could occur in the future despite not having occurred in this specific event so that any potential preventive actions can be evaluated and captured appropriately as a CAPA. To accomplish this, a systemic view should be taken when looking at the event/issue to help determine if any changes can be made to facilitate reduced risk of a similar event occurring in the future. The risk score and rationale should reflect this "what if"/future assessment to ensure risk has been assessed most completely. Additionally, if a single risk matrix attribute is scored 5 and no CAPA is launched, justification for the determination that a CAPA is not necessary will be required within the associated event. See Table 4.

8.2.3.2 Within a change control form, risk assessments should be conducted to help determine if any additional supporting work or documentation is needed to support the change or if an effectiveness check should be conducted following implementation of the change as detailed in Table 4. Additionally, if a single risk matrix attribute is scored 5 and no effectiveness check is deemed necessary, justification will be required within the associated event.

8.2.3.3 When applicable, initiators will address a review of any applicable risk assessment reports completed per COMM-QA-080 *Quality Risk Management*, to ensure consideration of how the event or change control impacts already established risks, and to ensure this is factored into the determination of the associated risk score. These supplemental risk assessments and associated report(s) 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.

8.3 There may be cases where a supplemental risk assessment method may be needed in addition to what is required in the relevant forms. COMM-QA-080 *Quality Risk Management* outlines the general MC3 approach to managing risk, including a process for conducting risk assessment outside of those that are part of the standard processes and matrix used for MC3 changes and events defined herein. Other tools can be utilized in these supplemental assessments as described in COMM-QA-080 *Quality Risk Management*.

8.3.1 When applicable, product specific overarching Risk Assessments that have been completed per COMM-QA-080 *Quality Risk Management*, should be reviewed on a periodic basis, minimally as designated by the associated review period of the MasterControl task, as part of the continued risk management lifecycle.

8.4 Maintenance of Records

8.4.1 All records are maintained according to the associated Program's Records Management or Records Retention procedure(s).

9 RELATED DOCUMENTS/FORMS

9.1 CCBB-QA-017 Complaint Management

9.2 CCBB-QA-017 FRM1 Complaint Form

9.3 COMM-PAS-004 Change Control

9.4 COMM-PAS-006 Product Complaint Management

9.5 COMM-PAS-006 FRM1 Product Complaint Form

9.6 COMM-QA-019 Change Control

9.7 COMM-QA-019 FRM1 Change Control Request (Effectiveness Check)

9.8 COMM-QA-019 FRM2 Change Control Request (no Effectiveness Check)

9.9 COMM-QA-042 Deviations and Investigations

9.10 COMM-QA-076 Corrective and Preventive Actions

9.11 COMM-QA-076 FRM1 CAPA Report

9.12 COMM-QA-080 Quality Risk Management

9.13 STCL-QA-007 Non-Conforming Products – Receipt, Processing, Distribution, and Disposition

10 REFERENCES

10.1 21 CFR 211.22(a) – Responsibilities of a Quality Control Unit

10.2 21 CFR 211.100 – Written Procedures; Deviations

10.3 21 CFR 1271 – Human Cells, Tissues, and Cellular and Tissue-Based Products

10.4 FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration; Current Edition

10.5 FACT Common Standards for Cellular Therapies; Current Edition

10.6 NetCord-FACT International Standards for Cord Blood Collection, Banking and Release for Administration; Current Edition

11 REVISION HISTORY

Revision No.	Author	Description of Change(s)
05	R. Bryant	• Major overhaul and redesign of risk assessment process; may be considered new SOP. • Incorporation of new risk matrix for probability and severity as well as adding detectability parameter. • Redefined Risk Score ranges and associated recommended actions for events and change controls. • Better clarify relationship between COMM-QA-080 and COMM-QA-077. • Align risk assessment processes between change controls and deviations/events.

Signature Manifest

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COMM-QA-077 Risk Assessment Procedure

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Sandy Mulligan (MULLI026)		27 Oct 2020, 02:13:23 PM	Approved