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COMM-QA-039
QUALITY SYSTEMS UNIT AUDIT

1 PURPOSE

1.1 To define the procedure for performing internal quality audits, facility qualification audits, facility requalification audits, and supplier qualification audits on programs and processes where the Quality Systems Unit (QSU) is responsible for overseeing quality functions.

2 INTRODUCTION

2.1 The QSU is required by the Code of Federal Regulations (CFR), current Good X Practices (cGXP), and several accreditation agencies to conduct independent examinations to ensure that quality systems and processes are being followed and are functioning effectively within established procedures, regulations, and guidance documents.

3 SCOPE AND RESPONSIBILITIES

3.1 This procedure applies to all programs/processes where the QSU is responsible for quality oversight.

3.2 This procedure applies to audits used for internal quality assessment, used to qualify or requalify suppliers/contractors when deemed necessary per Standard Operating Procedure (SOP) COMM-QA-002 *Supplier Qualifications*, and used to qualify/requalify facilities.

3.3 QSU personnel involved in planning, conducting or reporting quality system/process audits are responsible for SOP compliance and training. The QSU Director or designee is responsible for ensuring initial and ongoing training of QSU personnel.

3.4 The QSU Director or designee is responsible for communicating with applicable Program/Medical Directors and personnel when planning and reporting the results of a program/process audits.

3.5 Personnel involved in a program/process audit are responsible for complying with the requirements of this SOP. Program/Medical Director(s) are responsible for ensuring quality standards for their respective programs and complying with the principles of this SOP.

4 DEFINITIONS/ACRONYMS

4.1 APBMT: Adult and Pediatric Blood and Marrow Transplant

4.2 CAPA: Corrective and Preventive Action

4.3 CCBB: Carolinas Cord Blood Bank

4.4 CFR: Code of Federal Regulations

4.5 cGXP: Current Good X Practices. Encompasses all current Good (manufacturing, clinical, laboratory, tissue, etc.) practices to maintain quality of the process/product.

4.6 Control: Demonstrating continued safety, purity, and potency of the product, compliance with applicable product and establishment standards, and compliance with cGXP.

4.7 Critical Observation: A finding of a confirmed deficiency that requires immediate attention and/or intervention that affect SQIPP (Safety, Quality, Identity, Potency, and Purity) and/or reporting to external agencies.

4.8 Deviation: An unplanned or planned variance from a standard operating procedure (SOP) or other controlled document specified process.

4.9 External Audit/Inspection: Conducted by agencies or organizations (e.g. FACT, FDA) independent of the program being audited/inspected.

4.10 FACT: Foundation for the Accreditation of Cellular Therapy

4.11 FDA: Food and Drug Administration

4.12 IEC: Immune Effector Cell

4.13 Lead Auditor: The auditor most responsible for managing the audit, verifying the accuracy of audit related documents, and tracking related audit progress.

4.14 MC3: Marcus Center for Cellular Cures

4.15 Major Observation: A finding of a confirmed deficiency that is considered to be significant and may have a negative impact on the product, deliverable, service or contractual obligation. Repeated minor observations may also constitute a major observation, particularly when they indicate a more significant or systemic problem.

4.16 Minor Observation: A finding of a confirmed deficiency that does not necessarily have a negative impact on the product, deliverable, service, or contractual obligation.

4.17 PBMT: Pediatric Blood and Marrow Transplant

4.18 QA: Quality Assurance - QA provides information regarding levels of performance that can be used in setting priorities for process improvement. QA includes retrospective review and analysis of operational performance data to determine if the overall process is in a state of control and to detect shifts or trends that require attention.

4.19 QC: Quality Control - QC provides feedback to operational staff about the state of a process that is in progress. Product QC is performed to determine whether the product or service meets specifications.

4.20 QI: Quality Improvement - QI is intended to attain higher levels of performance either by creating new or better features that add value or by removing existing deficiencies in the process, product, or service. Observations do not require a written response, deviation, or CAPA, but should be discussed and considered.

4.21 Quality Systems: Encompasses all activities necessary to assure the finished product meet its predetermined design specification. This includes assuring manufacturing processes are controlled and adequate for their intended use, documentation is controlled and maintained, equipment is calibrated, inspected, tested, etc.

4.22 QSU: Quality Systems Unit - The designated unit responsible for ensuring quality system(s) are effectively established and maintained. QSU responsibilities may include sign-off authority for changes to documents, processes, or products; conducting system/process audits, assisting in the development, review, approval, and evaluation of effectiveness of corrective actions and preventive actions (CAPA), and ensuring completion of thorough investigations.

4.23 SME: Subject matter expert. An individual who has demonstrated a thorough understanding of a procedure or process.

4.24 SOP: Standard Operating Procedure - Detailed, written instructions to achieve uniformity on the performance of a specific function.

4.25 SQIPP: Safety, Quality, Identity, Potency, and Purity

4.26 STCL: Stem Cell Laboratory.

4.27 TED: Transplant Essential Data

5 MATERIALS

5.1 N/A

6 EQUIPMENT

6.1 N/A

7 SAFETY

7.1 The QSU will comply with Universal Precautions implemented at each facility or laboratory audited to uphold established requirements.

8 PROCEDURE

8.1 Audit Team

8.1.1 The audit team consists of a QSU lead auditor or a QSU designee, as well as other members of the QSU team, as needed. QSU is responsible for scheduling the audit and evaluating the number of resources needed based on the type and complexity of the audit being performed. SMEs will be asked to join the audit team for further expertise, as needed, and may lead content review, as applicable.

8.1.1.1 The QSU may work with and/or designate third party SMEs, consultants, or contractors, to audit on behalf of MC3.

8.2 Audit Frequency

8.2.1 The QSU will typically perform routine internal audits on the quality systems applicable to each program/process once during each calendar year.

8.2.2 The QSU may conduct internal audits with more frequency based upon observations from previous audits or unexpected events or concerns.

8.2.3 Facility qualification/requalification will be performed as needed and as appropriate to the program/process.

8.2.4 Supplier qualification audits will be performed based upon the outcome of the supplier assessment made in accordance with *COMM-QA-002 Supplier Qualifications.*

8.3 Focus of Quality Systems/Process Audits

8.3.1 The QSU will conduct audits on the following quality systems, where applicable.

8.3.1.1 Personnel/Training

8.3.1.2 Facilities

8.3.1.3 Environmental Monitoring

8.3.1.4 Equipment Management

8.3.1.5 Inventory Control/Supply Management

8.3.1.6 Document Control/Records Management

8.3.1.7 Process Management and Control

8.3.1.8 Product Release

8.3.1.9 Event Management

8.3.1.10 Quality Improvement

8.3.2 For the Stem Cell Laboratory (STCL) and the Adult and Pediatric Blood and Marrow Transplant (APBMT) Apheresis Programs, the QSU will conduct audits on the following systems in addition to the above quality systems audit, where applicable.

8.3.2.1 Donor/Recipient/Processing Files

8.3.2.2 Management of Cellular Therapy Products with Positive Microbial Cultures

8.3.2.3 TED Forms/Accuracy of Clinical Data

8.3.2.4 Donor Screening Testing

8.3.2.5 Chemotherapy Records and Prescription Ordering System against the Protocol

8.3.2.6 Immune Effector Cellular (IEC) Therapy Safety Endpoints and Toxicity Management

8.4 Scheduling the Audit

8.4.1 The QSU will notify, in writing, the program/process designee about the need to conduct an audit and will work with the designee to determine an acceptable timeframe. The receiving program/process designee is

asked to acknowledge receipt of the audit notification within 2 business days.

8.4.2 Audits may also be conducted without prior or with limited notification if deemed warranted by the QSU.

8.4.3 The program/process staff will make accessible to the auditor(s) all records, equipment, facilities, and applicable personnel involved with the program/process as appropriate to the scope of the audit.

8.5 Conducting the Audit

8.5.1 The audit team conducts an opening meeting with the program/process staff to review the objective and scope of the audit.

8.5.2 The audit team will conduct the audit and may ask for copies of documentation to attach to the final audit report.

8.5.3 *COMM-QA-039 JA6 Internal Quality Systems Facility Qualification/Requalification Audit Report JA6* may be used as a guide when conducting site visits for facility qualification or re-qualification.

8.5.4 *COMM-QA-039 JA7 APBMT Chemotherapy and Treatment Plan Audit* may be used as a guide when conducting audits on the chemotherapy records and prescription ordering system against the protocol.

8.5.5 *COMM-QA-039 JA8 Audit Guidance – Cord Blood Collection Site* may be used as a guide when conducting audits for relevant sites.

8.5.6 *COMM-QA-039 JA9 APBMT Immune Effector Cellular Therapy Safety Endpoints and Toxicity Management Audit* may be used as a guide when conducting the IEC therapy safety endpoints and toxicity management audit.

8.5.7 *COMM-QA-039 JA10 APBMT Transplant Essential Data (TED) Form Audit* may be used as a guide when conducting the TED form audit.

8.5.8 Once the audit is complete, the audit team will conduct a closeout meeting with applicable program/process personnel to discuss any observations.

8.5.9 Any issues found during the course of an audit that may affect the integrity of on-going activities will be brought to the attention of the QSU Director and applicable personnel.

8.5.10 Auditors will maintain the confidentiality of the audit and will only discuss outcomes of the audits with appropriate personnel.

8.6 Audit Report

8.6.1 Internal audit reports are documented on *COMM-QA-039 JA1 Internal Quality Systems Unit Audit Report JA1*, which is a template that can be modified to fit any number of observations.

8.6.2 Supplier qualification audit reports will be documented in a narrative style format on *COMM-QA-039 JA5 Supplier Qualification Audit*

Report JA5 and will describe the in place quality systems at the Supplier's organization.

8.6.2.1 When MC3 designates third party SMEs, consultants, or contractors, to audit on behalf of MC3, the associated audit reports may be captured on the external parties report template.

8.6.3 Site qualification/requalification audit reports will be documented on *COMM-QA-039 JA6 Internal Quality Systems Facility Qualification/Requalification Audit Report JA6.*

8.6.4 APBMT chemotherapy and treatment plan audit report is documented on *COMM-QA-039 JA7 APBMT Chemotherapy and Treatment Plan Audit*.

8.6.5 APBMT IEC therapy safety endpoints and toxicity management audit report is documented on COMM-QA-039 JA9 *APBMT Immune Effector Cellular Therapy Safety Endpoints and Toxicity Management Audit*.

8.6.6 APBMT TED form audit report is documented on COMM-QA-039 JA10 *APBMT Transplant Essential Data (TED) Form Audit, APPENDIX II.*

8.6.7 Documentation of the audit observations will be detailed, concise, and accurate.

8.6.8 The lead auditor ensures that the documented observations on the report are accurate and within the scope of the audit.

8.6.9 The lead auditor and QSU Director or designee will sign the audit report prior to distributing it to the representative of the audited program/process.

8.7 Audit Observations and Classifications

8.7.1 An audit observation constitutes the identification of a deviation, irregularity, or non-conformity to a specified requirement or operational process.

8.7.2 Internal observations are classified as Critical, Major, or Minor

8.7.2.1 A Critical Observation is a finding that affects SQIPP (Safety, Quality, Identity, Potency, and Purity). Thus, it requires immediate attention or intervention and/or reporting to external agencies. Critical observations may include but are not limited to those that:

8.7.2.1.1 Compose a threat against the life, health, or rights of patients or study subjects.

8.7.2.1.2 Pose a threat to employee safety.

8.7.2.1.3 May result in the severing of a contractual service agreement, loss of business, or assumed liability.

8.7.2.1.4 May result in regulatory, civil or criminal sanctions and/or penalties.

8.7.2.2 In situations with Critical Observations, the lead auditor will notify the QSU Director or designee, and the Supervisor/Manager and/or Program/Medical Director will be notified immediately.

8.7.2.3 A Major Observation is a finding of a confirmed deficiency or non-compliance that is considered to be significant and may have a negative impact on the product, deliverable, service or contractual obligation. Major observations may include but are not limited to those that:

8.7.2.3.1 Jeopardize the integrity of data.

8.7.2.3.2 Substantially reduce process quality and impede deliverable(s)/outcome(s).

8.7.2.3.3 Indicate the absence or breakdown of an element in the quality management system.

8.7.2.4 A Minor Observation is a finding that does not necessarily have a negative impact on the product, deliverable, service, or contractual obligation and/or any observation with a single or low frequency of occurrence that does not meet the criteria of a Major Observation.

8.7.2.4.1 Repeated Minor Observations may be escalated to a Major Observation, particularly when they indicate a more significant or systemic problem.

8.7.2.5 Remediation actions will be documented by the audit designee in the response section of the *COMM-QA-039 JA1 Internal Quality Systems Unit (QSU) Audit Report JA1*. The responses will be reviewed by the lead auditor for appropriateness prior closing the audit.

8.7.2.6 Remediation actions for observations labelled as Critical or Major must be verified by the lead auditor as being effective prior to closing the audit.

8.7.2.7 Remediation actions for observations labelled as Minor do not have to be verified prior to closing the audit.

8.7.2.8 Depending on the type and severity of the audit finding, further investigation and remediation actions may need to be documented per *COMM-QA-042 Deviations and Investigations* and *COMM-QA-077 Risk Assessment Procedure*. If needed, the QSU and lead auditor will work with the audit designee to ensure that a complete investigation has been performed and documented.

8.7.2.9 In the event that a CAPA is needed, documentation of the CAPA and the effectiveness of the CAPA will be performed and documented per *COMM-QA-076 Corrective and Preventive Actions.*

8.7.3 Supplier qualification observations do not have to be classified as Critical, Major, or Minor since observations are solely utilized in determining whether the Supplier is acceptable for use or continued use. However, all observations must be discussed and a remediation plan documented in consultation with the Supplier prior to approval. In situations where a supplier/vendor provides written responses and a remediation plan that is in process, the vendor/supplier may still be utilized by MC3, with continued follow-up by MC3 QSU as necessary. QSU reserves the option not to approve the supplier based upon the nature of the observation or the remediation action plan.

8.7.4 Observations discovered during site qualification or requalification will not be documented as Critical, Major or Minor, but must be discussed and a remediation plan documented prior to the site opening or continuing operations. In situations where a site provides written responses and a remediation plan that is in process, the site may still open or continue operations, with continued follow-up by MC3 QSU as necessary.

8.7.5 Observations discovered during the APBMT chemotherapy and treatment plan audit, or APBMT IEC therapy safety endpoints and toxicity management audit will not be documented as Critical, Major or Minor, but all the appropriate resolutions to any discrepancies must be remediated prior to closing the audit.

8.8 Audit Scoring and Audit Plan

8.8.1 Internal audits will receive a composite score of either Excellent, Satisfactory, Needs improvement, or Fail based on the number of Minor, Major or Critical Observations.

8.8.2 The following table describes how each internal audit will be scored.

SCORE	MINOR	MAJOR	CRITICAL	AUDIT PLAN
Excellent	≤5	0	0	Re-audit – 12 month period
Satisfactory	>5	0	0	Re-audit – 12 month period
Needs Improvement	Any	1	0	Re-audit – 12 month period
Fail	Any	>1	Any	Complete re-audit within 6 months

8.8.3 Supplier qualification audits will not receive a composite score but will only be documented as "approved for use/continued use" or "not approved for use/continued use." All observations must be addressed per section 8.7.3, and suppliers will be re-audited based upon the assessment made as described in section 8.2.4.

8.8.4 Site qualification/requalification audits will not receive a composite score but will only be documented as "approved for use/continued use" or "not approved for use/continued use." All observations must be addressed per section 8.7.4. Qualification/requalification audits will be performed as needed.

8.8.5 APBMT chemotherapy and treatment plan audit, or APBMT IEC therapy safety endpoints and toxicity management audit will not receive a composite score but will only be documented as "all follow-up items have been resolved, verified and the audit is now closed".

8.9 Audit Receipt and Responses

8.9.1 The audit designee should receive the audit report from QSU within 30 calendar days of the last day of the audit. If this is not feasible, the recipient should be notified within 30 calendar days of the audit and make them aware of when to expect the report. The recipient is asked to acknowledge receipt of the audit report via email within 2 business days.

8.9.2 If audit responses are needed, responses should be returned to QSU within 30 calendar days of receiving the audit report. If this is not feasible, QSU should be notified within 30 calendar days so that agreement can be reached on when the responses may be received.

NOTE: The remediation action does not need to be completed within 30 calendar days; however, a remediation plan must be described in the response.

8.9.3 The type of response will be dependent upon the observations observed. QSU will work with the audit designee in determining the most appropriate response to the observation.

8.10 Audit Closure

8.10.1 Once the audit responses have been reviewed and approved by QSU as required above based on the audit findings, the audit will be closed.

8.10.2 Completed audit documentation will be retained by the QSU.

9 RELATED DOCUMENTS/FORMS

9.1 COMM-QA-002 Supplier Qualifications

9.2 COMM-QA-042 Deviations and Investigations

9.3 COMM-QA-076 Corrective and Preventive Actions

9.4 COMM-QA-077 Risk Assessment Procedure

9.5 COMM-QA-039 JA1 Internal Quality Systems Unit Audit Report JA1

9.6 COMM-QA-039 JA5 Supplier Qualification Audit Report JA5

9.7 COMM-QA-039 JA6 Internal Quality Systems Facility Qualification/Requalification Audit Report JA6

9.8 COMM-QA-039 JA7 APBMT Chemotherapy and Treatment Plan Audit

9.9 COMM-QA-039 JA8 Audit Guidance – Cord Blood Collection Site

9.10 COMM-QA-039 JA9 APBMT Immune Effector Cellular Therapy Safety Endpoints and Toxicity Management Audit

9.11 COMM-QA-039 JA10 APBMT Transplant Essential Data (TED) Form Audit

10 REFERENCES

10.1 ICH Guideline for Good Clinical Practice

10.2 21CFR Parts 11, 50, 56, 312, 812 and 820

10.3 21CFR Parts 45 and 46

10.4 21CFR Part 210, Current Good Manufacturing Practice

10.5 21CFR Part 211, Current Good Manufacturing Practice for Finished Pharmaceuticals

10.6 21CFR Parts 600 - 680, Biological Products

10.7 21CFR Part 1271 Current Good Tissue Practice

11 REVISION HISTORY

Revision No.	Author	Description of Change(s)
10	B. Shen	-Added Section 4.27 TED acronym; -Added Section 8.5.7 to provide instructions on conducting TED form audit and renumbered the following Section 8.5.8 to Section 8.5.10; -Added Section 8.6.6 to define the documentation of the TED form audit report and renumbered following Section 8.6.7 to Section 8.6.9; -Added Section 9.11 to the related documents/forms.

Signature Manifest

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