Pediatric Blood and Marrow Transplant
Adult Blood and Marrow Transplant
Stem Cell Laboratory

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Change Control

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COMM-PAS-004
CHANGE CONTROL

1 PURPOSE

1.1 To describe the process required for initiating, completing, evaluating and approving a change control request (CCR).

1.2 To describe the functions of the CCR reviewers.

1.3 To identify and assess impact and risk(s) associated with a change.

1.4 To describe when an effectiveness check is required and describe the steps for completing an effectiveness check.

2 INTRODUCTION

2.1 Regulated environments require specific rules for processes including change control. The utilization of a change control system supports quality, consistency, and protects the integrity of controlled documents and validated systems.

3 SCOPE AND RESPONSIBILITIES

3.1 This procedure applies to the initiation, completion, evaluation, and approval of CCRs for the Adult Blood and Marrow Transplant (ABMT) Program, the Pediatric Blood and Marrow Transplant (PBMT) Program, and the Stem Cell Laboratory (STCL).

3.2 This procedure applies to the creation of or modification(s) to controlled documents, archiving controlled documents, and changes to working processes, design, software, equipment, materials, facilities, service provider, and/or other changes requiring review and approval through a proper change control process.

3.3 The process for handling emergency change control requests is addressed in Section 8.5.

3.4 The Medical/Program Director, Quality Systems Unit (QSU), Document Control Team, and all personnel involved in initiating, completing, evaluating and approving changes via the change control process are responsible for ensuring the requirements of this procedure are met.

3.5 Regulatory Affairs (RA) is responsible for reviewing all CCRs for the ABMT Program, PBMT Program and the STCL.

3.6 The Training Coordinator, as applicable, is included in the notification step when the CCR is approved to allow for early identification of training needs.

3.7 Document Control Operations (DCO) receives notification when a CCR is approved so that appropriate action can be taken in MasterControl (MC).

3.8 Initiators launch a Change Control Request on the appropriate form and populate information as detailed within this procedure. If one change affects multiples areas, initiators will engage applicable SMEs and may add these SMEs to the MasterControl form routing directly for review.

3.9 As part of the review process, QSU completes an assessment on all submitted change controls to determine the necessity for any external reporting to outside vendors/sponsors per the applicable quality agreement (s).

4 DEFINITIONS/ACRONYMS

4.1 **AR –** Annual Report

4.2 **ABMT –** Adult Blood and Marrow Transplant

4.3 **BLA –** Biologics License Applications

4.4 **CBE –** Changes Being Effected

4.5 **CCR –** Change Control Request

4.6 **Change Control –** The process of approving and documenting changes to controlled documents, processes, equipment, operations, design, and other change(s) to ensure compliance with applicable regulatory requirements.

4.7 **Controlled Documents –** Documents which are subject to review, approval, and version control. Includes, but is not limited to, Standard Operating Procedures (SOPs), forms, job aids, and validation documents.

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

4.9 **Design Change –** The disciplined approach and investment during the design phase that predicts the success of a change or innovation. Includes but is not limited to Program construction or remodeling.

4.10 **Document Control Operations (DCO) –** Consists of the MasterControl System Administrator and document control specialist(s).

4.11 **Effectiveness Check (EC) –** Process of evaluating a change after implementation to confirm the change has met the desired outcome. Requirements for each effectiveness check are agreed to before the change is approved and implemented.

4.12 **Emergency Request –** Allowed when Safety, Quality, Identity, Purity and Potency (SQIPP) is compromised.

4.13 **EMMES –** Dedicated, validated, web application, database, and online data entry system provided by EMMES Corporation also referred to as AdvantageEDC^{SM} database.

4.14 **Hazard –** The potential source of harm (ISO/IEC Guide 51).

4.15 **Initiator –** The author or owner of a change who is responsible for initiating the CCR.

4.16 **JA –** Job Aid

4.17 **MC –** MasterControl – A validated 21 CFR Part 11 compliant document management system.

4.18 **PAS –** Pediatric, Adult, and Stem Cell Laboratory

4.19 **PAS –** Prior Approval Supplement

4.20 **PBMT –** Pediatric Blood and Marrow Transplant

4.21 **Probability** – The likelihood of something happening or being the case.

4.22 **Quality Systems Unit** (**QSU**) – Responsible for ensuring quality system(s) are effectively established and maintained, and who reports on its performance to management with executive responsibility review. QSU has sign-off authority on new and changes to existing documents, processes, or products.

4.23 **RA** – Regulatory Affairs

4.24 **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.

4.25 **SCR** – System Change Request for EMMES

4.26 **Severity** – A measure of the possible consequences of a hazard.

4.27 **SME** – Subject Matter Expert

4.28 **Software Change** – Includes, but is not limited to, upgrades or changes in computer software/systems.

4.29 **SOP** – Standard Operating Procedure

4.30 **SQIPP** – Safety, Quality, Identity, Purity and Potency

4.31 **STCL** – Stem Cell Laboratory

5 MATERIALS

5.1 N/A

6 EQUIPMENT

6.1 Computer access to MasterControl and EMMES

7 SAFETY

7.1 N/A

8 PROCEDURE

8.1 Change Control Request Form

8.1.1 The Change Control Request form should be initiated in MasterControl and approval should be completed before implementing a change.

8.1.2 A change control form should be utilized when changes are planned for each of the following items listed below.

8.1.2.1 Revisions to a Standard Operating Procedure (SOP) and associated form or job aid, which may be combined in the same CCR if the change description can be clearly detailed/communicated within a single CCR.

8.1.2.2 Changes to facilities or equipment, including repairs (unless these are captured per existing, program specific procedures). The request should include applicable supporting documentation such as facility drawings.

8.1.2.3 Software changes.

8.1.2.4 Service provider changes.

8.1.2.5 Changes to critical supplies or material specifications that affect manufacturing (ex. a change that impacts a batch record, SOP, or process validation), as identified by the initiator and in consultation with quality, will be assessed through the review of the applicable Material Specification Form, if applicable, and will additionally require a separate Change Control Request Form to appropriately identify/evaluate all associated risks.

8.1.2.6 Note the following does NOT require a CCR form: Changes to non-critical supplies or material specifications that do not affect any other aspect of manufacturing (ex. a change that does not impact a batch record, SOP, or process validation) will be assessed and documented through the Material Specification Process, if applicable, and do NOT require a separate Change Control Request Form. Additionally, minor corrections, as determined by the initiator in consultation with quality, or clarifications on changes to critical material specifications, do not require submission of a change control, if applicable.

8.1.3 If multiple changes are required for any of the items requiring documentation via the CCR form, they should be documented on separate CCR forms; however, if the change description can be clearly documented together, they may be submitted on one CCR.

8.1.4 If one change affects multiples areas (for example, documents, equipment, and a service provider), one CCR is encouraged as long as the description of applicable changes is clear and all associated changes may be implemented in a similar timeframe. If implementing in a similar timeframe is not possible, multiple CCRs are acceptable, provided each change is implemented per the procedures detailing within this SOP.

8.1.5 The initiator completes *COMM-QA-019 FRM1 Change Control Request (Effectiveness Check) FRM1* or *COMM-QA-019 FRM2 Change Control Request (No Effectiveness Check) FRM2* in MasterControl.

8.1.5.1 *COMM-QA-019 FRM1 Change Control Request (Effectiveness Check) FRM1* can be routed if the initiator determines the risk associated with the change, per the assessment procedures/scoring detailed in *COMM-QA-077, Risk Assessment Procedure,* to be warranted. In addition to risk driven initiation, *COMM-QA-019 FRM1 Change Control Request (Effectiveness Check) FRM1* may be triggered from other quality systems, including, but not limited to, in response to internal/external audit findings, management review, risk assessments, and/or identified trends. Refer to Appendix I for specific routing structures for this form.

8.1.5.1.1 Refer to *COMM-QA-077 Risk Assessment Procedure* for assistance on evaluating and determining how to assess risk to facilitate completion of a risk assessment that is captured within *COMM-QA-0019 FRM1 Change Control Request (Effectiveness Check) FRM1.*

8.1.5.1.2 Examples of changes that require effectiveness checks include updates to critical equipment and changes to critical service providers.

8.1.5.2 *COMM-QA-019 FRM2 Change Control Request (No Effectiveness Check) FRM2* can be routed if the initiator determines the risk associated with the change, per the assessment procedures/scoring detailed in *COMM-QA-077, Risk Assessment Procedure,* to be warranted. In addition to risk driven initiation, *COMM-QA-019 FRM2 Change Control Request (No Effectiveness Check) FRM2* may be triggered from other quality systems, including, but not limited to, in response to internal/external audit findings, management review, risk assessments, and/or identified trends. This form contains the same information as *COMM-QA-019 FRM1 Change Control Request (Effectiveness Check) FRM1* excluding sections V and VI and their associated routing step in MasterControl. Refer to Appendix II for specific routing structures for this form.

8.1.5.2.1 Refer to *COMM-QA-077 Risk Assessment Procedure* for assistance on evaluating and determining how to assess risk to facilitate completion of a risk assessment that is captured within *COMM-QA-0019 FRM2 Change Control Request (No Effectiveness Check) FRM2.*

8.1.5.2.2 Examples of changes that do not require effectiveness checks include document title changes and changes associated with overall risk scores as defined in *COMM-QA-077 Risk Assessment Procedure*.

Note: Changes with an associated with *COMM-QA-076 FRM1 CAPA Report* should use this form, *COMM-QA-019 FRM2 Change Control Request (No Effectiveness Check) FRM2*, since the effectiveness check of the associated change will be tracked as part of the CAPA

8.1.5.2.3 QSU may determine during routing that an effectiveness check is required for the change. COMM-QA-019 FRM2 Change Control Request (No Effectiveness Check) FRM2 would be aborted and COMM-QA-019 FRM1 Change Control Request (Effectiveness Check) FRM1 would be

initiated to include an effectiveness check. QSU and the initiator would work with Document Control to determine a path forward for aborting the event in MasterControl and document accordingly.

8.1.6 The initiator of the CCR starts the appropriate form in MasterControl, selecting the associated program/department.

8.1.6.1 The CCR number and initiator auto-populates on the form.

8.1.7 Sections I and II are completed by the initiator by selecting applicable items and providing explanation where requested. Any sections that do not apply to the requested change should be checked N/A. Section V is completed by the initiator for *COMM-QA-019 FRM1 Change Control Request (Effectiveness Check) FRM1.*

8.1.8 Document Changes (Section I)

8.1.8.1 Designate whether requesting a new document or a revision or archival of an existing document. List all applicable document titles, document numbers, and revision numbers.

8.1.8.2 Collaborators for new or revised documents should include the Subject Matter Expert (SME) and/or personnel associated with the document who are trained in MasterControl as power users.

8.1.8.3 Under document training requirements, select if development of training tools is required (e.g., checklist, quiz, other).

8.1.8.3.1 The training coordinator will follow-up with the initiator in the document collaboration process to implement training tools.

8.1.8.4 The initiator of the CCR lists MasterControl job codes or personnel to ensure training assignments are appropriate and inclusive. Refer to *COMM-QA-069 Job Codes – Roles and Users within Job Codes.*

8.1.8.4.1 All new and revised SOPs, FRMs, and JAs require training in MasterControl.

8.1.8.4.2 For revised SOP/controlled documents, the initiator may select to utilize previously established training assignments if, after reviewing them, the initiator determines that there is no need to update the assignments.

8.1.8.4.3 Some documents in MasterControl, such as organizational charts for example, may not require training.

8.1.9 Process Changes (Section I)

8.1.9.1 List procedures associated with process, under the relevant sections(s).

8.1.9.2 If applicable, summarize how the specific changes identified within individual sections (document changes, equipment, software, etc.) impact the overall process.

8.1.9.3 If the change is to an existing process, document if the requested change affects the qualification status of the process.

8.1.9.4 Process qualification/validation status should be assessed upon changes to SOPs associated with the execution of the process.

8.1.9.4.1 Requalification may be warranted following any significant process alterations, replacement/adjustment of major process steps, or observation of drifts in performance trends.

8.1.10 Equipment Changes (Section I)

8.1.10.1 List Equipment Type, Name, and Serial Number, and Criticality as applicable under the relevant selection.

8.1.10.2 If equipment parts are being replaced per a standard, SOP-driven process (like for preventative maintenance) and are "like for like", submission of a Change Control is not required.

8.1.10.3 If the change is to existing equipment, document if the requested change affects the qualification status of the equipment.

8.1.10.4 If the change is to introduce new equipment, program specific SOPs will detail requirements for equipment management within the facility. Minimally, a CCR will be launched to capture this change.

8.1.10.5 Equipment qualification status should be assessed upon changes to SOPs associated with the use of the equipment.

8.1.10.5.1 Requalification may be warranted following any significant equipment repair, replacement of major components, relocation or observation of drifts in performance trends.

8.1.11 Software Changes (Section I)

8.1.11.1 List Software Type, Name, and Version Number of the requested change.

8.1.11.2 An EMMES change will also need to be accompanied by *STCL-FORM-034 Data Verification Form*. Refer to Section 8.4 below.

8.1.12 New Service Provide and/or Service Provider Changes (Section I)

8.1.12.1 List Service Provider Name,Type of service provided, and Criticality of the requested change.

8.1.12.2 If there is a change in scope of services provided by an existing service provider, list a summary of this change in scope.

8.1.13 Facility Changes (Section I)

8.1.13.1 If entering a facility shutdown, list planned shutdown date and the associated projected facility startup date.

8.1.13.2 If facility changes are occurring during the associated shutdown, indicate here and fill out corresponding sections (ex. equipment) as appropriate.

8.1.13.3 Indicate any areas, including location/room numbers, impacted by the proposed change.

8.1.14 Material Specification Change (Section I), if applicable

8.1.14.1 If updates are needed to a Material Specification Form for a critical supply/material, list new and replacement Material Specification Form number.

8.1.14.2 Describe the use of the associated supply in the description of change.

8.1.14.3 List quality documents available for review.

8.1.15 Explain any other requested changes that do not fall under the above categories.

8.1.16 The description and reason for the requested change(s) to a process, document, design, software, equipment, service provider, material specification change (if applicable), facility, or other, should include as much detail as possible.

8.1.16.1 Include applicable CAPA Report number in the description of change(s) if this change is a result of a CAPA.

8.1.17 Impact and Risk Assessment (Section II)

8.1.17.1 Documentation of impact and risk assessment is required for all changes.

8.1.17.2 Select all areas that could be affected by this change.

8.1.17.2.1 List specific projects, as applicable, to better categorize changes and determine reporting requirements.

8.1.17.3 Select any additional items that will need to be completed before the requested change can be implemented.

8.1.17.3.1 Validations/Qualifications may be required for any changes affecting the process, testing, or equipment used in GMP processing. List requested validation numbers.

8.1.17.3.2 External reporting may be selected when the department acts as a contract service provider to an external company. The service contract or quality agreement, as applicable, should be reviewed to determine reporting requirements.

8.1.17.3.3 Any change to the EMMES software also requires documentation and verification per *STCL-FORM-*

034 Data Verification Form. Refer to Section 8.4 below.

8.1.17.3.4 Supplier/Service Provider Qualification is required for any change to service providers.

8.1.17.3.5 In certain scenarios, per *COMM-QA-080 Quality Risk Management*, a supplemental risk assessment method (such as Risk Ranking and Filtering, FMEA, HACCP) and associated report, separate from the matrix described in *COMM-QA-077 Risk Assessment Procedure*, may be needed to support a change, in addition to what is required in the associated COMM-QA-019 Change Control Request forms. These supplemental risk assessments may involve a team of SMEs to facilitate a comprehensive risk assessment as described in *COMM-QA-080 Quality Risk Management.* Additionally, as change controls are developed, when applicable, initiators will address (Section II) a review of any applicable risk assessments completed per COMM-QA-080 *Quality Risk Management*, to ensure consideration of how the change impacts already established risks, and to ensure this is factored into the determination of the overall risk score associated with the proposed change.

8.1.17.3.6 All required items flagged in this section must be appropriately completed before the change is implemented

8.1.17.4 List all other documents as applicable, that also reference the same SOP, process, document, or other item that is the focus of this change .

8.1.17.4.1 This can be completed by running a search in MasterControl or contacting Document Control.

8.1.17.4.2 Review all identified documents to determine whether additional changes are needed.

8.1.17.4.3 Indicate for Document Control if any associated documents are required to be placed in collaboration. A new CCR will be needed for those documents.

8.1.17.4.4 If associated documents are not to be placed in collaboration, but will be updated at the next MC designated review cycle, list these documents within this section, explain this rationale.

8.1.17.4.5 If associated documents are not to be placed in collaboration, include rationale/justification.

8.1.17.5 Risk Assessment is determined by evaluating the severity, probability, and detectability of identified risks (Table 1-3).

8.1.17.5.1 See *COMM-QA-077 Risk Assessment Procedure* for further details on risk evaluation.

8.1.17.6 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 COMM-QA-077 *Risk Assessment Procedure*.

Risk Assessment Tables (per COMM-QA-077)

Table 1: Severity Risk Matric

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

8.1.18 The risk assessment score, per *COMM-QA-077 Risk Assessment Procedure,* is used to determine whether an effectiveness check (EC) is required.

8.1.18.1 Reference SOP COMM-QA-077 Risk Assessment Procedure to assess risk on all three parameters (severity, probability, and detectability). An individual score should be assigned and detailed rationale provided for that assigned score.

8.1.18.2 Within this field, a Risk Assessment Summary Conclusion is completed.

8.1.18.2.1 Use this field to populate a summary of the overall risk assessment if not sufficiently detailed in the individual parameter fields above; any additional information about the expanded risk assessment can also be described here.

8.1.18.2.2 As detailed in COMM-QA-077 *Risk Assessment Procedure*, if a single risk matrix attribute is scored 5 and no effectiveness check is deemed necessary, justification will be required and captured within this field, addressing specifically how the risk was evaluated to be at an acceptable level.

8.1.18.2.3 The field can be N/A if no additional details are needed.

8.1.18.3 In addition to risk driven initiation, *COMM-QA-019 FRM1 Change Control Request (Effectiveness Check) FRM1* may be utilized if an effectiveness check is seen as valuable tool to track the proposed changes and/or may be triggered from other quality systems, including, but not limited to, in response to internal/external audit findings, management review, risk assessments, and/or identified trends.

8.1.18.4 If the initiator determines an EC is required on *COMM-QA-019 FRM2 Change Control Request (No Effectiveness Check) FRM2*, the form should be aborted and *COMM-QA-019 FRM1 Change Control Request (Effectiveness Check) FRM1* should be initiated to include an effectiveness check. QSU and the initiator would work with Document Control to determine a path forward for aborting the event in MasterControl and documenting accordingly.

8.1.18.5 CCRs associated with a CAPA will record the EC solely in the CAPA Report.

8.1.19 Effectiveness Check Requirements (Section V)

8.1.19.1 This section is applicable to *COMM-QA-019 FRM1 Change Control Request (Effectiveness Check) FRM1* only.

8.1.19.2 The method to assess effectiveness of the change is selected based off the type of change and impact. This can include inspection, review of documentation, data analysis, etc.

8.1.19.3 An estimated completion date for the EC should be listed taking into account the method of the check and the time required to properly assess the effectiveness of the change.

8.1.20 The initiator submits the CCR in MasterControl after completion of Steps I, II, and V (Section V applies *to COMM-QA-019 FRM1 Change Control Request (Effectiveness Check) FRM1* only).

8.2 Change Control Plan Review and Approval

8.2.1 Change control routes are established within MasterControl based on the form and program/department. See Appendix I and II for detailed routing diagram. After the initiator submits the CCR in MasterControl, the review route consists of the following:

8.2.1.1 **Program/Medical Director –** Provides initial review of the CCR, approving or rejecting the request based on program need.

8.2.1.2 **RA –**Reviews all the CCRs for the ABMT Program, PBMT Program and the STCL.

8.2.1.2.1 RA documents an assessment in Section III, as necessary, to facilitate communication with Quality and Training Coordinator to ensure appropriate timing for release of documents and change implementation.

8.2.1.2.2 RA designates the appropriate classification of the change based on FDA requirements and the potential for an adverse effect on the product (Table 4 and 5).

8.2.1.2.3 If the CCR is not associated with a licensed product under a BLA, an investigational product under an IND, or an FDA Master File, RA selects No/N/A within each section.

Table 4: Change (s) Associated with a Licensed Product

Classification	FDA Requirement(s)	Reporting Type	Guidelines for Release
Major	Prior FDA approval required	PAS - Prior Approval Supplement	Wait for FDA feedback. Confirm release date with Regulatory Affairs (RA).
Moderate	Submit supplement	CBE 30: Changes Being Effected in 30 days	30 Days after FDA receipt of supplement. Confirm release date with Regulatory Affairs (RA).
Moderate	Submit supplement	CBE 0: Changes Being Effected immediately	Immediately after FDA receipt of supplement. Confirm release date with Regulatory Affairs (RA).
Minor	Submit change in Annual Report (AR)	Annual Report (AR)	Effective immediately. No confirmation required from Regulatory Affairs (RA).
N/A	Not applicable		

Table 5: Changes(s) Associated with a Master File or an Investigational Product Under an IND

FDA Requirement(s)	Reporting Type	Guidelines for Release
Submit amendment	Amendment	Confirm release date with Regulatory Affairs (RA).
Submit change in Annual Report (AR)	Annual Report (AR)	Effective Immediately. No confirmation required from Regulatory Affairs (RA).
Not applicable		

8.2.1.3 **Quality Review –** Completes final review on all initial CCR plans (during first routing) to ensure completeness and impact and risk assessment are documented. Additionally, this review will include an assessment that any external notifications, per the terms of the applicable quality agreement, are sufficiently documented. Final approval by Quality is required on all CCRs.

8.2.1.3.1 When a CCR is rejected, a comment is added by Quality to provide explanation to the initiator of the CCR.

8.2.1.3.2 Quality also ensures that an approved CCR is completed on all new and revised documents prior to release of the associated document InfoCard in MC .

8.2.1.3.3 The Quality review evaluates the CCR in terms of required corrective action or system/process

enhancement, technical design, risk and impact assessment, and proposed effectiveness checks.

8.2.1.3.4 If the CCR is incomplete or if additional risks are identified by the Quality review, the CCR will be rejected and sent back to the initiator with an explanation.

8.2.2 If the CCR is rejected, the initiator may discuss options with the Medical/Program Director and/or the QSU, as applicable for further guidance.

8.2.3 The initiator of the CCR is notified via MasterControl when the CCR plan is approved.

8.2.4 Final Approval to Implement Change (Section IV)

8.2.4.1 A second routing is required to document all requirements have been met before implementation of the change occurs.

8.2.4.2 The CCR routes back to the initiator after initial CCR plan approval.

8.2.4.3 The initiator reviews Sections II and III and performs all requirements attaching, when feasible, relevant documentation to the CCR form (e.g., validations).

8.2.4.3.1 The initiator of the CCR should include a projected effective date for any associated new or revised documents. This date is a projection contingent upon approval of the associated CCR.

8.2.4.3.2 At the time of implementation approval, if the original proposed effective date is not possible, in collaboration with QSU, a new date will be selected and reflected in Section IV of the associated CCR form

8.2.4.4 In situations in which the scope of the associated change expanded or changed slightly from the original changes proposed in the CCR plan, the initiator of the document may highlight this change in the comments field of Section IV before implementation of the change.

8.2.4.4.1 In these scenarios, QA will review the initial impact and risk assessment populated within the original CCR plan to determine if the additions to the change request are still applicable/appropriate and if any other additional reviews are needed before implementation (ex. RA).

8.2.4.5 When all required actions are completed, the initiator will submit for final approval to implement change.

8.2.4.6 QA reviews the CCR to ensure all requirements have been met.

8.2.4.6.1 If QA approves, the initiator may implement the change (ex. put equipment into use, make document effective).

8.2.4.6.2 If QA rejects, the CCR will be sent back to the initiator with a comment explaining why the change cannot be implemented. The initiator will collaborate with QA to determine a plan to move forward.

8.2.4.7 For *COMM-QA-019 FRM2 Change Control Request (No Effectiveness Check) FRM2*, this is the final step in the CCR process. The CCR is complete.

8.2.4.8 For *COMM-QA-019 FRM1 Change Control Request (Effectiveness Check) FRM1*, The CCR routes back to the initiator to hold until the EC is completed.

8.3 Effectiveness Check of Change (Section VI)

8.3.1 A third routing of the *COMM-QA-019 FRM1 Change Control Request FRM1* is required to document an effectiveness check of the change after implementation.

8.3.2 An effectiveness check is required only for changes as defined per the Impact and Risk Assessment above and *COMM-QA-077 Risk Assessment Procedure*. The method of the effectiveness check is approved in the initial routing of the form in Section V Effectiveness Check Requirements.

8.3.3 The Effectiveness Check Completion section of the *COMM-QA-019 FRM1 Change Control Request (Effectiveness Check) FRM1* will be completed by the initiator documenting the outcome of the check. Upon completion of the Effectiveness Check activities, the target timeline for routing of this form by the initiator is 30 days.

8.3.4 The change is determined to be satisfactory if it meets the desired outcome, which minimally involves a completion of the activities detailed in Section V, and may additionally involve a reduction in risk. If applicable, initiators should describe in the free text field in this section how the change reduced the risk highlighted in the prior sections of this same change control (Section II).

8.3.4.1 If the change is satisfactory, the CCR is closed and no further action is required.

8.3.4.2 If the change is not satisfactory, the initiator will document a plan of action of how to proceed. A new CCR may be initiated if a new change is required.

8.3.4.2.1 The Medical director and QSU will review the plan of action. If rejected, a comment is added providing explanation. The initiator and QSU will collaborate to determine next steps. The CCR is closed once an approved plan is reached.

8.4 Handling Controlled Document Changes Involving EMMES

8.4.1 When an author develops a new document that will be included in the EMMES System or identifies changes required to an existing document in EMMES, a *COMM-QA-019 FRM1 Change Control Request (Effectiveness Check) FRM1* must be submitted and approved in MasterControl.

8.4.2 The CCR must include detail in the description of change section of the CCR form; e.g., form change; verification required. Additionally, select "Other, Explain" and note generation of *STCL-FORM-034 Data Verification Form* on the Impact and Risk Assessment Section.

8.4.3 When the document is final in MasterControl, and prior to associated document becoming effective in MC, the supervisor/manager or designee must initiate the *STCL-FORM-034 Data Verification Form*.

8.4.4 The completed *STCL-FORM-034 Data Verification Form* with any supporting documentation are provided to the Quality Manager, or designee, for review and approval and is scanned and attached to the associated CCR on the EC.

8.5 Handling Emergency Change Requests

8.5.1 Emergency change requests will be allowed when SQIPP is compromised.

8.5.2 The person making the emergency request must consult with the Medical/Program Director, QSU and RA, if applicable, for consideration of how to proceed.

8.5.3 A CCR is submitted in MasterControl for documentation of the emergency approval and for tracking purposes.

8.5.4 Review by the Medical/Program Director and RA, if applicable and approval by the QSU are required prior to implementation of the emergency request.

8.6 The Supervisor/Manager is responsible for ongoing assessment and evaluation of the effectiveness of implemented changes by reviewing the change(s) and improving any area(s) not working as expected.

9 RELATED DOCUMENTS/FORMS

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

9.2 COMM-QA-019 FRM2 Change Control Request (No Effectiveness Check)

9.3 COMM-QA-069 Job Codes– Roles and Users within Job Codes

9.4 COMM-QA-076 FRM1 CAPA Report

9.5 COMM-QA-077 Risk Assessment Procedure

9.6 COMM-QA-080 Quality Risk Management

9.7 STCL-FORM-034 Data Verification Form

10 REFERENCES

10.1 American Association of Blood Banks. Standards for Hematopoietic Progenitor Cell and Cellular Product. Current edition.

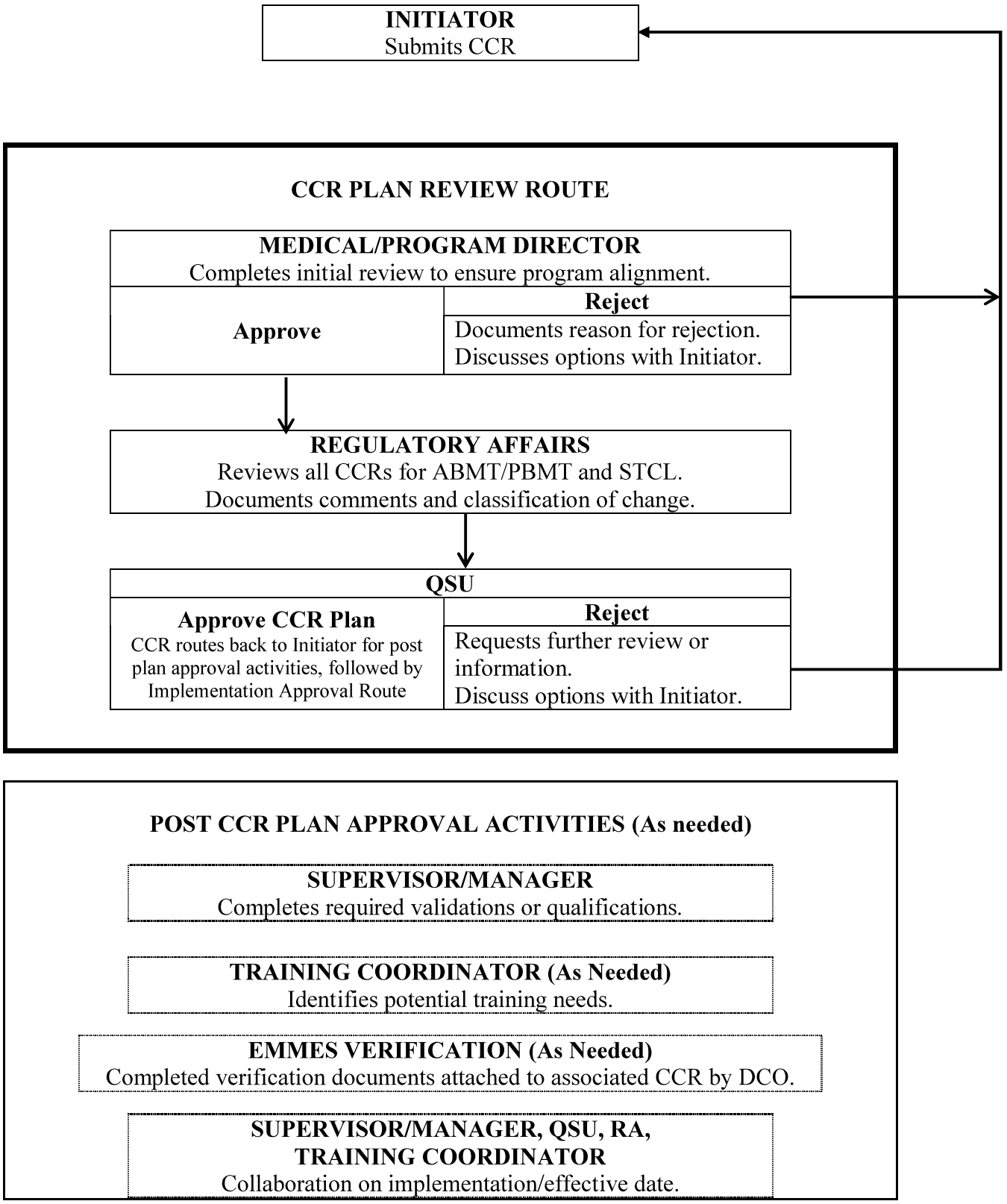
10.2 Foundation for the Accreditation of hematopoietic Cell Therapy (FACT). International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration. Current edition.

10.3 21CFR 211.22(c) The quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product.

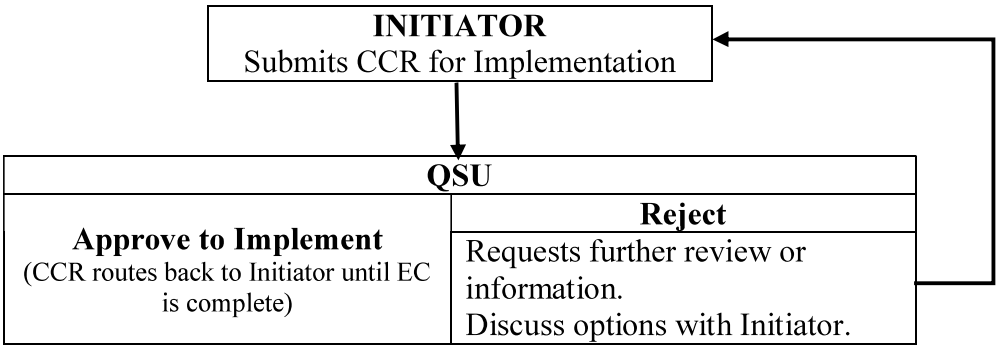
11 REVISION HISTORY

Revision No.	Author	Description of Change(s)
07	B. Shen	• Updated to include new risk assessment requirements and to align with revised COMM-QA-077. • Added Medical Director review/approval on FRM2. • Created new section on the CCR form for MSPEC changes, facility changes, as well as process changes. • Modified change control form to request projected effective date field on second routing. • Enhance linkage to more formal risk assessments through COMM-QA-080.

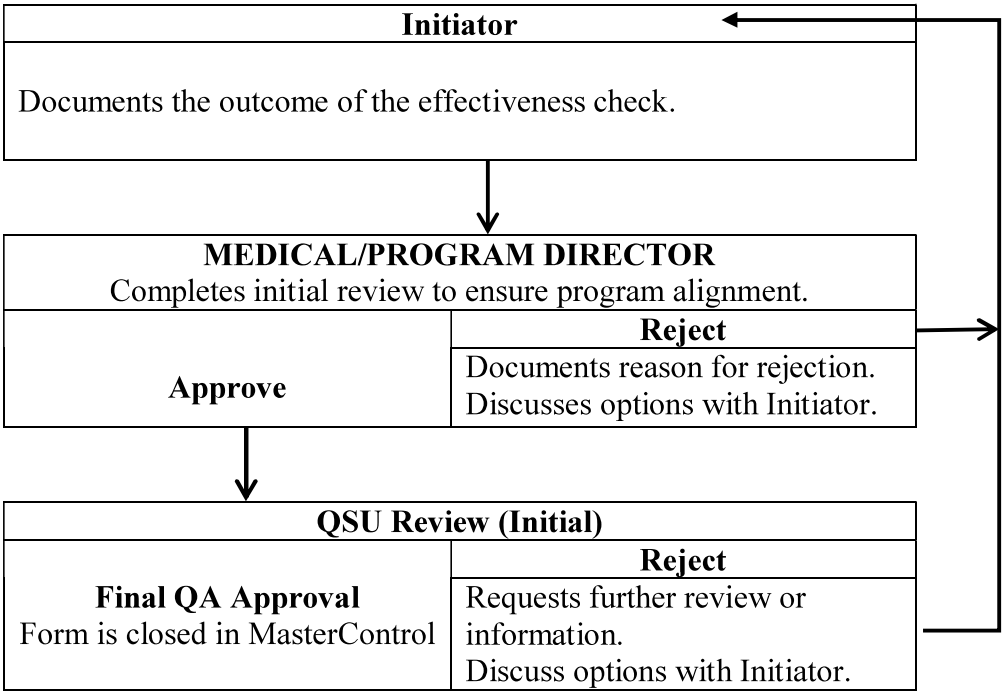
Appendix I
CHANGE CONTROL REVIEW PROCESS FRM1 (Effectiveness Check)



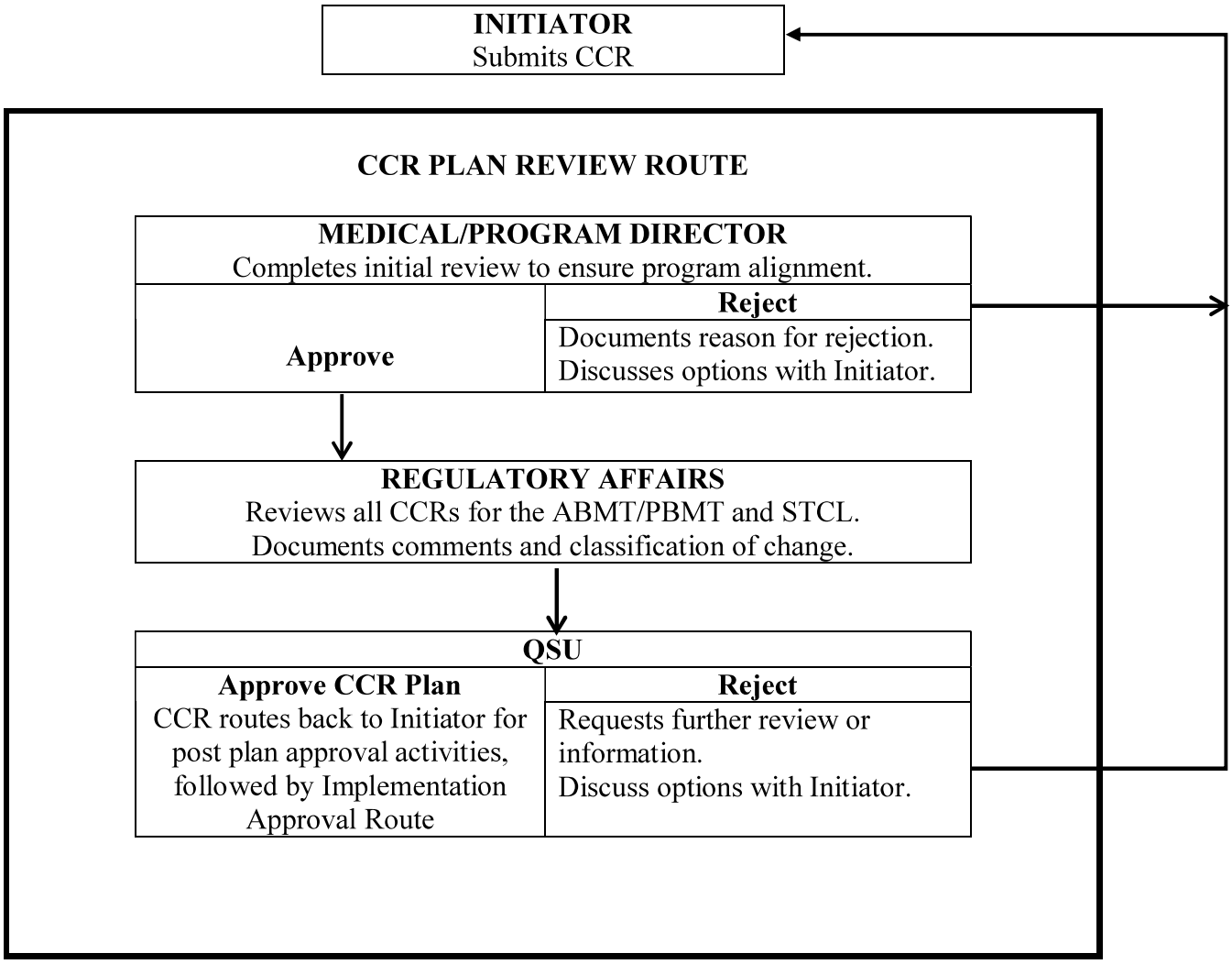
IMPLEMENTATION APPROVAL ROUTE

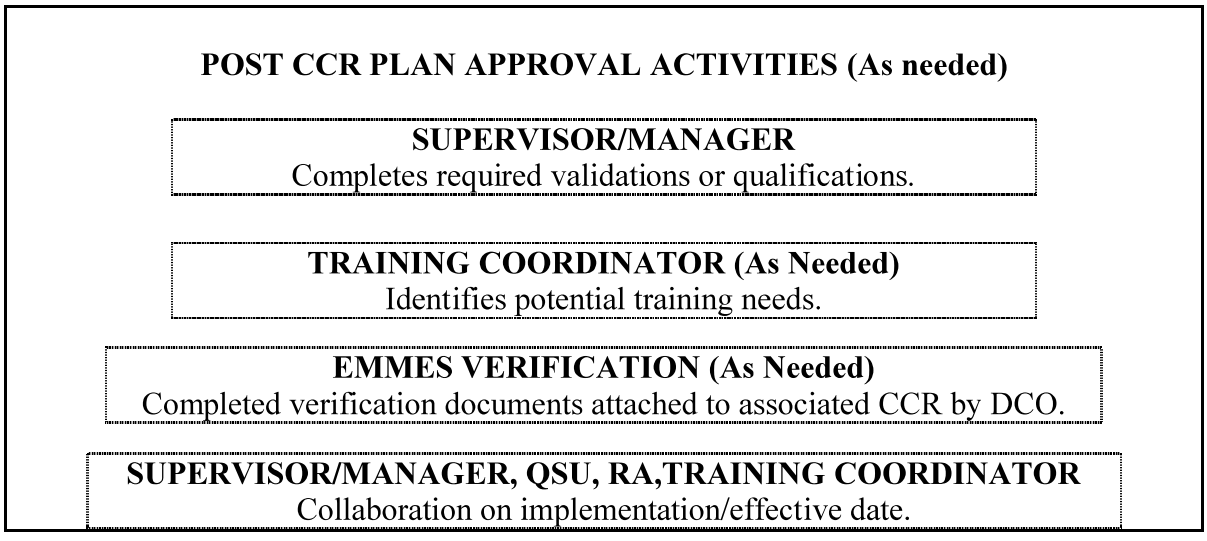


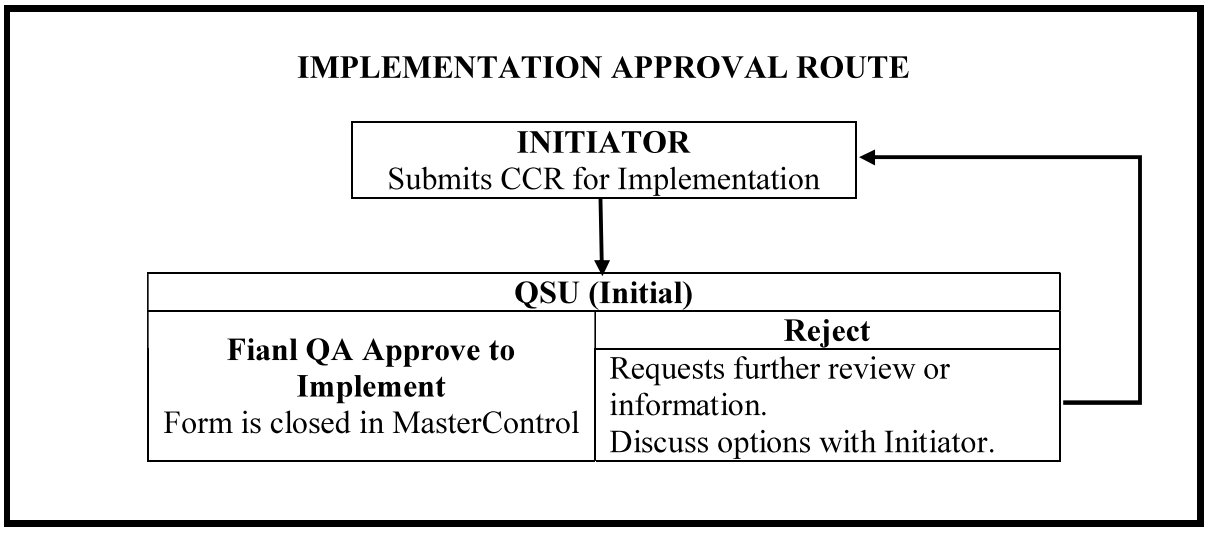
EFFECTIVENESS CHECK REVIEW ROUTE



Appendix II
CHANGE CONTROL REVIEW PROCESS FRM2 (No Effectiveness check)







Signature Manifest

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COMM-PAS-004 Change Control

Author

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Document Release

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