Kiniksa QMS SOP Review for 25Q2 KPL-387 Strategic Roadmap Project

**Scope Statement**

This Quality System Review evaluated the compliance and integration of the following quality management system (QMS) procedures and supporting documents from Kiniksa against applicable regulatory and standards requirements:

* **21 CFR Part 820** (Quality System Regulation for medical devices)
* **ISO 13485:2016** (Medical Devices – Quality Management Systems)
* **ISO 14971:2019** (Risk Management for Medical Devices)
* **21 CFR Part 4** (CGMP Requirements for Combination Products)

The evaluation covered the following procedures and associated work instructions:

* SOP-0035 Quality Risk Management
* SOP-0036 Design Control
* SOP-0028 Change Control
* SOP-0029 CAPA
* SOP-0019 Supplier Lifecycle Management
* SOP-0023 Quality Agreements Lifecycle Management
* SOP-0033 Supplier Auditing and Qualification

Emphasis was placed on the system’s ability to maintain regulatory compliance across device and combination product domains, traceability to risk management outputs, supplier oversight rigor, and integration between quality subsystems (e.g., CAPA ↔ Risk, Change Control ↔ Design Control).

**Document Reviewed: SOP-0035 Quality Risk Management**

**Reference Standards:**

* ISO 14971:2019
* 21 CFR Part 820
* 21 CFR Part 4 (Combination Products)
* ISO 13485:2016

**Findings Table – Gaps and Recommendations**

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| --- | --- | --- | --- | --- |
| Issue | Severity | Document Excerpt | Recommended Revision | Reference |
| Risk Management Plan not explicitly required as a documented deliverable | **Critical** | “Risk management activities shall be planned…” but no requirement for a documented risk management plan with defined content | Mandate a documented risk management plan including intended use, risk acceptability criteria, roles, responsibilities, methods for evaluation, and review criteria | ISO 14971:2019, Clause 4.4 |
| Overall residual risk evaluation not clearly described | **Critical** | No specific mention of evaluating overall residual risk or performing acceptability assessment | Add explicit steps for evaluating overall residual risk as per Clause 8, and defining acceptability criteria in the risk management plan | ISO 14971:2019, Clause 8 |
| Benefit-risk analysis process inadequately described | **Critical** | “Creates risk benefit analysis in accordance with this procedure” – vague, no defined methods or required documentation | Require a documented benefit-risk analysis aligned with Clause 7.4; define when it is required and how to perform it | ISO 14971:2019, Clause 7.4 |
| No requirement to analyze risks introduced by risk control measures | **Critical** | No mention of secondary risks introduced by controls | Add requirement to identify and assess risks arising from risk control implementation | ISO 14971:2019, Clause 7.5 |
| No defined method for ensuring completeness of risk control measures | **Moderate** | Risk control steps are present but lack verification of completeness | Require completeness verification before closing risk control actions | ISO 14971:2019, Clause 7.6 |
| Lack of detailed requirements for the contents of a Risk Management File (RMF) | **Moderate** | RMF is mentioned but not clearly defined or scoped | Require the RMF to include plan, analyses, evaluations, controls, residual risk decisions, and review records | ISO 14971:2019, Clause 4.5 |
| Post-market risk activities not fully aligned with ISO 14971:2019 Clause 10 | **Critical** | Mentions periodic reviews, but lacks specifics on data sources, triggers for action, or integration with PMS | Expand to include data sources (complaints, adverse events), frequency, triggers for update, and link to CAPA | ISO 14971:2019, Clause 10.1–10.4 |
| No process for evaluating risk from reasonably foreseeable misuse | **Moderate** | Foreseeable misuse not explicitly addressed | Add evaluation for misuse scenarios per Clause 5.2 | ISO 14971:2019, Clause 5.2 |
| Risk acceptance criteria not defined or documented | **Moderate** | “Top management shall define a policy…” – but no example or enforcement | Require documented, risk-based acceptability criteria tied to risk levels | ISO 14971:2019, Clause 6 |
| Risk control option analysis not structured | **Minor** | No defined approach for prioritizing inherent safety, protective measures, or information for safety | Add hierarchy per Clause 7.1 | ISO 14971:2019, Clause 7.1 |
| No clear link between combination product drug constituent and its risk controls | **Moderate** | Drug constituent out of scope; no bridging mention of how it is handled for combination product | Add statement on how device-side risk management interfaces with drug product risk analysis (e.g., per FDA’s 2019 draft guidance) | 21 CFR Part 4; FDA Combination Product Guidance (risk-based framework) |
| Competency requirements are described but not linked to risk management training | **Minor** | Mentions training but not specific to risk management methods (e.g., FMEA, FTA) | Specify required training and documentation of competency for personnel conducting risk activities | ISO 14971:2019, Clause 4.3 |

**System-Level Observations**

When cross-referenced with other procedures (Design Control, CAPA, Document Control, etc.):

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| --- | --- | --- | --- |
| Issue | Severity | Observation | Recommended System-Level Action |
| No defined interface between CAPA and risk management | **Critical** | CAPA Procedure does not reference feedback to RMF | Add requirement in CAPA to evaluate if nonconformance requires RMF update |
| Design Control references risk management but does not require RMF updates for changes | **Moderate** | Risk activities not clearly triggered by design change | Revise Change Control Process SOP and Design Control SOP to mandate RMF review/update |

**Combination Product Considerations**

The SOP references combination products and identifies that drug constituent risks are out of scope. However, **21 CFR Part 4** requires integrated consideration of both device and drug risks. Recommendations:

* Include interface mechanisms between the device RMF and drug development risk assessments.
* Define joint review expectations with drug safety teams.
* Require combination product RMF to include constituent-specific risks where device delivery affects drug safety or efficacy (e.g., leachables, dose accuracy).

**Conclusion**

The current SOP aligns partially with the intent of ISO 14971:2019 but omits multiple required elements, especially those related to:

* Comprehensive documentation (risk plan, risk file, residual risk evaluation)
* Risk control rigor
* Post-market integration
* Combination product bridging

To ensure regulatory compliance and audit readiness under ISO 13485, 21 CFR Part 820, and ISO 14971:2019, revision of the SOP is strongly recommended.

**Document Reviewed: SOP-0036 Design Control**

The table below provides a detailed, critical compliance review of the “SOP-0036 Design Control” procedure against the following regulatory and standards references:

* 21 CFR Part 820.30 (Design Controls)
* ISO 13485:2016
* ISO 14971:2019
* 21 CFR Part 4 (for combination products)

**Findings Table – Gaps and Recommendations**

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| --- | --- | --- | --- | --- |
| Issue Description | Severity Level | Original Excerpt | Recommended Revision | Applicable Standard or Regulation |
| Absence of explicit linkage between design control phases and risk management process. | **Critical** | The procedure lists phases like Design Input, Output, Verification, etc., but does not integrate risk identification or mitigation activities per phase. | Integrate ISO 14971 clauses 4.4 (Risk Management Plan) and 5.1–5.5 (Risk Analysis) across all design control phases. Each phase should document relevant risk assessment outputs in the DHF. | ISO 14971:2019 §4.4, §5; 21 CFR 820.30(g) SOP-0036 Design Control |
| No clear requirement for a design freeze pre design verification testing or requirement for change management post verification | **Moderate** | The procedure states that the intent of the verification phase is to complete the design but is not explicit as to what this means. | Provide direct requirements for no design changes pre-verification with a design review prior to verification start and change management required after design freeze. | 21 CFR 820.30 ISO 13485:2016 §7.3 |
| No reference to evaluation of risk control effectiveness during or after design validation. | **Critical** | Design validation is described, but there is no mention of ensuring that risk controls implemented during design are effective. | Add explicit requirement to evaluate and document the effectiveness of risk controls during design validation activities. | ISO 14971:2019 §7.2, §7.6; 21 CFR 820.30(g) |
| Limited consideration of combination product GMP alignment under 21 CFR Part 4. | **Moderate** | While 21 CFR Part 4 is cited, the SOP does not demonstrate how constituent part CGMPs (21 CFR 210/211) are met for drug-device combinations. | Include a matrix or cross-reference table linking 21 CFR Part 820 requirements with 21 CFR Parts 210/211 for combination product development. | 21 CFR Part 4.4(b)(3)21 CFR Part 4 (up to date as of 4-11-2025) |
| Design input requirements do not explicitly include usability/human factors analysis. | **Moderate** | Design inputs are defined as physical and performance requirements, but there is no mention of incorporating user interface safety or usability requirements (uFMEA or Task Analysis). | Revise the definition of Design Inputs to include usability/human factors requirements, in line with FDA guidance and IEC 62366-1. | 21 CFR 820.30(c); ISO 13485 §7.3.3; FDA Human Factors Guidance (2016) SOP-0036 Design Control |
| Lack of documented linkage from design inputs to outputs and verification via traceability matrix. | **Moderate** | No procedure requirement or description of how traceability from inputs to outputs and verification is maintained. Only reference to a trace matrix document. | Add requirement to generate and maintain a traceability matrix mapping design inputs to outputs and verification methods. | 21 CFR 820.30(f); ISO 13485 §7.3.6 SOP-0036 Design Control |
| Design transfer responsibilities and criteria are insufficiently defined. | **Minor** | Design Transfer is mentioned but lacks detail on deliverables, criteria, or personnel accountable for approving the transfer. | Expand the Design Transfer section to define deliverables, responsible roles, acceptance criteria, and approval processes. | 21 CFR 820.30(h); ISO 13485 §7.3.8 SOP-0036 Design Control |
| Design review team composition and independence not defined. | **Minor** | Design reviews are referenced but there is no requirement for an independent reviewer not directly involved in the design stage being reviewed. | Include requirement that each design review team must contain at least one independent reviewer in accordance with 820.30(e). | 21 CFR 820.30(e); ISO 13485 §7.3.5 SOP-0036 Design Control |
| Document does not specify retention policy for Design History File (DHF). | **Minor** | The DHF is mentioned as a compilation of design records, but no retention timeline or reference to record control procedure is given. | Add reference to document control or records retention procedure to clarify the duration and responsibility for DHF maintenance. | 21 CFR 820.30(j); ISO 13485 §4.2.5 SOP-0036 Design Control |
| Design control process overview waterfall does not align with defined process | **Minor** | Attachment 1 notes the FDA Design Control Process, however, the phase content, titles, and review elements are different in the current process. | Clearly define each phase to align with the waterfall design process using terms consistent with FDA and EU expectations. | 21 CFR 820, ISO 13485 |

**System-Level Observations**

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| System-Level Concern | Implication | Recommended Action |
| Lack of consistent linkage to risk management in all design-related SOP’s. | Risk control and risk file updates may be omitted during design changes or validations. | Ensure all WIs reference the Risk Management Procedure and ISO 14971 requirements explicitly. |
| Traceability matrix references are inconsistent or missing in SOP documents. | Regulatory risk of failing to demonstrate that all design inputs are verified/validated. | Mandate traceability matrix usage in all applicable WIs and include template reference. |
| Design Transfer expectations not uniformly defined across SOP documents. | Incomplete or inconsistent DMR and DHF population at hand-off to manufacturing. | Standardize Design Transfer deliverables across SOP-0036 and Design Transfer WI. |
| Human Factors (Usability Engineering) considerations not embedded across all design stages. | Potential compliance gaps with IEC 62366 and FDA Human Factors Guidance. | Embed Human Factors milestones into Design Input, Verification, and Validation procedures. |

**Next Steps & Recommendations**

Since this document is part of a larger system (and several other SOPs were submitted), a system-level consistency review is recommended to evaluate:

1. **Traceability and alignment across SOPs and Work Instructions:**
   * Inputs, outputs, and verifications mentioned in WI documents (e.g., Design Inputs, Outputs, Verification, Validation) must tie directly into this SOP and show traceability in the DHF.
2. **Cross-functional consistency:**
   * Confirm that risk management elements (as required by ISO 14971 and referenced in the Risk Management SOP) are integrated into design control deliverables and reviews.
3. **Combination product regulatory crosswalk:**
   * Explicit traceability to Part 210/211 requirements for combination products should be incorporated across relevant procedures.

**Confirmed Compatibility**

This SOP does include the following strengths:

* Proper citations to 21 CFR 820.30 and ISO 13485.
* Recognition of combination product scope.
* Inclusion of a Design and Development Plan (DDP).
* Delegation of cross-functional roles and responsibilities.

**Document Reviewed: SOP-0028: Change Control Process**

The document **SOP-0028: Change Control Process** was critically reviewed against:

* 21 CFR Part 820.30 and 820.100
* ISO 13485:2016, particularly clauses §6.2, §7.1, §7.3.9, and §8.5
* 21 CFR Part 4, for combination product considerations
* ISO 14971:2019 for risk-based design and process change management

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| Issue Description | Severity Level | Original Excerpt | Recommended Revision | Applicable Standard or Regulation |
| No explicit requirement for assessing impact on combination product CGMPs. | **Critical** | Changes are assessed for impact to quality systems and regulatory filings, but no criteria are provided for combination products governed by dual CGMPs. | Include mandatory assessment for changes impacting both device and drug/biologic constituent parts per 21 CFR Part 4. Clarify need to assess under 820 and 210/211 as applicable. | 21 CFR Part 4(b)(1); 21 CFR 820.30(i); 21 CFR 211.100(a) SOP-0028 Change Control Process |
| Risk management integration is inconsistently addressed. | **Moderate** | Risk assessment is listed as part of the change package, but the SOP does not reference ISO 14971 or define structured risk control documentation requirements. | Revise to require risk assessment per ISO 14971 for design, process, or supplier-related changes, with documented residual risk evaluation. | ISO 14971:2019 §7; ISO 13485:2016 §7.1 SOP-0028 Change Control Process |
| Absence of linkage to design control SOP when design is impacted. | **Moderate** | Design changes are mentioned in general, but there is no reference to initiating design control processes (e.g., verification/validation, DHF updates). | Add requirement to initiate procedures from Design Control SOP (SOP-0036) for any design change affecting form, fit, or function. | 21 CFR 820.30(i); ISO 13485:2016 §7.3.9SOP-0028 Change Control Process |
| Lack of defined acceptance criteria for effectiveness checks. | **Minor** | Effectiveness checks are required post-implementation but are not required to include measurable success criteria. | Mandate that effectiveness check plans include measurable acceptance criteria aligned with intended objectives of the change. | 21 CFR 820.100(a)(4); ISO 13485:2016 §8.5.2 SOP-0028 Change Control Process |
| Training assessment lacks integration with document control lifecycle. | **Minor** | Training impact is evaluated, but there's no link to document control system to ensure procedural revisions trigger training tasks. | Integrate document control SOP reference and require training task generation upon approval of changes impacting controlled documents. | ISO 13485:2016 §6.2; 21 CFR 820.25(b) SOP-0028 Change Control Process |

**Critical and Moderate Findings Summary**

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| Severity | Issue | Implication |
| Critical | No formal mechanism to assess change impact on combination product CGMPs | High compliance risk under 21 CFR Part 4 for dual-regulated products |
| Moderate | Risk management activities are inconsistently defined and lack ISO 14971 traceability | Risk documentation may be incomplete or inadequate |
| Moderate | No procedural trigger to engage design control requirements when design is affected | Risks omission of verification/validation and DHF updates |

**Document Reviewed: SOP-0029: Corrective and Preventative Action (CAPA) Procedure**

The table presented provides a detailed compliance assessment against:

* 21 CFR 820.100
* ISO 13485:2016, particularly clauses 8.4 and 8.5
* ISO 14971:2019, where risk management integration is relevant

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| Issue Description | Severity Level | Original Excerpt | Recommended Revision | Applicable Standard or Regulation |
| No requirement to analyze trends across CAPAs to detect systemic issues. | **Critical** | CAPA initiation is event-driven (e.g., deviations, audits), but there is no requirement to conduct trend analysis to identify recurring issues. | Include a section mandating trend analysis across CAPA sources to detect systemic issues, per 21 CFR 820.100(a)(1) and ISO 13485 §8.4. | 21 CFR 820.100(a)(1); ISO 13485:2016 §8.4SOP-0029 Corrective and Preventive Action (CAPA) Procedure |
| Lack of formal requirement to investigate root cause using defined methodology. | **Moderate** | Root cause is mentioned, but no structured investigation method (e.g., 5 Whys, Fishbone) is required. | Mandate use of a structured root cause analysis methodology and document the method used in each CAPA record. | 21 CFR 820.100(a)(2); ISO 13485:2016 §8.5.2 SOP-0029 Corrective and Preventive Action (CAPA) Procedure |
| Preventive action process is underdeveloped compared to corrective action. | **Moderate** | Preventive action is defined, but the SOP lacks a distinct workflow or criteria for identifying and initiating preventive actions proactively. | Define specific inputs or conditions that should trigger preventive action (e.g., audit trends, risk assessments) and clarify preventive vs. corrective actions. | 21 CFR 820.100(a)(1); ISO 13485:2016 §8.5.3 SOP-0029 Corrective and Preventive Action (CAPA) Procedure |
| No explicit linkage between CAPA records and risk management activities. | **Moderate** | While the CAPA procedure addresses risk via 'interim controls' and impact assessments, it does not reference the Risk Management Procedure or ISO 14971. | Cross-reference Risk Management Procedure and integrate ISO 14971 risk review when CAPA events are risk-driven. | ISO 13485:2016 §7.1; ISO 14971:2019 §6.3 SOP-0029 Corrective and Preventive Action (CAPA) Procedure |
| Effectiveness check success criteria not consistently defined in EC planning. | **Minor** | Effectiveness Check fields require justification, but not all examples define clear, measurable success criteria. | Standardize requirement for EC plans to include quantifiable/measurable success criteria, and link them to the original CAPA objective. | ISO 13485:2016 §8.5.2; 21 CFR 820.100(a)(4) SOP-0029 Corrective and Preventive Action (CAPA) Procedure |
| No requirement for management review of CAPA trends. | **Minor** | Management review is referenced as a CAPA source but not as a recipient of CAPA metrics. | Add requirement to summarize CAPA trends and metrics for management review meetings. | ISO 13485:2016 §5.6.2; 21 CFR 820.100(c) SOP-0029 Corrective and Preventive Action (CAPA) Procedure |

**Key Findings Summary**

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| Severity | Area of Concern | Impact |
| Critical | Lack of required trend analysis across CAPAs. | This poses a regulatory risk and is explicitly required by both 21 CFR 820.100(a)(1) and ISO 13485 §8.4. |
| Moderate | * Absence of a structured root cause methodology. * Underdeveloped preventive action process (as distinct from corrective action). * Missing explicit integration with risk management processes (i.e., ISO 14971 alignment). | This poses a regulatory risk |
| Minor | * Effectiveness check success criteria need standardization. * CAPA metrics should be formally routed to Management Review to meet ISO 13485 §5.6. | This poses a regulatory risk |

**Document Reviewed: SOP-0019: Supplier Lifecycle Management**

The compliance review for **SOP-0019: Supplier Lifecycle Management** has been completed with a focus on:

* 21 CFR Part 820.50 (Purchasing Controls)
* ISO 13485:2016 clauses §7.4 and §7.1
* 21 CFR Part 4 requirements for combination products
* ISO 14971:2019 for risk-based supplier qualification

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| Issue Description | Severity Level | Original Excerpt | Recommended Revision | Applicable Standard or Regulation |
| Combination product-specific supplier controls are not addressed explicitly. | **Critical** | The SOP applies broadly to GxP suppliers but does not address controls or dual compliance expectations for combination product suppliers under 21 CFR Part 4. | Include a section specifically addressing supplier controls for combination products, referencing both device (21 CFR 820.50) and drug (21 CFR 211.80, 211.84) requirements. | 21 CFR Part 4(b)(1); 21 CFR 820.50; 21 CFR 211.84 SOP-0019 Supplier Lifecycle Management |
| No requirement for documentation and evaluation of supplier-provided test methods or validation data. | **Moderate** | While supplier assessments reference quality certifications, there is no requirement to verify supplier-provided testing methods or validation reports for critical components. | Add a requirement to assess and document supplier test method validation or verification for critical raw materials or components. | 21 CFR 820.50(a); ISO 13485:2016 §7.4. SOP-0019 Supplier Lifecycle Management |
| No reference to supplier notification of changes to manufacturing processes or specifications. | **Moderate** | The SOP outlines surveillance and requalification but does not explicitly require suppliers to notify the organization of process or specification changes. | Require contractual obligations for suppliers to notify of any changes in manufacturing process, test methods, or specifications. | 21 CFR 820.50(b); ISO 13485:2016 §7.4.3 SOP-0019 Supplier Lifecycle Management |
| Approved Supplier List (ASL) lacks requirement to define supplier approval status rationale. | **Minor** | The SOP defines ASL status levels, but it does not require documentation of rationale for conditional approval or disqualification beyond narrative in a form. | Update procedure to mandate justification for all ASL statuses be recorded and traceable in quality records. | 21 CFR 820.50(a); ISO 13485:2016 §7.4.1 SOP-0019 Supplier Lifecycle Management |
| Risk management references ISO 14971 indirectly but lacks structured linkage. | **Minor** | Section 5.8 mentions following SOP-0035 for risk assessment, but does not directly link supplier evaluation criteria to ISO 14971 risk acceptability thresholds. | Ensure supplier risk evaluation incorporates defined risk acceptability criteria aligned with ISO 14971 for combination product suppliers. | ISO 14971:2019 §6.4; ISO 13485:2016 §7.1 SOP-0019 Supplier Lifecycle Management |

**Key Findings Summary**

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| Severity | Area of Concern | Impact |
| Critical | No explicit procedures addressing combination product supplier requirements | May result in regulatory noncompliance under 21 CFR Part 4 |
| Moderate | Missing requirements for:  • Reviewing supplier test methods/validation  • Supplier change notifications | Weakens control over component quality and traceability |
| Minor | Incomplete documentation standards in ASL and indirect ISO 14971 linkage | May reduce audit traceability and weaken risk justifications |

**Document Reviewed: SOP-0023: Quality Agreements (QAGs) Lifecycle Management**

The table presented contains a complete compliance evaluation of **SOP-0023: Quality Agreements (QAGs) Lifecycle Management** against:

* 21 CFR Part 820 (Quality System Regulation)
* ISO 13485:2016, with emphasis on §4.1, §7.1, §8.2, and §8.5
* ISO 14971:2019 on risk-based supplier and quality oversight
* 21 CFR Part 4, covering combination product CGMP responsibilities

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| --- | --- | --- | --- | --- |
| Issue Description | Severity Level | Original Excerpt | Recommended Revision | Applicable Standard or Regulation |
| Lack of required delineation of CGMP responsibilities for combination products under 21 CFR Part 4. | **Critical** | The SOP refers generally to GxP services and suppliers but does not specify how CGMP responsibilities are split between drug and device constituent parts in QAGs. | Require QAGs for combination products to clearly define which party is responsible for compliance with 21 CFR Part 820 (device CGMP) and Parts 210/211 (drug CGMP), per 21 CFR Part 4. | 21 CFR Part 4.4(b)(1); FDA Guidance on CGMP for Combination Products  SOP-0023 Quality Agreements (QAGs) Lifecycle Management |
| No requirement to document quality event escalation and notification timelines in QAGs. | **Moderate** | QAGs are said to align with regulatory expectations, but the SOP does not require inclusion of communication pathways for complaints, recalls, or serious adverse events. | Mandate inclusion in all QAGs of notification timelines and escalation requirements for significant quality events, in alignment with ISO 13485 and FDA expectations. | ISO 13485:2016 §8.2.1, §8.3; 21 CFR 820.198  SOP-0023 Quality Agreements (QAGs) Lifecycle Management |
| No integration with postmarket surveillance or field actions where contract partners are involved. | **Moderate** | The SOP is silent on responsibilities related to postmarket obligations such as field safety corrective actions (FSCA), MDRs, or recall coordination. | Add requirement that QAGs specify roles in postmarket surveillance, complaint handling, and field actions, especially for distributed combination products. | 21 CFR 820.198; ISO 13485:2016 §8.2.1, §8.5.1 SOP-0023 Quality Agreements (QAGs) Lifecycle Management |
| Risk management requirements are not clearly incorporated into QAG language. | **Minor** | The SOP references SOP-0035 for risk but does not define how risk controls, risk communication, or mitigation responsibilities are assigned through the QAG. | Include template guidance or checklist requiring QAGs to define how risk analysis results are communicated and managed across parties, referencing ISO 14971. | ISO 14971:2019 §6.3, §8; ISO 13485:2016 §7.1  SOP-0023 Quality Agreements (QAGs) Lifecycle Management |
| Supplier refusal to sign QAG triggers risk assessment, but no escalation or decision authority is defined. | **Minor** | If a contract acceptor refuses to sign a QAG, Quality is to perform a risk assessment, but there's no defined decision pathway or escalation to leadership or QA. | Clarify escalation mechanism and required approver (e.g., Head of QA or QP) for proceeding with vendors who refuse QAG execution. | ISO 13485:2016 §4.1.5; ISO 14971:2019 §3.4  SOP-0023 Quality Agreements (QAGs) Lifecycle Management |

**Summary of Critical & Moderate Issues**

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| Severity | Area of Nonconformance | Regulatory Gap |
| Critical | No definition of CGMP role delineation between drug and device components in QAGs | 21 CFR Part 4.4(b)(1) |
| Moderate | Missing quality event communication requirements in agreements | 21 CFR 820.198, ISO 13485 §8.2.1 |
| Moderate | Lack of postmarket or field action responsibility assignment | ISO 13485 §8.5.1 |

**Minor Issues**

* Insufficient procedural integration of risk controls into QAG development.
* Lack of escalation criteria when a supplier refuses to sign a QAG.
* All items are traceable to applicable clauses and support audit readiness.

**Document Reviewed: SOP-0033: Supplier Auditing and Qualification**

The review of **SOP-0033: Supplier Auditing and Qualification** has been completed in alignment with:

* 21 CFR Part 820 (Quality System Regulation),
* ISO 13485:2016 (Medical Devices – Quality Management Systems),
* ISO 14971:2019 (Risk Management for Medical Devices), and
* 21 CFR Part 4 (CGMP requirements for combination products).

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| Issue Description | Severity Level | Original Excerpt | Recommended Revision |
| No explicit auditing requirement for dual CGMP compliance for combination product suppliers. | **Critical** | The SOP includes broad language on GxP supplier auditing but does not reference 21 CFR Part 4 or the need to evaluate suppliers against both drug and device CGMPs. | Incorporate a requirement that suppliers involved in combination products be audited against applicable parts of 21 CFR 210/211 and 820 in accordance with 21 CFR Part 4.4(b). |
| Risk-based approach to auditing lacks formal integration with ISO 14971 principles. | **Moderate** | Supplier audits are prioritized based on risk level but ISO 14971 risk control, verification, and residual risk are not referenced. | Explicitly link supplier audit prioritization to ISO 14971-compliant risk assessments for critical suppliers impacting product safety or performance. |
| Auditor qualifications are defined, but not linked to training on combination product regulations. | **Moderate** | Auditor qualification per SOP-0076 is cited but there is no mention of specific training in dual CGMPs or combination product regulatory requirements. | Require auditor training to include understanding of combination product CGMP expectations and ISO 14971 risk control verification. |
| No instruction for evaluating quality agreement content during audits. | **Minor** | Auditors are directed to review QAGs (Section 5.4.1.4) but not to assess whether they cover essential GMP/GCP responsibilities. | Instruct auditors to assess whether quality agreements reviewed during audit include clear delineation of complaint handling, change control, traceability, and GMP/GCP obligations. |
| Surveillance audit triggers do not include supplier's change in regulatory scope or combination product engagement. | **Moderate** | Audit frequency adjustments are linked to product phase, audit history, and performance, but not to expanded supplier responsibility for combination products or regulatory certification changes. | Revise audit frequency criteria to include triggers such as entry into combination product supply or change in regulatory oversight (e.g., loss of GMP certification). |

The resulting compliance findings have been displayed above and categorized by severity. Notable Critical and Moderate gaps pertain to:

* Omission of dual CGMP requirements for combination product suppliers.
* Lack of auditor competency in combination product regulations.
* Absence of integration with ISO 14971 for supplier-related risk controls.
* Weak link between supplier risk profiles and regulatory scope changes.

If you are reviewing supplier controls systemically, it is strongly recommended to re-examine:

* SOP-0019: *Supplier Lifecycle Management*
* SOP-0023: *Quality Agreements Lifecycle Management*

for alignment with these audit triggers and risk factors, especially those related to combination products, dual CGMP environments, and interface responsibilities defined under Part 4.

**Conclusion**

The current QMS framework at Kiniksa demonstrates partial compliance with key requirements of ISO 13485:2016, 21 CFR Part 820, and ISO 14971:2019. Several procedures reflect foundational elements of a compliant system; however, the system as a whole exhibits critical integration gaps, particularly where combination products and risk-based decision-making are concerned.

**Critical System-Wide Observations:**

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| Category | Issue | Regulatory Risk |
| Risk Management | Lack of documented Risk Management Plan, overall residual risk evaluation, and postmarket surveillance alignment | ISO 14971 Clauses 4–10 |
| Combination Products | Procedures do not delineate drug/device CGMP roles nor audit or qualify vendors under dual-CGMP models | 21 CFR Part 4.4(b)(1); FDA Combination Product Guidance |
| Change Management | Design-impacting changes do not consistently trigger design controls or RMF updates | 21 CFR 820.30(i); ISO 13485 §7.3.9 |
| CAPA | No trend analysis, weak preventive action triggers, and missing integration with risk files | 21 CFR 820.100(a)(1); ISO 13485 §8.4–8.5 |
| Design Control | No documented traceability to risk activities or validation of risk control effectiveness | ISO 14971 §7; 21 CFR 820.30(g) |

**Overall Compliance:**

**Partially Compliant** – Requires targeted procedural revisions and cross-functional integration to close high-risk compliance gaps and align with dual CGMP requirements for combination products.