Leucine

FDA 483 Insights Report

Capricor Inc., California, USA (May 2025)

This report reflects Leucine's analysis and is shared for informational context only; it is not prescriptive.

483 Risk Summary

Facility Name	Capricor Inc., California, USA
Inspection Date	27-30 May, 2025
Subsystems Impacted	Area Qualification, Deviations, CAPA, Supplier Quality Management, Complaint Management, Returned and Salvaged Drug Products, Facility Design
Site History	Earlier Received 483 in Jan 2001

Observation		Scope	Patient Severity	Risk of Escalation	Cost of Remediation
1	Inadequate qualification of [facility/equipment] under dynamic conditions	Facility/Equipment Qualification, Manufacturing Operations	🔴	🔴	🟠
2	Written procedures not followed (Deviations, CAPA, NCPs, CARs overdue; ALCOA+ documentation gaps)	QA/QC Systems, Batch Release, Data Integrity	🔴	🔴	🟠
3	Lack of quality agreements with critical facilities/vendors	Vendor/Contract Management, QA Oversight	🟠	🔴	🟠
4	Absence of complaint handling & returned product SOPs	Quality Systems, Market Complaints, Pharmacovigilance	🔴	🔴	🔴
5	Facility/equipment not maintained in a state of repair.	Facilities & Utilities, Production Environment	🔴	🔴	🔴

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Carl Perez's Profile 🔴

Inspections	483s	Recent 483s
5	5	Janssen Pharmaceuticals Inc. (Nov 2024) Lonza Netherlands B.V. (Jul 2024) Roslin Cell Therapies Limited (Aug 2023) Berkshire Sterile Manufacturing, Inc. (Jan 2023) Krystal Biotech, Inc. (Nov 2022)

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This section provides actionable insights into root cause and CAPA strategy, ensuring transparency, regulatory compliance, and continuous improvement.

Observation 1

Inadequate Qualification of Equipment under Dynamic Conditions

Issue Description		Root Cause	- CAPA Actions
1.1	Qualification activities were executed under static conditions only, without simulating dynamic manufacturing operations (personnel/material movement, equipment in use).	Qualification protocols lacked worst-case scenario design; inadequate QA oversight during protocol development and execution.	- Revise qualification and validation protocols to include dynamic operating conditions. - Perform requalification of cleanroom/equipment under simulated production load. - Train QA and Validation teams on regulatory expectations for equipment/facility qualification. -
1.2	Risk assessments did not adequately account for contamination pathways during routine operations.	Incomplete integration of risk assessment with facility qualification activities.	- Conduct risk assessment focusing on personnel/material flow in cleanroom operations. - Align qualification outcomes with the site contamination control strategy.
1.3	Actual production workflows were not reflected in qualification studies.	Limited collaboration between Production, Engineering, and QA during qualification planning.	- Incorporate production process mapping into qualification protocols.

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Observation 2

Deviations, CAPA, and Documentation Failures

Observation Description		Root Cause	CAPA Actions
2.1	Deviations (27 cases of missing analytical data) were not trended or analysed over two years.	No established deviation trending mechanism in QA; lack of periodic quality review.	- Implement an electronic deviation management system with trending dashboards. - Mandate periodic QA review of deviation trends for recurrence.
2.2	Nonconformance reports (NCPs) were not closed within defined timelines, with no approved extensions.	Inadequate enforcement of closure timelines by QA.	- Enforce SOP-defined closure timelines for NCPs. - Establish an escalation matrix for overdue NCPs.
2.3	Corrective Action Reports (CARs) were overdue without documented extensions.	CAPA system follow-up was weak, with no automated reminders.	- Introduce the CAPA tracking system with automated alerts. - Require QA approval and justification for any extension.
2.4	Batch record entries showed unverified corrections, violating ALCOA+ data integrity principles.	Inadequate training in Good Documentation Practices (GDP) and insufficient QA review.	- Retrain analysts and operators on GDP and ALCOA+ requirements. - Conduct periodic QA audits of laboratory and production records.

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Observation 3

Missing Quality Agreements with External Facilities

Observation Description		Root Cause	CAPA Actions
3.1	No quality agreements with contract laboratories and contract manufacturers performing critical GMP activities (testing, release, manufacturing).	The vendor qualification program did not include mandatory quality agreements.	- Draft and execute quality agreements covering GMP activities with all vendors. - Define roles, responsibilities, and compliance requirements clearly.
3.2	Test data for raw materials and intermediates from external labs lacked oversight.	Absence of SOP governing review and approval of outsourced analytical data.	- Create SOP for oversight of contract testing laboratories. - Mandate QA review of all third-party results before use.
3.3	Contract laboratories were not audited for compliance with cGMP.	Lack of a structured vendor audit program.	- Set up vendor qualification and audit process. - Close audit findings with documented CAPA.

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Observation 4

Absence of Complaint Handling and Returned Product SOPs

Observation Description		Root Cause	CAPA Actions
4.1	No written procedures for the receipt, evaluation, and investigation of product complaints.	Lack of a structured complaint handling framework in the quality system.	- Develop a complaint handling SOP aligned with 21 CFR 211.198. - Train QA staff on complaint intake, categorisation, and investigation.
4.2	Returned products were not evaluated or documented under a controlled SOP.	Absence of a defined procedure for the disposition of returned drug products.	- Implement SOP for handling, evaluation, and disposition of returned products. - Require QA authorisation before disposition decisions.
4.3	No mechanism to test complaints or returned samples for root cause analysis.	Disconnection between complaint management and the laboratory investigation process.	- Update the complaint SOP to require laboratory analysis of returned/complaint samples. - Maintain complete records of complaint sample testing. - .

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Observation 5

Facility and Equipment Not Maintained in GMP Condition

Observation Description		Root Cause	CAPA Actions
4.1	Damaged equipment and facility areas were observed within the ISO-classified manufacturing suite.	Preventive maintenance program not effectively implemented.	- Establish robust preventive maintenance schedules. - Repair/replace defective equipment on priority.
4.2	QA was not verifying the adequacy of maintenance and repairs.	Lack of QA involvement in facility/equipment maintenance oversight.	- Introduce a QA verification step in maintenance activities. - Maintain maintenance records with QA review and sign-off.
4.3	Manufacturing operations continued in areas not maintained in GMP conditions.	No escalation or decision-making framework to halt production.	- Establish an escalation procedure for critical facility/equipment deficiencies. - Stop production activities until the facility is restored to GMP compliance. -

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Production Logbook Integrate Production Logbooks	**FDA Tracker** Track 483/WL data	**Media Fill Simulation** Validate aseptic processing

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Audit Checklist to prepare for Carl Perez

This section provides insights into the investigator's focus area, along with the audit checklist to follow in case the investigator visits the site.

Focus Area		CAPA Priority	Evidence Required	Preventive Actions
1	**Deviations**	Ensure all deviations, OOS, and NCPs are initiated, investigated, and closed on time with proper justification; conduct trending and periodic QA reviews.	Deviation logs, OOS investigation reports, nonconformance records, reconciliation records, closure timelines, and QA trending reports.	Implement electronic tracking, train staff on timely deviation handling, and conduct regular QA trending reviews.
2	**Facility Design**	Maintain facility infrastructure in compliance with GMP through scheduled inspections, repairs, and area qualification aligned to current processes.	Facility inspection logs, maintenance schedules, area qualification protocols, engineering change records, and environmental monitoring reports.	Perform routine inspections, periodic requalification, and keep facility SOPs updated to GMP standards.
3	**Batch Records**	Strengthen batch record control by ensuring OOS justifications, GDP compliance, and timely QA review for approval/release.	Batch records, review checklists, OOS justifications, correction logs, GDP audit findings, and QA approval records.	Train staff on ALCOA+/GDP, review batch records regularly, and enforce stricter error correction controls.
4	**Supplier Quality Management**	Ensure robust supplier oversight with executed quality agreements, updated SOPs, and documented vendor audits.	Quality agreements, vendor qualification records, supplier audit reports, SOPs for supplier management, and CAPA reports from supplier audits.	Execute vendor quality agreements, audit suppliers regularly with CAPA tracking, and maintain an updated qualification database.
5	**CAPA**	Ensure CAPA actions are linked to deviation findings, evaluated for effectiveness, and closed within timelines defined in SOPs.	CAPA logs, closure records, extension justifications, effectiveness review reports, and feedback loop documentation.	Link CAPAs to deviations and trends, enforce closure timelines with escalation, and verify effectiveness before closure.

Get Inspection Ready against this 483

This section helps in staying audit-ready for this particular 483's observations, along with recommended evidence.

Observation 1

Inadequate Qualification of Equipment under Dynamic Conditions

Questions		YES	NO	N/A	Recommended Evidence
1.1	Has the qualification protocol fully demonstrated equipment performance under dynamic, worst-case operating conditions?	☐	☐	☐	Qualification protocols and reports (static + dynamic).
1.2	Were personnel and material flow patterns formally assessed and included in the qualification design?	☐	☐	☐	Cleanroom/area qualification data with personnel/material flow simulations.
1.3	Was a structured risk assessment performed to evaluate potential contamination during qualification?	☐	☐	☐	Risk assessment reports linked to qualification activities.
1.4	Do qualification outcomes reflect the actual production workflows and operating practices?	☐	☐	☐	Cross-functional review approvals (QA, Engineering, Production).

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Observation 2

Deviations, CAPA, and Documentation Failures

Questions		YES	NO	N/A	Recommended Evidence
2.1	Is there a trending system in place that enables proactive identification of recurring deviations?	☐	☐	☐	Deviation logs, trending reports, and QA review notes.
2.2	Are nonconformance reports consistently closed within approved timelines, with extensions documented and justified?	☐	☐	☐	NCP closure logs with extension approvals.
2.3	Is the CAPA system effective in ensuring the timely completion of CARs with documented extensions where applicable?	☐	☐	☐	CAPA/CAR tracker with closure timelines.
2.4	Do batch records consistently comply with ALCOA+ and GDP principles, particularly for corrections and amendments?	☐	☐	☐	Batch records with correction logs, QA sign-off, and GDP audit reports.

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Observation 3

Missing Quality Agreements with External Facilities

Questions		YES	NO	N/A	Recommended Evidence
3.1	Are quality agreements formally executed with all contract manufacturers and testing laboratories involved in GMP operations?	☐	☐	☐	Executed quality agreements/contracts.
3.2	Is there documented QA oversight to ensure that all external testing data is reviewed and approved before use?	☐	☐	☐	SOPs for supplier oversight and outsourced testing review.
3.3	Are supplier and contractor audits conducted periodically, with CAPAs tracked to closure?	☐	☐	☐	Vendor qualification files, audit reports, and CAPA closures.

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Observation 4

Absence of Complaint Handling and Returned Product SOPs

Questions		YES	NO	N/A	Recommended Evidence
4.1	Is there a robust and approved SOP governing complaint receipt, logging, evaluation, and investigation?	☐	☐	☐	Complaint handling SOP and complaint register.
4.2	Are product complaints consistently documented, investigated, and trended for recurring issues?	☐	☐	☐	Complaint investigation reports, CAPA records, and QA review notes.
4.3	Is there a controlled process for the evaluation and disposition of returned products?	☐	☐	☐	Returned product handling SOP, disposition records.
4.4	Are complaint and returned product samples tested under GMP conditions, with results integrated into investigations?	☐	☐	☐	Lab test reports linked to complaint/returned product investigations.

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Observation 5

Facility and Equipment Not Maintained in GMP Condition

Questions		YES	NO	N/A	Recommended Evidence
4.1	Is there a defined and enforced preventive maintenance program for cleanrooms, utilities, and critical equipment?	☐	☐	☐	Preventive maintenance schedules, logs, and service records.
4.2	Are facility inspections routinely documented, with deficiencies escalated and tracked to closure?	☐	☐	☐	Facility inspection reports with corrective actions.
4.3	Does QA provide independent oversight to verify that all maintenance and repairs are completed effectively?	☐	☐	☐	QA verification records of maintenance/repairs.
4.4	Is production halted whenever facility or equipment conditions fall outside GMP compliance requirements?	☐	☐	☐	Escalation SOPs require a production stoppage under non-compliance.

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