

CRL Risk Analysis – A Deeper Dive into FDA’s Newly Published Letters

22 July 2025



REDICA
Systems

Agenda

- Recent FDA Announcement – What's in the Release?
- Redica Analysis of CRL Events 2022-Present
- Identifying CRL Events and Linking to Pre-Approval Inspections
- Analytics on Inspections and 483s
 - Identify Top Inspectors
 - 483 Cluster Analysis
- CRL Risk Model
- Looking Ahead – What's on the Horizon for CRLs

Radical Transparency A Step in the Right Direction

"...first ever centralized database of past CRLs"

(But most were already published in the drug approval packets... if you knew where to look)

The screenshot shows a document viewer interface for Redica Systems. The document title is "FDA Embraces Radical Transparency by Publishing Complete Response Letters". The interface includes a search bar, navigation tabs (Dashboards, Search, Spaces, Redica AI, Feeds), and document controls (Download, Source Link). The document content is a news release dated July 10, 2025, titled "FDA Embraces Radical Transparency by Publishing Complete Response Letters". The text discusses the FDA's decision to publish more than 200 complete response letters (CRLs) between 2020 and 2024, marking a significant step in modernizing and increasing transparency. It notes that this allows the public greater insight into the FDA's decision-making and the common deficiencies cited to sponsors. The release also includes a quote from Commissioner Marty Makary, M.D., M.P.H., stating that drug developers and capital markets want predictability and that this step is closer to delivering it to them. The release concludes by stating that because the FDA has historically refrained from publishing CRLs, sponsors often misrepresent the rationale behind FDA's decisions, and that this new transparency is a step towards sharing critical information and preventing similar mistakes.

<https://app.redica.com/regulatory-intelligence/documents/RDR500001508/snapshot>

Why It Matters? ~15-20% chance of Getting a CRL due to GMP

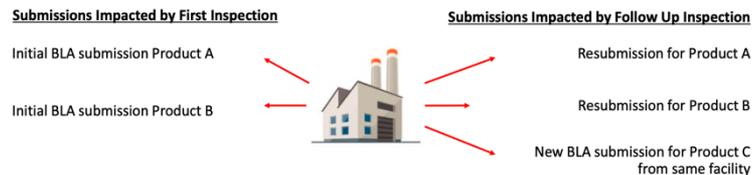
- *At least* 42% of applications lead to a Complete Response
- Over 1/3 of CRLs are due to GMP deficiencies
- Shared facilities (CMOs/CDMOs) are at elevated risk, a single site can impact multiple applications

NDA/ BLAs leading to CRLs

	2022	2023	2024	2025 (H1)
NDA / BLA PDUFAs	92	121	133	54
NDA / BLA CRLs	41 (45%)	60 (50%)	57 (43%)	11 (20%)
NDA / BLA GMP CRLs	18 (44%)	21 (35%)	16 (28%)	6 (55%)



Root causes of CRLs ¹



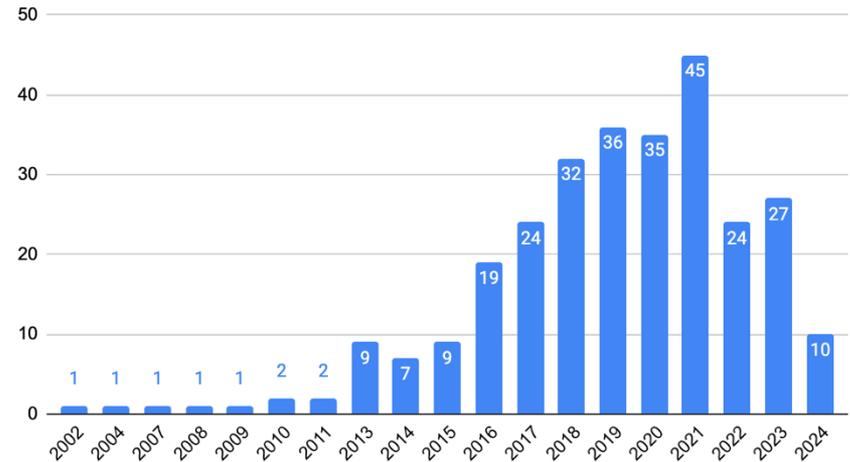
Source: Duke Margolis + FDA

¹Continual Improvement of CDER BLA Submission, Assessment, and Facility Readiness/Inspection: CMC for Biologics & Biosimilars

What's in the Central DB?

- 202 Total Files
- 286 Complete Response Letters
- 9 "Other" Letters
 - Tentative Approvals (2014, 2017, 2018, 2021)
 - Acknowledge Incomplete Response (2013)
 - Rescind Complete Response (2019)
 - Refusal to File (2012)
 - Provisional Determination (2024)
 - Corrected Provisional Determination (2024)

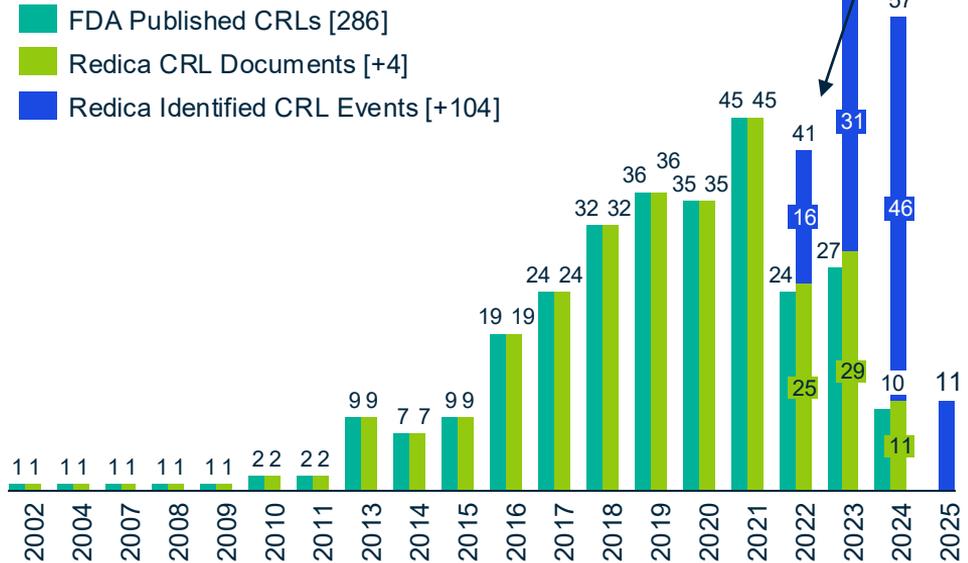
Complete Response Letters Published on openFDA, 2002-2024
CRLs



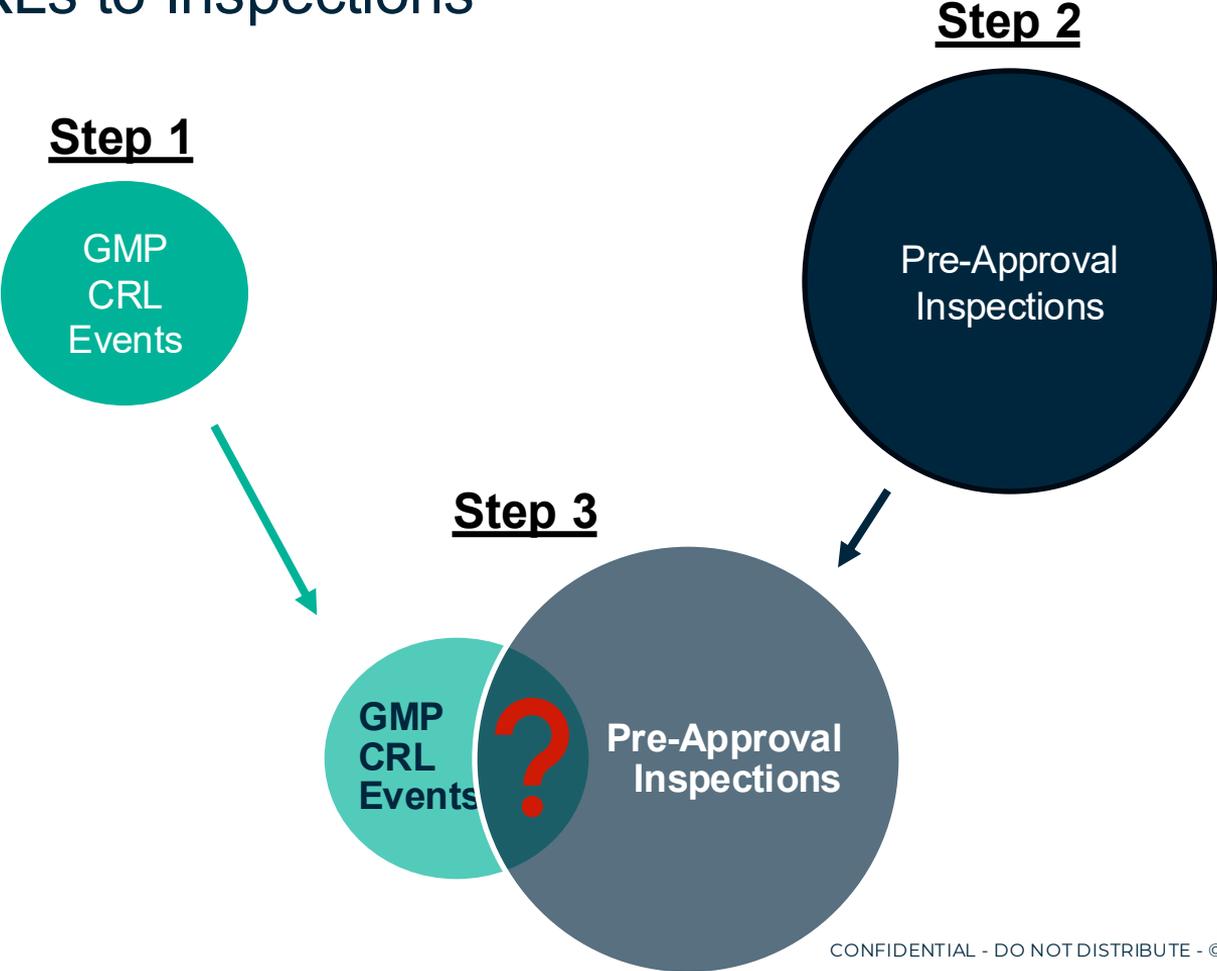
Redica Analysis Goes a Step Beyond (+108 events)

- Redica found 2(!) extra CRL documents in the latest FDA release
- Starting in 2022, Redica identified 169 CRL events from
 - Drug Approval Packages
 - Press Releases
 - Pink Sheet
 - FDA Release on openFDA

Redica CRL Database, 2002-2025
CRLs

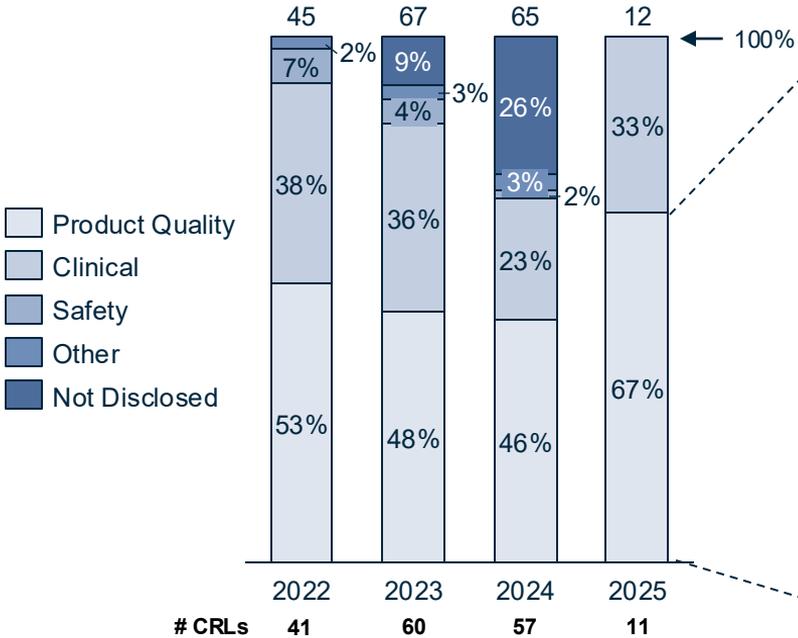


Linking CRLs to Inspections

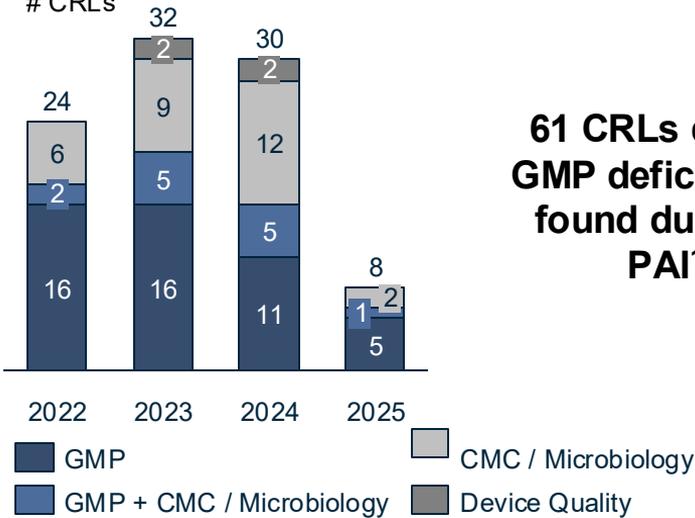


Step 1: Categorize CRLs – 61 GMP CRLs Identified

169 CRLs (189 CR Deficiencies), 2022-2025
% Deficiencies



94 Product Quality CRLs, 2022-2025
CRLs

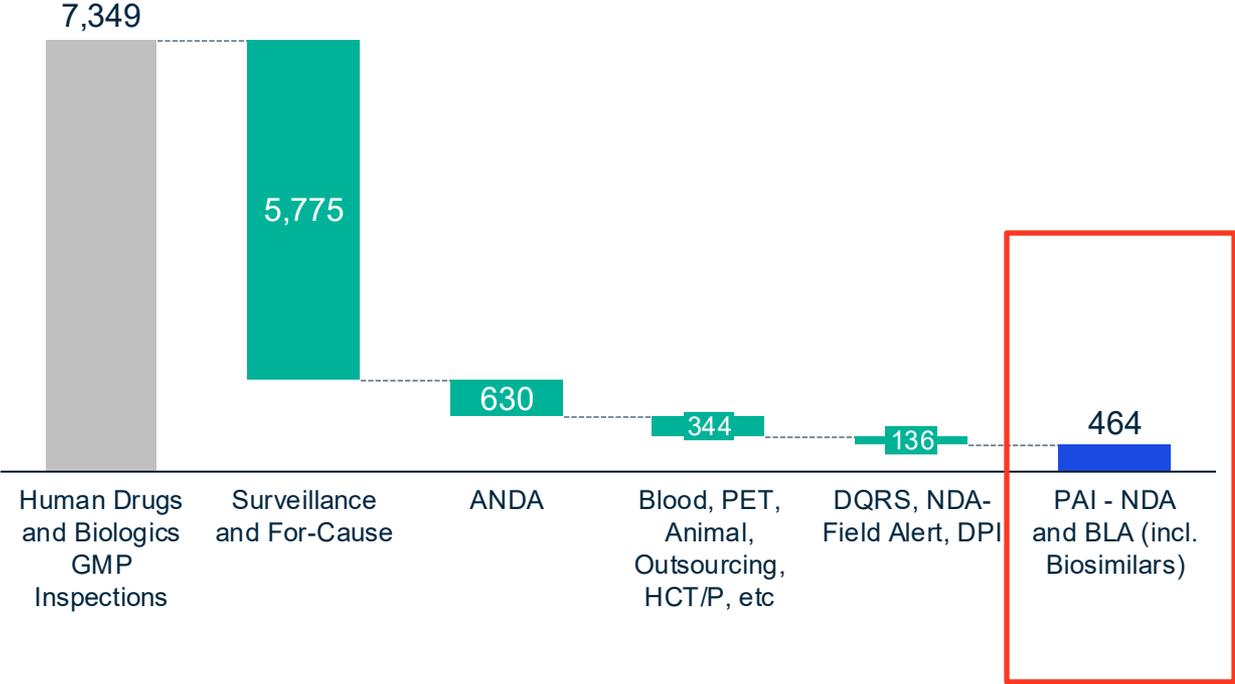


61 CRLs due to GMP deficiencies found during a PAI¹

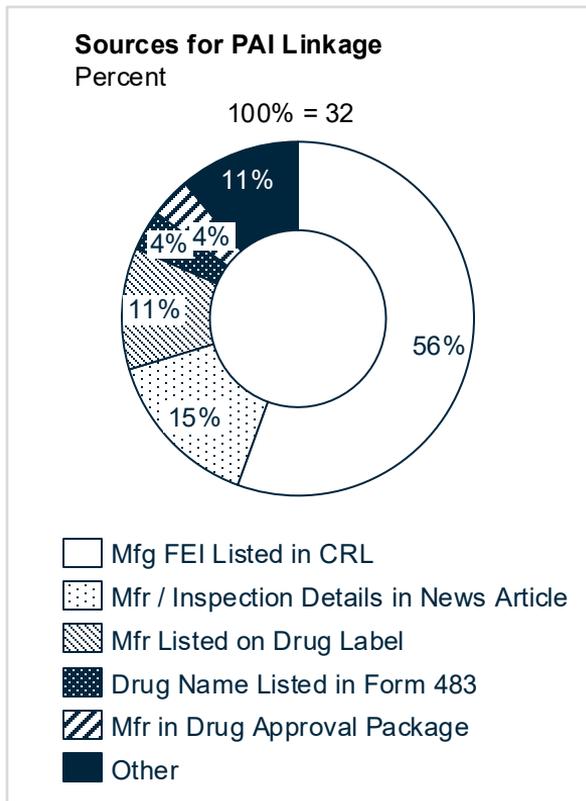
¹Three of the 61 GMP CRLs were issued because the FDA could not complete inspections as 'the facility was not ready for inspection.'

Step 2: 464 PAIs Identified That Could Be Linked to CRLs

FDA GMP Inspections Waterfall, 2022-Present
Inspections



Step 3: Link GMP CRLs to PAIs – 32 Matches Found



FACILITIES

Following inspections of Fresenius Kabi Austria GmbH, Graz, Austria (FEI: 3003708554) and application, FDA conveyed deficiencies to the representative of the facility. Satisfactory resolution.

FACILITY INSPECTIONS

1. Following pre-license inspection of CSL Behring GmbH, Emil-von-Behring-Strasse 76, Marburg, Hesse, Germany (FEI 3003098680), listed in this application, the FDA conveyed the deficiencies to the representative of the facility. The facility should the FDA office indicated on application. Your complete response to the FDA Form

Verrica Receives Complete Response Letter from the FDA for its NDA for VP-102 as a Direct Result of Deficiencies at General Reinspection of Sterling Pharmaceuticals Services, LLC

Pharm Country

Marketing Category	Application Number or Monograph Citations	Marketing Start Date	Marketing End Date
U.S.A.	81A93275		07/10/2024

Labeler = Fresenius Kabi USA, LLC (322547657)

Name	Address	ID/FEI	Business Operations
FRESIUS KABI AUSTRIA GMBH	SEIBENSTRASSE 76	3003708554	MANUFACTURING (322547657, 322547657)

Name	Address	ID/FEI	Business Operations
STERLING PHARMACEUTICALS SERVICES, LLC	43706368	322547657	MANUFACTURING (322547657, 322547657)

Form 483, 2023-11-10

US - FDA | Form 483 | Issuance Date: Nov 10, 2023 | Inspection Date: Nov 10, 2023

1 Keyword matches

[Redacted Drug Name]

Stability testing studies for [Redacted Drug Name] substance at the proposed stress conditions are not properly performed. Specifically, on November 10, 2023, the facilities and...

GMP Pre-Approval Inspections Linked to CRLs

Request for Data



<u>Site Display Name</u>	<u>Site Country</u>	<u>Inspection</u> <u>End Date</u>	<u>Inspection / Site Type</u>	<u>CRL Risk Factors*</u>	<u>483</u> <u>Available</u>
	Austria	11/12/24	Sponsor	3, 7, 10, 13	Y
	Switzerland	9/23/24	Sponsor	3, 7, 10, 12, 13	Y
	Germany	9/20/24	CMO/CDMO	1, 2, 3, 7, 10, 13	Y
	Italy	6/19/24	CMO/CDMO	2, 3, 6, 8, 11, 12, 13	Y
	Germany	4/30/24	Sponsor	3, 7, 10, 11, 12, 13	Y
	China	12/14/23	Sponsor	3, 7, 10, 11, 12, 13	Y
	United States	11/10/23	CMO/CDMO	1, 2, 3, 6, 7, 10, 11, 12, 13	Y
	India	10/12/23	Sponsor	3, 5, 10, 11, 12, 13	Y
	South Korea	9/1/23	CMO/CDMO, Biosimilar	2, 3, 4, 6, 7, 11, 12, 13	Y
	China	8/7/23	Sponsor	3, 7, 10, 11, 12, 13	Y
	United States	7/27/23	Sponsor	1, 3, 6, 7, 10, 11, 13	Y
	Spain	5/19/23	CMO/CDMO	1, 2, 3, 5, 11, 12, 13	Y
	United States	5/12/23	CMO/CDMO	1, 2, 3, 7, 10, 13	Y
	Italy	5/10/23	Sponsor	1, 3, 7, 10, 12, 13	Y
	Austria	3/28/23	CMO/CDMO, Biosimilar	2, 3, 7, 10, 13	Y
	Iceland	3/17/23	Biosimilar	1, 3, 7, 10, 11, 12, 13	Y
	South Korea	3/10/23	Sponsor	3, 7, 10, 12, 13	Y
	United States	2/9/23	CMO/CDMO	1, 2, 3, 8, 10, 11, 12, 13	Y
	United States	1/24/23	CMO/CDMO, Biosimilar	1, 2, 3, 5, 6, 7, 13	Y
	United States	11/14/22	CMO/CDMO	1, 2, 3, 4, 6, 8, 11, 12, 13	Y
	United States	11/14/22	CMO/CDMO	1, 2, 3, 6, 8, 13	Y
	United States	10/21/22	Sponsor	3, 6, 7, 10, 12, 13	Y
	Belgium	8/19/22	CMO/CDMO	1, 2, 3, 4, 11, 12, 13	Y
	Malaysia	8/30/22	Biosimilar	1, 3, 6, 7, 10, 11, 12, 13	Y
	India	8/26/22	Biosimilar	3, 7, 10, 11, 12, 13	Y
	India	8/26/22	Biosimilar	1, 3, 4, 5, 6, 7, 11, 12, 13	Y
	Spain	6/29/22	CMO/CDMO	1, 2, 3, 5, 7, 13	Y
	Spain	6/27/22	CMO/CDMO	1, 2, 3, 5, 7, 13	Y
	Spain	6/20/22	CMO/CDMO	2, 3, 5, 7, 12, 13	Y
	Iceland	3/17/22	Biosimilar	1, 3, 5, 8, 11, 12, 13	Y
	United States	2/18/22	CMO/CDMO	1, 2, 3, 4, 9, 12, 13	Y
	Belgium	2/4/22	Sponsor	3, 7, 13	Y

*** CRL RISK FACTORS**

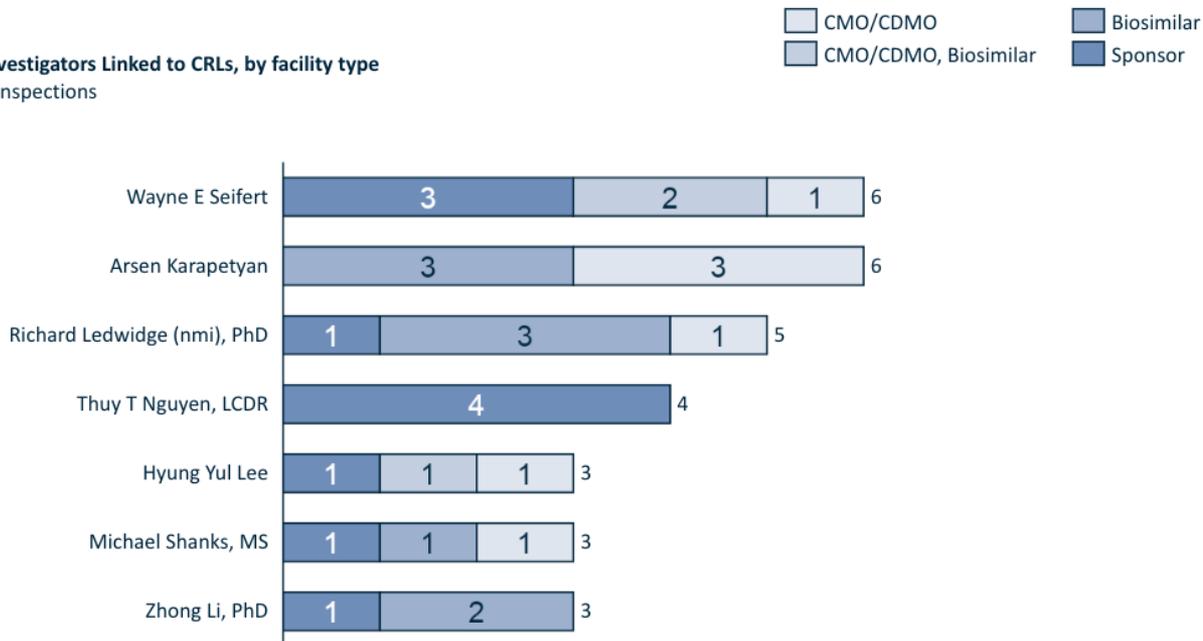
1. Redica Site Score - Poor / Very Poor
2. Facility Type - CMO / CDMO
3. Inspection - NDA / BLA
4. Inspection - Parenteral
5. Inspection - For-Cause
6. Inspection - > 3 Investigators
7. Investigator has been linked to > 2 CRLs
8. Investigator has been linked to > 1 CRL
9. Inspection Outcome - WL / OAI
10. OPMA Issuing Office
11. 483 had > 5 Observations
12. 483 had Critical / Major Obs > 2
13. 483 Issued
14. 483 Not Available (delayed)

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Who Were the Inspectors Associated with CRLs?

Investigators Linked to CRLs, by facility type
inspections



483 Obs Cluster Analysis

ROVI PHARMA INDUSTRIAL SERVICES S.A. [San Sebastián De Los Reyes / Spain]

NOTICE This is the primary document within the cluster. There is 1 duplicate: 703dd987-064e-4b23-b969-4754f028285c

Field Review Section Review **Enriched Data Review**

Search keyword > - 150 % + 1 / 6

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER 12420 Parklawn Drive, Room 2032 Rockville, MD 20857	DATE(S) OF INSPECTION 6/6/2022-6/20/2022*
IDENTIFICATION NUMBER 3016688535	
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED Guillermo Paraja Arrechea, Site Director	
FIRM NAME Rovi Pharma Industrial Services S.A.	STREET ADDRESS Paseo De Europa 50
CITY, STATE, ZIP CODE, COUNTRY San Sebastian De Los Reyes, Madrid, 28703 Spain	TYPE ESTABLISHMENT INSPECTED Sterile Drug Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:
OBSERVATION 1
Written records are not always made of investigations into the failure of a batch or any of its components to meet specifications.
Specifically,
A. A significant number Out-of-Specification (OOS) and Out-of-Trend (OOT) investigations were not initiated and investigated by your firm's Quality Unit (QC and QA) involving microbiological test items for bioburden, endotoxins, total aerobic carbon (TOC), and conductivity for the (b)(4) for annual years 2021 and 2022 (January - March): Per the firm's deviation investigation provided during the inspection, for annual year 2021, approximately 137 laboratory test results were over the action limit, which should have been reported as OOS results, and 35 test results were over the alert limit, which should have been reported as OOT results. Similarly, from January 2022 to March 2022,

Document AI Summary

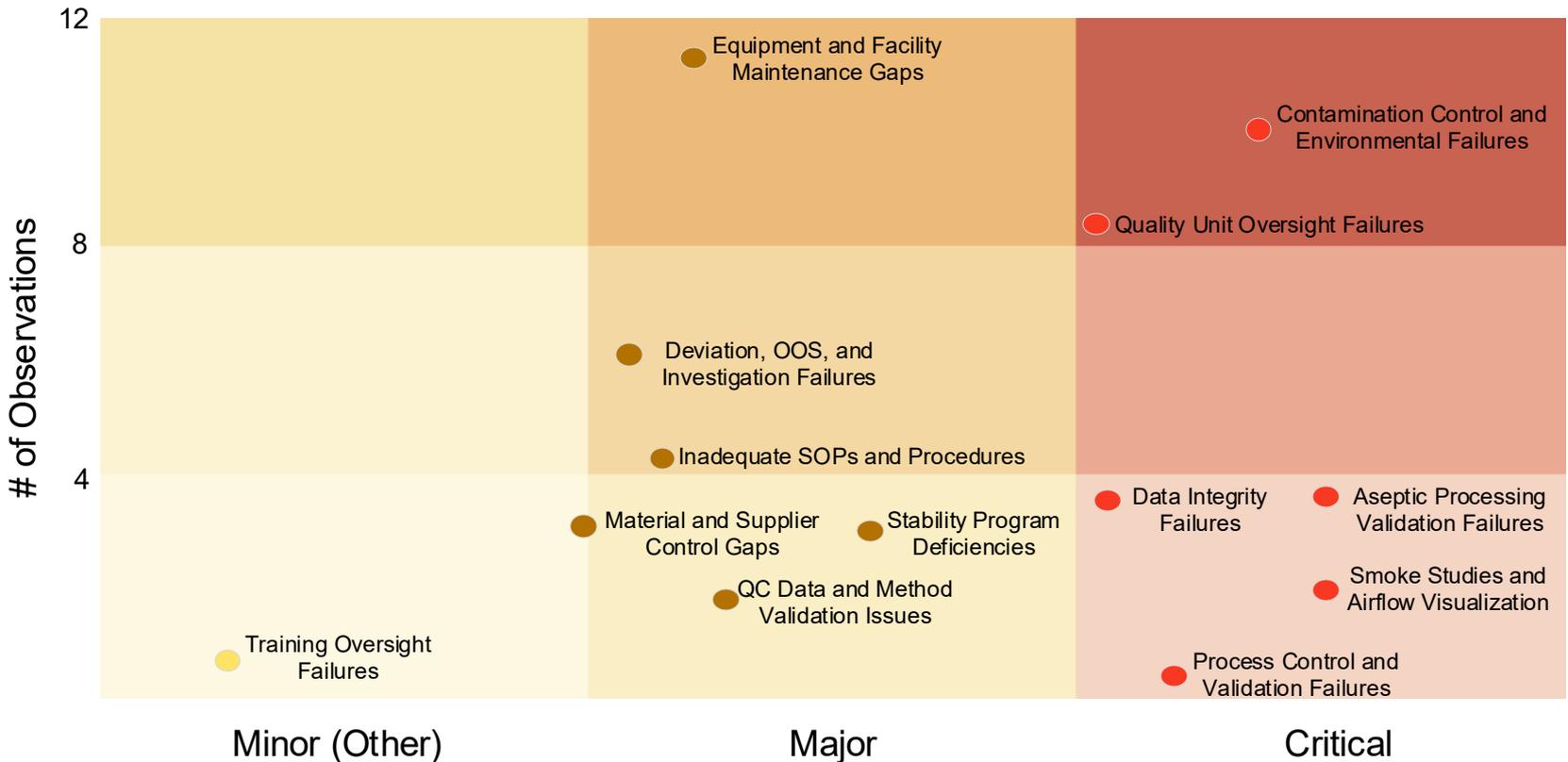
AI Summary

This is a 483 document for Rovi Pharma Industrial Services S.A. issued on 2022-06-20, following an inspection that began on 2022-06-06, with four observations: A significant number of OOS and OOT investigations involving microbiological test items were not initiated or investigated by the firm's Quality Unit. Procedures designed to prevent microbiological contamination of sterile drug products were not always followed, including inadequate documentation of interventions during filling processes... [Show more](#)

Total Observation Count - 4 8 / 8 columns

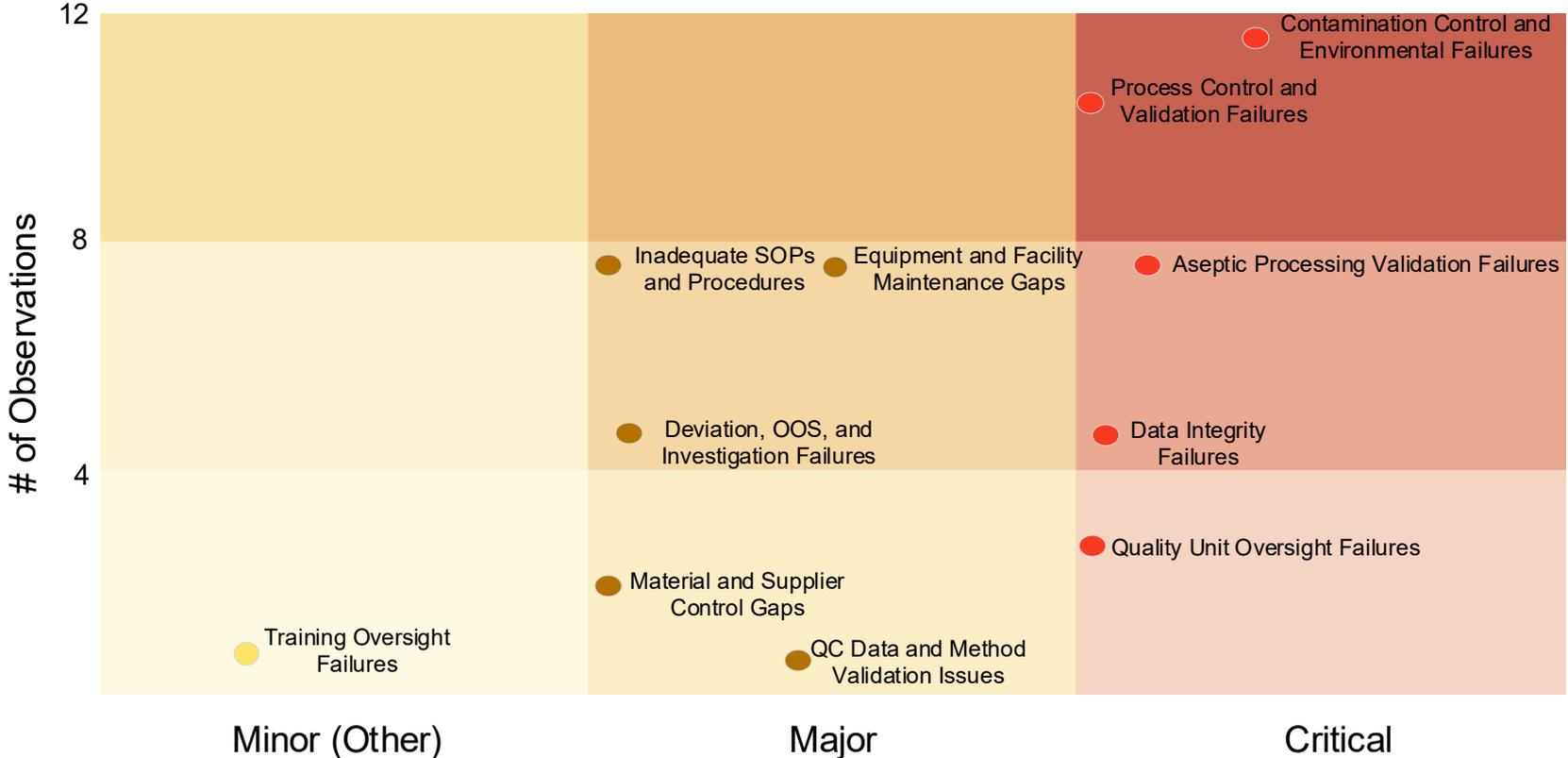
Obs #	Raw Observation Text	Human Retyped Observation Text	AI Summary	HD-GMP Area	HD-GMP L1	Data Integrity Label(s)	Search Index
1	OBSERVATION 1 Written records are not always made of investigations into the failure of a batch or any of its components to meet specifications. Specifically, A. A significant number of Out-of-Specification (OOS) and Out-Of-Trend(OOT) investigations were not initiated and investigated by your firm's Quality unit (QC and QA) involving microbiological test items for bioburden, endotoxins, total aerobic carbon (TOC) and conductivity for the (b)(4) for annual years 2021 and 2022 (January - M... Show more	OBSERVATION 1 Written records are not always made of investigations into the failure of a batch or any of its components to meet specifications. Specifically, A. A significant number of Out-of-Specification (OOS) and Out-Of-Trend(OOT) investigations were not initiated and investigated by your firm's Quality unit (QC and QA) involving microbiological test items for bioburden, endotoxins, total aerobic carbon (TOC) and conductivity for the (b)(4) for annual years 2021 and 2022 (January - M... Show more	The firm failed to investigate a significant number of OOS/OOT results for microbiological tests, including bioburden, endotoxins, TOC, and conductivity, from 2021 to March 2022. For 2021, approximately 137 laboratory test results exceeded action limits and 35 exceeded alert limits, but were not appropriately investigated. Procedures for endotoxin and conductivity OOS investigations were also not scientifically sound.	Quality Unit	Reviews and Approvals		Quality Unit > Reviews and Approvals > Analytical Testing > Production > Sterile Environment, Laboratory > Deviation Investigations, Laboratory > CAPA
	OBSERVATION 2 Procedures designed to prevent microbiological	OBSERVATION 2 Procedures designed to prevent microbiological					Production > Sterile Products, Production and

CMO Inspections



Redica AI (Beta) was used to analyze **14 CMO Form 483s** associated with CRLs, including **62 observations**. The analysis included topic labeling, clustering, summarization, risk ranking, and comparative insights.

Sponsor Inspections



Redica AI (Beta) was used to analyze **11 Sponsor Form 483s** associated with CRLs, including **66 observations**. The analysis included topic labeling, clustering, summarization, risk ranking, and comparative insights.

Differences Between CMOs and Sponsors



CMOs

- Equipment and Facility Maintenance Gaps
- Quality Unit Oversight Failures
- Smoke Studies and Airflow Visualization



Sponsors

- Process Control and Validation Failures
- Aseptic Processing Validation Failures
- Inadequate SOPs and Procedures

~ Same

- Contamination Control and Environmental Failures
- Data Integrity Failures
- Training Oversight Failures
- Deviation, OOS, and Investigation Failures
- Material and Supplier Control Gaps
- QC Data and Method Validation

483 Content Analysis for CMOs – 14 inspections, 62 Observations with linked CRLs (1/3)*

Contamination Control and Environmental Failures

Failures to prevent, detect, or control microbial and particulate contamination through proper aseptic technique, sanitization, or environmental monitoring in sterile drug production areas.

- **Inadequate environmental and equipment monitoring** during aseptic operations, including missed non-viable particle counts, unsanitized RABS curtains, and unmonitored high-risk areas.^{3,10}
- **Operator interventions were poorly simulated and documented** in media fills, with limited personnel involved, unqualified operators, and no worst-case scenarios tested.^{4,5}
- **Aseptic practices compromised unidirectional airflow**, with blocked first air, non-sanitized equipment transfers, and contact with non-sterile surfaces during critical operations.^{10,12}
- **Storage and disinfectant practices failed to control bioburden**, including outdated cardboard in aseptic areas and inadequate contact times in disinfectant studies.¹⁰
- **Sterility assurance was compromised by glove breaches, unvalidated sterilization processes, and missing environmental monitoring coverage**, even as affected batches were released.^{11,12}

Quality Unit Oversight Failures

Failures by the Quality Unit to implement, document, or enforce controls over product review, deviation handling, facility oversight, or data verification.

- **Deviation handling and CAPA execution were ineffective or delayed**, with missed maintenance follow-ups, uninvestigated environmental deviations, unresolved non-conformances, and ineffective corrective actions.^{2,7,10}
- **Written and procedural gaps weakened quality oversight**, including reliance on external certificates, failure to assess contract manufacturer data, omitted assessments of objectionable conditions, and incomplete audit coverage (e.g., audits not addressing device regulations for combination products).^{1,4,5}
- **Oversight during aseptic and analytical operations was inadequate**, as shown by unvalidated equipment use, poor gowning deviation follow-up, missed microbial monitoring, and insufficient visual inspection controls.^{3,11}
- **Facility and lab oversight were weak**, with no trending of pest control data and use of unqualified chemical storage areas, risking environmental control failures.¹⁴

Aseptic Processing Validation Failures

Failures in establishing, executing, or maintaining validated aseptic processes that reliably prevent contamination and ensure consistent product quality under routine conditions.

- **Media fill simulations were unrepresentative or incomplete**, lacking documentation of filled units, incubation, or coverage of routine production conditions—undermining sterility assurance.^{3,9}
- **Validation studies did not account for major system or process changes**, such as HVAC or HEPA replacements, and failed to consider variability introduced by atypical fill volumes or speeds.¹
- **Procedures for aseptic validation were not followed or lacked controls**, including missing video evidence, poor equipment transitions, inadequate fingertip and container integrity monitoring, and improper calibration.^{7,9}

Data Integrity Failures

Failures to protect, verify, and restrict access to critical electronic and raw data, compromising its accuracy, completeness, and reliability for GMP data.

- **No review or verification of electronic raw data** from QC instruments; printed reports are relied upon instead of audit trails.¹
- **Backups of analytical instrument data are unverified**, lacking confirmation of completeness or restorability.¹
- **Insufficient system access controls allowed unauthorized changes or deletions** of lab data used for in-process and release testing.¹⁰
- **Data integrity controls were missing in the MSAT lab**, including shared passwords, lack of data backups, and absence of third-party assessments to ensure reliability of application testing results.⁷

Smoke Studies and Airflow Visualization

Deficiencies in performing or documenting airflow visualization (smoke) studies to confirm unidirectional airflow and contamination control in aseptic processing areas.

- **Smoke studies failed to demonstrate adequate airflow** from HEPA filters to critical Grade A zones and did not confirm proper air velocity or direction across work surfaces.¹
- **Airflow visualization was incomplete or missing for required interventions**, and documentation lacked clarity on inspection frequency and hold time controls for open vials and surfaces.⁷

* Leverages Redica 483s, labeling, and proprietary AI analytics model (Beta)

483 Content Analysis for CMOs – 14 inspections, 62 Observations with linked CRLs (2/3)*

Process Control and Validation



Failures to implement or comply with production process controls necessary to maintain consistent product quality and adherence to validated procedures.

- **Production controls were not followed**, including improper sanitization, misclassification of material movement areas, poor equipment handling, and failure to document aseptic non-conformances.¹³

Equipment and Facility Maintenance Gaps



Failures in the proper design, qualification, cleaning, maintenance, or revalidation of equipment and facilities, compromising their suitability

- **Equipment was poorly designed or inadequately qualified**, with deviations in PQ, missing scientific justification, or workarounds used in place of proper repairs.^{1,2,4,5}
- **Cleaning and revalidation practices were deficient**, including missed revalidation intervals, unscientific equipment use, and missing bioburden verification in cleaning reports.^{6,7,13}
- **Facility and equipment maintenance was visibly inadequate**, with dislodged fixtures, degraded components, rust, missing seals, and contamination-prone surfaces observed.^{7,13,14}
- **Preventive maintenance was overdue or not enforced**, with missed PM deadlines and failure to assess contamination risk in unkept areas.^{8,9}

Deviation, OOS, and Investigation Failures



Failures to adequately investigate deviations, OOS/OOT results, or process failures, including lack of root cause analysis, incomplete follow-up, or ineffective CAPAs.

- **Deviation and batch failure investigations lacked root cause analysis, follow-up, or product disposition decisions**, risking recurrence and CGMP non-compliance.^{1,3,4}
- **OOS/OOT test results for critical quality attributes were not properly investigated**, and associated procedures for endotoxin and conductivity testing lacked scientific justification.⁵
- **CAPAs failed to correct repeat deviations** like mold and water leaks, and new SOPs were not implemented in subordinate procedures to improve effectiveness.⁸
- **Final reports for process qualification batches overstated control**, despite multiple lots exceeding defect limits and requiring amendments and CAPAs.¹²

Inadequate SOPs and Procedures



Failures to establish, document, or follow standard operating procedures (SOPs) and GMP instructions

- **SOPs were missing, poorly defined, or not followed**, affecting areas such as change control, pest control, preventive maintenance, calibration, and GMP walkthroughs.^{8,14}
- **Inspection and transfer procedures lacked defined criteria**, including unclear stopper sterilization validation and vague SOPs for product transfer line inspection.⁹
- **Visual inspection protocols lacked specificity**, including undefined movement parameters, unqualified inspectors, and kits that did not represent relevant defect types.¹¹
- **No procedures were in place to establish and maintain a Design History File (DHF)** for combination product components, reflecting gaps in document control for design and specification management.¹

Stability Program Deficiencies



Deficiencies in the design, execution, or control of stability programs, including improper storage conditions, inadequate stress testing, or insufficient analytical methods.

- **Stability storage conditions were not qualified or maintained**, including unverified temperature distribution in stability cages and humidity deviations without change control.^{6,8}
- **Test methods used in stability studies were unreliable**, with impurity assays lacking sensitivity to detect degradation products during stress testing.¹¹

* Leverages Redica 483s, labeling, and proprietary AI analytics model (Beta)

483 Content Analysis for CMOs – 14 inspections, 62 Observations with linked CRLs (3/3)*

Material and Supplier Control Gaps

Gaps in the control, qualification, labeling, or verification of incoming materials and supplier-provided data, affecting material traceability

- **Supplier controls were weak**, as the firm relied on certificates of analysis without verifying results (e.g., microbiological testing), and failed to enforce material specifications through procedures, purchase orders, or QC inspections.^{1,6}
- **Labeling and storage conditions for raw materials were inadequate**, including unlabeled materials and missing environmental controls (e.g., temperature), compromising material traceability and CGMP compliance.⁸

QC Data and Method Validation

Deficiencies in laboratory test methods, standards, or procedures that compromise the ability to validate, verify, and ensure the reliability of QC data for product release or in-process control.

- **In-process testing lacked hold time standards**, as SOPs did not define scientifically sound parameters for endotoxin testing, violating basic laboratory control expectations.¹⁰
- **Critical QC test methods and controls were unvalidated**, including environmental monitoring and bioburden tests, microbial plate review procedures, and visible particulate matter determination.¹¹

Training Oversight Failures

Failures to maintain timely, accurate, and complete training records or to integrate critical procedures into the training program, undermining staff readiness

- **Employee training was overdue or incomplete**, with misaligned training schedules, late completion of required modules, and delays in implementing SOPs into the training system.⁸

Footnote Key

- 1.
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- 14.

Request for Data



* Leverages Redica 483s, labeling, and proprietary AI analytics model (Beta)

483 Content Analysis for Sponsors – 11 inspections, 66 Observations with linked CRLs (1/3)*

Contamination Control and Environmental Failures

Failures to prevent, detect, or control microbial and particulate contamination through proper aseptic technique, sanitization, or environmental monitoring in sterile drug production areas.

- **Disinfection programs and cleaning validation were scientifically unsound**, lacking sporicidal coverage, validated methods, or swab sampling of product-contact surfaces. Some procedures failed to control specific organisms, and certain agents were not proven effective for critical areas.^{2,3,6,9,10}
- **Poor aseptic practices during setup and filling**, including use of non-sterile gloves, uncovered stopper bowls, unprotected critical parts, and improperly handled sterile parts.^{5,7}
- **Post-run and routine monitoring were inconsistent or missing**, including insufficient sampling contact times, skipped glove and surface monitoring, and lack of monitoring during critical operations. Environmental monitoring procedures missed critical locations or organisms and had poorly executed glove monitoring steps.^{3,4,7,10}
- **Facility mold control, microbial testing, and viral contamination prevention were inadequate**, with 696 mold recoveries going unaddressed, lack of bioburden/endotoxin testing during storage, and no adventitious virus testing for shared equipment batches.⁹

Process Control and Validation

Failures to implement or comply with production process controls necessary to maintain consistent product quality and adherence to validated procedures.

- **Critical process controls and validation steps were missing or ineffective**, including inadequate hold time assessment, poor filling line practices, and uncontrolled parameters like pressure and droplet formation.^{1,9}
- **Sterilization validation studies lacked scientific justification**, with poor bioindicator placement/incubation and failure to demonstrate sterility of medical devices or product-contact components.^{6,9}
- **Container closure and product control strategies were flawed**, including unrepresentative sample sizes for closure integrity testing and risky practices like adding excipients before endotoxin test clearance.^{5,6}
- **Manufacturing processes lacked consistency and traceability**, with high termination/rejection rates, unresolved deviations, and approval of batches following questionable investigational requalifications.^{9,10}
- **Commercial validation and documentation were incomplete**, with no full-scale validation of labeling/packaging, an exhausted cell bank in use, and undocumented rework activities contradicting formal procedures.¹¹

Aseptic Processing Validation Failures

Failures in establishing, executing, or maintaining validated aseptic processes that reliably prevent contamination and ensure consistent product quality under routine conditions.

- **Operators routinely violated aseptic technique**, including handling sterile components with unsterile tools, blocking first air, and failing to sanitize gloves before aseptic connections.^{2,3,11}
- **Environmental and personnel monitoring practices were inadequate**, with examples of improper glove sanitization timing, absence of anaerobic monitoring, and insufficient surface sampling.^{2,3}
- **Intervention controls and fill line setup lacked aseptic safeguards**, including high-risk interventions performed without proper decontamination and poor equipment design requiring potentially contaminating actions.^{5,6}
- **Aseptic process design and simulations were inadequate**, such as transporting sterilized bulk drug product without terminal sterilization, relying on insensitive integrity tests, and using non-evaluated media simulations.¹⁰

Data Integrity Failures

Failures to protect, verify, and restrict access to critical electronic and raw data, compromising its accuracy, completeness, and reliability for GMP data.

- **Lack of audit trails and user access controls compromised electronic records**, including elevated privileges for QC staff, absence of unique user IDs, and no review of audit trails, allowing undetected data modification.^{4,11}
- **Procedural and spreadsheet controls were insufficient**, with uncontrolled templates lacking password protection or audit trails, deleted original entries, and no second-person verification.^{3,5}
- **Instruments and data acquisition systems lacked compliance controls**, including disabled pH meter user settings, no raw data capture, and missing reproducibility instructions for manual integrations.⁵

Quality Unit Oversight Failures

Failures by the Quality Unit to implement, document, or enforce controls over product review, deviation handling, facility oversight, or data verification.

- **Oversight of critical system validations and process control was inadequate**, with unvalidated data acquisition systems, unresolved software bugs, and poor monitoring of cleaning effectiveness and in-process control results.³
- **The quality unit failed to enforce proper release procedures**, allowing unreleased drug substances to be used in manufacturing prior to full QC review.⁵
- **GMP abnormalities and batch deviations were not adequately documented or assessed**, including unaddressed material color changes and missing hold time documentation in batch records.⁹

* Leverages Redica 483s, labeling, and proprietary AI analytics model (Beta)

483 Content Analysis for Sponsors – 11 inspections, 66 Observations with linked CRLs (2/3)*

Equipment and Facility Maintenance Gaps

Failures in the proper design, qualification, cleaning, maintenance, or revalidation of equipment and facilities, compromising their suitability

- **Maintenance programs failed to address deterioration and contamination risks**, including widespread discoloration on equipment, rouging, cracked RABS enclosures, and unsealed utility lines lacking back-siphonage protection.^{1,4,7,8}
- **Cleaning validation and verification were incomplete**, with missing swab samples from hard-to-clean areas and no precision studies to assess cleaning consistency across operators.¹¹
- **Facility and utility systems were poorly maintained or unqualified**, including unsealed wall-ceiling junctions, unqualified water systems, and lack of validation for point-of-use distribution lines.^{1,8}

Inadequate SOPs and Procedures

Failures to establish, document, or follow standard operating procedures (SOPs) and GMP instructions

- **Visual inspection procedures were poorly defined, inconsistently implemented, and inadequately supported by training**, affecting batch release decisions. SOPs lacked criteria for particle types and visible defect acceptance (e.g., size, color, shape); inspectors were not provided with representative training kits; and inspection times were insufficient.^{1,4,5,7,10}
- **SOPs failed to define inspection and rejection criteria for incoming materials**, allowing use of visibly dirty or poor-quality containers without documentation or rejection requirements.⁴
- **Aseptic setup and sterilization procedures lacked adequate control**, including insufficient guidance on stoppering assembly, sterile holder installation, and validation of sterilization processes.⁹
- **Alarm management procedures were vague and non-actionable**, failing to define time limits or responses for process deviations once alert or action levels were breached.¹¹

Deviation, OOS, and Investigation Failures

Failures to adequately investigate deviations, OOS/OOT results, or process failures, including lack of root cause analysis, incomplete follow-up, or ineffective CAPAs.

- **Investigations into discrepancies and OOS events lacked thorough root cause analysis and justification for retesting**, with repeat tests initiated without scientific basis or conclusive investigation.^{4,11}
- **Visual defect investigations were unresolved despite recurring issues**, including extrinsic fibers and particles in drug product vials. Corrective actions were ineffective, and associated sterility assurance concerns remained unaddressed.⁹
- **Deviation records lacked impact assessments and quality linkage**, with abnormal conditions and equipment failures documented without evaluating potential effects on product quality.⁵
- **Deviation tracking was inconsistent and overdue**, with major deviations missing closure plans, timelines, or reassessments. Nearly two-thirds of major deviations were unresolved for multiple years.¹⁰

Material and Supplier Control Gaps

Gaps in the control, qualification, labeling, or verification of incoming materials and supplier-provided data, affecting material traceability

- **Raw material controls were insufficient to prevent market-specific mix-ups**, resulting in use of a Chinese-market-only material in a US-bound batch. The ERP system lacked functionality to restrict or flag inappropriate usage.⁵
- **Product-contact equipment shared between US and Chinese batches posed cross-contamination risks**, as adventitious agent testing used non-equivalent methods (Chinese Pharmacopeia vs. USP), and cell banks and drug substances were released without proper control.¹¹

QC Data and Method Validation

Deficiencies in laboratory test methods, standards, or procedures that compromise the ability to validate, verify, and ensure the reliability of QC data for product release or in-process control.

- **Recurrent sample and inventory control failures impacted QC reliability**, including missing reference standards, assay controls, stability and release samples, and improper disposal. Discrepancies in LIMS records and failure to execute change-controlled transactions further disrupted sample traceability.⁴

* Leverages Redica 483s, labeling, and proprietary AI analytics model (Beta)

483 Content Analysis for **Sponsors** – 11 inspections, 66 Observations with linked CRLs (3/3)*

Training Oversight Failures



Failures to maintain timely, accurate, and complete training records or to integrate critical procedures into the training program, undermining staff readiness

- **GMP training was incomplete or missing for dozens of personnel**, including a case where an analyst conducted 15 assays without required training (TR# 40525237), along with 40 other missed training completions prior to GMP activity.⁴

Footnote Key

- 1.
- 2.
- 3.
- 4.
- 5.
- 6.
- 7.
- 8.
- 9.
- 10
- 11

Request for Data



* Leverages Redica 483s, labeling, and proprietary AI analytics model (Beta)

Agenda

- Recent FDA Announcement – What's in the Release?
- Redica Analysis of CRL Events 2022-Present
- Identifying CRL Events and Linking to Pre-Approval Inspections
- Analytics on Inspections and 483s
 - Identify Top Inspectors
 - 483 Cluster Analysis
- **CRL Risk Model**
- Looking Ahead – What's on the Horizon for CRLs

CRL Risk Model

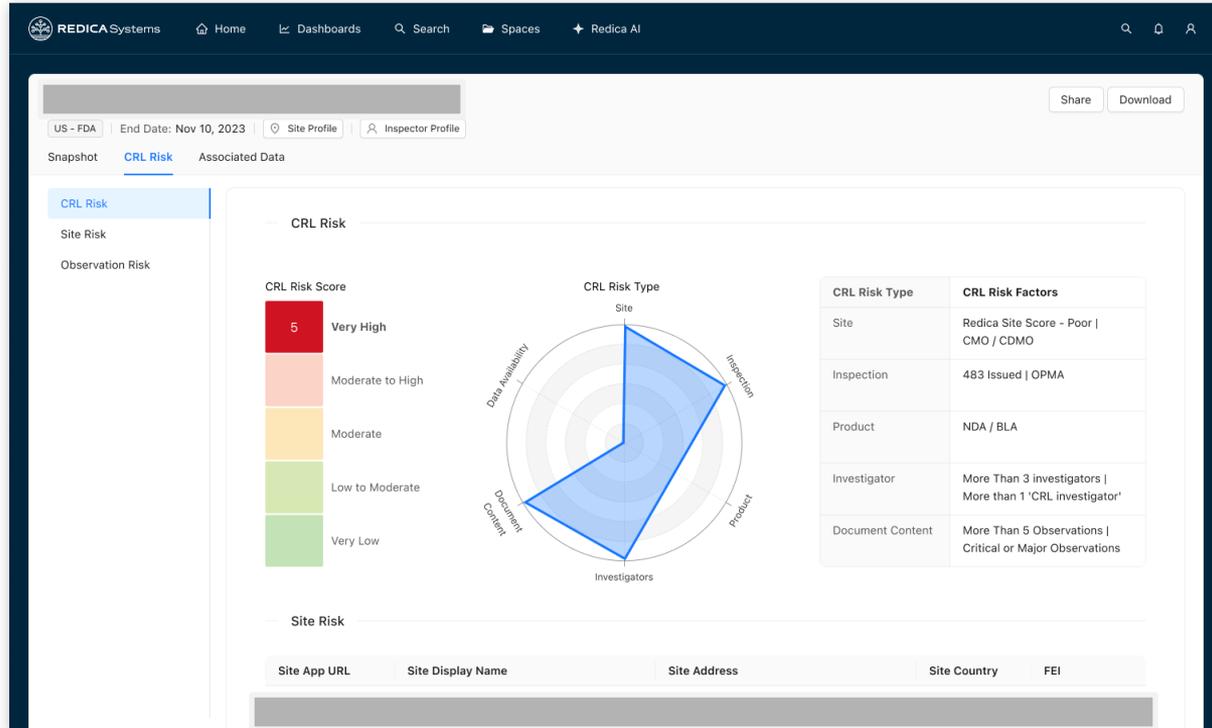
The CRL risk model is a multifactorial system that assigns risk weights to various inspection and 483 document parameters, helping to identify inspections with a higher likelihood of resulting in a CRL.

CRL risk analytics can be integrated into the Redica Platform on PAI profiles, facilitating early risk identification.

Ongoing integration of new CRL data and inspection linkages ensures continuous model refinement and improvement.

* CRL RISK FACTORS

- 1.Redica Site Score - Poor / Very Poor
- 2.Facility type - CMO / CDMO
- 3.Inspection - NDA / BLA
- 4.Inspection - Parenteral
- 5.Inspection - For-Cause
- 6.Inspection - > 3 Investigators
- 7.Investigator has been linked to > 2 CRLs
- 8.Investigator has been linked to > 1 CRL
- 9.Inspection Outcome – Red WL / OAI
- 10.OPMA issuing office
- 11.483 had > 5 Observations
- 12.483 had Critical / Major Obs > 2
- 13.483 Issued
- 14.483 Not Available (delayed)



High-Risk Inspections Identified by Our CRL Risk Model



<u>Site Display Name</u>	<u>Site Country</u>	<u>Inspection End</u> <u>Date</u>	<u>Inspection / Site Type</u>	<u>CRL Risk Factors*</u>	<u>483</u> <u>Available</u>
	India	7/26/24	Sponsor	1, 3, 4, 5, 6, 7, 11, 12, 13	Y
	South Korea	2/27/24	CMO/CDMO, Biosimilar	1, 2, 3, 4, 6, 7, 11, 12, 13	Y
	Lithuania	1/31/24	CMO/CDMO	2, 3, 6, 7, 10, 11, 12, 13	Y
	Denmark	11/12/24	CMO/CDMO	1, 2, 3, 6, 7, 10, 13	Y
	United States	9/24/24	CMO/CDMO	2, 3, 4, 6, 7, 10, 13	Y
	Germany	8/27/24	CMO/CDMO	1, 2, 3, 7, 10, 11, 12, 13	Y
	South Korea	7/30/24	CMO/CDMO, Biosimilar	2, 6, 7, 10, 11, 12, 13	Y
	Italy	7/16/24	CMO/CDMO	2, 3, 7, 10, 11, 12, 13	Y
	United States	7/12/24	CMO/CDMO, Biosimilar	2, 3, 6, 7, 10, 13	Y
	South Korea	6/20/24	CMO/CDMO, Biosimilar	2, 3, 6, 7, 10, 13	Y
	United States	6/18/24	CMO/CDMO	2, 3, 6, 7, 10, 13	Y
	United States	3/27/24	CMO/CDMO	1, 2, 3, 6, 7, 10, 13	Y
	Switzerland	2/28/24	CMO/CDMO	2, 3, 7, 10, 11, 12, 13	Y
	United States	1/26/24	CMO/CDMO	1, 2, 3, 6, 9, 11, 13	Y
	Ireland	12/13/24	Sponsor	1, 6, 7, 13, 14	N
	Taiwan	11/7/24	Biosimilar	1, 6, 7, 13, 14	N
	United States	6/28/24	CMO/CDMO	1, 2, 3, 4, 5, 12, 13	Y
	United States	6/7/24	Sponsor	3, 6, 7, 10, 13	Y
	Singapore	5/14/24	Biosimilar	3, 6, 7, 10, 13	Y
	Netherlands	3/8/24	CMO/CDMO	1, 2, 3, 7, 10, 13	Y
	Italy	2/29/24	CMO/CDMO	1, 2, 3, 7, 10, 13	Y

Looking Ahead

- FDA’s “Radical Transparency” Paradigm
 - The FDA will (probably) provide more detailed communication on reasons for not approving an application, including posting more CRLs
- Manufacturing and CMC Issues
 - Product Quality Issues including CMC and GMP deficiencies will most likely continue to be a top reason for CRLs, particularly for complex biologics and biosimilars.
- Impact of PDUFA Deadlines on CRL Timing
 - CRL issuance will continue to cluster around PDUFA deadlines. Historical data shows spikes in CRLs near PDUFA dates.
- Redica Data Roadmap
 - CRLs coming to the App Soon!
 - Enhanced Predictive Models with Expanded CRL Data

**Redica Systems Product
Roadmap Updates – July 2025**

Thank you

**Request Redica's
CRL Datasets**

