REDICA SYSTEMS LABELING AND ANALYSIS

Cipla Limited

FDA 483 Issued June 21, 2024

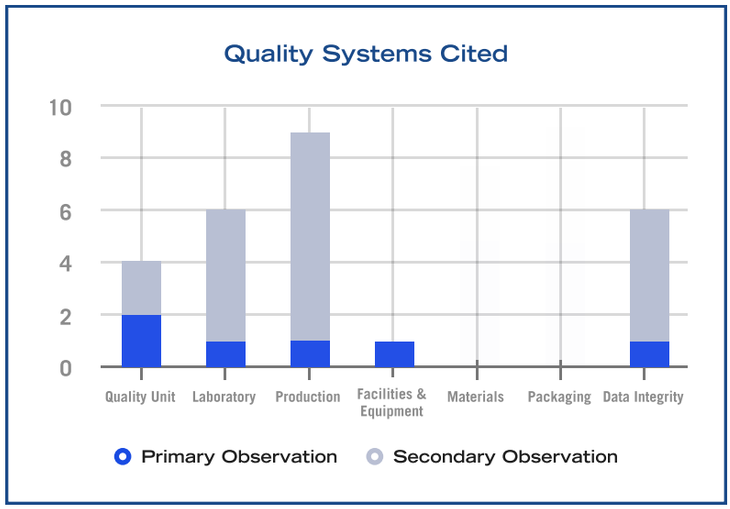

FIGURE 1 | REDICA SYSTEMS LABELING OF QUALITY SYSTEMS CITED IN 483

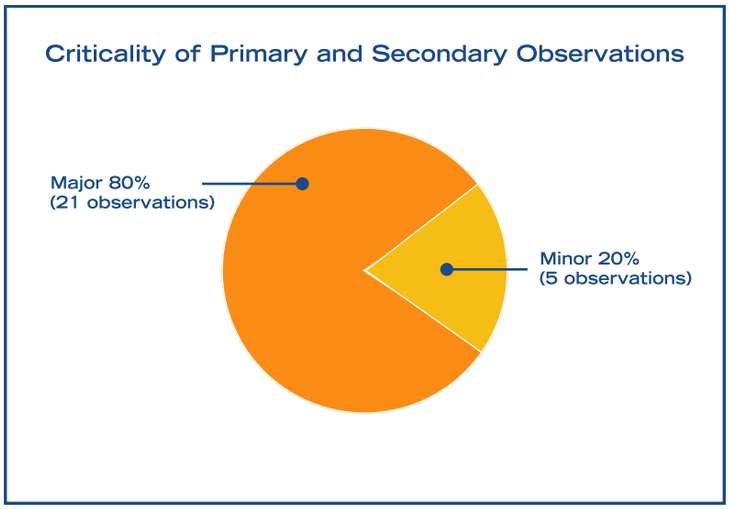

FIGURE 2 | REDICA CRITICALITY SCORES OF PRIMARY AND SECONDARY OBSERVATIONS

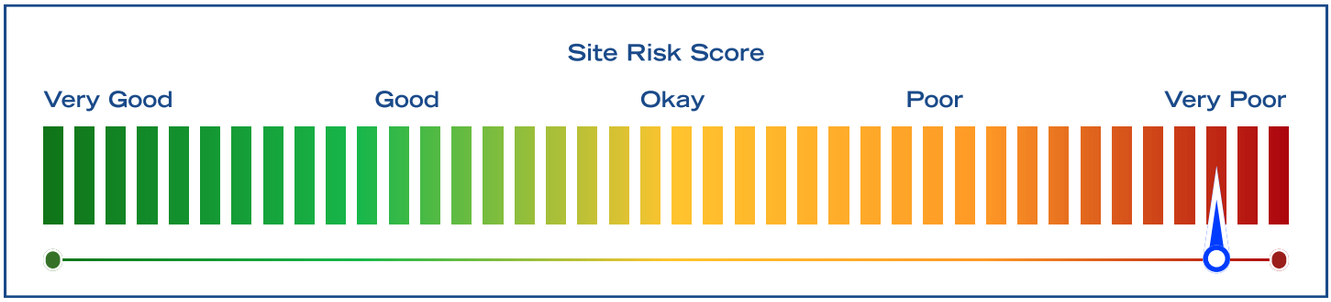

FIGURE 3 | CIPLA LIMITED SITE RISK SCORE FROM REDICA SYSTEMS

In June 2024, the U.S. FDA issued a 483 to a Cipla site in the Indian state of Goa. This 483 is noteworthy for a few reasons, which prompted this analysis.

It repeats observations seen at the same site two years ago, and similar observations were noted at other Cipla sites recently. So there's a broader pattern here, as well as a lack of evidence of improvement. We believe that a more serious enforcement action like a Warning Letter may soon follow.

Furthermore, a high percentage of the observations are classified as "Major" by Redica Systems, meaning that there is substantial risk.

Company Background

Cipla Limited (Cipla) is an Indian multinational pharmaceutical company headquartered in Mumbai and is the third-largest drug producer in India and one of the largest generic drug manufacturers in the world. In addition to finished drug products, Cipla produces active pharmaceutical ingredients (APIs) that it sells to other companies. It primarily focuses on developing medication to treat respiratory disease, cardiovascular disease, arthritis, diabetes, depression, and various other medical conditions, and is the largest manufacturer of antiretroviral drugs. Cipla has 47 manufacturing locations across the world and sells its products in 86 countries.

Analyzing the June 2024 483 (Goa)

The Cipla Verna, Salcette, Goa, India site has had at least 51 regulatory agency inspections since 2004, including 15 by the US FDA, 26 by the European Medicines Agency (EMA) and its competent country authorities, 17 by Great Britain's Medicines and Healthcare products Regulatory Agency (MHRA), and 18 by Health Canada. The inspections resulted in 14 FDA 483s, one FDA warning letter, and ten instances in which deficiencies were reported by MHRA.

FDA performed a 10-day inspection of the company's Verna, Salcette, Goa, India site in June 2024 and issued a 15-page, six-observation 483. FDA investigators were Tamil Arasu and Eileen A. Liu from the agency's Dedicated Drug Cadre, and Joseph A. Piechocki. The FDA's Dedicated Drug Cadre is a specialized group within the agency's Office of Regulatory Affairs (ORA) and the Center for Drug Evaluation and Research (CDER) focused exclusively on conducting foreign inspections of drug manufacturing facilities. This cadre is part of FDA's broader efforts to ensure the safety and quality of pharmaceuticals imported into the United States.

Analyzing the 483 using the Redica Systems Quality Systems Labeling (QSL) model, 25 deficiencies were identified in the text of the observations that mapped to the following areas:

Quality System Area	Deficiency Count
Production	9
Laboratory	6
Data Integrity	5
Quality System	4
Facilities & Equipment	1

FIGURE 4 | CIPLA LIMITED 483 OUTPUT FROM REDICA SYSTEMS PLATFORM

From a risk perspective, 80% of the deficiencies are in the Major category, 20% are Minor, and none are Critical.

The first observation in the FDA form 483 issued to Cipla after a recent inspection focuses on a lack of verification and

validation of the company's laboratory test methods. The first observation in a 483 generally focuses on the area agency investigators have the biggest concern about. Investigators listed the impacted drug products and methods in a redacted table that takes up more than six pages of the 483, which indicates the large number of products that likely have not been properly tested.

2022 Inspection of the Same Site

Nearly two years earlier, in August 2022, noted FDA investigator Justin Boyd along with Teresa I. Navas, and Jonah S. Ufferfilge performed a nine-day for-cause inspection of the same site that resulted in an 11-page, six observation 483.

Similar areas were found to be deficient, although the 2022 inspection did not note issues in the Laboratory system. One observation in the 2024 inspection was noted as a repeat finding from the 2022 inspection, "the observed spraying process has not been qualified to demonstrate it is effective for intended use," which our QSL maps to Production > Cleaning Validation or Verification > Disinfectants, with a risk level of Major.

In addition, the 2022 inspection included one observation our model classifies as Critical: "Procedures designed to prevent microbiological contamination of drug products purporting to be sterile did not include adequate validation of the aseptic process."

This maps to: Production > Process Monitoring > Process Validation > Sterile Products

Observation Areas in Common in Both the 2022 and 2024 Inspection

The 483s that resulted from the 2022 and 2024 inspections of this Cipla site shared observations in the following areas as mapped by the QSL model:

- Production > Sterile Environment > Environmental Monitoring
- Facilities and Equipment > Equipment > Design > Contamination Control
- Data Integrity > System Controls
- Quality Unit > Inadequate > Responsibilities

Two Other Cipla Sites Inspected by FDA in 2024

In addition to the Cipla site discussed above, the company also had FDA inspections of two other of its Indian sites earlier in 2024. An eight-day inspection of its Raigad, Maharashtra, India site two months earlier (April 2024) produced a five-page 483 that found deficiencies in these areas:

Quality System Area	Deficiency Count
Facilities & Equipment	5
Production	4
Laboratory	2
Quality System	2

FIGURE 5 | CIPLA LIMITED 483 OUTPUT FROM REDICA SYSTEMS PLATFORM

One month later, in May 2024, FDA performed an eight-day inspection of a Cipla site in Kurkumbh, Maharashtra, India that resulted in a one-page, one observation 483 focused on the responsibilities of the quality unit and document control, although our QSL model also tagged issues in the areas of data integrity and stability testing in the text of the examples noted in support of the observation.

Common Deficiency Areas in the Four Inspections

Areas investigators found deficient in at least two of the four inspections of Cipla sites listed above map to the following:

- Data Integrity > System Controls
- Facilities and Equipment > Equipment > Design > Contamination Control
- Laboratory > Stability > Stability Testing
- Production > Cleaning Validation or Verification > Validation > Procedures
- Production > Deviation Investigations
- Production > Sterile Environment > Environmental Monitoring
- Quality Unit > Inadequate > Responsibilities
- Quality Unit > Reviews and Approvals > Deviation Investigations

One Possible Scenario

Major Issue: Language from the most recent 483 includes the following observation:

- Because the firm's environmental monitoring SOP "lacks sufficient details on how to swab" and "there is no systematic sampling plan to ensure uniform coverage" and
- "test methods were not validated or verified appropriately"

In these circumstances microbiological contamination can occur without detection in the final product released and sold to patients.

Where the firm did investigate microbial contamination, the 483 states that "the investigation was inadequate in that you failed to provide conclusive evidence that the observed microbial contamination was the result of damaged and leaking containers and was not the result of failures in the aseptic filling process." Indicating that investigations are not adequate.

Repeat Observations and Systemic Issues:

- One direct repeat observation in the June 2024 inspection from the August 2022 inspection of the same facility, i.e., was not corrected after the previous inspection as FDA expected it would be
- Common areas were discovered by the QSL model in both the June 2024 and the August 2022 inspections of the same facility by different investigators:
  - Production > Sterile Environment > Environmental Monitoring
  - Facilities and Equipment > Equipment > Design > Contamination Control
  - Data Integrity > System Controls
  - Quality Unit > Inadequate > Responsibilities
- Similar issues were found in inspections at two other Cipla sites indicating the possibility of systemic issues in the company.
- Inspections of three Cipla sites in India by US FDA over a three-month period
- A high percentage of the observations fall into the "Major" risk category
  - Taken together these would indicate a high probability of an enforcement action by FDA such as a Warning Letter sooner rather than later.

Obs #	Primary Sentence	Human Drugs GMP Tag	Criticality	Inferred 21 CFR
1	**The accuracy, sensitivity, specificity and reproducibility of test methods have not been established or documented**	**Laboratory > Analytical Testing > Method Accuracy, Sensitivity, Specificity, and Reproducibility**	**Major**	**211.165(e)**
1.1	commercial drug products…in-house and compendial test methods were not validated, verified, or transferred appropriately	Laboratory > Analytical Testing > Method Validation	Major	211.160(b)
1.2	Active pharmaceutical ingredients (API)…test methods including in-house and compendial test methods were not validated or verified appropriately	Laboratory > Analytical Testing > Method Validation	Major	211.160(b)
1.3	in-process test methods including in-house and compendial test methods were not validated or verified appropriately	Laboratory > Analytical Testing > Method Validation	Major	211.160(b)
2	**Aseptic processing areas are deficient regarding the system for monitoring environmental conditions**	**Production > Sterile Environment > Environmental Monitoring**	**Major**	**211.42(c)(10)(iv)**
2.1	viable surface monitoring conducted in(b)(4) Line (b)(4) does not always ensure microbial contamination in the critical Grade A areas will be recognized	Production > Sterile Environment > Environmental Monitoring > Surfaces	Major	211.42(c)(10)(iv)
2.2	1. viable surface monitoring are conducted at random. There is no systematic sampling plan to ensure uniform coverage	Production > Sterile Environment > Environmental Monitoring > Surfaces	Major	211.42(c)(10)(iv)
2.3	2. swabs are used to conduct Grade A viable surface monitoring…no limit of detection was established during validation	Laboratory > Analytical Testing > Method Validation	Major	211.160(b)
2.4	3. swab validation failed to include testing of Grade A (b)(4) flexible pipes (b)(4) surfaces	Production > Sterile Environment > Environmental Monitoring > Surfaces	Major	211.42(c)(10)(iv)
2.5	4. Monitoring procedure UQCP 158…lacks sufficient details how to swab	Production > Sterile Products > Microbiological Contamination > Procedures	Major	211.113(b)
3	**Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room and equipment to produce aseptic conditions**	**Facilities and Equipment > Equipment > Design > Contamination Control**	**Major**	**211.42(b)(c)**
3.1	1. The observed spraying process has not been qualified to demonstrate it is effective for intended use*	Production > Cleaning Validation Or Verification > Disinfectants	Major	211.67(a)
3.2	2. SOP CT-413…lacks requirement and details for how to clean the Grade A (b)(4) formation interior machine bed	Production > Cleaning Validation Or Verification > Validation > Procedures	Major	211.67(a)
3.3	3. Operators did not always follow SOP CT0413	Production > Cleaning Validation Or Verification > Validation > Procedures	Major	211.67(a)
4	**There is a failure to thoroughly review the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been distributed.**	**Quality Unit > Reviews and Approvals > Deviation Investigations**	**Minor**	**211.192**

EXHIBIT A | CIPLA LIMITED 483 OUTPUT FROM REDICA SYSTEMS PLATFORM

Obs #	Primary Sentence	Human Drugs GMP Tag	Criticality	Inferred 21 CFR
4.1	1. investigation was inadequate in that you failed to provide conclusive evidence that the observed microbial contamination was the result of damaged and leaking containers and was not the result of failures in the aseptic filling process	Production > Deviation Investigations	Minor	211.192
4.2	2. Long term stability at 36M (25°C / 60% RH) gave an OOS value of (b)(4) for assay	Laboratory > Stability > Stability Testing	Major	211.166(a)(3)
5	**Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel**	**Data Integrity > System Controls**	**Major**	**211.68(b)**
5.1	A. User privileges assigned within the manufacturing equipment used for products intended for the US market are not appropriate for the job functions being performed nor are they adequately defined.	Data Integrity > System Controls	Major	211.68(b)
5.2	A. 1. Quality Assurance personnel are assigned "Admin" privileges...including but not limited to modifying the date and time, creating and modifying users, and deleting batches.	Data Integrity > Attributable > Batch Records	Minor	211.188(b)(11)
5.3	B. User access for equipment...is not adequately reviewed to ensure proper and approved access to the systems is maintained.	Data Integrity > System Controls	Major	211.68(b)
5.4	B. 2. There is no requirement to ensure that each user is assigned only one login account per system.	Data Integrity > Attributable > General	Minor	211.101(d)
6	**The responsibilities and procedures applicable to the quality control unit are not fully followed.**	**Quality Unit > Inadequate > Responsibilities**	**Major**	**211.22(a)**
6.1	1. No change control or action item specific to the drug substance...was initiated as required by procedure.	Quality Unit > Reviews and Approvals > Change Control	Minor	211.100(a)
6.2	2. ensure that the material received from the sending unit has been tested per specification, all results are satisfactory, and tests are performed per the US market requirement.	Quality Unit > Reviews and Approvals > Batch Release	Major	211.192

EXHIBIT A | CIPLA LIMITED 483 OUTPUT FROM REDICA SYSTEMS PLATFORM

Exhibit B

Minor

Definition:
– Issues that pose minimal risk to product quality, patient safety, or data integrity.
– Typically involve isolated or infrequent deviations from SOPs.
– Corrective actions are straightforward and can be implemented quickly without significant resource allocation.

Examples:
– Minor documentation errors that do not impact product quality.
– Isolated instances of equipment not being calibrated on schedule.
– Small deviations in environmental monitoring that are easily corrected.

Major

Definition:
– Issues that pose a significant risk to product quality, patient safety, or data integrity.
– Involve serious deviations from regulatory requirements or SOPs that have the potential to lead to product recalls or serious health consequences.
– Require immediate and comprehensive corrective actions, often involving cross-functional teams and substantial resource allocation.

Examples:
– Significant deviations from manufacturing processes that impact product sterility or potency.
– Systematic failures in quality control procedures that could lead to widespread product defects.
– Major lapses in data integrity, such as unauthorized data manipulation or loss of critical data.

Critical

Definition:
– Issues that pose an immediate and severe risk to patient safety, product quality, or data integrity.
– Represent blatant non-compliance with regulatory requirements and could result in enforcement actions, product recalls, or serious public health threats.
– Require urgent and extensive corrective actions, potentially including halting production and comprehensive review and overhaul of processes.

Examples:
– Production of contaminated products that have reached the market.
– Gross failures in aseptic processing leading to widespread contamination.
– Falsification of data in regulatory submissions or quality control records.