REDICA Systems

Intas Pharmaceuticals Troubles with FDA Continue

EXPERT ARTICLE

WRITTEN BY

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INTAS WARNING LETTER FOCUSES ON DATA INTEGRITY

On July 28, 2023, Indian drug maker Intas Pharmaceuticals received a warning letter from the FDA detailing serious concerns with its Gujarat manufacturing facility and the drugs the company produces.

The first citation states, "You failed to ensure reliability of data relating to the quality of medicines produced at your facility. Our inspection revealed serious deviations, including but not limited to, inadequate oversight of original CGMP documents, deficient controls over computerized systems, insufficient laboratory investigations, and aborted chromatographic sequences."

The letter points to several serious deficiencies related to Good Manufacturing Practice (GMP), including numerous references to data integrity lapses throughout the letter (**see Figure 1**).

In its April 2016 guidance, Data Integrity and Compliance With CGMP, FDA notes that it has "increasingly observed CGMP violations involving data integrity during CGMP inspections. This is troubling because ensuring data integrity is an important component of industry's responsibility to ensure the safety, efficacy, and quality of drugs, and of FDA's ability to protect the public health."

It defines "data integrity" as "the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA)." Data integrity related CGMP violations have led to numerous regulatory actions, including warning letters, import alerts, and consent decrees.

MANAGEMENT RESPONSIBILITY FAILURES AT INTAS

In December 2018, FDA released a Question and Answer document to accompany the 2016 guidance, in which it clarified its expectations regarding company implementation of systems to ensure the integrity of data and detect data issues and its expectations for the role of company management:

Data Integrity Issues Cited in the Intas Warning Letter

The July 2023 FDA warning letter to Intas includes at least 40 phrases indicating concerns with the integrity of data, including its reliability and accuracy, retention, completeness, and sources. The following phrases are quoted directly from the letter:

Integrity:

- data integrity (occurs 15 times)
- integrity of data
- integrity of your company's data
- integrity of analytical testing data
- integrity of all data

Reliability and Accuracy:

- reliability of data
- adequacy and reliability of CGMP data
- compromises the reliability of data
- inaccuracies in data records and reporting
- data inaccuracies

Raw/Source Data:

- printout of raw data in laboratory records
- unreported raw data

Retention:

- retention of all source data
- data retention or reliability
- full retention of laboratory data
- data retention measures
- retention of all CGMP data
- retain batch-related data

Completeness:

- complete data derived from all tests
- lacked complete and accurate data
- laboratory raw data was missing
- complete records of data and testing conditions
- missing laboratory data
- completeness of all the data you generate
- adequate data to support their capabilities

FIGURE 1 | DATA INTEGRITY ISSUES CITED IN THE INTAS WARNING LETTER

"CGMP regulations and guidance allow for flexible and risk-based strategies to prevent and detect data integrity issues. Firms should implement meaningful and effective strategies to manage their data integrity risks based on their process understanding and knowledge management of technologies and business models.

"Management's involvement in and influence on these strategies is essential in preventing and correcting conditions that can lead to data integrity problems. It is the role of management with executive responsibility to create a quality culture where employees understand that data integrity is an organizational core value and employees are encouraged to identify and promptly report data integrity issues. In the absence of management support of a quality culture, quality systems can break down and lead to CGMP noncompliance."

In the warning letter to Intas, the agency points to a failure of management to fulfill these responsibilities.

"Senior facility managers failed to exercise their authority and responsibility to ensure reliable data, leading to severe data integrity deficiencies in your production and laboratory departments. These findings also indicate that your quality assurance function is not exercising its responsibilities, including but not limited to, oversight and control over the adequacy and reliability of CGMP data used throughout your operation."

The Redica Systems analysis of the last 22 years of drug GMP 483s in its platform found data integrity issues of various types in about 7% of them. Here is a three-minute video detailing the data integrity findings.

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Intas Pharmaceuticals Warning Letter Predicted by Red Flag Models

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As covered, the warning letter cites the Intas quality control unit for failing to perform its duties as well as for errors and omissions in data used to make critical decisions and the reliability of laboratory tests. These findings call into question the safety and quality of the medicines the company produces and ships to the United States. Of interest is that the issuance of the letter could have been predicted by a careful and detailed examination of the company's storied inspection history.

According to public inspection data accumulated, stored, and analyzed by Redica Systems, the Intas location in Gujarat, India, has been inspected 24 times since 2011, including eight times by the U.S. FDA, eight times by Health Canada, seven times by the U.K. Medicines and Healthcare products Regulatory Authority (MHRA) and once by a European Medicines Agency (EMA) competent authority (Poland).

At least six of these inspections raised concerns about the company's ability to produce safe, high-quality products. This history and pattern of findings indicate that without remediation of the quality gaps found during the inspections, it was only a matter of time before an FDA warning or a serious product defect or contamination issue occurred.

RED FLAGS ABOUND

Redica Systems has developed a "Red Flag" model computer algorithm that weighs the relative seriousness of inspection findings and related factors to gauge the relative risk of products produced at a particular manufacturing site.

Evaluation of risk by the model is based on many factors, some obvious and others subtle. Here are some examples of potentially problematic issues contrasted with similar issues that are less so:

- An inspection conducted "for cause" vs. a routine surveillance inspection;
- An FDA inspection that resulted in a 483 vs. one that did not;

- A lengthy inspection vs. a short inspection;
- An inspection finding on product sterility vs. on employee training; or
- An inspection conducted by an expert investigator vs. one less experienced (when FDA assigns an expert investigator it generally indicates a heightened concern for issues occurring at the site in question).

Signals produced by the model, called "flags," can be categorized as critical (red), major (orange), or minor (yellow). More flags indicate a higher potential for serious issues occurring.

APPLYING THE MODEL TO INTAS

Redica's analysis indicates nine red flags from FDA inspections since 2011 – six of them from the December 2022 inspection that preceded the July warning letter, one from a 2019 FDA inspection, and two an inspection in 2016. That many red flags indicate a high likelihood of a critical impact to product quality or a product safety issue in the near term.

Also noted since 2011 were 13 orange flags (potentially major issues) from FDA inspections and one from an MHRA inspection, each of which indicates a quality or management system that could be heading toward failure and should warrant further review. Many of the issues found recurred over the 12-year timeframe being examined. During the same timeframe, 16 yellow flags were cumulatively noted from FDA and MHRA inspections (**see Figure 2**).

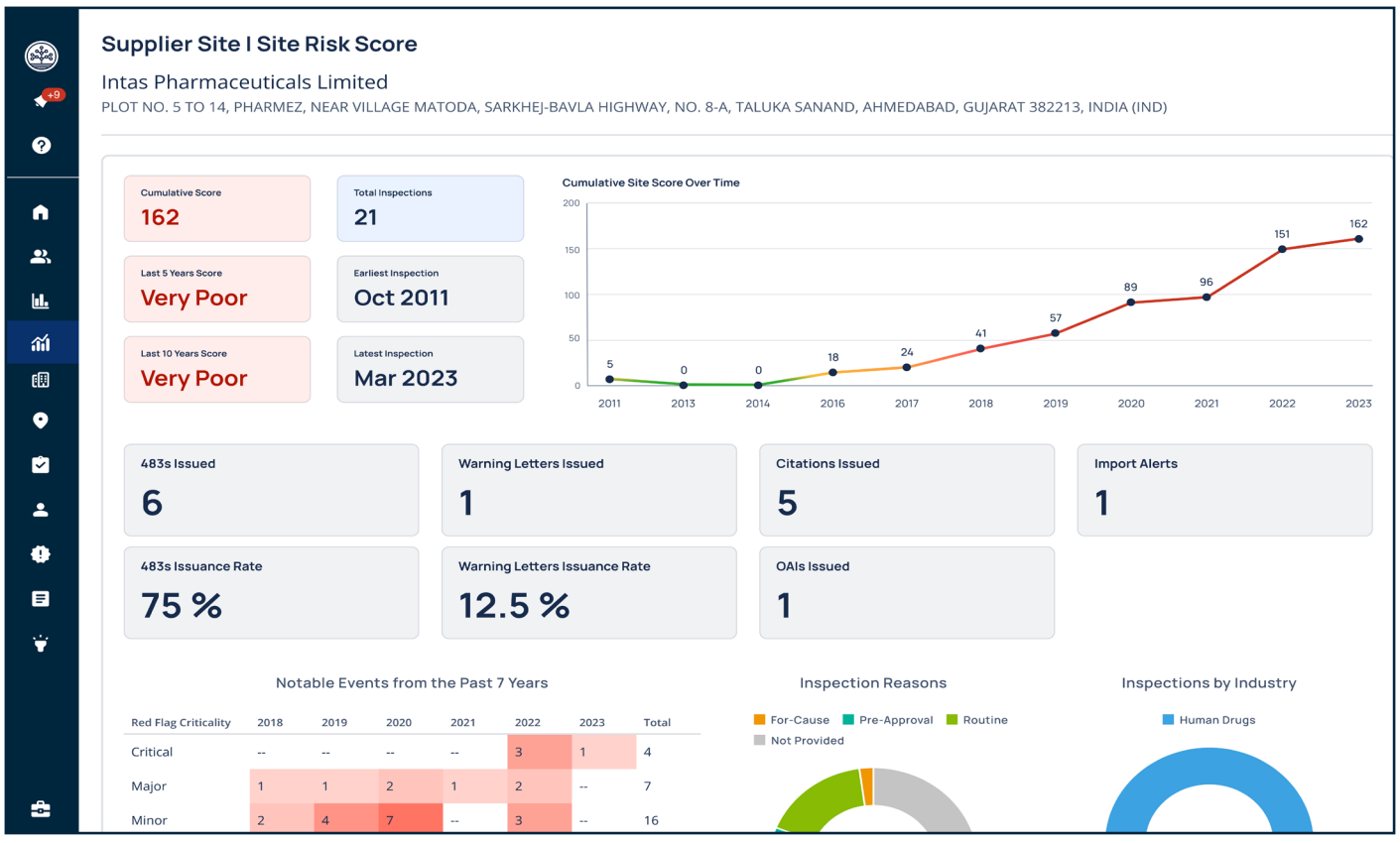

FIGURE 1 | INTAS SITE PROFILE FROM REDICA SYSTEMS PLATFORM

Intas Inspection Timeline Summary, 2011 – 2022

Date	Critical Issue	Major Issue	Minor Issue	None	Agency
12-02-2022	🚩🚩🚩🚩🚩🚩	🚩🚩🚩🚩	🚩🚩		U.S. FDA
05-21-2021				✅	Poland
05-17-2021				✅	Health Canada
07-14-2020			🚩		MHRA
06-25-2020				✅	Health Canada
06-23-2020				✅	MHRA
02-28-2020		🚩🚩🚩	🚩		U.S. FDA
01-17-2020				✅	Health Canada
01-17-2020		🚩			MHRA
05-28-2019	🚩	🚩🚩🚩	🚩		U.S. FDA
05-28-2019				✅	Health Canada
11-30-2018			🚩		MHRA
02-02-2018				✅	Health Canada
06-19-2017			🚩	✅	MHRA
06-19-2017			🚩🚩	✅	U.S. FDA
10-19-2016	🚩🚩	🚩🚩	🚩🚩		U.S. FDA
02-19-2016				✅	Health Canada
02-19-2016				✅	Health Canada
02-19-2016			🚩		MHRA
12-19-2014		🚩			U.S. FDA
06-27-2013				✅	Health Canada
06-27-2013			🚩		U.S. FDA
01-11-2013			🚩		MHRA
10-21-2011			🚩🚩		U.S. FDA

🚩 Potential Critical Issue observed
🚩 Potential Major Issue observed
🚩 Minor Issue observed
✅ No issue observed (or not enough data from the agency to determine)

FIGURE 2 | DATA INTEGRITY ISSUES CITED IN THE INTAS WARNING LETTER

When reviewing **Figure 2** it is worth remembering that agency inspections are only snapshots in time, that the level of compliance can ebb and flow over time, and that the purpose of a particular inspection and its length and intensity can vary as does the skill and experience of the investigator conducting the inspection.

WHAT DEFICIENCIES WERE FOUND?

Although FDA 483s do not cite the Code of Federal Regulations (CFR), language used can be mapped to the FDA Quality Systems using the Redica Systems Quality System Labeling (QSL) model. Using this model, inspection deficiencies can be mapped to the 6+1 quality systems – the six FDA Quality Systems plus data integrity – and often two and three levels deeper (**see What is "Quality and Regulatory Intelligence"?**).

Where did FDA observe deficiencies during its inspections of Intas according to the QSL model? (**See Figure 3.**) Although deficiencies in a 483 are numbered, each generally includes additional "for example" or supporting text where our models often find "observations hiding in plain sight" – deficiencies included in the text of the 483 but not specifically called out as a numbered observation.

Where Does Language in the Intas FDA 483s Map?

Quality System > Qualified Personnel > Personnel (2)
Quality System > Quality Unit Inadequate > Procedures not followed (3)
Quality System > Quality Unit Inadequate > Other (2)
Quality System > Deviations > Investigations (3)
Quality System > Records and Reports > Procedures
Quality System > Records and Reports > Batch Release
Quality System > Agency Notification > Recalls
Quality System > Complaint Management

Data Integrity > Data Manipulation
Data Integrity > Testing into Compliance
Data Integrity > Data Destruction
Data Integrity > System Controls (2)
Data Integrity > Contemporaneous

Production > Sterile Products > Environmental Monitoring (2)
Production > Process Validation inadequate or missing > Sterile (3)
Production > Cleaning validation or verification
Production > Process Monitoring > Continued Process Verification

Laboratory > Stability > Stability Program
Laboratory > Records and Reports
Laboratory > General Requirements > Laboratory controls
Laboratory > General Requirements > Laboratory Controls > Scientifically Sound

Facilities and Equipment > Maintenance > Equipment > Written Program

FIGURE 3 | DATA INTEGRITY ISSUES CITED IN THE INTAS WARNING LETTER

OTHER TROUBLING ISSUES

The FDA recognized many of the company's deficiencies as recurring. In the July 2023 warning letter, FDA states, "In previous inspections, including the inspection of May 20-28, 2019, FDA cited similar CGMP observations. You proposed specific remediation for these observations in your response. Repeated failures demonstrate that executive management oversight and control over the manufacture of drugs is inadequate."

On June 1, 2023, FDA placed the firm on Import Alert 66-40, "Detention Without Physical Examination of Drugs from Firms Which Have Not Met Drug GMPs." The import alert bars the importation of drugs from the firm into the U.S. until further notice and is generally issued when the agency has evidence from a manufacturing site inspection that the firm is not operating in conformity with current good manufacturing practices (GMPs).

This action took place after the December 2022 inspection in advance of the July 2023 warning letter. An FDA import alert represents another red flag in Redica's Intas site profile.

HOW CAN I USE THE RED FLAG ANALYSIS?

In the case of Intas, a 12-year Red Flag analysis points to many potentially serious concerns that, taken together, produce a profile of a manufacturing site with a high risk for serious or critical issues. The June 2023 FDA Import Alert and July 2023 FDA Warning Letter confirm what the Red Flags in the inspection history up to that point predicted.

In addition to the cautions indicated by the Red Flag report, an analysis of the July 2023 warning letter reveals a deep concern by FDA with data integrity lapses at the Intas facility (**See Intas Pharmaceuticals' Troubles with FDA Continue article above**).

Redica Systems has the ability to generate Red Flag reports on virtually any FDA-regulated manufacturing site. Use cases for a pharma manufacturing company include commissioning a Red Flag report covering:

- Specific manufacturing sites in your company
- An aggregate of your sites for a compilation of overall company risk
- Partner/CMO sites you are currently doing business with
- Sites/companies under consideration for partnership/outsourcing as part of due diligence
- Benchmarking your sites with competitor sites

These analyses can be used to target internal improvement efforts, get a comparison with how the company stacks up against its competitors, understand the relative regulatory risk in outsourced and partner/supplier operations, and inform decisions regarding the selection of new partners and CMOs. They include not only the Red Flags as shown in Figure 1, but the detail behind how each was determined.

Contact Redica Systems for more information.

ABOUT THE AUTHOR

Jerry Chapman is Senior GMP Quality Expert at Redica Systems. He brings over 40 years' experience in the pharma industry, including 31 years at Eli Lilly, where he worked in product development, biosynthetic human insulin manufacturing, and site and corporate quality. He designed and implemented a comprehensive GMP Intelligence process to identify, analyze, and archive pertinent drug GMP regulations, inspection findings, trends, and best practices in the U.S. and internationally.

Chapman has been an invited speaker at PDA, AAPS, ISPE, and RAPS events and has served as a consultant to the animal health and compounding pharmacy industries. He founded the Midwest Discussion Group GMP-Intelligence sub-group and chaired it from 2004-2009. At Redica Systems, Chapman works with the machine learning and data science teams building computer models that examine enforcement actions and other data to produce insightful expert analyses. His articles appear on the Redica Systems Conference Spotlight page.