



## Overview of Data Integrity issues in the Pharmaceutical industry

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### ABSTRACT

In the recent few years, the most discussed topic in the pharmaceutical / healthcare industry is the DATA INTEGRITY. Many former pharmaceutical giants were collapsed due to Data integrity issues. Hence the senior management of the organizations should take data integrity issues seriously and work on how to resolve them to avoid destructive things in terms of business, reputation, trust, market value and many others by getting Warning letters or non-compliance reports issued from the regulatory agencies. This document will provide information about data integrity, regulatory requirements of data Integrity, consequences of data integrity issues, steps to be taken to prevent data integrity Issues and discussion on Warning letters issued by regulatory authorities with graphical representation.

**Keywords:** Data integrity, ALCOA, warning letter, 21 CFR, Audit trails.

### INTRODUCTION

Data has never been easy to manage as it contains various steps right from generation to destruction i.e. throughout its life cycle. It is important that data are not only stored but also protected from various means. The process of generating, processing, archiving, retrieving and destructing a data is called as data life cycle. The extent to which all data are complete, consistent and accurate throughout the Data Lifecycle is called as Data Integrity.<sup>1</sup>

Data means all original records and certified true copies of original records, including source data and metadata and all subsequent transformations and reports of this data, which are recorded at the time of the GxP activity and allow full and complete reconstruction and evaluation of the GxP activity.<sup>2</sup> Metadata are data about data that provide the contextual information required to understand those data. Typically, these are data that describe the structure, data elements, interrelationships and other characteristics of data. They also permit data to be attributable to an individual.<sup>2</sup>

Data Integrity is equally important to both Paper (manual) and electronic data. In the recent years, Regulatory Authorities have put more stress on Data Integrity Issues because they found some serious cGMP violation which could alter the product quality, safety and efficacy. It is always better to take proactive action against data integrity issues, rather than taking action as a part of compliance.

### DISCUSSION

Good Documentation practices (GDP) is key to ensuring data integrity and is a primary part of Quality management system. The applications of GDP may vary depending upon the medium used to document the data

(i.e. Paper based or electronic based) but principles are applicable to both.

Both FDA and MHRA have specified that a data should be ALCOA i.e. Attributable to the person generating the data, Legible and permanent, contemporaneous, Original Record (or true copy) and Accurate. In Addition to ALCOA, following things are added and termed it as ALCOA+; these are Complete, Consistent, Enduring and Available. ALCOA and ALCOA+ will ensure that events are properly documented and can be used to support the decisions in future.

### Regulatory Requirements

Data integrity is critical to Regulatory Compliance. As discussed in various guidelines and regulations such as 21 CFR parts 211, 21 CFR part 11, EU Guideline on Good manufacturing practices, EU Annexure 11 and ICH Q7; following are the few regulatory requirements but not limited to,

1. There must be written procedure designed to carry out each activity, followed in the execution and such activities shall be documented contemporaneously.
2. For both Paper and electronic data, a backup procedure must be in place. The records shall be maintained for certain time period (retention period).
3. If a computer or computer system is used for data generation or processing, then appropriate control measure shall be applied on such systems to ensure that only an authorized person can make changes in the master documents.



4. Documents shall be designed, prepared, reviewed, and distributed with care. Documents containing instruction shall be approved by an authorized person only. All the documents within Quality management system shall be reviewed periodically.
5. Good documentation practices shall be strictly followed while documenting an event.
6. If electronic signatures are used on documents, they shall be authenticated and secure.
7. Computerized systems shall be validated to ensure accuracy, reliability, consistent performance, and the ability to detect invalid or altered records.
8. Audit trail function shall be enabled to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information.
9. The use of scribes to record activity on behalf of another operator should be considered 'exceptional', and only take place where :
  - The act of contemporaneous recording compromises the product or activity e.g. documenting line interventions by sterile operators.
  - To accommodate cultural or staff literacy/language limitations, for instance where an activity is performed by an operator, but witnessed and recorded by a Supervisor or Officer.
  - In both situations, the supervisory recording should be contemporaneous with the task being performed, and should identify both the person performing the task and the person completing the record. The person performing the task should countersign the record wherever possible, although it is accepted that this countersigning step will be retrospective. The process for supervisory (scribe) documentation completion should be described in an approved procedure, which should also specify the activities to which the process applies.<sup>1</sup>

#### Consequences of Data Integrity Issues

There are many consequences of data integrity issues which can affect the various stakeholders directly and indirectly such as regulators, patients, and customer. The worst case scenario is impact on patient safety and the loss of lives.

Although not regulated by the FDA or subject to cGMPs, the New England Compounding Pharmacy incident in the United States can be used as an example of the

consequences of fraudulent activity. Here, 64 patients died and over 750 were sickened from fungal meningitis as a result of sterility negligence and data integrity issues. In this case, a FDA official said pharmacy technicians were instructed to lie on cleaning logs, showing rooms as being properly cleaned when they had not been.<sup>3</sup>

#### a. Warning letters, statement of non-compliance and consent Decrees

Several warning letters, statement of non-compliance and consent Decrees have been issued to pharmaceutical manufacturing facilities after identifying data integrity issues by the regulatory Authorities. When such types of actions are taken by the regulatory authorities, it will affect the ability of company to get approve new drug product for marketing, loss of regulatory authority trust. Additionally there may be a condition in which company has to reduce the production or hold the products at site. This will result in shortage of drug product and lack of consumer confidence.

#### b. Import Alert, Product Recalls and Seizure of Products

Drug product which has data integrity issues are considered as adulterated drug products. For such adulterated drug products, US FDA can restrict them from being allowed in USA market. In some cases, FDA can mandate that the drug product be recalled and Subject to seizure of drug products.

Import alerts inform FDA field staff and the public that the agency has enough evidence to allow for Detention without Physical Examination (DWPE) of products that appear to be in violation of FDA laws and regulations. These violations could be related to the product, manufacturer, shipper and/or other information.<sup>4</sup> When an FDA-regulated product is either defective or potentially harmful, recalling that product—removing it from the market or correcting the problem—is the most effective means for protecting the public.<sup>5</sup>

#### c. Need to appoint Third Party Consultants for Data Integrity

Once a warning letter has been issued by US FDA to the pharmaceutical facility, FDA suggest to hire a third party consultant who is experienced in detecting data integrity problem to assist the company with this evaluation and to assist with company's overall compliance with CGMP. The process of identifying data integrity issues and complying with the regulatory requirement through a consultant is usually time consuming and expensive too.

#### d. Loss of Regulatory Trust

When data integrity issues arise, they are expected to result into Loss of regulatory trust. This can be resulted in more repeated inspections of the facility, expecting to see more data to support claims, and make it unlikely for a company to obtain approval for average issues that they may wish to perform.



### e. Debarment and imprisonment (for individuals involved in data integrity issue)

How data integrity issues can affect to the individuals who were involved in the data integrity issues is well understand by a case study. A former Vice President in charge of the Quality Control Department and three supervisory chemists at now-defunct New Jersey generic drug manufacturer Able Laboratories pleaded guilty to a conspiracy involving the extensive falsification and manipulation of testing data of its drugs. Due to this all the 500 employees of Able laboratories, Inc had lost their job.

All four face a statutory maximum penalty of five years in federal prison and a \$250,000 fine. All four had not been previously charged, and thus their guilty pleas were their first appearances in court. Judge Wigenton set bail for Shah at \$500,000 secured by equity in his home; the other defendants' bail was set at \$100,000 unsecured. "The damage from the fraud at Able Labs was devastatingly complete," said Christie. "Consumers were put at risk, a company that employed 500 people was destroyed, and shareholders were left with nothing in the end. This is the legacy of the fraud perpetrated at Able Labs by these defendants."<sup>6</sup>

#### Reasons of Data Integrity Issues to Occur

There is a general misconception that the Data integrity Issues arises only from acts of deliberate fraud. Act of deliberate fraud is a single element due to which data integrity issues could occur, but there are many other elements which are equally responsible for data integrity issues to occur. A Few elements are mentioned below,

- Time / Work Pressure
- Insufficient education and understanding
- Fear for Mistakes
- Performance pressure
- Am told by Leader / Manager to do the activity which is against cGMP procedures
- Reputation
- Money
- Company Culture or Accepted behavior
- And others...

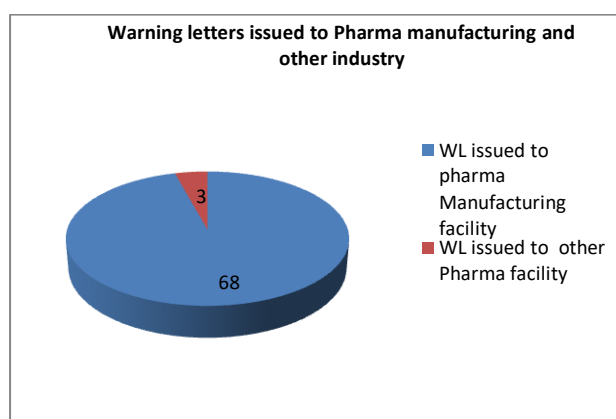
#### Data Integrity Warning Letters Issued by FDA

This is mainly issued when serious defects were identified but also if the answer to the form 483 is classified as inadequate. It is release after a review by the answered responsible centre / district offices, not the inspector himself / herself. The company must respond within 15

working days and explain in details how to resolve the deficiencies on the one hand and how a recurrence can be prevented on the other hand.

The author has reviewed FDA website for 'pharmaceutical warning letter on data integrity' and found that total 71 data integrity Warning letters were issued worldwide to pharmaceutical industry during a period from 2013 to 2017.<sup>7</sup>

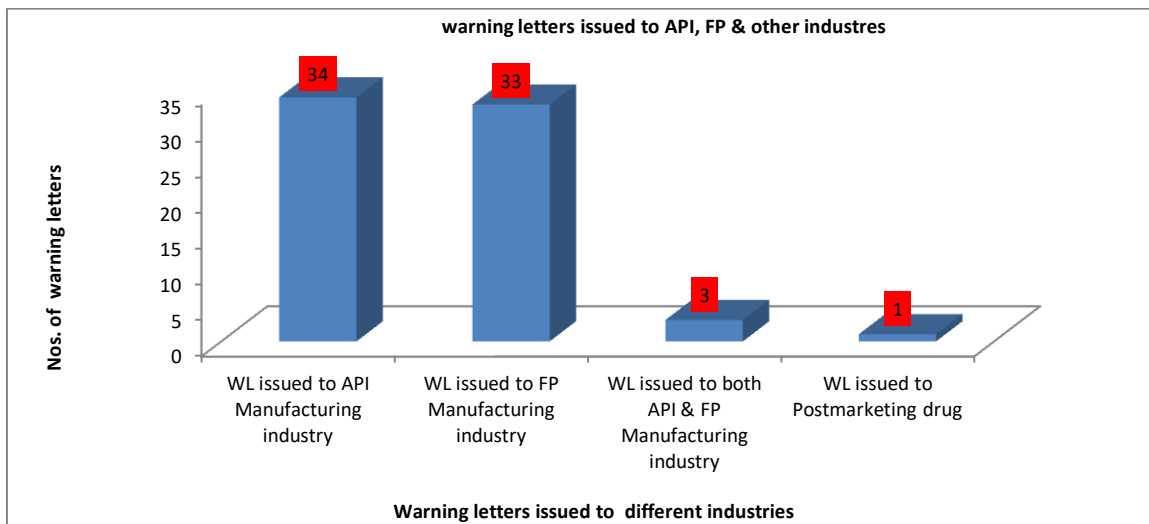
The Figure-1 shows a graphical representation of warning letters issued to pharma manufacturing facility and other facilities such as Contract testing laboratories, packaging and labeling industry and others. Out of total 71 warning letters 68 warning letters were issued to pharmaceutical manufacturing facilities and 3 were issued to other facilities such as packaging and labeling, contract testing laboratories and other.



**Figure 1:** FDA Warning letters – Pharma Manufacturing and other facilities

The Figure-2 shows a graphical representation of warning letters issued to API mfg. industry, FP mfg. facility and others pharma industry. Out of total 71 warning letters 37 warning letters were issued to API manufacturing industries, 33 were issued to finished product (FP) manufacturing facilities, 3 were issued to both API and FP manufacturing industry and 1 was issued to other having post marketing drug violation issue.

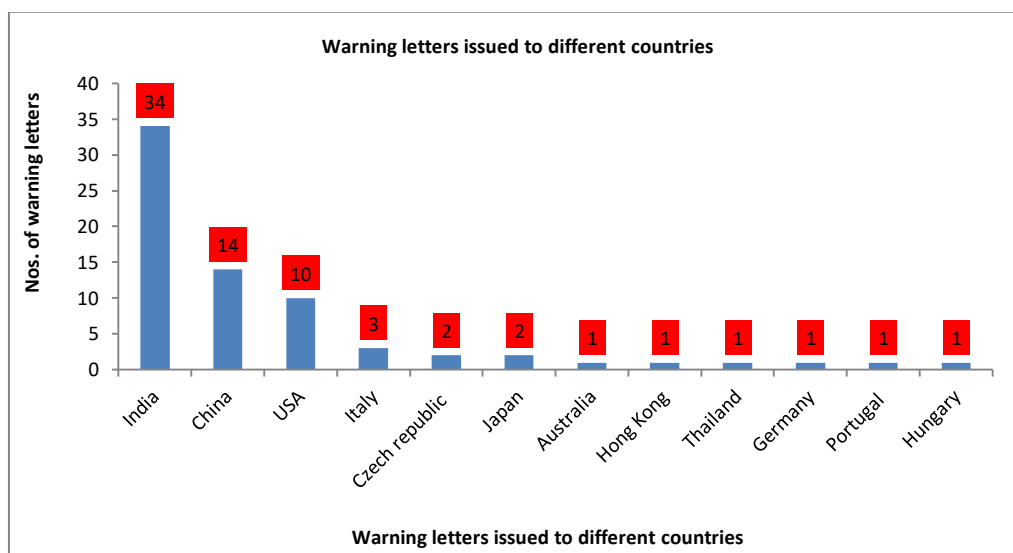
The Table-1 indicates the numbers of warning letters issued to different countries and Figure-3 shows a graphical representation of Data integrity warning letters issued to different counties worldwide. Out of total 71 warning letters, India had received the maximum numbers of warning letters i.e. 34 numbers of warning letters, China had received total 14 Numbers of warning letters and it is at second position after India and USA had received 10 warning letters.



**Figure 2:** FDA Warning letters – API manufacturing, FP Manufacturing and other industry

**Table - 1** Warning letters issued to different countries

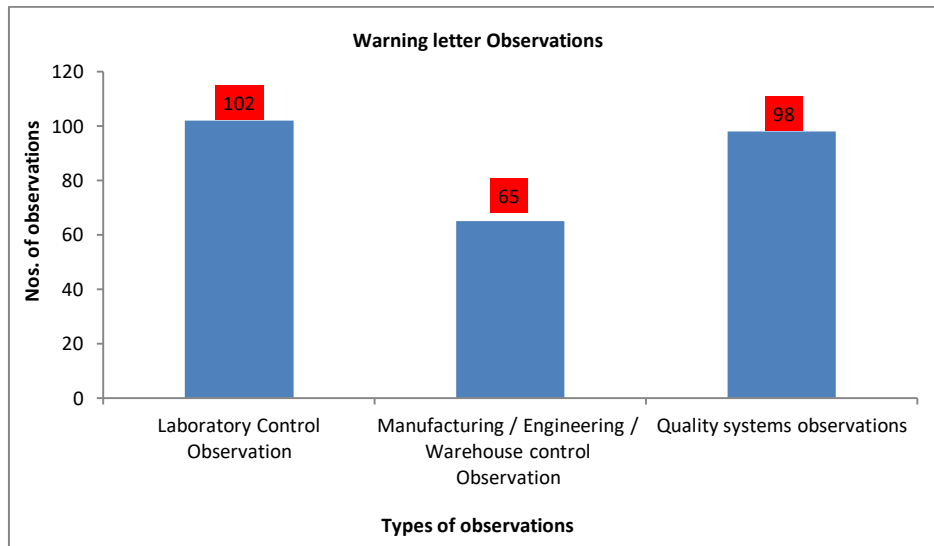
Country	Nos. of warning letters
India	34
China	14
USA	10
Italy	3
Czech republic	2
Japan	2
Australia	1
Hong Kong	1
Thailand	1
Germany	1
Portugal	1
Hungary	1
<b>Total</b>	<b>71</b>



**Figure 3:** FDA Warning letters – issued to different countries

In the warning letters, the observations are classified in to three major categories such as Laboratory control observations, Manufacturing / engineering / warehouse

control Observations and Quality System Observations. The Figure-4 shows a graphical representation of observations in to three major categories.



**Figure 4:** FDA Warning letters – Observations

#### a. Laboratory Control Observations

The observations related to laboratory controls are found with maximum numbers. In the total 71 numbers of warning letters, 102 observations were related with Laboratory control observations. Following are the examples.

- Failure to maintain laboratory control records with complete data derived from all tests,
- Failure to adequately investigate out-of-specification results,
- Failure to ensure that, for each batch of intermediate and API, appropriate laboratory tests are conducted to determine conformance to specifications and many others.

#### b. Manufacturing / Engineering / Warehouse Control Observations

Out of total 71 warning letters, 65 observations were related with Manufacturing / Engineering / Warehouse Control. Following are the examples.

- Your firm failed to maintain the buildings used in the manufacture, processing, packing, or holding of a drug product in a clean and sanitary condition (21 CFR 211.56(a)).
- Your firm failed to have separate or defined areas or such other control systems necessary to prevent contamination or mix-ups (21 CFR 211.42(c)).
- Failure to control the API repackaging, relabeling, and holding operations in order to avoid mix-ups and the loss of the API identity.

- Your firm did not follow written procedures regarding storage and warehousing of drug products (21 CFR 211.142) and many others.

#### c. Quality System Observations

Total 98 observations related to Quality System were found in 71 numbers of warning letters. Following are the examples.

- Your firm failed to review and investigate production and QC laboratory deviations.
- Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192) and many others.

#### Strategies to Avoid Data Integrity Issues

Pharmaceutical companies need to ensure that all the data generated during the manufacturing and testing of the drug products are original, accurate, correct and integral.

Given the increased scrutiny for data integrity, companies are well advised to establish internal competency, assessment and monitoring programs, and assure data integrity is an integral part of their internal audit / self-inspection program<sup>8</sup>

Following are the few ways by which pharmaceutical companies can avoid any data integrity issues and avoid any regulatory impact during the audits.

#### a. Establishing Quality culture in the organization

Culture is the backbone of the organization.<sup>9</sup> Culture is responsible for overall growth of not only employees but the organization too. A quality culture means where each employee must feel that my work is responsible for company's growth and I should work as per the Company's rules and regulations. Sometimes due to poor quality culture and lack of encouragement by the senior management, employees try to hide their mistake, and ultimately it leads to the data integrity issue. Because of this senior managements are responsible to develop and sustain a culture where reporting mistakes is encouraged without retaliation.

Management should aim to create a work environment (i.e. quality culture) that is transparent and open, one in which personnel are encouraged to freely communicate failures and mistakes, including potential data reliability issues, so that corrective and preventative actions can be taken. Organizational reporting structure should permit the information flow between personnel at all levels.<sup>10</sup>

Organizational culture is not just addressed by senior management putting the right words in a mission statement but communicating expectations clearly to staff at all levels in the company, and then living by these principles, is the key to success. Leadership, engagement and empowerment of staff at all levels in the organization can then combine to identify and deliver systematic data integrity improvements where good practice becomes automatic.<sup>11</sup>

#### b. Control by Procedure

If procedures are appropriately controlled, data integrity issues can be minimized. There shall be written procedure available for data generation, processing, archival, retrieval and destruction. Where paper based documentation system is followed, it is important that the issuance of documents shall be in control of quality unit to avoid any manipulation.

#### c. Control by Design

Data integrity issues can be controlled by the design. If control measures are in place, then it is impossible to manipulate data or making data integrity issues. For electronic data integrity issues, following are the controls to maintain data integrity in a system.

- **Computerized System validation**

While doing validation of a computerized system, one must ensure that the validation should be performed for its intended use along with computer system.

If you validate the computer system, but you do not validate it for its intended use, you cannot

know if your workflow runs correctly.<sup>12</sup> Computerized system validations should ensure that all necessary technical and procedural controls are implemented ensuring compliance with good documentation practices for electronic data generated by the system.<sup>13</sup> A formal risk assessment shall be done in computerized system validation considering potential of the system to affect quality, safety and record integrity.

- **Audit Trails**

Audit trail function shall be enabled for all the chromatographic and other systems where applicable. Majority warning letters related with data integrity issues states that the Audit trail function is kept disabled and due to this there is a chance where data can be reprocessed again and again or repeat testing of failed samples or deletion of results which are out of specification.

There shall be computer- generated, time-stamped audit trails, for example - date, time, or sequencing of events, as well as any requirements for ensuring that changes to records do not obscure previous entries to ensure the trustworthiness and reliability of the records.<sup>14</sup> The use if audit trails help to ensure that the only authorized activity i.e. addition, deletion or modification of GMP related electronic record have been done.

- **Personnel**

Only authorized personnel shall have authority for addition, modification and deletion of GMP related documents. There should be close cooperation between all relevant personnel such as Process Owner, System Owner, Qualified Persons and IT Persons. All personnel should have appropriate qualifications, level of access and defined responsibilities to carry out their assigned duties.<sup>15</sup>

- **Security**

Strong computer security is another way to control data integrity issues. Strong computer security will ensure that the only authorized personnel have added, modified or deleted GMP data. Also it will ensure that the unauthorized personnel have attempted to access the computer system or data storage devices. Computer security shall also include procedures for periodic electronic data backup, storage, and migration, archival.

- **Electronic signature**

Electronic records may be signed electronically. Electronic signature with appropriate control shall be used instead of handwritten signatures



in any GMP records. Firms using electronic signatures should document the controls used to ensure that they are able to identify the specific person who signed the records electronically.<sup>12</sup>

Electronic records may be signed electronically. Electronic signatures are expected to:

- a. have the same impact as hand-written signatures within the boundaries of the company,
- b. be permanently linked to their respective record,
- c. includes the time and date that they were applied.<sup>15</sup>

#### d. Control by Monitoring

Data integrity issues can also be controlled by the monitoring the process. Independent data review and internal audits are the two ways of monitoring the process. In case of independent review, after completion of any analysis for example, an independent reviewer team must review the hard data comparing with electronic data to ensure completeness, accuracy and traceability find out any changes have been made since the time of electronic data generated.

Internal Audit is a promising tool to control data integrity issues. Using this tool manufacturing facilities can find out and control the potential data integrity issues proactively. Data integrity verification activities shall be implanted into internal audit process and shall be performed periodically.

#### e. Training

Data Governance systems should include staff training in the importance of data integrity principles and the creation of a working environment that enables visibility of errors, omissions and aberrant results.<sup>1</sup> Create awareness among staff so they can assist with this Endeavour, and report concerns before they become full-fledged issues. Train the internal auditors to understand what to look for when detecting data integrity deficiencies.<sup>8</sup>

#### CONCLUSION

Data integrity is an important aspect for the pharmaceutical industry and industry should able to express the integrity of their data during regulatory audits. Warning letters issued to various pharmaceutical industries reveals that the industries have compromises with data integrity issues and resulted into serious implications such as Import ban, consent decree, Debarment and life imprisonment for individuals who involved in data integrity issues, loss of market value, Loss

of customer trust and many others. With proper strategic planning, it is possible to overcome with data integrity issues such as building and sustaining Quality culture, control by design, control by procedure, cGMP training and by other ways.

As increased focus on data integrity during the audits, companies are advised to start internal assessment and periodic monitoring by the quality unit. It will ensure the trust and confidence of the regulators in the pharmaceutical Industries and continuity of the business.

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