REVIEW ARTICLE

Data Integrity Violations: A Challenge to the Pharmaceutical Industry

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Received: 26th Dec, 2019; Revised: 28th Jan, 2020; Accepted: 20th Feb, 2020; Available Online: 25th Mar, 2020

ABSTRACT

Data integrity refers to data reliability throughout the data lifecycle. Terminology "ALCOA" means that the data should be attributable, legible, contemporaneously recorded, original, and accurate. "ALCOA Plus" was introduced later. Violation of the integrity of data is termed as a breach of data integrity. It can take place in various fields, but not limited to manufacturing, quality control (QC), quality assurance (QA), and research. Some of the reasons for breach in data integrity are fabrication or duplication of data, out of specification, out of trend, back-dating, manipulation of data, inadequate standard operating procedures (SOPs), common usernames, and shared passwords. A study to assess the impact of data integrity violations based on the US FDA warning letters was conducted. The majority of data integrity breaches belonged to QC. The frequency of letters based on the country has been presented in the form of a graph. China and India received the highest number of letters for breach of data integrity in the year 2018 and 2017 respectively. It can be concluded that it is important to enforce data integrity and develop strategies for the same. The study is beneficial to understand the reason, affected field of work and remediation methods for data integrity, and improve regulatory compliance.

Keywords: ALCOA, Compliance, Data integrity, US FDA, Warning letters and standard operating procedures.

International Journal of Pharmaceutical Quality Assurance (2020); DOI: 10.25258/ijpqa.11.1.30

How to cite this article: Jaiswal H, Muddukrishna BS, Kulyadi GP. Data Integrity Violations: A Challenge to the Pharmaceutical Industry. International Journal of Pharmaceutical Quality Assurance. 2020;11(1):193-195.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Data integrity refers to the completeness, consistency, and accuracy of data during the data lifecycle. The term ALCOA stands for attributable, legible, contemporaneously recorded, original or a true copy, and accurate data.[1] ALCOA Plus, a new terminology includes words about the quality of documentation that are enduring, available, complete, consistent, credible, and corroborated.[2] (Refer Figure 1a, Figure 1b and Table 1).

Five W's of Data Integrity

Five W's are discussed in FDA Data Integrity and Compliance with current Good Manufacturing Practices (cGMP's). The questions associated with five W's of data integrity are:

- WHAT is raw data, metadata, audit trail?
- WHO generated the data, owns the data, made changes, reviewed the audit trails[3]?

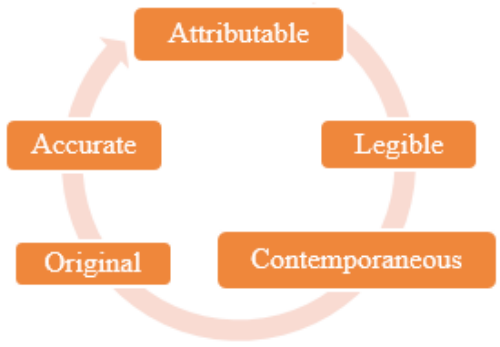

Figure 1a: ALCOA

Figure 1b: ALCOA Plus

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Table 1: Concept of ALCOA and ALCOA Plus

ALCOA	
Attributable	Identification of the user who performed the action
Legible	Clear and understandable
Contemporaneous	Documentation during the activity
Original	A true copy
Accurate	Without editing or errors
ALCOA Plus	
Enduring	Maintainable and true
Available	Easy to access
Complete	Does not lack anything
Consistent	Done in the same sequence over time
Credible	Convincing and effective
Corroborated	Support or provide evidence

- WHEN was it done or processed, or when were the changes made?
- WHERE were the changes made?
- WHY were the changes made?

Breach of Data Integrity

Breach of data integrity refers to the violation of the integrity of the data. This shows that reality and truth are not reflected in the records and documents.[4] This applies to the entire drug discovery and development process, which includes:

- Research and development
- Quality control
- Quality assurance
- Manufacturing
- Clinical trials
- Inspection
- Post-inspection activities[2]

Problems associated with data integrity are mainly related to technical, organizational, or human factors. Organizational factors are related to the management of audits, documents, and quality. Technical factors may include non-compliance with computerized systems with data integrity requirements.[5,6] Human errors may result in data integrity violations.[7] Training on ethics and data integrity should be organized for the employees.

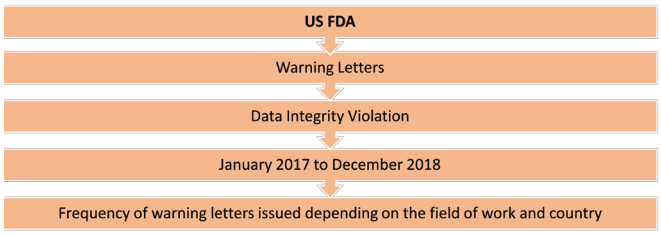


Figure 2: Methodology

Table 2: Number of observations in warning letters based on the field

Year	*Field*	*Number of observations*	*Percentage (%)*
2017	Quality control	13	41
	Quality assurance	5	16
	Manufacturing	10	31
	Clinical trial	4	12
	Total	32	100
2018	Quality control	27	53
	Quality assurance	9	18
	Manufacturing	14	27
	Research	1	2
	Total	51	100

Objective

The objective of the current study is to assess the impact of data integrity breaches in the pharmaceutical industry.

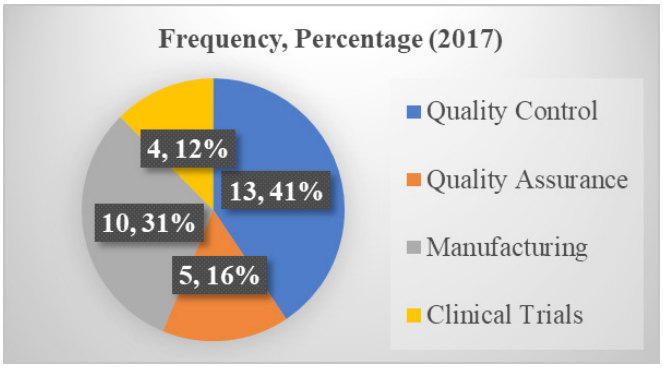
METHODOLOGY

In the present study, breach of data integrity is determined based on the US FDA warning letters issued between January 2017 to December 2018. The assessment was done based on the frequency of warning letters issued, depending on the field of work and country (Refer Figure 2).

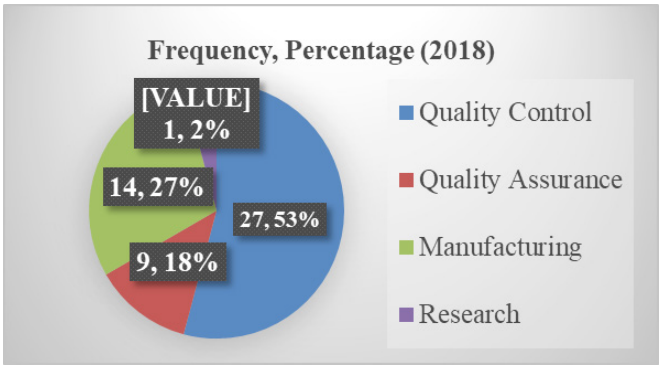
FINDINGS

The study is based on the 21 warning letters issued in 2017 and 33 warning letters issued in 2018 for the violation of data integrity (Refer Table 2). A warning letter may have data integrity issues in more than one field of work. Graph 1a and 1b depict the number of observations in a department, followed by percentage contribution (Refer Graph 1a and Graph 1b).

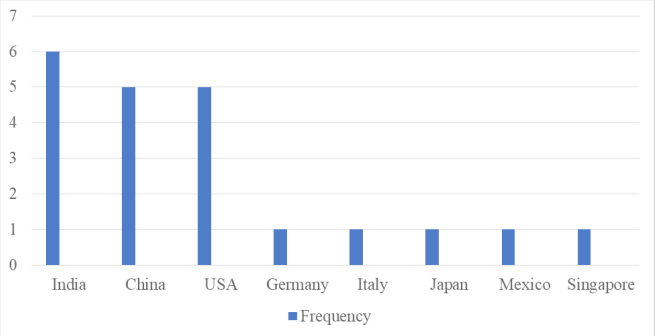
The major reasons behind the breach of data integrity in the field of QC are out of specification (OOS), out of trend (OOT) results, audit trails, back-dating, advance-dating, duplication of data, falsification of data, fabrication of data, manipulation of data, discarding data, inadequate employee training, unjustified reworking, shared passwords, common



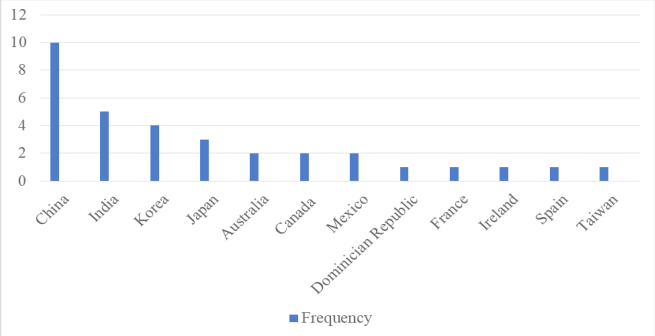
Graph 1a: Number of observations in warning letters based on the field of work in 2017



Graph 1b: Number of observations in warning letters based on the field of work in 2018.



Graph 2a: Frequency of letters based on the country in 2017



Graph 2b: Frequency of letters based on the country in 2018

usernames, and audit trails. Data integrity violations in manufacturing field may result from lack of data, inadequate SOPs, employee training, recording wrong data, not recording data contemporaneously, failure to keep complete records of equipment maintenance, insufficient batch record or annual product review, and when a site does not manufacture the drug as prescribed in the drug master file.[8]

DISCUSSION

The study shows that China in 2018 and India in 2017 received the maximum number of warning letters for breach in data integrity[9] (Refer Graph 2a and Graph 2b). The majority of them were related to the quality control department. The firms are suggested to submit comprehensive investigation into inaccuracies in data recording and reporting, corrective risk assessment and corrective and preventive action (CAPA) plan as a part of data integrity remediation.

Data assures the quality and efficiency of innovation in the pharmaceutical organization.[10] Data integrity is applicable for both electronic as well as manual records.[11] Absence of data integrity may impact the organization and result in the statement of non-compliance, warning letters, importation ban, fines and penalties,[12] reputation damage, safety alerts, share price reduction, business damage,[13] product recalls market withdrawals and sometimes closure of companies losing thousands of jobs.

CONCLUSION

Data integrity and accuracy prove the safety, efficacy, and quality of the manufactured drug. Comprehensive investigations should be done by the firm to understand the extent of inaccuracies as expected by the US FDA. Risk assessment for the lapse of data integrity and its impact must be carried out. The firm should establish a reliable corrective and preventive action (CAPA) plan.[14] To enforce data integrity, it is important to develop strategies and manage the data lifecycle. Hence, effective and justified remediation of data integrity should be established for regulatory compliance.

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