CURRENT STATUS, CHALLENGES AND PREVENTIVE STRATEGIES TO OVERCOME DATA INTEGRITY ISSUES IN THE PHARMACEUTICAL INDUSTRY

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ABSTRACT

The pharmaceutical industry is currently one of the most dynamic among all industries. At present, it is striking with various compliance challenges like never before there is increased regulation, acquisitions, push toward harmonization and endemic in a Data Integrity (DI) concern. DI weakness is identified, either as a result of an audit or a regulatory inspection, companies with multiple sites should ensure that appropriate corrective and preventive actions are implemented across the organizations and appropriate notification to regulatory authorities should be made wherever applicable. The objective of the study carries the number of issues involved within data integrity in current GMP aspects, the root causes were addressed based on warning letters. This review intends to study the concept of data integrity holistically in all aspects, regulatory expectations and to evaluate the state of compliance and challenges that explore to suggest appropriate remedial and proactive measures to avoid DI issues. There were many challenges involved to overcome the issues, which are all about the one's handling by maintaining good documentation practice. The importance, strategies and recommendations were discussed to overcome from the repeated data integrity mistakes.

This review was carried out by systematic searches of data integrity in relevant guidelines, published articles, reviews and abstracts in Google scholar, Pubmed, Science direct, Embase, Web of science, Cochrane database of systematic reviews of articles up to March 2020. The keywords used for gathering information were listed below.

Keywords: Data integrity, Root causes, ALCOA, Recommendations

INTRODUCTION

Data integrity (DI) is the assurance of data records that are complete, accurate, intact, and maintained within the original circumstance, including their connectivity to relevant data records and focuses to prevent unwanted changes to the required information [1]. DI is much important for the management of a quality system in the pharmaceutical industry, which ensures that medicines are safe based on the evidence of data. Due to issues with DI, there was a considerable increase in enforcement actions taken by regulatory bodies [2]. With faster growth in the generics market, economical and regulations on pharmaceutical manufacturers is increasing nowadays. In recent years there has been a significant increase in the number and types of data integrity issues that have been cited in regulatory inspections [3]. The DI related cGMP violations have leads to several regulatory actions, including warning letters, import alerts and seizures. There were many uncovered serious cases on DI related problems. Companies often have DI issues, which are hazardous to the company's long-term prospects and a demoralizing effect on the company culture [4]. Managing data is challenging in the pharmaceutical industry, especially when a firm's growth was emerging on a volume of data at a rapid rate. Distrustful data quality

can result in severe consequences for the responsible organization that destroys the reputation of the organization [5]. Implementing controls and management of data without understanding the regulatory and business processes can result in the questionable validity of data and may lead to regulatory action. DI is the map of maintaining and ensuring the accuracy and consistency of data over its lifecycle [6]. Good data storage and record management are vital elements of the pharmaceutical quality system. DI refers to maintaining and assuring the accuracy and consistency of data over its entire life cycle in compliance with its suitable regulatory requirements [7]. Organizations expect that pharmaceutical organizations have to hold exact records and every single data will be accessible to controllers [8]. There are many chances of getting corrupted results if there is no proper measures are taken to ensure the safety of data. Errors of DI generally arise from human error, uncooperative operating procedures, data transfers, defects in software and physical negotiation to devices [9]. DI maintenance is an essential part of the industry's accountability to ensure the safety, effectiveness and quality of the drug products. Data integrity is a serious part of regulatory compliance [10].

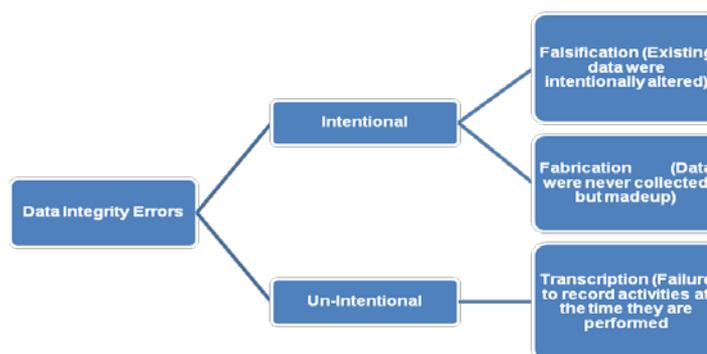Errors involved in the DI system were classified in fig. 1.

Fig. 1: Lapses in data integrity [11]

Common data integrity issues

1. Personnel

- Personnel qualification

- Unqualified persons performing critical tasks

- Inadequate training

- No demonstration of competency

- Using improper techniques

- Inexperienced reviewers

- Differences between the site contract labs personnel and systems

- Not enough qualified personnel

- Active fraud/falsification [12]

2. Task preparation and execution

- Unapproved suppliers

- System/equipment

- Not calibrated/validated-accuracy and reliability issues

- Lack of appropriate access controls

- Overwrite/delete information [13]

3. Materials

- Unlabeled samples

- Processing equipment

- Unapproved/unverified materials used [14]

4. Procedures

- Not thorough enough, leading to variability in performance

- Missing equipment for data recording

- Missing data capture [15]

5. Data collection (Capture/Interpretation/Review)

- Lack of handling with the deviations tends to fail to record, report, investigate or covering up out of specifications (including discarding/not documenting failing results)

- No proper documentation and compilation

- Inadequate investigations, including a failure to identify root cause

- Use of un-validated analytical methods

- Inaccuracies between data systems and specification documents [16]

6. Handling issues

- Personnel overloaded and cutting corners

- Documenting changes to approved records without re-approval

- Failure to follow procedures

- Lack of verification

- Mislabeling/not labeling samples

- Not completing documentation

- Running trial samples [17]

7. Data management and archiving

- Ability to edit data/delete methods

- Lack of backups/protection of records from loss

- Failure to retain raw data/complete data as generated

- Incomplete files/records of data acquired

- No backup or backups that overwritten earlier data

- Hybrid systems of both paper/electronic record [18]

Consequences of data integrity noncompliance

➢ Loss of trust

➢ Recalls

➢ Warning letter/483 observations

➢ Import alert/injunction

➢ Seizure

➢ Non-compliance report

➢ Loss of job/loss of business [19]

Elements of data integrity

The regulated bodies and industries followed a term called ALCOA (Attributable, Legible, Contemporaneous, Original and Accurate) a USFDA guidance since 1990, for ensuring data integrity and which is a key to handling Good Documentation Practice (GDP) [20].

Table 1: Required elements for ensuring data integrity

Elements	Abbreviation	Explanation	Comments
A	Attributable	Action that who performed and when? If anyone was changed the record, who did it and why?	Who did it?
L	Legible	Recorded data must be permanent, readable and durable medium	Can you read it?
C	Contemporaneous	Date and time should be affixed whenever the recorded data was performed	Was it done in real-time?
O	Original	Is the obtained results are original data?	Is it original or true copy?
A	Accurate	Without documents amendments no editing/modification to be done	Is it accurate data?

Example for attributable

- During an approval work out, test results ought to be initiated and dated by the individual who run the test.

- Adjustment of a set point on a procedure or checking framework ought to be made by an approved client and the details of the modifications signed in a review trail [21].

Note: It is imperative to guarantee a mark log is kept up to recognize the marks, initials or potentially assumed names of individuals finishing paper records.

Example for legible

- The use of permanent ink is recommended when finishing the records.

- During a correction process to a record, a single line is always preferable to strike out the old record. This procedure ensures the record is still legible [22].

Note: Should be readable and permanent

Example for contemporaneous

- Electronically performed data, ought to make some date/time stamp joined to the record.

- Ensure electronic frameworks that log information has their framework and in synchronized format [24].

Note: Data should never be backdated, documented at the time of activity
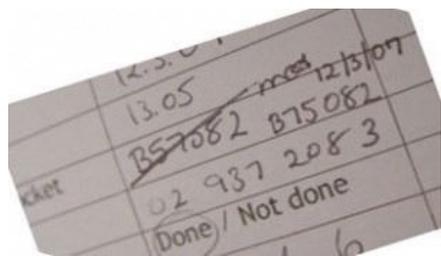
Fig. 2: Legible criteria [23]

Example for original

• Ensure approved test results are recorded on the endorsed convention. The recording brings about a note pad for translation later that can present blunders.

• If unique information is written by hand and should be put away electronically, guarantee a genuine duplicate is created, the duplicate is confirmed for fulfilment and afterward relocated into the electronic framework [25].

Note: Reliable written printout and certified data

Example for accurate

• Use an observer verify for basic record assortment to affirm the exactness of the information.

• Consider how to catch information electronically and check its precision. Incorporate precision checks with the plan of the electronic framework.

• Place confirmation on manual information passage, for instance, temperature results must be entered inside a pre-defined scope of 0-100 °C [26].

Note: Should complies with actual value and error-free

USFDA prohibits the following

• Recording of the data on pieces of paper

• Storing the data in temporary memory

• Sampling and testing to achieve a specific result or to overcome an unacceptable result as this is not as per the cGMP standards

• Actual samples to be used to perform system suitability (system suitability tests should be done by using written procedures and data should be recorded for scientific justification for exclusion) [27].

Minimum data integrity requirements

• Data should be secure from alteration, accidental erasures or loss

• Backup data should be exact and complete

• Data should be stored to prevent loss

• Performed tasks should be documented at the time itself and controlled laboratory practices to be maintained [28]

• The records should be retained as original records and true copies

• FDA requires data to record complete information, a complete record of all data from all the tests performed and no test or data should be failed to record [29].

Why DI issues happen (Root causes)?

Shortage of manpower

Shortage of staff and unnecessary work weight can prompt off base and inadequate documentation [30].

Quantity over quality

Employees might be compelled to bargain the adequate quality levels to meet creation targets or dispatch courses of events [31].

Lack of awareness

Often, representatives are not prepared or insufficiently prepared to understand GMPs. This makes workers consider exercises as a task as opposed to understanding their significance by considering GMP [32].

Effectiveness of training

While the organization may procure the best worldwide mentors, representatives referenced that there were language and highlight obstructions, which kept the workers from understanding the substance, in this manner making the preparation repetitive [33].

Preventing data integrity issues

Information respectability disappointments have prompted organizations losing their licenses, consent orders, cautioning letters, import alarms, summon of the application uprightness arrangement, terrible exposure when issues become newsworthy and more. Assessing at any rate the components introduced in these 5 significant regions in the process will help recognize where any likely information and honesty issues may exist, just as giving plans to upgrades [34].

Personnel preparation

The personnel involving in generating, reviewing and approving data must have adequate knowledge and skills to generate GMP environment and keep up to the data integrity expectations, which includes:

• GMP and 21 CFR Part 11 expectations

• Change control and validation

• Good documentation practices

• Root cause analysis, deviations and investigations

• Data integration and their guidance documents [35]

Procedures

One should ensure that the procedure that,

• Accurately defines the validated process

• It is performed in clear and unambiguous language

• To assure proper execution accurately and constantly by all the personnel involved in performing the task [36]

Equipment/System

The key elements that guarantee the accuracy and control of equipment and systems should be verified, which includes:

• Equipment must be validated, test strategies, information computation/data move systems to guarantee accuracy and right execution preceding use

• The operating systems should be updated from the existing one

• There should be limited access for the data [37]

Being proactive

Being proactive in detecting the potential data integrity issues and upholds the civilizing elements supports data integrity in the organization. Frequent audits on data integrity should be performed and issues in potential or questionable practices should be identified [38].

Recommendations

Based on the detailed study of various aspects of DI issues, regulatory guidelines, expectations and learning from various regulatory inspections/warning letters, the below following are the recommendations to prevent and proactively avoid DI issues to safeguard the company's image and reputation for long-lasting, sustainable business [39]. Recommendations were determined below:

- Organizations should focus on long term sustainability instead of short term gains

- Focus on systems and procedures

- Focus on QBD-Quality by Design/RFT-Right First Time concepts

- Focus on better process understanding than traditional trial and error approach

- Engage SME-Subject Matter Experts/third party DI consultants

- Do not put undue pressure on output/yield improvement, which may force the people to indulge in DI issues.

- Enrich internal audit scrutiny/involve cross-functional experts for self-inspections and ensure self-inspections are for the improvement

- Provide required and adequate management support in terms of resources

- Nurture knowledge sharing practices and create an appropriate platform and share the learning across the various manufacturing sites of the same company

- Learn from mistakes of self and mistakes of other companies

- Actively watch the happenings in the industry and keep updating the skills and knowledge of the core people

- Focus on effective training and evaluate to measure the benefit of training [40]

CONCLUSION

The integrity of data performed by any pharmaceutical organization is a topmost factor for trustworthiness. The finding of a solitary example where information respectability is undermined throws a shadow over the entire of the information produced. Discovering the occurrence of adulteration brings up the reason for more number of cases for such non-compliance on guidelines. Therefore ensuring data integrity is a major importance to any pharmaceutical organization as the consequences of getting it wrong are very costly and it will take a long time to rebuild the trust. Among 1000+manufacturers in generic pharmaceuticals across the globe, it is unclear how many operate in such a way that ensures compliance with current and future regulatory agencies in data integrity expectations. Getting data integrity right is a huge credit. It needs a concentrated, continuous effort to improve and maintain the policies involved and discipline culture to avoid regulatory issues. The time, hard costs, open door costs and key interruption of fixing a DI administrative lack fundamentally exceed the venture of time and vitality to make proper DI frameworks and controls. By putting up resources into an arrangement of precise, compelling and practical consistency will secure productivity and integrity in maintaining the quality of data standards.

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CONFLICTS OF INTERESTS

None

REFERENCES

1. Jain Sanjay Kumar. Strategy to avoid data integrity issues in the pharmaceutical industry. Pharma Innovation J 2017;6:110-5.
2. SLM, Gupta NV. Quality management system in change control at industry level: an overview. Int J Pharm Pharm Sci 2015;7:13-9.
3. Agarwal P, Mishra A. Pharmaceutical quality audits a review. Int J Appl Pharm 2019;11:14-22.
4. Alamelu R, Amudha R. Pharma export: comforts and confronts in India. Asian J Pharm Clin Res 2016;9:24-6.
5. MN Raviteja, N Vishal Gupta. A review on electronic data management in pharmaceutical industry. Asian J Pharm Clin Res 2013;6 Suppl 2:S38-42.
6. Koshechkin K, Lebedev G, Tikhonova J. Regulatory information management systems, as a means for ensuring the pharmaceutical data continuity and risk management. Intelligent Decision Technol 2019;14:265-74.
7. Wen MM, Aref H, Abozaid A, Kandil NH, Elsobky YH. Quality evaluation and survey of the essential need for drug information centers. Int J Pharm Pharm Sci 2016;8:137-43.
8. Valentin Steinwandter, Christoph Herwig. Provable data integrity in the pharmaceutical industry based on version control systems and the blockchain. PDA J Pharm Sci Technol 2019;73:373-90.
9. Kumar S, Tanwar D, Arora N. The role of regulatory GMP audit in pharmaceutical companies. Int J Res Dev Pharm Life Sci 2013;2:493-8.
10. Bhatia K. Current scenario and future challenges in pharma segment; 2014. Available from: http://www.pharmabiz.com/ NewsDetails.aspx?aid=79940andsid=9. [Last accessed on 05 Jun 2020]
11. Anu Linna, Mirka Korhonen, Marja Airaksinen, Anne Mari Juppo. Experiences of using the GMP audit preparation tool in pharmaceutical contract manufacturer audits. Drug Dev Ind Pharm 2010;36:632-7.
12. Rohit A Patil, Shruti N Patil. Data integrity and worldwide regulatory guidance. Pharma Tutor 2016;4:20-4.
13. P Kiruba Rachel, N Vishal Gupta. Data integrity-regulations and current scenario. Int J Pharm Sci Rev Res 2017;43:16-22.
14. Abhishek Kumar Pandey, Asif Irshad Khan. Key issues in healthcare data integrity: analysis and recommendations. IEE Xplore 2020;8:40612-28.
15. Joanna Gallant. Identifying and preventing common data integrity issues; 2016. Available from: https://www.mastercontrol.com/gxp-lifeline/identifying-and-preventing-common-data-integrity-issues. [Last accessed on 05 Jun 2020]
16. Jill Wechsler. Data integrity key to GMP compliance. Pharma Technol 2014;38:1-2.
17. Grant. Ensuring Data Integrity through ALCOA. Pharmout; 2016. Available from: https://www.pharmout.net/data-integrity-alcoa/. [Last accessed on 05 Jun 2020].
18. U.S. Food and drug administration. FDA Form 483 Frequently Asked Questions; 2017. Available from: https://www.fda.gov/ iceci/inspections/ucm256377.htm. [Last accessed on 05 Jun 2020].
19. Rattan AK. Data integrity: History, issues, and remediation of issues. PDA J Pharm Sci Technol 2018;72:105-16.
20. David Churchward. Good Manufacturing Practice (GMP) data integrity: a new look at an old topic, part 1; 2015. Available from: https://mhrainspectorate.blog.gov.uk/2015/06/25/ good-manufacturing-practice-gmp-data-integrity-a-new-look-at-an-old-topic-part-1/. [Last accessed on 05 Jun 2020]
21. Anil K Rattan. Data integrity: history, issues, and remediation of issues. PDA J Pharm Sci Technol 2018;72:105-16.
22. Paul Smith. Data integrity in the analytical laboratory. Pharm Technol 2014;38:2-4.
23. Valentin Steinwandter, Christoph Herwig. Provable Data integrity in the pharmaceutical industry based on version control systems and the blockchain. PDA J Pharm Sci Technol 2019;73:373-90.
24. U.S. Food and drug administration. data integrity and compliance with drug CGMP questions and answers guidance for industry; 2018. Available from: https://www.fda.gov/ downloads/drugs/guidances/ucm495891.pdf. [Last accessed on 05 Jun 2020]
25. Medicines and Healthcare Products Regulatory Agency. GXP Data Integrity Guidance and Definitions; 2018. Available from: https://assets.publishing.service. gov.uk/government/uploads/system/uploads/attachmentdata /file/68724 6/MHRA_GxPdata_integrityguideMarchedited Final.pdf. [Last accessed on 05 Jun 2020]
26. Vignesh M, Ganesh GNK. Fixed-dose combinations banned in an india-a review. J Pharm Sci Res 2020;12:987-91.

27. Bramstedt KA. A study of warning letters issued to clinical investigators by the United States food and drug administration. Clin Investigative Med 2004;27:129-34.
28. Gogtay NJ, Doshi BM, Kannan S, Thatte U. A study of warning letters issued to clinical investigators and institutional review boards by the United States food and drug administration. Indian J Med Ethics 2011;8:211-4.
29. Saiyed AA, Shetty YC. Analysis of warning letters issued by the US Food and drug administration to clinical investigators, institutional review boards and sponsors: a retrospective study. J Med Ethics 2015;41:398-403.
30. Garmendia CA, Bhansali N, Madhivanan P. Research misconduct in FDA-regulated clinical trials: a cross-sectional analysis of warning letters and disqualification proceedings. Ther Innovation Regulatory Sci 2018;52:592-605.
31. Ni A Khin, Gail Francis, Jean Mulinde. Data integrity in global clinical trials: discussions from joint us food and drug administration and uk medicines and healthcare products regulatory agency good clinical practice workshop. Clin Pharmacol Ther 2020;107:1-15.
32. RD McDowall. Are you controlling peak integration to ensure data integrity? LCGC Europe 2020;38:346-54.
33. Bhuvaneswari VS, Chandan RS. Review on safety assessment of a cosmetic product. Int J Curr Pharm Res 2018;10:1-6.
34. B Kapre Varad, SK Sekar. Quality analysis and quality control in building construction with six sigma approach. J Crit Rev 2020;7:412-8.
35. Ronald L Deffenbeugh. Total quality management at construction jobsites. J Management Eng 2017;9:15-24.
36. E Sweetline Priya, G Suseendran. Cloud computing and big data: a comprehensive analysis. J Crit Rev 2020;7:185-9.
37. K Makesh Babu, K Mohan Kumar. Data profiling on big data using key dependencies to improve the quality of metadata. J Crit Rev 2020;7:1423-30.
38. Z Abedjan, L Golab, F Naumann. Profiling relational data: a survey. Int J Very Large Data Bases 2015;24:557-81.
39. K Ganga Devi, R Renuga Devi. Cloud data integrity security by using blockchain. J Crit Rev 2020;7:2884-7.
40. J Li, W Yao, Y Zhang, H Qian, J Han. Flexible and fine-grained attribute-based data storage in cloud computing. IEEE Transactions Services Computing 2017;10:785-96.