AN APPROACH OF DATA INTEGRITY IN PHARMACEUTICAL INDUSTRIES

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ABSTRACT: Data Integrity assures that the information is traceable, readable, current, unique, and correct. It is an essential aspect of the industry's obligation to assure the safety, efficacy, and quality of their products. In pharmaceutical industry it plays a vital role and it is an important current issue for regulators around the world. During inspections a multiple of problems being found by the pharmaceutical regulatory agency all over the world. There are many regulatory guidelines on data integrity. The objective of this study carries number of issues involved within data integrity in current GMP aspects, the root causes were addressed grounded on warning letters. In this article we study about types, advantage and disadvantage, factors affecting, ALCOA concept, and their limitations.

KEYWORDS: Data integrity, ALCOA, WHO, Retrieval and storage.

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INTRODUCTION:

Data Integrity (DI) refers to accuracy and consistency of data, also it assures that data are accurate, consistency, safe and complete in terms of regulatory guidelines. It plays a major role in pharmaceutical industries as it helps in prevention of stealing and systematic storage along with arrangement of data. It supports to create a trust between industry and regulatory agency in terms of storage and retrieval of data in precise order. In pharma industry as a part of Quality Attribute to ensure that final products meet all the quality attributes; integrity of data in chronological order makes the system flawless in terms of storage and retrieval process of data. The DI is used to protect original data from accidental modification, intentional adjustment, and falsification and deletion. In recent years, USFDA observed that cGMP violations occur due to data integrity during cGMP inspections. Regulatory bodies issued many warning letters to the pharmaceutical industries that violated DI. The organization expects that data should be reliable and accurate.[1]

DI plays a vital role in US FDA audit. It is customary to back up the data containing valid reports from all of the department. Incase of failure to back up the data consisting of vital information regarding quality of the product may lead to product termination.[2]

DI forms an important part of internal audit conducted by working staff of quality assurance department with respect to that pharmaceutical company. In case of invalid DI, the supervisor from quality assurance department is liable to suspension or penalty. The supervisor has an authority to issue command with respective department subjected to invalid data integrity, excessive adulteration and data manipulation.[3]

Integrity:

DI refers to maintaining and assuring the accuracy and consistency of data. A variety of mechanisms used to assure the integrity of a data unit or stream of data units. Integrity can be classified into five types: they are 1) Logical integrity 2) Referential Integrity 3) User-Defined Integrity 4) Domain Integrity 5) Physical Integrity.

Logical integrity [LI]:

It is an important part of DI has it involves a process of physical integrity, protects information from human error, piracy and data hackers. Logical integrity plays a vital role in storage and analysis of data retrieved from respective department in pharmaceutical industry. A major threat to data integrity occurs via human error vial manually entering vital information into storage data base. DI is suspectable to bugs and malware while transferring and storage of data information from one sitewithin a data base to another field of storage data base. In pharmaceutical industry there is a certain work which hasbeen allocated to quality assurance department; the supervisor involved in such department has a varying number of responsibilities regarding analysis and storage of data retrieved from quality control department. The logical integrity helps in minimizing error generated within the data obtained from quality control department.[4]

Referential integrity [RI]:

Integrity can be of varies types involving process and implementation of rules involved in data storage and retrieval process. Referential integrity consists of imperative element such as foreign keys. This foreign key consists of various principles regarding valve between two states. The states consist of foreign key valve; which can also be termed as primary key valve of another table, or it can be null. The referential Integrity isan important part of implementation of gathering of data generated across various department in pharmaceutical industry. The various norms issued by regulatory bodies emphasis on data safety and protection against safety of such vital components by using Referential Integrity method. All the procedures and rules enforced to deliver proper implementation and gathering of data in accordance with standard operating procedure by using foreign key as a tool.[5]

User-defined integrity [UDI]:

In pharmaceutical industry data retrieved from post marketing surveillance and information gathered from pharmacovigilance supervisor is respective to particular set of individuals. In such peculiar scenario the data needs to be user defined for the process of integration. With implementation of user defined integrity in accordance with standard operating procedure has set by regulatory guidelines; Data generated from variousindividuals can be protected and stored with implementation of data integration or user defined integrity process respectively. In case detection of errorif reported; the data retrieval process is simplified by the application of user defined integrity.[6]

Domain integrity [DOI]:

In presence of various set of rules and procedures present in operational records of pharmaceutical industry; this data can be simplified and stored by the execution of DOI procedure. Information consisting of various variables and constant such as places, name, number, value generated, profit and loss can be arranged in chronological series by the implementation of domain integrity. The domain integrity plays a vital role in data storage and retrieval process involving various combination of constant and variables. Such constant andvariables can be separated by the application of data retrieval process via using data integrity in such respective scenario. If any error generated while gathering and processing of respective data in system assigned by the respective departments involved in domain integrity, can be easily detected and solved.[7]

Physical integrity [PI]:

There can be various way in variable factors which affect data integrity process and storage, Natural calamity is among one of the factors which is beyond the control of one's wishes. Natural calamity such as earth quake, flood, tsunami, tornado and hail storm can disrupt the course of action of storage and retrieval of data integration. With the implementation of physical integrity and its working methodology can play a vital role in data storage and its protection. Multiplication of data stored in the system along with process of duplication is a part of physical integrity process. Concrete walls along with various kinds of physical barrier protection can be provided in data storage facilities in order to protect against various unpredictable natural circumstances.[8]

Advantages:

DI used to protect the data during end-to-end transmission via transmission medium, backup system for emergency purpose, internal and external audit conducted by the regulatory body. The integration of data helps in technology transfer from pilot to large scale manufacturing unit in pharmaceutical industry [scale-up technology]. DI helps in problem solving and analysis of essential data required by the respective supervisor. Artificial intelligence and block chain technology made the data integrity helps in further facilitating advancement in data retrieval from the respective system.[9]

Disadvantages:
The data integrity is susceptible to data stealing, piracy and manipulation of its content by hackers. Increases in data storage servers, globally makes the vital data prone to hacking. Data integrity is an old school and outdated methodology in pharmaceutical industry. Weak hardware quality leads to physical damage so that it reduces the chances of data retrieval and its protection. The artificial intelligence is more advance method when compared to the data integrity. The block chain technology is much more advance in its protection facility than data integrity. It has several kinds of limitation which prevents its usage globally. Data which is generated by old school handwritten method is not eligible for data storage and its integrity process in pharmaceutical industry.[10]

Common data integrity issues:
Some of the common issues that repeatedly come up in FDA warning letters are:

1. Common passwords- Where analysts share passwords, it is not possible to identify who creates or changes records, thus the A in ALCOA is not clear.
2. User privileges the system configuration for the software does not adequately define or segregate user levels and users have access to inappropriate software privileges such as modification of methods and integration.
3. Computer system control Laboratories have failed to implement adequate controls over data, and unauthorized access to modify, delete, or not save electronic files is not prevented; the file, therefore, may not be original, accurate, or complete.
4. Processing methods Integration parameters are not controlled and there is no procedure to define integration. Regulators are concerned over re-integration of chromatograms.
5. Incomplete data- The record is not complete in this case. The definition of complete data is open to interpretation see references 13 and 14 for a detailed analysis of FDA 483 observations
6. on complete data (21 CFR 211.194 and sub parts).

7. Audit trails- In this case, the laboratory has turned off the audit-trail functionality within the system. It is, therefore, not clear who has modified a file or why.[11]

Causes of data integrity issues:

1. Data review limited to printed records- No review of e-source Data.
2. Shared identity and passwords.
3. Effective training to new entrants.
4. Adherence to procedures and Standard Operating Procedures (SOPS).
5. Following regulations and cGMP requirements.
6. Lack of quality culture.
7. No verification during self-inspections.
8. Incomplete or altered data
9. Backdating/Fabricating/Discarding
10. Testing into compliance.
11. Changing integration parameters of chromatographic data to obtain passing results.
12. Turning off Audit trails capabilities
13. Password sharing
14. Inadequate controls for access privileges
15. One batch Test results were used to release other batches. [12]

Error due to human: There are various kinds of error among which cannot be prevented to a great extent involves human error. This type of error comes under non-recurring and unavoidable factor which cannot be minimized to a great extent. Human error can be caused due to various factors such as: excessive adulteration, in accuracy in working methodology, attention deficient of working individual, lack of precision while collecting and integration of data, and physical factor such as natural calamity and accident etc.[13]

Errors in the transfer: Transferring of data is an important part in pharmaceutical industry as it has wider application accordingly. There can be various factors which influence transfer of data thereby leading to error in the system; It can be also be known as transfer error. For example; there is set of variables, constant and numbers which gets changed in course of action while transmitting it from one department to another in pharmaceutical industry. This change occurred while transferring of data is termed as transfer error. Transfer error can be off three types; small transfer error, large transfer error and intermediated transfer error.

Small variation transfer error means the variation in variable, constant and numbers in transferred file is less different from those original files. The extent of deviation in value is small.

Large variation transfer error means the variation in variable, constant and numbers in transferred file is more different from that of original files. The extent of deviation is large.

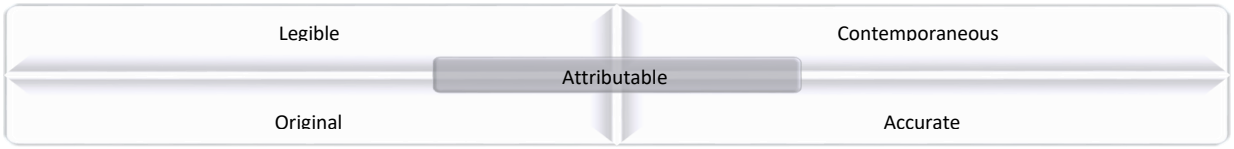
Intermediated transfer error means this type oftransfer error is caused due to poor calibration of instruments, human error, poor research methodology or not following proper guidelines mentioned in standard operating procedure.[14]

ALCOA concept:

The FDA was the first to use the acronym ALCOA,which stands for [Accountable, legible, Contemporaneous, Original, and Accurate].[15]

Attributable: Who obtained the data or performed the action, and when was it obtained.[16.] **Example:** During an approval process, the person who runs the test should begin and mention the date at which the work has been done. An approved client should make changes to a procedure or testing framework, that specifics the changes can be documented in a review trail.

Note: It is critical to keep a mark log to identify the markings, initials or maybe assumed identities of persons finishing paper documents. When the record has been completed, it is advised that you use permanent ink. When an entry has been corrected, a single sentence is always preferred over the original record. This method guarantees that the record remains readable. It should be persistent and readable in all scenarios.[17]



Legible: Data must be accessible along with durability during the course of action involved in data integrity.

Contemporaneous: At the period of the activity, data was documented.[18] **Example**: The word Contemporaneouscan be seen in such case- when vital information is obtained from multiple sources is synced and compiled into proper useable data in chronological series.

Original: Raw or raw data must be provided in original or true copy form. **Example:** When a series of raw data needs to be processed into useable forms of binary numbers, table and columns etc.; the original data is misplaced by the process data.[19]

Accurate: Data must include meaning full information.[20]**Example**: To ensure the accuracy of the information, use an observation check for basic record collection. Consider electronic methods to capture and verify information. Integrate accuracy checks into every part of electrical framework's design. Confirm manual information flow, for example; temperature data must be recorded within a pre-defined range of 0-100 °C.

Now ALCOA plus:

Some more words were included to define the attributes of

good documentation practice. They are: Easy or feasible to obtain or use, or existing or prepared to use, **Accessible:** Capable of being accessed or sought, or of being utilized or gained,[21]**Complete:** There is nothing missing, Consistent: Consistently performing or behaving in the same manner, **Credible:** Capable of being believed or effective, **corroborated:** To corroborate or contribute to the proof by adding facts or evidence.[22]

Examples:

Data discarding, incorrect data recording, back-dating versus forward-dating, making a misleading or incorrect statement, omitting a fact, or making a statement that lacks evidence of an actual occurrence, providing untrustworthy information, replacing old data with fresh.

USFDA prohibits the following:

1. Recording of the data on pieces of paper.
2. Storing the data in temporary memory.
3. Sampling and testing to achieve a specific result or to overcome an unacceptable result as this is not as per the cGMP standards.
4. 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).[23]

Minimum data integrity requirements:

1. Data should be secure from alteration, accidental erasures or loss.
2. Backup data should be exact and complete.[24]
3. Data should be stored to prevent loss.
4. Performed tasks should be documented at the time itself and controlled laboratory practices to be maintained.
5. The records should be retained as original records and true copies.
6. 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.[25]

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. Recommendations were determined below:[26]

1. Organizations should focus on long term sustainability instead of short-term gains.
2. Focus on systems and procedures.
3. Focus on QBD-Quality by Design/RFT-Right First-Time concepts.
4. Focus on better process understanding than traditional trial and error approach.
5. Engage SME-Subject Matter Experts/third party DI consultants.
6. Do not put undue pressure on output/yield improvement, which may force the people to indulge in DI issues.
7. Enrich internal audit scrutiny/involve cross-functional experts for self-inspections and ensure self-inspections are for the improvement.
8. Provide required and adequate management support in terms of resources.
9. Nurture knowledge sharing practices and create an appropriate platform and share the learning across the various manufacturing sites of the same company.
10. Learn from mistakes of self and mistakes of other companies.
11. Actively watch the happenings in the industry and keep updating the skills and knowledge of the core people.
12. Focus on effective training and evaluate to measure the benefit of training.[27]

Importance of Data Integrity:

Regulators increased attention to data integrity for several years, the FDA and other global regulatory bodies have emphasized the importance of accurate and reliable data in assuring drug safety and quality.[28]

World Regulatory Guidance on Data Integrity:

USFDA: 21-CFR:

21-CFR (Code of Federal Regulation) is a codification of the general and permanent rules published in the federal register by the executive departments and agencies of the Federal Government. Title 21 of the CFR is reserved for rules of the Food and Drug Administration. Each title/volume of the CFR is revised once each calendar year on approximately April 1st of each year.[29]

MHRA:

MHRA guidance on GMP data integrity expectations for the pharmaceutical industry the guidance is intended to complement existing EU GMP relating to active substances and dosage forms. Data integrity is fundamental in the pharmaceutical quality system which ensures that medicines are of the required quality.[30]

TGA:

Australian regulatory body Therapeutic Goods Administration (TGA) give the requirement of data integrity in the form of deficiency. A deficiency in a practice or process that has produced, or may result in, a significant risk of producing a product that is harmful to the user. Also occurs when it is observed that the manufacturer has engaged in fraud, misrepresentation or falsification of products or data.[31]

cGMP:

As a reflection of the importance of this issue FDA released guidance on Data Integrity and Compliance with cGMP within the guidance itself the FDA notes the trend of increasing data integrity violations.[32] cGMP compliant record-keeping practices prevent data from being lost or obscured. FDA's authority for cGMP comes from FD&C Act section 501 a drug shall be deemed adulterated if "the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirement of the act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess".[33]

Good Documentation Practices.

In the context of these guidelines, good practices are those

measures that collectively and individually ensure documentation, whether paper or electronic, is attributable, legible, traceable, permanent, contemporaneously recorded, original and accurate.[34]

WHO:

Essential medicines and health products, WHO launches data integrity guidelines to protect patients all over the world. WHO proposed a guideline on international good practice for regulatory authorities and inspectors that can help reduce incidents of incomplete presentation of data by manufacturers or deliberate data falsification? While us developing a medicine and bringing it to market. It involves a multitude of actors and activities; a fundamental step is linked to the robustness and accuracy of the data submitted by manufacturers to national regulatory authorities. That data must be comprehensive, complete, and accurate and true to assure the quality of studies supporting applications for medicines to be put on the market. It also must comply with a number of standards, namely: good manufacturing practices (GMP), good clinical practice (GCP) and good laboratory practices (GLP).[35]

EME:

The European Medicines Agency (EMA) has released new Good Manufacturing Practice (GMP) guidance to ensure the integrity of data that are generated in the process of testing, manufacturing, packaging, distribution, and monitoring of medicines. Regulators rely on these data to evaluate the quality, safety, and efficacy of medicines and to monitor their benefit-risk profile throughout their life cycle. Good controlling of data records helps to ensure that the data generated are accurate and consistent and help to take good decision making by pharmaceutical manufacturers and regulatory authorities.[36]

Eight ways to reduce data integrity risk:

Since data integrity risks are so detrimental to enterprises and data-driven operations, a variety of strategic steps must be implemented to mitigate these threats. However, it is very hard to reduce data integrity risks with a single strategy, making it preferable to employ a combination of strategies. Among the most effective methods for reducing data integrity concerns are: [37]

Encourage an integrity culture:

In every pharmaceutical organization the integrity culture places a vital role in developing, formulation, product development and marketing of the product respectively. With each penury there come challenges, problems and hardships which can be solved using proper integration of data in required manner. The integrity culture has many vital points among which data integrity places an important role in developing of product and minizine error. Every pharmaceutical organization has to develop and promote a strong integrity culture for its future growth and development. Every department in pharmaceutical industry especially quality assurance department has to focus on various principles of integration of data collected from varying departments having different functions. With strong, resilient and consistent process of data integrity will lead to minizine error prospects in near future.[38]

Put quality control measures in place:

As we know that quality of product may get affected with improper data management and replacement, the data obtained from quality control department may affectthe product quality to a great extent. The data obtained from quality control department in pharmaceutical industry plays an important role in integration of data and analysis for future prospects accordingly. Proper quality control measures are vital up to a great extent for the proper product development along with arrangement of obtained data in required manner.[39]

Create an audit trail:

In accordance with standard operating procedure obtained from different regulatory bodies; a proper and consistent audit trial has to be conducted in regular interval of time.[40] Periodic audit trial in pharmaceutical industry will check various parameters including data integrity, arrangement of data as specified in sop, quality of product and analysis of data obtained from quality control department. With each audit trial, the pharmaceutical industry makes a better arrangement in terms of data integrity and minimization of error.[41]

Create flow charts for all important data:

In pharmaceutical industry a proper road map has to be planned ahead in accordance with management of appropriate data in precise and accurate manner. By creating various flow chart of integrated data and its summit will lead to good manufacturing practice, good laboratory practice, approval of guidelines from WHO and ICH regulatory body. Creating a flow chart will also help in problem solving ability, planning of future prospects, knowing its weak and strong areas in respective pharmaceutical industry. Integration of data obtained from various sources in pharmaceutical industrycan be arranged by using flow chart and its analytical operating procedure.[42]

Address known security vulnerabilities:

In present scenario, there is "n" number of possibilitiesof hacking into data base obtained from pharmaceutical industry. The vulnerabilities further increase upon compiling of data and transferring it from one database to another. Hacking, pricey theft, inducing virus and bugs may lead to breakdown of firewall in security patch system. With proper malware security system installed and runed for a particular duration of time interval may route to be significant in minimizing vulnerabilities in security patch system.[43]

Comply with the software development lifecycle:

With each passing day in pharmaceutical industry, the implementation of latest technology facilitates the growth and development of the product. The software used in pharmaceutical sector plays an important function of data complaining and its integration for further research analysis. This software needs to be updated on regular basis for smoothening the process of data collection, storage and retrieval method. The software development takes places after old software has been declared obsolete from respective governing bodies in pharmaceutical industries.[44]

Test your computer system:

The IT department present in the pharmaceutical industry is given an important role of maintaining, storage and retrieval method in both hardware as well as software system. The staff, supervisor and software engineers working in information technology system needs to be regularly trained, updated to latest technology and be ready to implement latest updates in related/required fields. The regular maintenance of hardware disk, personal computer and storage drives may keep the core computer system away from viruses and bugs.[45]

Use error detection software:
Anomaly detection tools and services can assist in monitoring and isolating outliers, determining why mistakes happened, and demonstrating how to prevent them from near future. This entire procedure is crucial for keeping data security risk under control.[46]

CONCLUSION:

In pharmaceutical sector, data integrity and its management playa vital role in its functioning, operation and manufacture of its product respectively. The steps followed in integration of data involve process of preservation, protection, duplication, storage and retrieval methodology followed by the pharmaceutical industry to obtained optimum result. Audit trails along with proper preservation of data obtained across various department in pharmaceutical industry needs to be properly arranged as mentioned in standard operating procedure and follow the rules implemented by the regulatory bodies. In above review article we have discussed about data integrity, its advantages and disadvantages, challenges faced by pharmaceutical industry regarding data integration, causes of improper management of data, warning letter regarding the subject and its solution respectively.

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