Review of Data Integrity in Pharmaceutical Industry

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ABSTRACT

Data integrity has been in the world for a quite some time. In the pharmaceutical industry, it has been playing a major role in ensuring the correctness and truthfulness of the data. The industry has been upgrading the technologies for the production of drugs, storage and distribution. In the past, the man-made workforce has been upgraded to the machine that too Artificial Intelligence machine, computers etc. In such a case integrity of data is utmost priority for ensuring correctness. Machine and the computer are built to reduce the workforce and make the work convenient for workers. It is helpful in reducing the time load of work but to ensure the honesty of the work; data integrity came into effect. A company which runs with the full GMP regulations will get less warning letter during the audit trials, but a company with proper GMP as well as proper implementation of data integrity will percolate into the audit trials successfully. Ensuring data integrity will help the firm to acquire a smaller number of warning letters or form 483. Efficacy; quality and safety of the drug can be easily achieved by data integrity. Data integrity has revolutionized the pharmaceutical industry. Terms such as ALCOA ALCOA+ plays a major role in the integrity of data and been used by various regulatory agencies such as FDA MHRA etc.

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INTRODUCTION

In the present scenario, when the world is moving towards the digital platform, data integrity plays a major role. Data integrity simply means the accuracy and reliability of data. It is important in industry, academic as well as research field also, but it plays a major role in the healthcare sector. Be it submission of CTD (eCTD) to final sell of drug product everything is recorded for its safety and authenticity, here comes data integrity ensuring the safety of data, protecting it from accidental or intentional modification or falsely changing of data. There are many instances where data integrity leads to issuing of warning letters, from 483 to subsequently closing of big firms. Data have been effective for all the processes; small data integrity issue may lead to small injuries to big problems such as life-threatening as well as may lead to the death of a person. Data integrity is important for electronic submission to paper-based data. To overcome this issue, regulatory bodies have come up with their data integrity guidelines as well as to maintain the safety of data throughout their lifecycle.

Back in the 1700s and 1800s, paper-based work was done. Depending on the company, black or blue ink so that information could not be erased or lost when got wet. It was secured by putting the documents in locked cabinets. If copies were issued, it

was stamped with "COPY" ensuring it was copied. If data was to be changed; it was changed in such a way that visibility of original data was visible, apart from that who changed it, when it was changed and, in some cases, why the change was made must be mentioned.

Poor collection of data, lack of guidance or training may provide a high risk of the data integrity issue. Unintentional modification of data if not found primarily, may lead to serious consequences. Earlier the regulatory process of a quality system in the firm was recorded and written on paper, binders, lab notebooks etc. The detail was specified with the help of data and signature. But nowadays the industry is digitalized and there are many advantages of it. Data integrity license us to look around the data in a faster way from a wide variety of devices. We may sit in one corner of the world and ensure that the firm running with its full potential. We can easily make the required copies of data for further work process. The data can be easily shared through the various platform when even required. Data integrity practices have improved and revolutionized the pharmaceutical industry. (Kumar, 2016)

Good documentation practices protect all form of data starting from raw data which is otherwise called as Metadata. Firms are required to practice good documentation practices to ensure that their data is well protected and preserved. With the advancement in technology, good documentation practices also have evolved into various GxP like good clinical practice, good laboratory practices, good manufacturing practices, which all tends to improve the integrity of data. Apart from this, ALCOA & ALCOA+ have been implemented for better data integrity in the data. (WHO, 2020)

Importance of data integrity

1. Product efficacy, quality and safety can be made certain with authenticate and accurate data provided through data integrity.

2. Due to the integrity of data, the trust between the firm and regulatory agencies improve and grow.

3. Inspection of every process from the production till the supply lessens, ensuring less amount of workload.

4. It helps recall products complying with the regulations and improving company image in the industry.

5. To summarize data integrity helps by providing data that is completely accurate and consistent. (Pharmaceutical Guidelines, 2020)

History

The 1980s- Basic GMP

The 1990s- Part 11 –computer control

The 2000s- Quality system/OOS/CAPA

2015- MHRA- GMP Data integrity definition and guidance for industry.

2016-{April} FDA- (draft) data integrity and compliance with cGMP guidance for industry.

2016-{June} WHO-(draft) guidance on good data and record management practices.

2016-{August} EMA- Question & answer- good manufacturing practices- data integrity compliances

2016{July & August} PIC/S-(draft) Good practices for data management and integrity in regulated GMP/GDP environment.

2018{March} MHRA-GxP – data integrity guidance and definition.

2018{November} PIC/S-(draft) - good practices for data management and integrity in regulated GMP/GDP environment.

2018{December}-FDA- data integrity compliance with drug cGMP.

Regulatory parameters

Data integrity is a critical regulatory parameter. Various guidance and regulations such as FDA's 21 CFR part 211, 21 CFR part 11, EU Annexure 11, ICH Q7 all have a significant role in establishing the integrity of data and ensuring that data is accurate and consistent. Few regulatory parameters are as follows

1. Management should be responsible for the integrity of the data. They should ensure proper training of staff to make them competent.

2. Using a network system with a database. Ensuring system configuration for protection of data.

3. Providing unique identities for electronically working to staff for ensuring that if changes made it can be evaluated properly. The electronic signature used in the document must be authenticated.

4. SOP (standard operation procedure) per the company must be properly followed.

5. Both papers, as well as electronic data, must be approved by authorized person only. All the documents must be evaluated by the quality management system periodically.

6. Good documentation practices should be strictly followed.

7. Validation and Calibration of laboratory apparatus must be done properly to ensure that there is a low risk for error in the reading and measurements.

8. Proper audit trails must be done even if the proper SOP is followed, ensuring compliances with the regulation and help in maintaining the record. (Bhadrashette, 2018)

Data

Data are any sort of information, facts, figure, numbers collected together. All the original data, values that are generated during any activity that is recorded or maintained for any future reference. The information can be recorded on paper or electronically in either of the case the data must be accurate. If data is recorded in the paper the data should be legible and stored properly, the computer-related data must be accurate and saved properly with date-time, it should be also authenticated with the person in-charged. Data should be correct and should be up to date with the specified time zone. It should be always complete reflective and truthful. (MHRA, 2018) As shown in Figure 1, Confidentiality, integrity and availability is the common feature of data. All these components are useful to main the data.

Raw data

Raw data is defined as the original record (data) which can be described as the first-capture of information, whether recorded on paper or electronically. Information that is originally captured in a dynamic state should remain available in that state.

Raw data must permit full reconstruction of the activities. Where this has been captured in a dynamic state and generated electronically, paper copies cannot be considered as 'raw data'. (MHRA, 2018)

Metadata

Metadata gives the background of data. Metadata without data is useless and data without metadata is useless. Metadata is any data that describe the main data. These are an element that helps us understand the data more clearly. These can be the date, units, and measurements, file name, file size etc. (MHRA, 2018)

Static data & Dynamic data

Static data are the data that are fixed; these data cannot be changed or allows very limited user interaction.

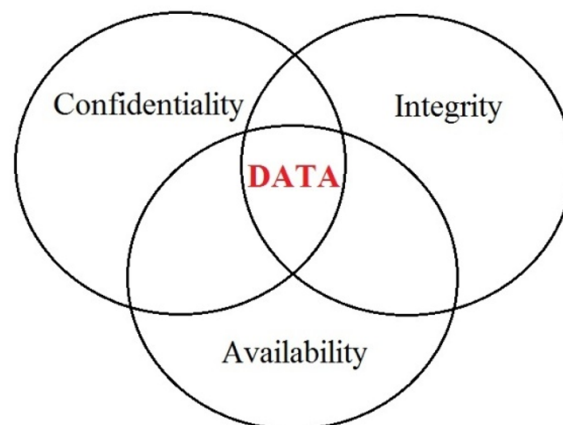Dynamic data are the data that can be altered electronically; it allows the user interaction to alter the

Figure 1: Common features of data

result. (MHRA, 2018)

ALCOA

This 1st introduced in the pharmaceutical industry by USFDA which are simply acronyms, i.e. Attributable, Legible, Contemporaneous, Original, Accurate. ALCOA was coined by *Stan Wollen*. It is the part of data lifecycle whether the data is recorded in paper or electronically. ALCOA helps the data to be complete, consistent & accurate throughout the data lifecycle from the beginning of data generation and recording throughout the process (including transformation or migration) use, retention, achieving retrieval and destruction.

A-Attributable

It indicated clearly who recorded the data or performed the activity, who wrote the document when it was written. Every single data collected written must be able to trace back to the person in-charged. For the data to be attributable, the in-charged person signature must be used. The date-time of creation modification deletion every aspect must be recorded. Every person should use their own login credentials & passwords. Sharing of personal login credentials and passwords must be avoided in any circumstances.

L-Legible

The data for paper-based records must be easy to read & interpret after the data is recorded. The records should be permanent and it should not be damaged throughout the data life cycle. Handwritten documents often tend to have grammatical and spelling errors; it should be properly checked and corrected if required. The documents should not contain any unexplained hieroglyphics. For computer-based data, it should be stored in permanent memory. The data from the permanent memory should not be deleted during changing or cor-

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recting data.

C-Cotemporaneous

It means data must be recorded at the time of generation. Data recorded should be close to the location where data is generated. If there is any change in time of recorded data and generated data, proper and validated, a reason must be provided. If needed validation protocol can be executed.

O-Original

Source data or original data must be preserved in the unaltered state. If the data is recorded in the paper, the original copies of it should be maintained. If the data is recorded electronically, the data should be stored as it is. If there are changes made to original data, it should be properly explained and evaluated. The proper protocol should be established to ensure unwanted changes. Properly certified copies of the original data must be maintained in separate file or folder.

A-Accurate

Accuracy means truthfulness; data recorded or stored must correctly reflect the action or observation made. It should be error-free. Data should be checked properly if changes are made proper explanation with evidence is required. (Ahmad *et al.*, 2019)

ALCOA+

ALCOA+ was introduced by EMA. Currently, USFDA, EMA, WHO, PIC/S, MHRA, TGA every regulatory body is focusing on ALCOA+. It applies for basic ALCOA along with some more attributes, i.e. Complete, Consistent, Enduring, and Available.

Complete

It means all the data recorded must be complete, including test, reanalysis, performance, sampling etc. the complete set of data is necessary for its integrity.

Consistent

It means the data should be in chronological order, i.e. data and time-stamped should be in a sequence.

Enduring

Enduring emphasis on preserving the data for a long duration of time. In some cases, the data must be preserved for a decade.

Available

This is a continuation of ENDURING, i.e. data should not only be preserved, it must be available in a certain time, e.g. during an inspection, audit trials over the data lifecycle. (Ahmad *et al.*, 2019)

Regulatory challenges due to data integrity issues

In recent years many challenges are faced by big firms like warning letters and compliances issues, import and recall of products, losing regulatory body's trust which in turn causes a lot of capital loss and dishonor to the firm. To overcome such challenge data integrity is a must be strictly followed by the companies. According to USFDA, 95% of data integrity issues arise due to poor data integrity and data management practice. (Nikam *et al.*, 2020)

Major issues of data integrity

Backup Data

Most of the companies do not preserve the back up for data; this intern leads to failure during the inspection. According to the regulatory bodies, the data must be stored at least five years for pharmaceutical drug products. Regulatory agencies also say that the paper records must be well preserved and electronic data must have a proper backup.

Sharing Login Credentials

In most of the analytical laborites, the login IDs and the password are shared within the colleague. This, in turn, creates the problem in analyzing the changes during the process as individuality is not maintained. The A in ALCOA is affected if login credentials are shared. (Guidance for Industry Part 11: FDA, 2003)

Audit Trails

Various instruments contain the audit trail which is sometimes disabled or not properly maintained. The management or the laboratory in charge is responsible to ensure that the instruments have proper audit trails. (CGMP, 2016)

User Access

Some of the analysts have access to the documents which they can edit or delete. The user access must be granted to the higher officials and if any kinds of changes are made, they must be noted.

Copying of Data

Regulatory bodies have proper guidance documents on the copying of data. The data copied from the source data must have a proper label as "COPY" to ensure that documents can be differentiated between the original & copies. (European Commission, 2017)

Strategies s to prevent data integrity issues

Quality Control Management Within Organization

We often think that data integrity persists because of fraud data, but the majority of issues exists because

of poor quality behaviours within the organization. The company can practice proper quality management system and remove these issues. Work ethics, proper training, values may lead to good functioning. Data governance can be implemented and used for ensuring more integrity in data. It is arrangements to ensure that data, irrespective of the format in which they are generated, are recorded, processed, retained and used to ensure the record throughout the data lifecycle. (MHRA, 2018)

Control by Design

Various designs may be implemented within the organization to ensure data integrity. These measures can be designed according to the convenience according to the organization. Following are some measures of control by design.

Computer System Validation

It is an important aspect of control by design. If the computer is not validated properly, the result may vary. A computer system validation ensures technical and procedural control over the process.

Personnel

Proper training must be provided to each person working in the organization. The person must follow the validated protocol according to the company. Changes like addition, modification, or deletion of any GMP related documents must be done by authorized personnel only. Every person working in the industry must be qualified appropriately and must work responsibly.

Audit Trails

Audit trails are computer-generated date time and sequence of the workflow. Major of data integrity issue warning letters are issued because of failure of audit trails. The organization should ensure that the audit trails are enabled in each of the systems such as chromatography, HPLC etc. It helps in the authorization of the workflow. (CGMP, 2016)

Security

The premises of the organization must have appropriate security. Any breach of security may lead to data integrity issues. Access to an unauthorized person must be taken care of. Security should be high where data are stored, data backup area or archival areas. In the case of cloud computing, special attention must be given to understand the service provider, ownership, retrieval, retention and security of data. (Kumar et al., 2017)

Control by Monitoring

Proper monitoring in the process can also have a good impact on the integrity of data. Internal audits, third party audits. Internal audits are carried out within the internal auditing committee. In a third-party audit, teams of reviewer are hired, who review the accuracy, authenticity and traceability of data and give the report. Now a day when the data is all on the computer, the auditing is also done electronically. Some issues to be considered during auditing are

1. An electronic record is focused within the system.

2. Paper is incidental to the inspection.

3. Configuration of ER/ES software is essential.

4. Inspection of audit trials entries.

5. Electronic signature within a document is also focused. (Kumar et al., 2017)

CONCLUSIONS

Data integrity is an important parameter within a pharmaceutical firm. Data integrity should be followed by the manufacturing process until the distribution of the product. Various warning letters issues states that there are breaches in data integrity which in turn leads in a poor quality of products. By following the ALCOA & ALCOA+, integrity of data can be maintained. Nowadays, in audit trial, data integrity is more focused. By following the protocols and proper training may help in achieving proper integrity. With the advancement in technology, the companies are moving towards cloud computing, where proper attention should be given on the location, ownership, laws including in the storage of data. All big pharmaceutical firms follow and practice data integrity ensuring quality of products. Applying proper QMS/QCS can help in preventing and controlling the risks.

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