Data Integrity Issues, Statistical Trends and Utilization of ALCOA+ in Pharmaceutical Industry

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**ABSTRACT**

**Background:** Data integrity is critical to regulatory compliance, and the fundamental reason for 21 CFR Part 11 published by the U.S. Food and Drug Administration (FDA). In pharmaceutical industry good documentation frames, a crucial part of good manufacturing practices (GMP)as it plays an indispensable part for the integrity of data maintenance and its development, certifications, registrations, commodification, and life-cycle governance for pharmaceutical products. Data integrity is a major concern in the regulated pharmaceutical industry due to observations and results of poor record management practices or falsification of data.

**Main Body of the Abstract:** In the present review article, data is collected from various online sources which includes articles, CFR and WHO guidelines and statistical data from Blogs. Various articles published in indexed journals and other databases have been collected and reviewed systematically.

**Short Conclusion:** A rise in the number of data integrity breeches during 2019 encouraged regulatory bodies, such as the WHO and FDA, to publish guidelines on good documentation practices. The present review article will help researchers to understand what is data integrity? Its importance in pharmaceutical industry, ways to reduce the data integrity issues by utilizing concept if ALCOA+ and recent WHO guidelines for data integrity issues.

**Key Words: Data Integrity, 21 CFR Good Documentation Practices, Regulatory Bodies, ALCOA +, WHO**

**I. INTRODUCTION**

Data has always been an important part of in pharmaceutical manufacturing and research activities. The importance of data is growing tremendously in range of different factors in pharmaceutical manufacturing. During recent cGMP inspections FDA has observed numerous data integrity associated violations. Ensuring data integrity is vital component in pharma sector as it directly impacts the efficacy, safety and quality of drugs. Increasing data integrity issues, questions FDA’s ability to protect public health. These data integrity issues have led regulatory bosies to carry out stringent actions which include warning letters, import alerts, form 483’s and mutual agreement on termination[1]

Data integrity is a major concern in the regulated pharmaceutical industry due to observations and results of poor record management practices or falsification of data.  This has resulted in numerous FDA warning letters as well as guidance for data integrity issued by regulatory agencies such as MHRA, WHO, FDA and PIC/S, industry associations.[2]

Every healthcare industry deals with Good Documentation Practices (GDP) inside the organization to lead the outside market of high-quality drugs or medical devices. The procedures also include a high level of documentation activities to make sure they are audit-ready and have trace-able records. [5,6]

During recent years, healthcare industries especially in India frequently have received warning letters for data integrity issues resulting in huge losses for example [7]:

1. Restrictions imposed by regulatory bodies such as WHO, FDA, etc.
2. Due to lack of traceability, organisations are unable to respond to agencies
3. Constrained reputation in the market
4. Loss of customer trust means losing business
5. Questions on the marketed product regarding authenticity
6. Major deprivation in trades and share market

Huge number of companies have suffered serious regulatory and financial consequences as a result of false and unacceptable pharmaceutical data integrity practices.

Major issues for why we are dealing with data integrity are:

1. Senior management who doesn’t themselves learn and don’t support data integrity. They don’t promote support or guide the employees for following correct procedures.
2. Employees who lack technical and regulatory knowledge of process or product hence cannot perform their jobs adequately and accurately.
3. People don’t understand importance of cybersecurity and data completeness[8]

Data integrity is critical to regulatory compliance, and the fundamental reason for 21 CFR Part 11 published by the U.S. Food and Drug Administration (FDA). Since the time FDA published the first guideline in 1963, FDA in collaboration with European Union published number of guidelines on multiple subjects associated to data integrity for pharmaceuticals firms. Data integrity is security of data from unintentional changes to information protecting data from unauthorised parties.[9]

Integrity stems from the Latin word ‘integer’ which means whole and complete. So, integrity requires an inner sense of ‘wholeness’ and ‘consistency’ of character. Integrity is not possible without compassion and makes it clear that doing the right thing includes doing it for the right reason [10]

Integrity, ethically can be defined as “the honesty and truthfulness or accuracy of one’s actions and a concept of consistency of actions, values, methods, measures, principles, expectations, and outcomes.[11]

Data can be defined as attributes or details, usually numeric, collected as a result of various observations. Data in more technical sense may be defined as collection of qualitative or quantitative variables about one or more persons or objects.

In complete sense data integrity is characteristics or information which is complete, accurate and reliable.

“Integrity is doing wright thing when no one is watching”

* *C. S. Lewis*

**II. DEFINITIONS**

**A. Meta Data**

Metadata is a contextual data that depends on the preceding or following parts of a text to clarify meaning. In short it is a set of data that describes and gives information about other data. It helps organize electronic resources, provide digital identification, and archive and preserve resources. For example, to denote file size number 23 is meaning less without metadata i.e., the unit KB. Other examples of metadata may be ID given to a person, time or date of activity performed. Many distinct types of metadata exist, including descriptive metadata, structural metadata, administrative metadata, reference metadata and statistical metadata.  [12]

**B. Raw Data**

Raw data, also known as primary data, are data (e.g., numbers, instrument readings, figures, etc.) collected from a source. In the context of examinations, the raw data might be described as a raw score. **Raw data** is primarily unstructured or unformatted repository data. It can be in the form of files, visual images, database records or any other digital data.[13]

In a lab when performingexperiment if a provision is made to note the temperature in a reaction mixture every minute and recorded in computer system or record sheet are called raw data.

**C. Static Data**

It is a fixed data document (e.g., paper record or an electronic image). It is the data which does not change after recording such as a paper or pdf record which allows little or no interaction between the user and the record matter. For example, once printed or converted to fixed or constant pdfs, chromatography records lose their tendency of being recovered or allowing more detailed survey of baselines. [14]

**D. Dynamic Data**

It is data layout which allows recording of fundamental interrelation between the user and the content recorded. (e.g., a chromatogram where the integration parameters (peaks) can be modified). It also permits the user to make modifications in entries or formulas in a record sheet for computing analytical results or other data such as calculated yield. [1, 9,14]

**E. Electronic Data**

Digitalization for raw materials maintenance can take many shapes from online certificates of analysis (CoAs) to electronic batch records (EBR). Companies in the pharma industry are now approaching towards more digitalization at various stages of manufacturing.

Automated systems benefit us by minimizing the double verification which is mandatory for manual papers. Electronic data includes data from ERP software for controlling lab scale data, quality systems data warehousing data and other records maintained in pharmaceutical industry. [14, 25]

**F. Audit Trail**

It a system that traces the detailed transactions relating to any item in an accounting record.   
It is secure, computer-generated, time-stamped electronic record of the changes that have been made to a database or file. An Audit trail is source of progressive, sequential, consecutive set of records that furnishes secured documentary evidences for series of activities that may have altered or modified at any time of specific procedure, test, operation or event. E.g., For system-based record: In generation and issuance of Batch manufacturing record from software audit trail will include the record of date and time, BMR number, which regulated market it belongs to, Batch size, product name etc. For a paper record: an audit trail of a change would be documented via a single-line cross-out that allows the original entry to remain legible and documents the initials of the person making the change, the date of the change and the cause for the change, as required to authenticate and ratify the change. [1, 14]

**G. Backup**

If in any case of system crash or corruption of disk there is necessity for an alternative data, this data is called as backup data. A backup means one or more duplicate copies of electronic files in event of losing the original data or system or in the case of data is not traceable. It is important to note that these backup files are stored only for temporary period and should not be relied upon as archival mechanism. [1, 14]

**H. Computerized System**

A Computerized system includes software, hardware, application software, operating system software, supporting documentation. e.g., manuals and standard operating procedures, automated laboratory systems, control systems, manufacturing, clinical, or compliance monitoring database systems A computerized system collectively controls the performance of one or more automated processes and/or functions.[14]

**I. Corrective and Preventive Action (CAPA)**

CAPA term indicates actions taken to eradicate or minimize an organization's non-conformities or other unwanted, disagreeable, objectionable, unacceptable, unsuitable, out of place situations. CAPA is a most common concept common across the GxPs (good laboratory practices, good clinical practices and good manufacturing practices), and number of ISO (International Organization for Standardization) business standards. It is a set of actions, laws or regulations required by an organization to account in manufacturing, documentation, analytical procedures, or computed systems to rectify and eradicate duplicating non-conformance. Nonconformity can occur when a manufacturing procedure results in a reduction of quality and does not get immediately addressed. Non-conformance may be a market complaint or customer complaint or machine failure or a failure in total quality management system, or misapprehension of written instructions to carry out work. Corrective action means an action taken to eliminate the cause of a nonconformity and to prevent recurrence. Preventive action means action to eliminate the cause of a potential nonconformity or other potential undesirable situation. In short, preventive action prevents occurrence and corrective action prevents recurrence, while correction basically refers to containment.[14]

**J. Data Governance**

Data governance means a method to retain the data in the format in which they are generated, recorded and processed to ensure their completeness, consistency and accuracy at all time for data life cycle. [14]

**K. Data Life Cycle**

The data life cycle is the series of events that a specific unit of data goes through, from beginning of its generation or manifestation to its ultimate recording, documentation and/or deletion, withdrawal and clearance. Data life cycle management inculcates all the aspects of data generation, collection, processing, storing, retrieval, analysing, visualizing, interpretation and its archival. For assessing, monitoring and managing data there should be a planned approach so that the risks associated with data in a manner of corresponding with its potential impact on product quality, patient safety throughout all phases of the data life cycle can be minimised.The data life cycle serves as a navigation tool for facilitating users in discovering recommendations on how to effectively work with their data across all stages the data life cycle. [14]

**L. Good Documentation Practices**

Good documentation is described as standards by which data is collected and framed into document. It can be defined as measures taken safe guard the data collected whether on paper or digitalized system continue to exist as traceable, legible, attributable, intact, permanent, original and accurate throughout the document longevity. [14]

***M.* GxP**

GxP the acronym is a set of regulations and quality guidelines formulated to ensure the safety of life sciences products while maintaining the quality of processes throughout every stage of manufacturing, control, storage, and distribution. GxP is a shared term for guidelines and regulations under good practices which ensures the quality in many domains of globally recognised paradigm such as GMP (Good Manufacturing Practice), GCP (Good Clinical Practices), GLP (Good Laboratory Practice), GDP (Good Documentation Practice), GSP (Good Storage Practice), GDP (Good Distribution Practice) and GRP (Good Review Practice) [14]

**N. Hybrid Approach**

Hybrid approach is a mix up computerized system where combination of original electronic records and paper records that combine to give information about the complete data set which is then reviewed and maintained. E.g., while doing analysis the analysts, with generated electronic record even takes a print of the result for summarizing the total data. When hybrid approach is used its mandatory to use appropriate controls for recording data like templates, master documents, recording sheets according to SOP. The link between the original record and paper record should be such that they be legible throughout data life cycle. [16]

**O. Master Controlled Documents**

Mater controlled documents are approved documents which are in custody of QA department and can be issued for operational work after doing requisite issuance formalities. Examples of such documents are master SOP, Validation Protocols, Manufacturing\Production Records, master packing record QC specifications etc.[16]

**P. Original**

Original record means the first generation of the information and is the preferred version of a record. Archival of records should be the maximum extent possible for an original records.[16]

**Q. Post-Dating**

Post-dating means assign a date later than the actual one to (Enter a data before activity is performed).[16]

**R. Back- Dating**

It means is executing a document and then dating it with an earlier date than the actual date of execution.[16]

**S. True Copy**

A true copy is a copy made from the original record. It is a certified document showing all the details of the original documents but is not original document. It confirms that the it contains the same data or exact data mirror imaging to original data.[16]

**Pharmaceutical industry is the vital segment of health care system** as it deals with manufacturing of medication for patients intended for safe and therapeutically active with good consistent quality. Good documentation frames, a crucial part of good manufacturing practices (GMP) as it plays an indispensable part for the integrity of data maintenance and its development, certifications, registrations, commodification, and life-cycle governance of pharmaceutical products. The GDPs aid us to prevent the erroneous data collection during the manufacturing and the analysis of pharmaceutical products. This would directly or indirectly impact product quality, and safety for the patients. Both US and European regulatory authorities i.e., USFDA (United states of Food and Drug Administration) and EMA (European Medicines Agency) require mandatory compliance with GDPs. International organisations such as World Health Organisation (WHO), Health Canada and EudraLex (European union collection of standards for fundamental regulation governing medicinal products) accompanying with United States of Pharmacopeia (USP) have published certain guidelines corresponding to GDPs. Not only the regulatory requirements but maintenance of authentic records is also important as documentations of activities in the pharmaceutical industry allows critical evaluation of internal procedures and continuous improvement of process and minimizes the time for repetitive detailed study from start to end.[17]

As per the WHO, the purpose of Good Documentation Practices helps to:

1. Set a predefined specifications and operational strategies for all materials and processes of manufacturing and analysis,
2. Set job responsibilities of employees based on their expertise field
3. Ensures release of a product to be done after all the necessary information to authorized persons
4. Maintain documented evidence for future investigations and audits in a legible manner
5. Maintain constant availability of data for statistical and validation analysis.

For an organisation to be compliant with regulatory authorities and to enhance market value it is important to:

1. Provide requisite resources for fulfilling complete documentation,
2. Ensure that the documents are prepared with concept of ALCOA+. (Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring and Available)
3. Fill the gap of any missing data for existing documents providing basis of forecasting what is to be done in future
4. Continuous training should be provided to employees on existing and current GDPs to be followed in manufacturing ang quality control departments.

Quality Assurance department needs to review all the documents before release of product to market [17].

**III. TYPES OF DOCUMENTATION IN PHARMACEUTICAL INDUSTRY** [18]

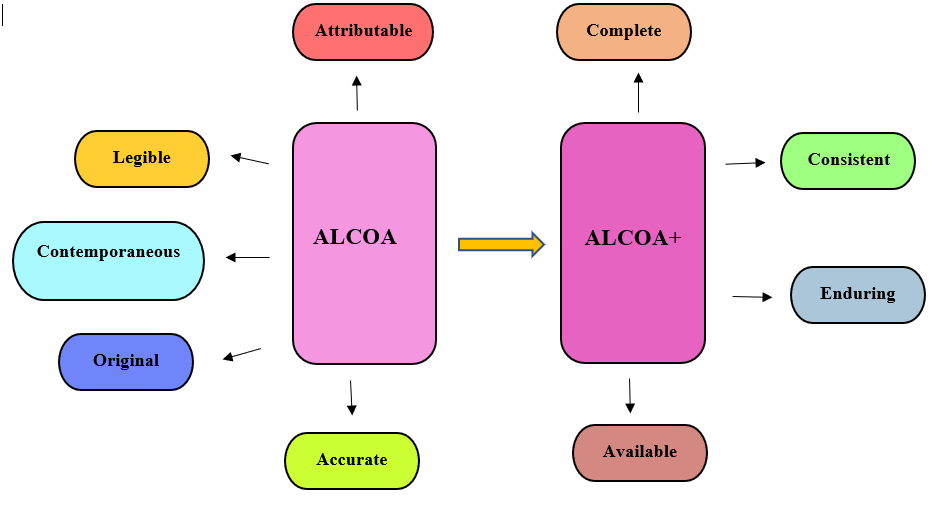
Documentation refers to both printed electronic forms and electronic systems.

1. Standard Operating Procedures (SOP)
2. Records/Worksheets
3. Annexures
4. Quality management system documents
5. Production and packaging instructions
6. Standard operating procedures
7. Records.
8. Licencing documents
9. Master documents
10. Technical agreements
11. Confidentiality agreements
12. Training records
13. Qualification Documents (including URS, DQ, FAT, IQ, OQ, PQ)
14. Quality Manual
15. Issuance Documents
16. Annual product quality review (APQR) documents
17. BMR/BPR
18. Validation protocols and reports
19. Deviation reports
20. Audit plans
21. Validation Master Plans and validation documents
22. Test material related documents including product specification, test material receipt, and reports
23. Personnel related documents including training records
24. Documents related to facility which includes floor plans, HVAC plans, and environmental specifications
25. Planned Deviation, unplanned deviations and system failure investigation
26. Change control
27. Worksheets, notebooks, and logbooks

In pharmaceutical industry it is said that “**If It Is Documented It Is Done**”. So, recording and maintenance of data plays a very important part in pharmaceutical industry.

**IV. CONCEPT OF ALCOA TO ALCOA+**

For prevention of data integrity issues concept of ALCOA was utilized by pharmaceutical companies. ALCOA is concept to implement for the data guarding and sturdiness in pharmaceutical industries.In 1990’s Stan Woollen used the acronym ALCOA when he worked for the agency to help him remember compliance terms relevant to data quality which has been widely associated with data integrity by FDA. [19]ALCOA defines a framework to achieve and maintain data integrity, especially important for ensuring good manufacturing practices in regulated industries. The theory of ALCOA can aid to furnish an audit trail data that encapsulates details such as additions, deletions, or alterations of data in an electronic record without obscuring the original record. [20]As an improvement over this, additionally, new characteristics were identified which are critical to data integrity apart from regular good documentation practices core characteristics. This launched the improved ALCOA now known as ALCOA (+).[21]The term ALCOA which is acronym stands for Attributable, Legible, Contemporaneous, Original and Accurate. Later ALCOA was outstretched to ALCOA-C or ALCOA+ (Fig 1). Complete, Consistent, Enduring and Available (CCEA) was added to ALCOA in 2010. They are considered as the heart of Good Documentation Practices because of the specific significance they hold. [22]



**Figure 1: Outstretching to ALCOA to ALCOA+**

Following are the features for Quality records considering Good Documentation Practices in place.

**A. Attributable –** When and Who performed an activity?

It indicates that the any data should be traceable and determinable regard of when it is performed and who performed it. It should be capable to discover and find out the emergence and the past of data. The document should be also capable to refer to the individual responsible for theinitiation, collection, preservation, or managing the record. In critical times, this results in trace-ability. Therefore, sometimes **attributable is**considered as **traceable**. [[22, 23, 24]

**E.g.:** System user ID sharing and password sharing, Analysis done by two person and one person signing

**B. Legible –** Is the data file readable throughout the data life cycle?

Data should be readable throughout life span of data. The document should be is easy to read, valid and understandable. i.e., Readable and Relatable. This is because it must be possible for data to be read and understood years and even decades after it’s recorded. History for the particular data should be relevant and understandable even after a gap of long time period. [19, 25]

**E.g.:** Hand writing should be readable by others, Write over’s- usage of pencils or erasers/ correction fluids

**C. Contemporaneous –** Is the documented at the time of the activity?

Contemporaneous means Parallel, Simultaneous, or Concurrent. The data should be recorded at the time when activity is performed. Data should be recorded at the same time they are generated, collected and observed (include time and date stamps for electronic records). Data should never be backdated, or forms completed with expected results prior to execution.[26, 30]

**E.g.:** Data should be recorded at the time of activity, Back dating or forward dating (Non-compliance with GDP)

**D. Original –** Is the data collected an original record or a certified copy?

The original term refers to the obtainability or existence of data in its raw form, whether it is on paper or electronic data. Sometimes the prints which are generated electronically or digitally fade away over a period of time, in those cases the document should be scanned or photocopied and saved for future references. Original data is the paper or electronic medium in which the data point is initially recorded including protocol, notepad, logbooks, registers, worksheet, data archives or software tools. Practice should be made to report the data in the original notebooks or main registers rather than noting them on piece of paper with intention of completing them later in the main register/logbook. This can create more errors and hamper the authentication of original data. When data or information is recorded at first sight capture of data generation and includes all subsequential data required to ensure quality and good conduct of GxP activities is called as original data. Certified Copy is verified by a 2nd person who compares the copy to the original, confirms that the copy is accurate, correct & complete and sustains original Content & significance as it is. [27, 30]

**E.g.:** Altering/ modifying and deleting original data, Analytical results written on new worksheet as original data got impaired (smudged or torn off or discarded)

**E. Accurate –** Are there any errors or editing without documented amendments?

Consistent, factual, error free and recorded as it is. For validity of data, it should be error free. In case of amendments there should be evidence for accompanying support for changes made. The quality of data should be maintained such that any changes made during any time of data life cycle has enough proof for supporting the change made. If any editing is done it should be done considering GDP.[26, 27]

**E.g.:** System adjusted to get passing results to avoid OOS (out of specification), Data from passing run analysis is used for another sample to expect a result within specification

**E. Complete –** Is all data documented viz. any test, repeat or re-analysis performed?

Data for any repeat or reanalysis performed on the sample should be noted correctly. Evidences of the data for any reanalysis performed should not be deleted (Evidence: Audit Trail). Evidence should be such that, when reconstructing or reforming the events, data must be sufficient and complete for required information. This means that there should not be any breach when remodelling of requisite information. All paper and electronic data including all tests (original and retest) must be properly recorded clearly identifying when and who performed the test making sure everything is included, and nothing is missing. [25, 30]

**E.g.:** Information worksheets without name of person, instrument ID, date and time etc, meta data support is not mentioned for the original raw data collected

**F. Consistent –** Whether all the components of the investigations are always carried out similarly?

Consistent with reference to the events in chronological order. Records should be maintained in such a way that data should reproduce correct information consistently at any time. Any data which will be written to the database must be valid maintaining all the defined rules of a particular system. Data consistency is not an assurance of correctness of the transaction in all ways. It is mostly for identifying any programming errors resulting in the contravention.[21, 23]

Data should be gathered using a system that enforces the use of approved data acquisition and analysis methods, reporting templates, and laboratory workflows.

**E.g.:** Batch records not filled on time by the operators, Flash results which tend to disappear before analysts can jot down the result.

**G. Enduring –** Is all the data recorded systematically in laboratory notebooks or in validated systems?

The data or information must be maintained in such a way that it should remain unviolated, pristine, approachable and accessible throughout their specified retention period. Paper or electronic data should be transcribed in validated software systems and defined laboratory notebooks, registers, log books, spreadsheets, worksheets, annexures etc. Data should not be recorded in any scrap papers.[19]

**E.g.:** Tampered batch records, deletion or modification of existing system data due to upgradation of system.

**H. Available –** Can the data be accessed for review, audit or inspection over the lifetime of the record?

Availability of the data severs the basic purpose of saving it so that it can be referred when needed. Data should be readily available when required for inspection and audit purposes. During regular inspection of authorities, the requested data should be produced instantaneously in legible format. Paper and electronic data should be neatly arranged in a manner so that retrieval and recovery is easy. [19, 30]

**E.g.:** Back up for the files are not available and deleted in case of OOS results, Archival of data is not done until data retention period

**V. SIGNIFICANT ISSUES OF DATA INTEGRITY**

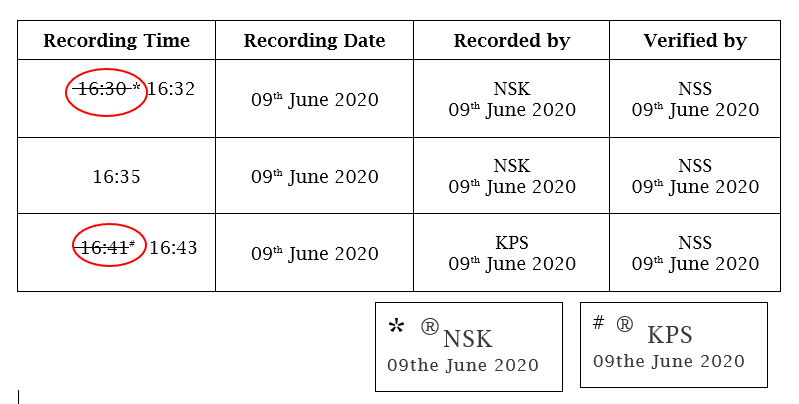
Majority of the data integrity issues and Form 483 are due failure in quality control instruments.

**A. There is various reason for data integrity issue some of them write the following [28]:**

1. No support record for raw data or loss of data during changes made in digitalized system
2. Inaccurate and incomplete records or discarding the data of repeated tests, trial runs, sample runs
3. Using CoA (Certificate of Analysis) of one batch to release another
4. Backdating
5. Manipulating integration parameters of chromatogram to get pass results
6. Deletion/manipulation of electronic records
7. Shutting down audit trail
8. Signing instead of concerned person authorized for the work
9. Deficient/In complete computer validation.
10. Activities not recorded contemporaneously
11. Sharing Login IDs by other analysts. By doing this work done by individual analyst cannot be identified.
12. Usage of ditto marks
13. Usage of signature stamp
14. Failure to use ink as specified by procedure
15. At the time of spillage Incorrect ink used for entries causing illegible data
16. Failure to identify person who made corrections of changes in logbooks
17. Arcane original data
18. Usage of pencil
19. Erroneous/ Fallacious records
20. Correct dating of handwritten changes not done
21. Write-overs, multiple line-through, and use of "white-out" or other masking device.

The most common GDP violations occur when corrections of the errors are done during recording of information.

**B. Following methods should be carried out for Correction of documentation (Fig 2):**

1. One should draw a single line over the error,
2. Mention the correction next to the error,
3. Explain the error,
4. Date and sign of the individual carrying out the correction
5. Mention time in 24 hr format

**Figure 2: Method for correction of document**

**These common errors should be highlighted in training of good documentation practices.** [9, 28]

As it is said **“Prevention is better than cure”** industries must follow the Good Documentation Practices actively.

**VI. WAYS TO REDUCE DATA INTEGRITY RISK**

**A. All computer systems should comply to 21 CFR Part 11 guidelines:** [21 CFR Part 11](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=11&showFR=1) is an FDA regulation that is concerned to electronic records. One should ensure that the electronic data are true, relatable, and parallel to paper record. Data stored in digital systems must comply to quality aspects making it reliable to store data.

**B. Software development lifecycle must be followed:** To supervise the quality task performance, a software development lifecycle methodology can be followed. This methodology aids to investigate different functions of software lifecycle phases which embodies software testing, software development, installation and amalgamation of ongoing system maintenance. All digitalised systems should be appropriately developed, qualified, quantified, analysed, investigated, and validated on a routine basis.

**C. Validate your computer systems:** Validation of Software systems is necessary as it provides documented evidence that a particular process consistently manufactures a product which conforms with pre-determined specifications and quality standards.

**D. Implement audit trails:** The individuality, date, and time of data entries, changes, and deletions made should be recorded by a secure, digitally-generated, time-coined audit trail. Audit trails provides evidence that data entered in electronic records are true, ethical, meets necessary data conversation, and promises that information recorded have not been modified, edited or deleted.

**E. Error detection software should be implemented:** There must be an incorporation of automated inspection software that will authenticate critical documents which will assure systems meticulousness. [Manual examining](https://blog.globalvision.co/company/proofreading-software-why-it-is-better-than-your-english-teacher/) or inspections are not sufficing to furnish that data are error-free.

**F. User system access should be maintained to secure your records:** To assure data integrity a secured login should be made available for all systems with at least two distinct pieces of information and provide access only to concerned individuals.

**G. Maintenance of backup and recovery procedures are important:** In case of unexpected data loss or system errors backup and recovery strategy are necessary. This practice guarantees the physical and critical recovery of database ensuring veracious restoration of data.

**H. SOPs and logical controls should be followed to design a Quality Management System (QMS):** Standard operating procedures and guidelines collectively builds a [Quality Management System](https://blog.globalvision.co/quality/a-new-era-for-quality-management-systems/) which lays foundation for ensuring quality into process by systematically organising the process. For ensuring clear liability it is mandatory to follow efficient procedures.

**I. Establishment of a vendor management qualification program is necessary:** For ensuring that all the products manufactured are genuine and authentic it is mandatory to examine all the vendors supplying raw materials. Initial validation followed by continuous verification must be carried for ascertaining quality production. Organizations must interact with vendors for new or updated data integrity procedures they follow.

**J. Training of users and maintenance of records must be done appropriately:** For a job to be performed in predetermined manner precise and appropriate training must be given with the help of expertise’s. Proof of the training delivered must be documented.

**K. Conduct Internal Audits to evaluate procedures:** For a company to thrive in competitive business environment, routine internal audits aids to understand the flaws in regime followed by the firm which empower firms to continuously prosper. Self-inspection by the company under an internal auditor who is trusted consultant assigned for advising upper management on how to best manage the company’s quality management system (QMS). **[29, 30]**

**VII. CODE OF FEDERAL REGULATIONS (CFR) AND DATA INTEGRITY [31-36]**

With respect to 21 CFR Guidelines includes:

* Part 210 – Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General.
* Part 211 – Current Good Manufacturing Practice for Finished Pharmaceuticals.
* Guidance for Industry Part 11, Electronic Records; Electronic Signatures — Scope and Application. Table 1 represents data integrity issues related to 21 CFR guidelines in pharmaceutical industry. [23]

**Table 1: 21 CFR Guidelines associated Data integrity issues**

|  |  |  |  |
| --- | --- | --- | --- |
| Sl. No. | 21 CFR Guideline No. | Guidelines | Data integrity issues in Pharmaceutical Industry |
| 1 | 211.192 | Failure 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 | The investigations for a tablet with specified unit dose(mg)were incomplete which resulted in OOS and partial batch rejection. On investigation an OOS was observed for the thickness of tablets for particular lot. The investigation failed to include an assessment of the manufacturing operations and the partially released finished lot which was not placed on stability. |
| 2 | 211.188(b)(11) | Failure to prepare batch production and control records for each significant step in the manufacture, processing, packing, or holding of the batch of each batch of drug product that include documentation of the accomplishment. | Batch Manufacturing Record of the firm lacks to include appropriately statement and control of the processing steps at each stage of manufacturing/ production of products. |
| 3 | 211.194(a)(8) | Failure to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards | In a laboratory for Viscosity testing the quantity samples is critical. Results will be low if sample is too less and results will be high if sample is more. But the firm failed to mention the amount of the sample used for the test. |
| 4 | 211.68 | Failure 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 | * For computer or digitalized systems there is not much appropriate controls on its utilization by individuals. A software system designed for validation protocol used for drug material and inventory control, drug production scheduling and control on distribution of finished product failed to ensure the validation for user access controls or password protection, specifically relating to the status of products in inventory. |
| 5 | 211.100(b) | Failure to follow written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess, and to document same at the time of performance. | Firm fails to follow manufacturing process and online entry control parameters that will define the quality and purity of the product to conform with predetermined specifications. |
| 6 | 211.160 | Failure to follow and document at the time of performance required laboratory control mechanisms | Firm has to include any additional test or procedures carried out in Supplemental Method Information Sheet (SMIS) which is not present in a client specific procedure. A SMIS then becomes part of the firm's official procedure used to perform testing. In method of bulk release testing laboratory information includes that the sample should be added to the viscometer in small portions distributed around the cone and plate, rather than in one single portion in the centre. In addition to this information lab SMIS also indicates that the amount on sample cup is critical with units of measurement |
| 7 | 211.165(a)). | Your firm does not have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release | Sampling plan allows for potency results to be reported as the average of three samples tested for each batch. Firm did not establish an acceptance criterion for the results of each individual test or for the standard deviation of the test results. Therefore, current practice allowed the release of sterile drug products despite individual potency test results being sub-potent or super-potent compared to the potency release specification of the finished drug product. |

**VIII. STATISTICAL TRENDS OF DATA INTEGRITY VIOLATIONS IN PHARMACEUTICAL INDUSTRIES**

**A. Statistical Trends of Data Integrity Issues**

Warning letters and closeout letters issued by the Food and Drug Administration’s Bioresearch Monitoring (BIMO) Program between US fiscal years 2007–2018 were analyzed by categorizing regulatory violations into violation themes. A combined total of 300 warning letters were analyzed as a part of this study. The most common violations found in all warning letter categories included failing to follow and maintain procedures and poor documentation practices. Although the number of warning letters has decreased over the past decade and inspection results have been improving, there are still significant data integrity and other regulatory compliance issues found in the premarket side of the pharmaceutical industry [37].

Table 2 and Figure 3 unveils Data Integrity Associated Warning Letters by different countries for the calendar year 2008 to 2018, along with a cumulative total [38]. The pie chart Figure 3 signifies that nearly 80% of data integrity-related warning letters accounted since 2008 occurred in the past four calendar years. of countries associated with these warning letters continues to increase. In 2018, the sites that were the subject of warning letters were in 11 different countries. The number peaked in Calendar Year 2017, and it will be interesting to see if the number decreases again in Calendar Year2019, as it did in Calendar Year 2018 [38].

**Table 2. Data Integrity Related Warning Letters by different countries**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | Total |
| China | 1 | 1 | 3 | 1 |  |  | 2 | 2 | 14 | 19 | 15 | **58** |
| India | 1 | 1 |  | 2 |  | 6 | 7 | 10 | 9 | 12 | 6 | **54** |
| US | 1 | 2 | 1 | 1 | 1 |  |  |  | 7 | 15 | 8 | **36** |
| Europe |  | 1 |  |  |  |  | 1 | 2 | 6 | 3 | 1 | **14** |
| Japan | 1 |  |  |  |  |  |  |  | 2 | 1 | 3 | **7** |
| South Korea |  |  |  |  |  |  |  |  |  | 2 | 4 | **6** |
| Canada |  |  | 1 | 1 |  |  |  |  |  | 2 | 1 | **5** |
| Mexico |  |  |  |  | 2 |  |  |  |  | 1 | 1 | **4** |
| Brazil |  |  |  |  |  |  |  |  | 3 |  |  | **3** |
| Thailand |  |  |  |  |  |  |  | 1 |  |  |  | **1** |
| UAE |  |  |  |  | 1 |  |  |  |  |  |  | **1** |
| Jamaica |  |  |  |  | 1 |  |  |  |  |  |  | **1** |
| Singapore |  |  |  |  |  |  |  |  |  | 1 |  | **1** |
| Australia |  |  |  |  |  |  |  |  |  |  | 1 | **1** |
| Taiwan |  |  |  |  |  |  |  |  |  |  | 1 | **1** |
| Dominican Republic |  |  |  |  |  |  |  |  |  |  | 1 | **1** |
| Total | **4** | **5** | **5** | **4** | **6** | **6** | **10** | **15** | **41** | **56** | **42** | **194** |

**Figure 3: Pie chart for Data Integrity related warning letters of different countries**

Table 3 displays a clear picture of major of countries involved in data integrity warning letters viz. CHINA, INDIA and UNITED STATES. FDA did not identify many violations as “conclusions’ or data integrity remediation’ to which the pharmaceutical companies need to respond. Warning letters issued to API manufacturers do not identify 21 CFR 211. The citation of regulations continues to follow the FDA’s stated goal of focusing on the evaluation of predicate rule requirements. [38]

**Table 3: Data integrity related warning letters with reference to geographical locations**

|  |  |  |
| --- | --- | --- |
| Country | Total Number, 2008-2018 | % of Total, 2008-2018 |
| China | 58 | 30% |
| India | 54 | 28% |
| United States | 36 | 19% |
| Europe | 14 | 7% |
| Rest of the World | 32 | 16% |

The most common violations found in all warning letter categories included failing to follow and maintain procedures and poor documentation practices Table 4. Roughly around 50% of all global drug 483s which have been issued over the period of 2014-2018 have reported for data integrity concerns. This data was found by the Big Data and AI Analytics firm Govzilla. 79% of global drug warning letters during this period cited data integrity issue. In recent years it is noticed that there is substantial increase in data integrity deficiencies[39].

**Table 4 Most recurrent data integrity related warning letters**

|  |  |  |
| --- | --- | --- |
| 21 CFR Reference | Frequency of citations | Caption of CFR Section |
| 211.194 | 10 | Review of entire data, Lab Records |
| 211.188 | 6 | Batch Manufacturing and control records |
| 211.165(a) and (b) | 5 | Testing and release for distribution |
| 211.192 | 5 | Deviations, Risk managements, Investigations, Production records review |
| 211.68 | 2 | Automatic, Mechanical and Electronic Equipment |

Very rare form 483s and warning letters were cited for deficiencies with 21 CFR Part 11. Most of the deficiencies were cited for non-compliance with cGMP rules (specifically, 21 CFR Parts 210, 211 and 212).

**B. Two major violations were cited for CFR code 211.68 and 211.194.**

1. Part 211.68 specifies requirements for “Automatic, Mechanical and Electronic Equipment.” Frequent citations in this area include:

* Mismatch of the printed data with actual audit trail.
* Data was not legible and correctly backed up for future reference.

1. Part 211.194 is cited when companies do not review and include all relevant data when making lot release decisions. Frequent citations in this area include:

* For meeting the predefined acceptance criteria laboratory analysts delete or manipulate data.
* Identification for out of specification results becomes difficult for investigations since companies fail to review critical data and/or metadata
* The test results of analysis are either deleted or corrupted by company which do not have sufficient supportive data.

**C. Other recently cited deficiencies include:**

* Utilizing “pre-injections” of product samples outside of full sample sets to determine if results pass acceptance criteria, and then deleting/ignoring results if they fail.
* Shutting down the audit trails to conceal results
* Deletions or modifications of results
* Minimizing the data with use of integration suppression settings that would likely cause an OOS result
* No proper justification for Aborting test runs

FDA has encouraged on utilization of “independent” data integrity assessments as part of the strategy for remediating identified issues. A few examples include:

* A warning letter was issued on august 10th, 2018, to the manufacturing unit of Kyowa Hakko Bio Co., Ltd. in Japan that stated: “We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.”
* A warning letter was issued on march 26th, 2019, to the manufacturing unit of Winder Laboratories, LLC in Georgia that stated: “Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture…. We strongly recommend that you retain a qualified consultant to assist in your remediation.”
* A warning letter was issued on june 13th 2019to the manufacturing facility of Akorn Inc. in Illinois that stated: “Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture…. We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements.”

**D. Benefits Data Integrity Assessment:**

1. Builds up focus of Organization on Data Integrity issues– Braces the fact that all employees are focused on compliance of data integrity concerns.
2. Satisfaction of identifying data integrity concerns – Once the data integrity issues have been identified it becomes easy to work on compliance.
3. Expenditure reductions and Time saving – Data integrity issues identified and rectified internally are much more significant than identified by regulatory authorities and are also less time consuming for redrafting.
4. Can concentrate on enhancing Business – Can stay focused on well-being of business in effective way rather than spending time and expenditure on data integrity issues if solved proactively.[39]

A rise in the number of Data Integrity breeches during 2019 has encouraged regulatory bodies, such as the WHO and FDA, to publish guidelines on good documentation practices and how data should be inputted and handled. Draft document of guideline on data integrity (October 2019) by WHO included the following scope:

**IX. HIGHLIGHTS OF WHO GUIDELINE ON DATA INTEGRITY** [40]

1. Guideline covers basic concepts, information and recommendations for promoting GxP in documentation and record keeping which will facilitate compliance with Data Integrity.
2. This guideline does not cover Data integrity on medical devices, however designated as ‘GxP’.
3. This guideline should be read with WHO GxP guidelines and publications, considering it has been harmonised with other published documents.
4. Data integrity risk assessment should be carried out along with current practices in GMP facilitating risk-based approach over the life cycle of data which will help to find and assess risk areas.
5. This guideline is applicable to contract givers and contract acceptors. Contract acceptors are the one providing the data to contract acceptors; hence it completely demands for the contract giver to ensure that contract acceptor complies principals underlined in this guideline.
6. The effectiveness of controls can be verified by identification and review of data with risk-based controls.

**X. CONCLUSION**

In pharmaceutical industry data integrity plays an important role in regard of maintaining quality product because improper practice allows inferior quality of product to reach patients, so it becomes mandatory responsibility of pharmaceutical industry to ensure efficacy, safety and quality of products. Data Integrity is the most common issue with majority of pharmaceutical industries. Concept of ALCOA+ helps maintain data integrity necessary for following Good Manufacturing Practices. Now a day pharmaceutical industry has started relying on digital and automated systems, hence it becomes necessary to validate them for minimizing errors related to addition or deletion of data. It eliminates the need for inspecting each and every process involved in the production and supply of drugs. Following the ALCOA+ principles is the best way to achieve this goal. Numerous regulatory bodies suggest of using ALCOA as tool to reduce errors and ensure GDP. Warning letters and closeout letters issued by the Food and Drug Administration’s Bioresearch Monitoring (BIMO) Program, Big Data and AI Analytics firm Govzilla and article by Barbara Unger suggested most of the form 483 citations were due to data integrity issue. An inflation in multiple numbers of data integrity related violations during recent years roused a vital requisite to publish guidelines on good documentation practices by regulatory bodies.

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**XII. ABBREVIATIONS**

FDA- Food and Drug Administration

cGMP- Current Good Manufacturing Practices

MHRA- Medicines and Healthcare Products Regulatory Agency

WHO- World Health Organisation

PIC/S- Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme

GDP- Good Document Practices

CFR- Code of Federal Regulations

KB- Kilobyte

ID- Identity

ERP- Enterprise Resource Planning

BMR- Batch Manufacturing Record

GxP- Good Practices. (x-Variables)

SOP- Standard Operating Procedures

OOS- Out Of Specification

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