

# A Perspective Study of Warning Letters on Data Integrity Issued by FDA between 2017 and 2019

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## ABSTRACT

Data integrity credential is a good stride to the pharmaceutical industry and also helps for the prospective market growth of the industry by increasing the public trust, reputation. Data integrity is a head way for maintaining quality systems and controlling deviations, minimizing errors that occur frequently in the industry. It ensures the lab records and good outcome in inspections, audits, and to get excellent market division in terms of share and also makes the industry flawless. Data integrity includes the complete, consistent data that should be attributable, legible, contemporaneous, and original, accurate data and should be recorded and maintained in-depth periodically. This article mainly emphasizes on the approaches for data integrity, background, challenges faced by company, consequences of data integrity failures, remediation measures for data integrity, new FDA (Food and Drug Administration) guidelines on data integrity. In order to ensure data integrity in industry quality culture should be maintained, electronic signatures, personnel, giving training to employees to ensure quality system in the industry.

**KEYWORDS:** Close out letters, Data integrity failures, New FDA guidelines, Quality culture, Risk factors

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## INTRODUCTION

**Data Integrity:** Data Integrity refers to the extent to which the data is complete, consistent and accurate throughout the data lifecycle. Data includes all original records and true copies, including raw data, metadata and all subsequent transformations and reports of the data. [1, 2]

The warning letters are under the control of the CDER (Centre for Drug Evaluation and Research) and in office of regulatory affairs under the division of pharmaceutical quality programs. The data integrity process followed by FDA is shown in the Fig.1.

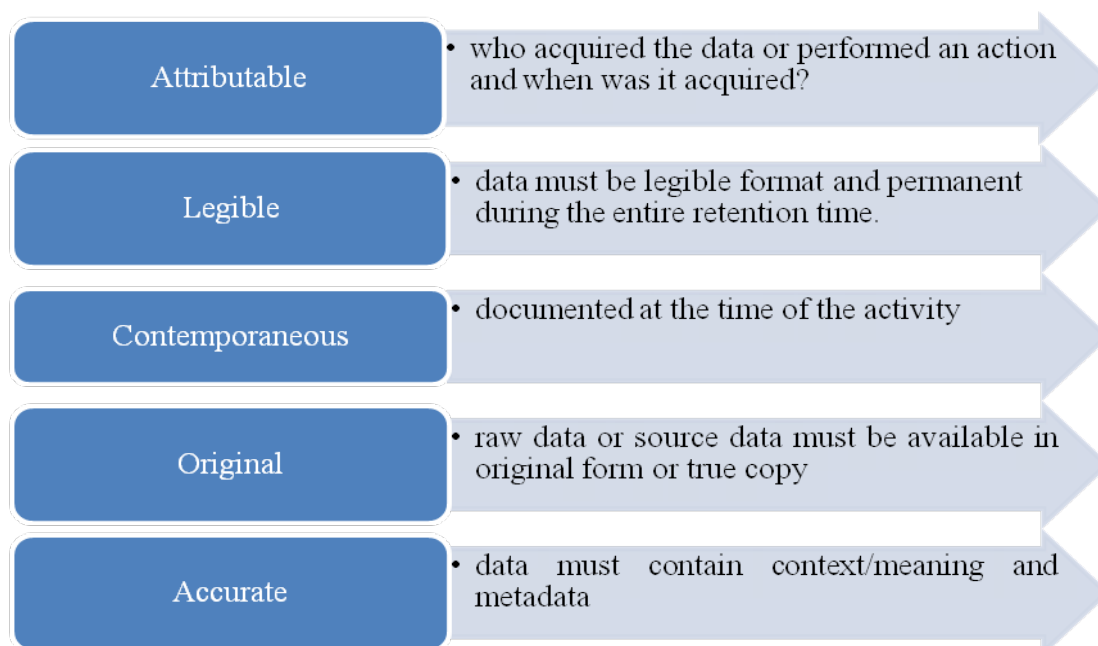


Fig. 1: Data integrity follows ALCOA

Why is data integrity needed?

1. It assures the quality, safety and efficacy of the drugs.
2. The documented data is the only record of the activity presenting the quality of the product.
3. Reliability of the data presented.
4. Submitting false data to the FDA is a criminal violation under FD&C act (CGMP/adulteration provisions)

#### **Metadata:**

metadata is structured information that describes, explains, or otherwise makes it easier to retrieve, use, or manage data. Metadata is often described as data about data. Data should be maintained throughout the record's retention period with all associated metadata required to reconstruct the CGMP activity (e.g., §211.188, 211.94).the relationships between data and their metadata should be preserved in a secure and traceable manner.

#### **Audit trail:**

audit trail means a secure, computer-generated, time-stamped electronic record that allows for reconstruction of the course of events relating to the creation, modification, or deletion of an electronic record.

Audit trails include those that track creation, modification, or deletion of data and those that track actions at the record or system level.

CGMP-complaint record-keeping practices prevent data from being lost or obscured and ensure that activities are documented at the time of performance (§§ 211.68, 211.100, 211.160(a), 211.188 and 211.194).electronic record-keeping systems, which include audit trails, can support these CGMP requirements.

#### **Static record format:**

static is used to indicate a fixed data record such as paper record or electronic image.

Dynamic record format: dynamic means that the record format allows interaction between the user and the record content.

**Backup data:** according to §211.68(b) backup refers to a true copy of the original record that is maintained securely throughout the record retention period (e.g., §211.180).

The backup file should contain the data along with metadata and should be in original format and compatible with the original format.FDA uses the term "backup" as it is consistent with the term archive as used in guidance for industry and FDA staff General Principles of Software Validation. Temporary backup copies (e.g., in case of a computer crash or other interruption) would not satisfy the requirement in §211.68(b) to maintain a backup file of data.

Computer related systems: the American national standards institute(ANSI) computer related systems can refer to computer hardware, software, peripheral devices, networks, cloud infrastructure, personnel, and associated documents(e.g., user manuals and standard operating procedures).[3]

#### **Regulations and Guidelines of Data Integrity:**

21 CFR Part 11- Electronic records and electronic signatures

21 CFR Part 210- cGMP in manufacturing, processing, packing and holding of drugs, generalDraft Guidance- Data Integrity and compliance with cGMP

21 CFR Part 211- cGMP for finished pharmaceuticals

§211.68 requires that backup data are complete and accurate and secure from alteration, inadvertent loss

§212.110(b) requires that data be stored to prevent deterioration or loss

§211.100 and 211.160 require that certain activities are to be documented at the time of performance and that laboratory controls should be scientifically strong.

§211.180 requires true copies or other accurate reproductions of the original records and;

§211.188, 211.194 and 212.60(g) require complete information, complete data derived from all tests, complete record of all data, and complete records of all tests performed.

#### **APIs-ICH Q7:**

- Computerized systems (5.4): GMP-related computerized systems should be validated.
- Appropriate installation and operational qualifications should demonstrate the suitability of computer hardware and software to perform assigned tasks.
- Incidents related to computerized systems that could affect the quality of intermediates or APIs or the reliability of records or test results should be recorded and investigated.

### FORM 483:

An FDA Form 483 is issued to firm management at the conclusion of an inspection when an investigator has observed any conditions that in their judgment may constitute violations of the Food Drug Cosmetic (FD&C) Act and related acts. FDA investigators are trained to ensure that each observation noted on the FDA Form 483 is clear, specific and significant.

The purpose of Form 483 is to encourage companies to respond to FDA Form 483 in writing with their corrective action plan and then implement that corrective plan expeditiously. FDA Form 483 notifies the company's management of objectionable conditions. At the conclusion of an inspection, the FDA Form 483 is presented and discussed with the company's senior management.

### Close out letter:

a close out letter will be issued by FDA based on its evaluation; the firm has taken corrective action to address the violations contained in the warning letter. This process applies to warning letters issued on or after September 1, 2009. The corrective actions must have actually been made and verified by FDA. Usually, the standard for verifying that corrections have been implemented will be a follow-up inspection. If the warning letter contains violations that by their nature are not correctable, then no close-out letter will be issued. [4]

**Import alerts:** import alerts inform the FDA's field staff and the public that the agency has enough evidence to allow for Detention without Physical Examination (DWPE) of products that appear to be in violation of the FDA's laws and regulations.

### The purpose of an import alerts is to:

- Prevent potentially violative products from being distributed in the United States.
- Free-up agency resources to examine other shipments
- Provide uniform coverage across the country
- Place the responsibility back on the importer to ensure that the products being imported into the United States are in compliance with the FDA's laws and regulations. [5]

### Background:

Data integrity assurance is a component of data management and equally applies to paper records and electronic records. The "generics scandal" of the 1980's raised the issue of falsified data submitted to FDA in support of drug approvals. One outcome of this scandal was the shift in focus of the FDA pre-approval inspection (PAI) to evaluate raw laboratory data included in the marketing application and evaluate whether the site was capable of manufacture as described in the application. This scandal also promoted implementation of the application integrity policy in 1991 which "describes the agency's approach regarding the review of applications that may be affected by wrongful acts that raise significant questions regarding data reliability." [6]

FDA recognized the increased reliance on computerized systems within the pharmaceutical industry. They developed and published 21CFR Part 11, the final rule on electronic records and electronic signatures in 1997. In 2003 FDA published a guidance for industry, part 11, electronic records; electronic signatures-scope and application to address enforcement priorities. FDA continues to communicate their interpretations in compliance actions such as Form 483, warning letters, podium presentations and on their Q&A website page.

How can we find warning letters in FDA official page?

- Firstly in FDA's electronic reading room we should search based on some keywords
- Then we should select the "sort by" - means by date, or by month etc.
- Then we should proceed to the "select sort criteria" - like ascending or descending order.
- Then select "GO"
- We should select "ALL" to view pages relating to the warning letters
- Select warning letters to open-use ctrl+F to find key words

### Example of warning letter:

This is a warning letter issued by USFDA to Reine life science, Gujarat, India last year in MAY, 2019.

Stating that "failure to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data, and failure to have adequate controls to prevent omission of data".

### FDA mentioned in the warning letter as:

Our investigator observed that the audit trail feature was disabled on instruments you use for quality control testing of your API, including your high performance liquid chromatographic system. Your analytical systems also lacked controls to prevent users from deleting or altering electronic data. For example, your quality assurance executive, who also performed your analytical tests, had administrator access to each system.

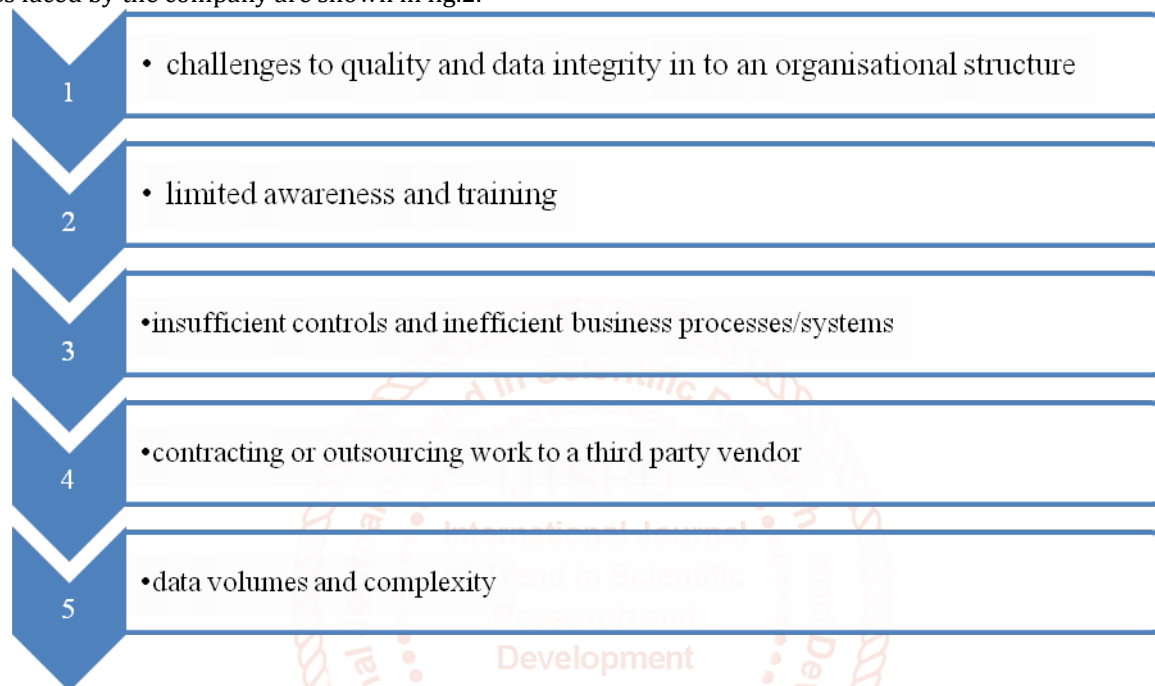
In your response, you committed to validating all computerized systems with incorporation of audit trails, restrictions on data, and user-access controls by March 31, 2018.

Your response is insufficient because it does not include interim control measures and procedural changes for the control and review of analytical data. You also do not specify who will have administrator privileges on your analytical instrument systems used for cGMP quality control testing.

In response to this letter:

- Provide a summary of your interim controls to prevent deletion and modification of data,
- Define the roles and responsibilities of personnel who have access to analytical instruments and data,
- Provide a standard operating procedure (SOP) that ensures that all quality control tests are performed by an analyst and receive second-tier review (e.g., by a manager) from a separate individual;
- Detail the associated user privileges for each analytical system;
- Provide a detailed summary of your procedural updates and associated training for user role assignment and controls; and
- Provide detailed procedures for your review of audit trail data

Challenges faced by the company are shown in fig.2.



**Fig.2: Key Challenges Company is facing in implementing data integrity**

#### **Common data integrity violations:**

- Failure to maintain complete data derived from all laboratory tests conducted to ensure compliance with established API standards. e.g.: this failure included the discovery of residual solvent testing data in the recycle bin folder, and failure to retrieve test data upon request.[7]
- Failure to prevent unauthorized access or changes data, and failure to provide adequate controls to prevent omission of data. This failure in one case, included the discovery that chromatography metadata (e.g.: time and data) could be changed without the changes being reflected in the audit trail. In another case, analysts deleted unknown peaks without justification, making the drugs in question paper to conform to their specifications. One of these peaks was for a residual solvent known to be a genotoxic impurity.[8]
- Failure to record activities at the time they are performed and destruction of original records. In one case, this failure involved the back dating of batch production records, and the destruction of original records after being manually transcribed.[9]
- Failure to train employees on their particular operations and related GMP practices.eg includes the declaration by employees that they had not received training for their production operations. The company in question was not able to produce any training reports for inspectors, despite the generation of training reports being part of company policy.[10]

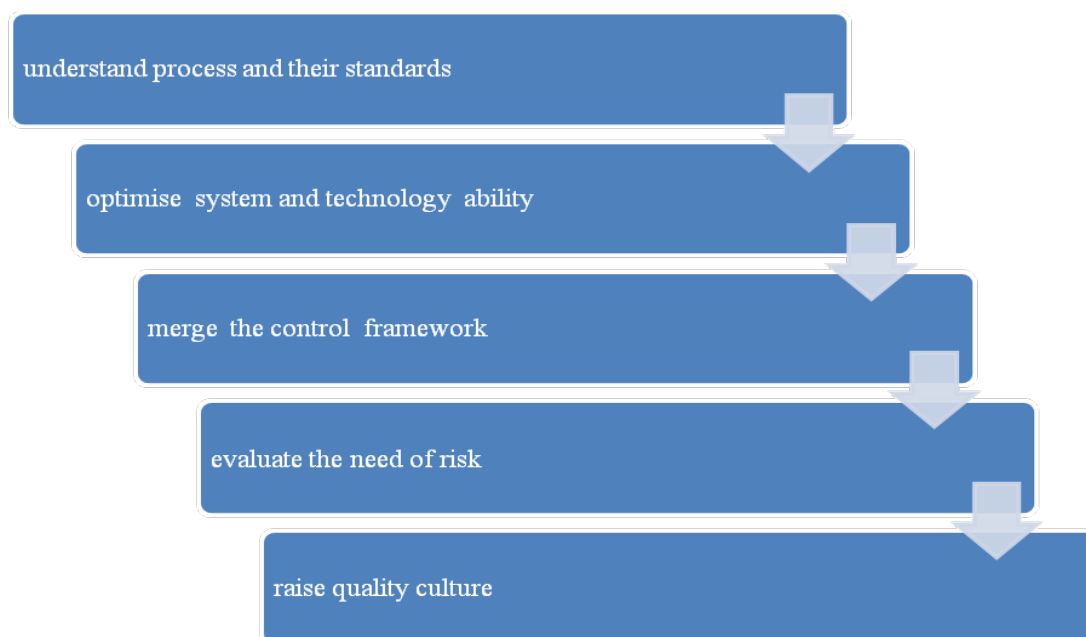
#### **Consequences of data integrity failure:**

Data integrity can result in the following regulatory and non regulatory consequences: [11]

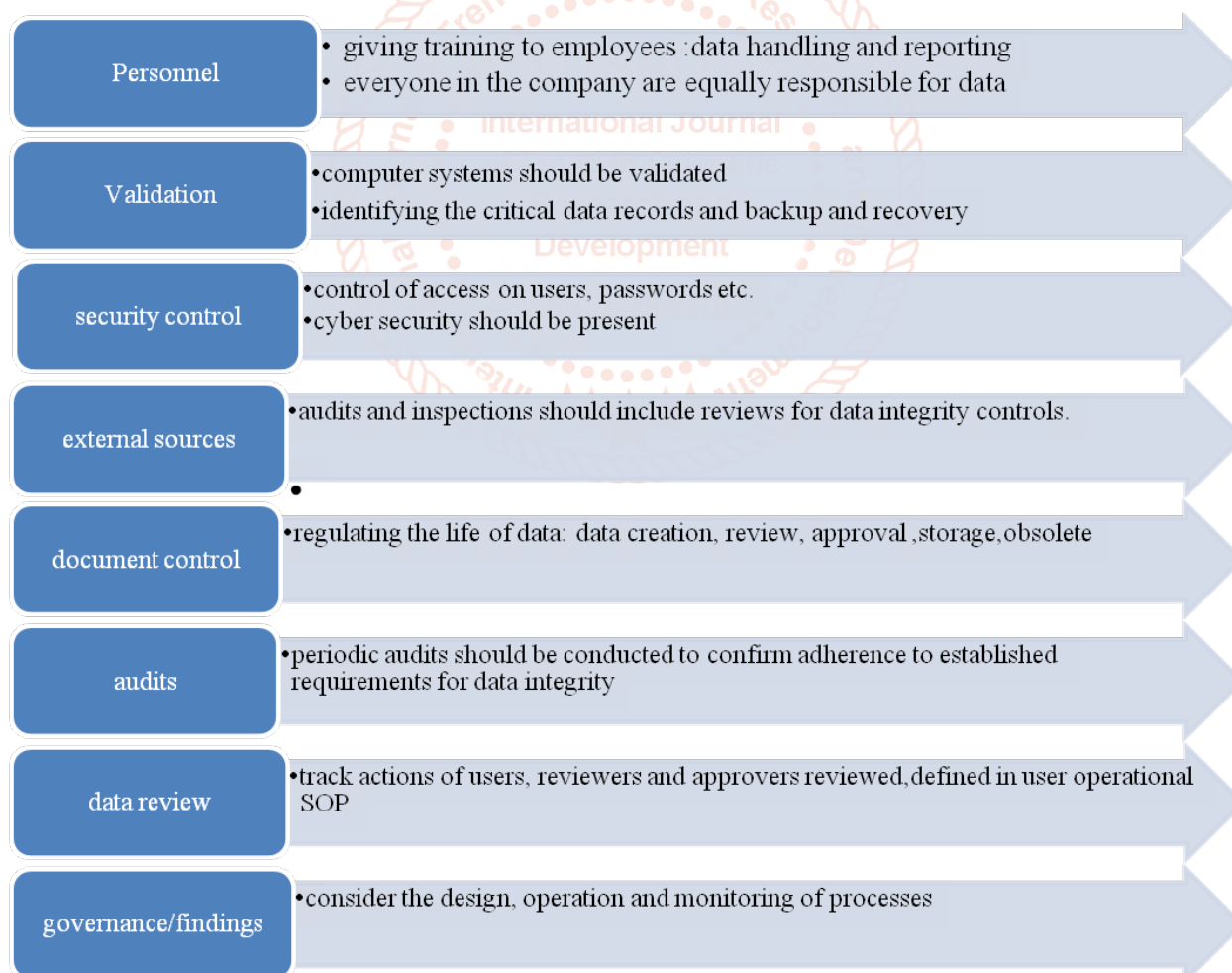
- The regulatory body can, at its own discretion, punish even technical violations which may not result in obvious threats to patient health. In addition to warning letters, the available enforcement actions include approval withdrawals, plant shutdowns, injunctions or penalties and debarment of individuals. The regulatory body has also resorted to suspending drug sales when it discovered that the integrity of the underlying data was compromised.[12,13]
- Criminal enforcement- the New England compounding centre manufactured drug products that resulted in a number of individuals dying from meningitis. During an inspection by a regulatory agency, the investigators found numerous cases of negligence and data integrity issues, for example, falsified cleaning logs to show cleaning was performed when it was not performed. Following the investigation, criminal charges were filed against 14 employees from high level executives to operators in the clean room.conviction on these types of charges can result in prison terms in addition to large fines.[14]



- Loss of reputation and public trust- the publication of warning letters in newspapers and consumer domains, can significantly tarnishes the reputations of a company. There have recently also been high profile warning letters from the regulatory body for a serious GMP violations which can result in adverse publicity.[15].organization's approach in implementing data integrity is shown in the fig.3.the risk factors are shown in the Fig.4.



**Fig.3: Organization's approach in implementing data integrity**



**Fig.4: Data Integrity Risk Factors**

#### Implementing Data Integrity:

- Record all the data in contemporaneous manner and sign
- Enter the data and time as per procedure
- Errors if any should be corrected as per Good Distribution Practices
- Any changes should be noted with reason

- Data should reflect the person who performed the activity or entered the results or verified the accuracy of entries. Never record the signature of another person
- Never pre-date or back date entries on any record
- Computer system shall be trustworthy, validated, ensure access control and audit trail
- QMS Modernization
- Computer system validation
- Quality risk management processes
- Strengthen internal audit
- Identifying risk factors
- Technical/QA/training/Education
- Promoting and supporting quality culture
- Effective CAPA assessment
- Control of documents/records

#### Data Integrity Remediation:

##### FDA warning letter recommendations:

1. investigate extent: investigate extent includes
  - Scope of investigation protocol/methodology
  - Root cause: interview current employees/former employees
  - Report all deficiencies: extent
  - Third party: deeper investigation of breaches
2. risk assessment: it includes
  - On drug quality: impact of data integrity lapses
3. management strategy: it is very much important and should be considered for future purposes
  - To ensure reliability and completeness: detailed corrective action
  - Root causes: comprehensive description
  - Actions: interim measures and long term measures
  - Report the status
  - The FDA regulators want that there should be no data- falsification, omission, hiding, and substitution.
  - perform GAP analysis
  - implement a corrective action plan(global) & prevent the integrity
  - Remove the individuals responsible for problems from cGMP positions
  - Complete a satisfactory inspection
  - increase the frequency of review
  - do surprise or spot checks
  - have a checklist for review mechanism
  - compare hand writing styles and signatures
  - verify attendance and presence of the persons
  - verify the traceability and logbook entries
  - trend the observations and provide the training
  - Define a clear policy on various activities like password policy
  - Have a clear procedure and controls over the electronic data and software administration
  - Cross check privileges and job responsibilities
  - Check the adequacy of the procedures.

The graphs representing the warning letters on data integrity and deviations are shown in fig.5 respectively.

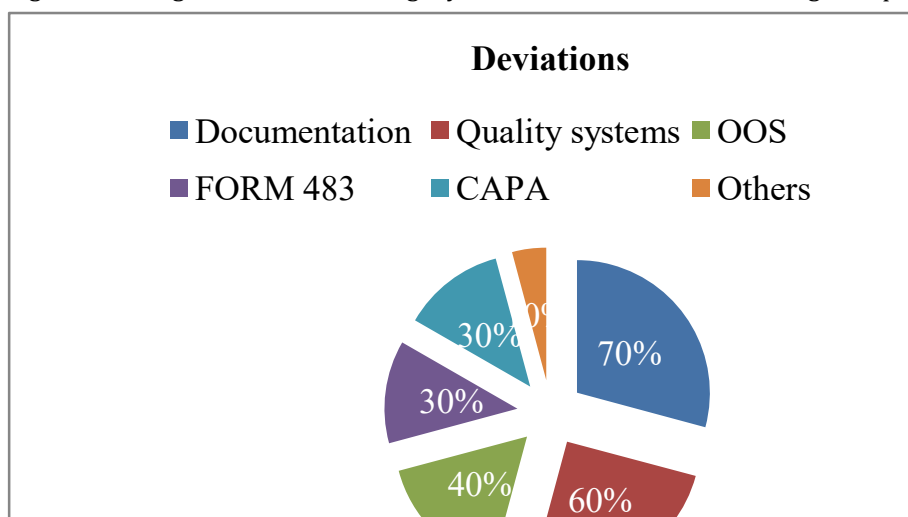


Fig. 5: Bar graph depicting the deviations in data integrity observed by USFDA

## CONCLUSION:

Data integrity is a crucial part in industry in maintaining the data during the regulatory audits. Data integrity is attained by having data recorded and documented and ensuring quality systems to be maintained. The perfect strategic planning ensures the audit trails, internal assessment of records, training of employees, electronic signatures, data review etc. data integrity mainly occurs due to improper documentation of records, lack of quality system, inadequate control over computer systems, unauthorized access to accounts, Form 483, lack of inspectional observations, corrective and preventive action measures are not properly implemented. To ensure successful implementation of data Integrity Company should maintain quality culture to get reputation, trust and market value and confidence of regulators and successful business organizations. In this we have observed that U.S have received more warning letters when compared to other countries and the number is enormously increasing day-by-day.

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