Data Integrity Issues & Concerns

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Objectives

- What is Data Integrity?

- Regulations

- Why is Data Integrity Important?

- Significant Issues

- Warning Letter (W/L) / Untitled Letter (U/L) charges and some FDA 483 examples.

What is Data Integrity?

- **Complete, consistent, and accurate data to assure patient safety and product quality.**

- Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a 'true copy', and accurate (**ALCOA**).

- Good Documentation Practices for Static and Dynamic Records.

- Data integrity should be maintained throughout the **data life cycle**, including, but not limited to data creation, processing, archiving and disposition after record's retention period.

Use of "static" and "dynamic" in relation to record format

- Static: fixed data document (e.g., paper record or an electronic image)

- Dynamic: record format allows interaction between the user and the record content (e.g., a chromatogram where the integration parameters can be modified)

Trustworthy Record Characteristics

- Reliabile: complete & accurate
- Authentic: proven to be what it purports to be
- Integrity: Complete & unaltered
- Usable: can be located, retrieved, presented & interpreted

ALCOA

- **A**ttributable – Traceable to a unique individual
- **L**egible – Data must be recorded permanently and be readable
- **C**ontemporaneously – Activities must be recorded at the time they occur
- **O**riginal or a true copy – first capture of data (not transcribed data), must review the original record, must retain the original or certified copy* of the original record.
- **A**ccurate – records must be accurate, which is achieved thru the Quality Management System

*Certified Copy is verified by a 2nd person who compares the copy to the original, confirms that the copy is accurate & complete and preserves Content & meaning (i.e., all data and metadata; documents the verification)

What is Metadata?

- Contextual information required to understand data (i.e., data about the data)
- Structured information that describes, explains, or otherwise makes it easier to retrieve, use or manage data
- Examples: date/time stamp, user ID, instrument ID, audit trails, etc.
- Relationships between data and their metadata should be preserved in a secure and traceable manner

What is an Audit Trail?

- Secure, computer-generated, time-stamped electronic record that allows for reconstruction of events relating to the creation, modification, or deletion of an electronic record
- Chronology: who, what, when, and why of a record
- Track actions at the record or system level
- CGMP-compliant record-keeping practices prevent data from being lost or obscured

Audit Trail captures…

- Overwriting
- Runs that have been aborted
- Testing into compliance
- Deleting data
- Backdating
- Altering data

(not an all-inclusive list)

How often should audit trails be reviewed?

- FDA recommends that audit trails capturing changes to critical data <u>be reviewed with each record and before final approval of the record</u>.

- Audit trails subject to regular review should include, for example, changes to: finished product test results, sample run sequences, sample identification, critical process parameters.

- FDA recommends routine scheduled audit trail review based on the complexity of the system and its intended use.

What are the Regulations?

FDA

Data in accordance with CGMP requirements for drugs (i.e., as required by 21 CFR parts 210, 211, and 212).

- Part 210 – Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General.
- Part 211 – Current Good Manufacturing Practice for Finished Pharmaceuticals.
- Part 212 – Current Good Manufacturing Practice for Positron Emission Tomography Drugs.
- Q7A – Active Pharmaceutical Ingredients.

Regulations – Data Integrity

Requirements with respect to data integrity in parts 211 and 212 continued:

- 211.188, 211.194, and 212.60(g) (requires "complete information," "complete data derived from all tests," "complete record of all data," "original records have been reviewed for accuracy, completeness, and compliance with established standards," and "complete records of all tests performed").

- 211.192 (requires production and control records be "reviewed")

- 211.101(c) and (d), 211.103, 211.182, 211.186(a), 211.188(b)(11), and 211.194(a)(8) require records be "reviewed" by a second person.

Regulations – Data Integrity

Requirements with respect to data integrity in parts 211 and 212 include:

- 211.68 (requires "backup data are exact and complete," and "secure from alteration, inadvertent erasures, or loss;" and that "output from the computer" "be checked for accuracy";
- 212.110(b) (requires data be "stored to prevent deterioration or loss");
- 211.100 and 211.160 (requires that certain activities be "documented at the time of performance" and that laboratory controls be "scientifically sound");
- 211.180 (requires records be retained as "original records," "true copies," or other "accurate reproductions of the original records");

Regulations – Data Integrity

- Electronic signature and record-keeping requirements in 21 CFR part 11 apply to certain records subject to record requirements set forth in the regulations (i.e., 210, 211, and 212).

- Guidance for Industry *Part 11, Electronic Records; Electronic Signatures — Scope and Application*.

How does FDA use the term "backup" in 211.68(b)?

- True copy of the original data that is maintained securely throughout the records retention period and reviewed by QCU.

- Electronic CGMP data should include relevant metadata.

- To exclude data from the release criteria decision-making process, there must be a valid, documented, scientific justification for its exclusion.

How should access to CGMP computer systems be restricted?

- Appropriate controls to assure only authorized personnel change computerized: For examples, MPCRs, Input of laboratory data into records, etc.
- Recommend restricting the ability to alter:
    - Specifications
    - Process parameters
    - Manufacturing or testing methods

How should access to CGMP computer systems be restricted cont.

- Recommend system administrator role, including any rights to alter files and settings, be assigned to personnel independent from those responsible for the record content

- Recommend maintaining a list of authorized individuals and their access privileges for each CGMP computer system in use

- May not be practical for small operations with few employees

Why is FDA concerned with the use of shared login accounts for computer systems?

A firm must

- Exercise appropriate controls to assure that only authorized personnel make changes to computerized records.

- Ensure actions are attributable to a specific individual.

Paper Record Comparison

- If actions are not attributable to a specific individual, a BPCR would look like all the values were entered but the people who performed and reviewed every step would be empty.

- Firm would not know if the unidentified individuals are authorized to perform the activity.

How should Blank Forms be controlled?

- Blank forms (e.g., worksheets, laboratory notebooks, and MPCRs) should be controlled by the quality unit or by another document control method

- Numbered sets of blank forms may be issued and should be reconciled upon completion of the activity

- Incomplete or erroneous forms should be kept as part of the permanent record along with written justification for their replacement

Paper Record Comparison

- Bound paginated notebooks, stamped for official use by a document control group, allow detection of unofficial notebooks as well as of any gaps in notebook pages.

- An electronic document management system could have the capability to reconcile and document the number of copies printed.

When does electronic data become a CGMP record?

- When it is generated to satisfy a CGMP requirement.

- You must document, or save, the data at the time of performance.

- Not acceptable to store data in temporary memory; this allows for manipulation, before creating a permanent record.

When does electronic data become a CGMP record continued…

- You may employ a combination of technical and procedural controls to meet CGMP documentation practices

- Computer systems, such as LIMS or EBR systems, can be designed to save after separate entries.

Paper Record Comparison

- This is similar to recording each entry contemporaneously on a paper batch record

FDA

Is it acceptable to only save the final results from reprocessed laboratory chromatography?

- No
- Analytical methods should be capable and stable
- If reprocessed, written procedures must be established and followed
- FDA requires laboratory records include complete data derived from all tests

Why is Data Integrity Important?

- FDA CGMP inspection(s) have uncovered violations with data integrity issues.

- Data integrity is an important component of industry's responsibility to ensure the safety, efficacy, and quality of drugs, and of FDA's ability to protect the public health.

- Data integrity-related cGMP violations may lead to regulatory actions, including warning letters, import alerts, and consent decrees.

- The underlying premise in 210.1 and 212.2 is that CGMPs sets forth minimum requirements to assure drugs meet standards of the Federal Food, Drug, and Cosmetic Act (FD&C Act) regarding safety, identity, strength, quality, and purity.

Why is Data Integrity Important?

- FDA's authority for CGMP comes from FD&C Act section 501(a)(2)(B).

- 501(a)(2)(B) states: 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."

Why is Data Integrity Important?

- FDA expects data to be reliable and accurate. CGMP regulations and guidance allow for flexible and risk-based strategies to prevent and detect data integrity issues.

- Firms should implement meaningful and effective strategies to manage their data integrity risks based upon their process understanding and knowledge management of technologies.

Why is Data Integrity Important?

- Reliability on the information used to ensure the quality of the drugs that consumers will take

- Data integrity problems break trust

- FDA rely on firm's to do the right thing when FDA is not present.

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Examples of significant issues

- No raw data to support records
- Creating inaccurate and incomplete records
- Test results for one batch used to release other batches
- Backdating
- Fabricating data
- Discarding data

Examples of significant issues

- Repeated tests, trial runs, sample runs (testing into compliance)
- Changing integration parameters of chromatographic data to obtain passing results
- Deletion/manipulation of electronic records
- Turning off audit trail
- Sharing password
- Inadequate controls for access privileges
- Inadequate/incomplete computer validation

Examples of significant issues

FDA

- Inadequate investigations
- Inaccurate reporting of microbial, sterility, or endotoxin data results
- Loss of data during changes to the system
- Activities not recorded contemporaneously
- Employees that sign that they completed manufacturing steps when the employees were not on premises at the time the steps were completed.

Things to consider…

FDA

- Is data integrity a problem at your facility? What measures are in place to prevent data integrity problems?

- Are internal audit procedures adequate? What measures are in place and will they detect data integrity issues?

- Does senior management cultivate adequate and accurate reporting of events when things go wrong during manufacturing…during testing?

- Train personnel to detect and prevent data integrity as part of routine CGMP training.

Data Audit Considerations

- Is the data being accurately interpreted?

- Is the data set accurately calculated and accurately reported?

- Does source data support the reported data and conclusions?

- Was there relevant data generated that should have been included but was not?

Where does the Agency find Data Integrity Issues?

- Domestic and International facilities
- Small and Large pharmaceuticals companies
- Manufacturing operations
- Quality units, including quality control laboratories (chemistry and microbiology)
- Clinical Trials

WL/ULs charges cited

- Failure to prepare batch production and control records for each batch of drug product that include documentation of the accomplishment of each significant step in the manufacture, processing, packing, or holding of the batch (21 CPR 211.188(b)).

WL/ULs charges cited

- Failure to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).

- 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 (21 CFR 211.68(b)).

FDA 483 Example 1
Reference 21 CFR 211.194(a)(3)

FDA

Laboratory records do not include a statement of the weight or measure of sample used for each test, where appropriate.

Specifically, the firm's Supplemental Method Sheet for Pharmaceutical Methods *** Pouch Testing approval date 05/07/** indicates for viscosity the amount on sample cup is critical try 0.12 mL using 3 cc syringe. **If there is too little sample, result will be low. If there is too much sample results will be high.**

For *** Pouch Testing (Viscosity Testing) the firm did not document the measure of sample used in their laboratory note book pages for the following samples:

- Sample NS-*****119
- Sample NS-*****120
- Sample NS-*****121
- Sample NS-*****122
- Sample NS-*****123

FDA 483 Example 2
Reference 21 CFR 211.68 – Validated for intended use

Appropriate controls are not exercised over computers or related systems...Specifically, the ***** software system has not been validated for its intended use**. Per the validation protocol, this software is used for drug material and inventory control, drug production scheduling, and control of finished product during distribution. **The validation does not address user access controls or password protection, specifically relating to the status of products in inventory**. A summary report, dated ***, in the validation material **states the *** software has, "been validated in order to see if it is manageable and user friendly**."

WL/ULs charges cited

- 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 (21 CFR 211.192).

- Failure to follow and document at the time of performance required laboratory control mechanisms (21 CFR 211.160(a)).

FDA 483 Example 3
Reference 21 CFR 211.192

There is a failure to thoroughly review any unexplained discrepancy for the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed. Specifically,

The investigations for *** tablets *** mg resulting in OOS and partial batch rejections were incomplete, for the following:

For Investigation ID #XXX, dated *** OOS was observed for the thickness *** tablets *** mg, Lot 123. **The investigation did not include an assessment of the manufacturing operations and the partially released finished lot 123 was not placed on stability.**

For Investigation ID #YYY, dated *** OOS was observed for the thickness ***tablets *** mg, Lot 456. **The investigation did not include an assessment of the manufacturing operations and the partially released finished lot 456 was not placed on stability.**

FDA 483 Example 4
Reference 21 CFR 211.160(a)

The establishment of test procedures including any changes thereto, are not reviewed and approved by the quality control unit.

Specifically, the firm's Supplemental Method Information Sheet (SMIS) is used to document information which is not present in a client specific procedure. A SMIS becomes part of the firm's official procedure used to perform testing. The following **SMIS reports were not reviewed or approved by the firm's quality assurance group:**

a. Version Number 10-02 for method ***Bulk Release Testing; Method Number ATM ***. Laboratory information indicates 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 center. In addition, lab info also indicates that the amount on sample cup is critical (try 0.12 mL using 3 cc Syringe).

b. Version Number 10-04 for method ***Pouch Testing; Method Number ATM ***. Laboratory information indicates 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 center. In addition, lab info also indicates that the amount on sample cup is critical (try 0.12 mL using 3 cc Syringe).

WL/ULs charges cited

- 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 (21 CFR 211.100(b)).

WL/ULs charges cited

- 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 (21 CFR 211.165(a)).

FDA 483 Example 5
Reference 21 CFR 211.165(a)

Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the final specifications prior to release. Specifically,

a.) Your **sampling plan allows for potency results to be reported as the average of three samples tested for each batch**. You have not established acceptance criteria for the results of each individual test or for the standard deviation of the test results. Therefore, your **current practice allows for 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.**

For example, potency sample #2 of ***, lot 567, 16.0 mg/mL was found to have an active ingredient concentration of 17.0 mg/mL. Potency sample #3 of the same batch was tested and found to have a concentration of 14.9 mg/mL. Your release specification for potency of is 15.2 - 16.8mg/mL. Within this batch you received potency test results that were both above and below the release specification range. Lot 567 was approved for release and distributed.

b.) You have not conducted testing of the preservative content or determined the effectiveness of the preservatives in your products. For examples, *** 100 mg/mL vials which contain preservative ***.

WL/UL for APIs

- Failure to ensure that laboratory records included complete data derived from all tests necessary to ensure compliance with established specifications and standards.

- Failure to protect computerized data from unauthorized access or changes.

- Failure to follow and document quality-related activities at the time they are performed.

WL/UL for APIs

- Failure to maintain and make available for inspectional review production and control reworks for currently marketed APIs.

- Failure to perform laboratory testing of APIs to ensure conformance to specifications and to accurately report results on Certificates of Analysis (CoA).

- Failure to investigate and document out-of-specification results.

WL/UL for APIs

- Failure to maintain complete records for APIs.
- Failure to include adequate documentation during complaint investigation.

Things to consider…

- Existing systems should be able to ensure data integrity, traceability and reliability

- Firms who outsource operations should have robust systems in place to verify and compare data generated by the contractor

Conclusion

- Once data integrity issues are found during an inspection, a change to a written procedure or firing an employee is not enough

- Quality Risk Management approaches to prevent, detect and control potential risk are essential

FDA recommends that data integrity problems identified during inspections be addressed?

The firm should demonstrate **effective remediation. For example,** By:

- Hire a third party auditor

- Determine the extent/scope of the problem

- Implement a global corrective action plan

- Removing individuals responsible for problems from CGMP positions

Acknowledgements

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Thank you