Top 10 DI citations in production systems

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Examples of Data Integrity Citations and their Possible Mitigations

Top 1 Audit Trai

"There are total (b)(4) standalone manufacturing equipment which are not equipped with HMI/PLC/SCADA system. There is no time stamped audit trail, data management, alarm management, archival and retrieval of records on these standalone manufacturing equipment." [33]

"Our investigator found that your (b)(4)system used for (b)(4) and (b)(4) testing lacked access controls and audit trail capabilities."檢查員發現用於（b）（4）和（b）（4）檢測的（b）（4）系統缺乏存取管控和審計追蹤功能

For example, all employees had administrator privileges and shared one user name, so actions could not be attributed or traced to specific individuals. This exposed your electronic data to manipulation and/or deletion without traceability." [34]

Possible Mitigations/ Controls

- Master and reference data review
- CQA/CPP identified and risk assessed
- Data mapping
- Deviation/incident Reports
- Report approval
- Including audit trail review as part of the batch report where exceptions are reported
- Technical controls to ensure audit trails are always active

Top 2 Calibration

"You failed to calibrate and maintain written records for the scale used to weigh components, including active ingredients, prior to their addition into the manufacturing process (21 CFR 211.68(a))." [35]

Possible Mitigations/ Controls

- Implement calibration management procedures
- Periodically review that they are effective
- Automatic system indication of calibration state

Top 3 Security and Access Controls

"Our investigators observed that information technology (IT) staff at your facility share usernames and passwords to access your electronic storage system for (b)(4) data. Your IT staff can delete or change directories and files without identifying individuals making changes. After a previous inspection in which FDA observed similar deficiencies, you committed to eliminate these and other data integrity vulnerabilities." [36]

"…the computer in your quality unit area did not have controls to restrict access and prevent unauthorized changes to data files and folders. All employees had access to your Annual Product Review (APR) spreadsheet. The desktop computer containing the APR was not locked." [37]

"The Electronic Logbook (eLog) System V1.0.0. is used for Instrument, Equipment, Area Operation and Cleaning usage log for Production, Warehouse, and Quality Control departments…" "The review of the audit trail for Electronic Logbook (eLog) System Version 1.0.0 in Unit 2 revealed that the "Reviewer" role has more (full) rights to the system than the "Administrator" and the system is managed by QC." [38]

Possible Mitigations/ Controls

- Access and security management
- Segregation of duties
- Data securely stored, use of relational databases in place of flat file storage
- System periodic review

Top 4 Manipulation of System Time

"Specifically, your Quality Control (QC) analysts used administrator privileges and passwords to manipulate your high performance liquid chromatography (HPLC) computer clock to alter the recorded chronology of laboratory testing events." [39]

Possible Mitigations/ Controls

- Lock down access to clocks
- Synchronize time Automatically

Top 5 Retention

"Your firm failed to maintain production, control, or distribution records associated with a batch of a drug product for at least one year after the expiration date of the batch (21 CFR 211.180)." [40]

"Our investigator also noted that your firm copied raw data to a CD and then deleted the data from the system to free space on the hard drive. Files copied to the CD were selected manually; the selection process was not supervised. Without audit trail capabilities or supervised file selection, there was no assurance that all raw data files were copied to the CD before they were permanently deleted from the system."[34]

Possible Mitigations/ Controls

Retention procedure, including the need to verify readability of archived data after any software upgrades/ downgrades

Top 6 Failure to record activities at the time they are performed.

"Our investigator found numerous examples of your failure to record manufacturing operations contemporaneously with their performance. For example, our investigator discovered blank batch production records that were pre-signed by your operator, partially-completed batch records, and batch records with data changes in pencil without any justification." [41]

"Your employees did not complete batch production and control records immediately after activities were performed. When QA reviewers noticed missing entries in the batch records, they made a list of all the missing items on separate, uncontrolled pieces of paper that were provided to the production manager. Data were later entered into CGMP documents after operations had already ended as though they had been entered at the time of the operation." [42]

"FDA investigators identified instances of non-contemporaneous documentation of batch production activities. Two uncontrolled Excel spreadsheets were used to record discrepancies and

certain in-process drug quality data. This data was initially missing in the batch manufacturing record. Your firm later entered this data into batch records and backdated them." [43]

"A critical deficiency was cited with regardsto data integrity of GMP records, entries were seen to be made when personnel were not present on site, documentation was seen that was not completed contemporaneously despite appearing to be completed in this manner."[44]

Possible Mitigations/ Controls

- Second person verification of results
- Data auditing
- User SOP
- Training on Good Documentation Practices
- Use MES that forces contemporaneous recording and sequence of steps
- Move spreadsheets to a validated EDMS or replace with avalidated application

Top 7 Batch Data Review

"Your firm's Quality Control Unit (QCU) failed to review and approve drug product production and control records. For example, your QCU did not identify discrepancies between your batch production records and your product labeling for the type and concentration of active ingredient in your (b)(4) gel and lotion products." [45]

"Our inspector reviewed several batch records and found use of white-out correction liquid, unintelligible data, and/or missing information such as density test results and the date of approval of the batch. Several entries were over written and crossed out with no signature, date, or explanation.

In addition, laboratory test results (e.g., viscosity, density, appearance, and odor) lacked initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards." [46]

Possible Mitigations/ Controls

- Batch data review Procedure
- Data auditing
- Second person verification of results
- Manual data/ transcribed data review
- Training on Good Documentation Practices
- Automated Data checks
- Validation of accurate transfer of data across interfaces

Top 8 Deliberate Falsification

"Our investigator discovered that your firm was destroying original batch records and backdating revised replacement pages. For example, our investigator found original pages from five (b)(4) batch records (batches(b) (4) to (b)(4)) discarded outside your facility. Your quality control unit approved revised and backdated master batch record pages that your firm created to replace the discarded pages. The original data were subsequently transcribed and backdated to the time of production. Quality and production managers allowed this practice." [47]

"Furthermore, your quality unit failed to identify data integrity issues in 11 batch production records reviewed by our investigator. Your production manager admitted that he falsified the signatures of other employees in the "Prepared By," "Reviewed By," "Approved By," and "Authorized By" sections." [48]

"Severe GMP violations related to the implementation of sound computerised systems in the quality control facilities were committed, that could lead/could have lead to the falsification of data. It was impossible to verify that the decision to approve raw material and final API was based on valid and accurate data" [49]

Possible Mitigations/ Controls

- Data integrity awareness training
- Open culture
- Data auditing
- Automated entries and automated data capture to secure records
- Assessment of system prior to purchase, followed by best practices for system implementation and validation
- Implement a data integrity policy that clearly states the consequences for deliberately falsifying records or intentionally disregarding procedures

Top 9 Incomplete Records Kept

A. Discarded training records

Our investigators observed discarded original personnel training records. Your procedure 3-040-127, Use of the Schulungs daten bank (Learning Management System) in the Supply Center Leverkusen requires these records to be maintained. In your response, you committed to retain original training records. However, you did not reassess your program to ensure that personnel were trained and capable of performing their assigned functions.

B. Discarded automated visual inspection machine parameters

In a (b)(4) department office waste bin, our investigators observed discarded forms used to document and set inspection parameters for your automated tablet visual inspection machinery. These parameters are used to accept or reject tablets. In your response, you noted that you documented and approved final set-up parameters, "but historically the calculations generated in support of those parameters have not been preserved."

You indicate that programming the visual inspection machine to detect defects may not be a CGMP activity. We note that the parameters of this machinery are used to discriminate between acceptable and unacceptable tablets. Accordingly, entering reliable settings into machine programming is part of CGMP." [50]

"Your electronic data logs did not retain alarm messages indicating when certain manufacturing parameters exceed their limits during production operations. Specifically, you did not maintain electronic log records of the in- process control alarms for your(b)(4) hydrogel coating machine, your (b)(4) checkweigher, and your (b)(4) packager." "In your response, you provided a list of equipment you will review for electronic data controls, but your response did not address the need to maintain a record of all deviations in the batch record in accordance with 21 CFR Part 211.188, and it lacked a global remediation to ensure electronic record retention." [51]

Possible Mitigations/ Controls

- Traceability
- Master data definition (routings / recipes, metadata)
- System configuration and exception reporting
- Collation of completed data into batch record
- Automation of data routings
- Training on Good Documentation Practices

Top 10 System Data Integrity Functions Not Validated

"Electronic records are used, but they do not meet systems validation requirements to ensure that they are trustworthy, reliable and generally equivalent to paper records." [52]

"Computer system validation for the Win KQCL software (endotoxin testing) is deficient in that the functionality testing related to user access and data security did not include challenges to demonstrate that data cannot be altered, manipulated or deleted."[53]

"Your firm utilizes Electronic Logbook (e-Log) System Version 1.0.0 in Unit 2 facility to document the all activities including results of analytical data for laboratory equipment and production. Your firm processed Change Control #CCP-IO-135-14-0009 to implement Logbook System Version 1.0.0 in Unit 2. Your firm did not execute a validation protocol including a validation summary report for the software Electronic Logbook System Version 1.0.0." [38]

Possible Mitigations/ Controls

Computerized systems validation life cycle to be followed for all GMP systems.

Source: 生產系統十大數據完整性問題！ (qq.com)