Detecting GMP Data Integrity Issues

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Outline

- Definitions and Regulations
- Regulatory Perspectives and Consequence
- Data Integrity Audit Techniques
- Points to Consider
- Questions

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Definition and Primary Concerns

- **Data Integrity** is "The degree to which a collection of data is complete, consistent, and accurate" Source: FDA Glossary of Computer Systems Software Development Terminology (8/95)
- **Two areas of concern regarding data integrity in daily CGMP operations:**
  - Submission or providing data to a health authority as a result of an inspection
  - Part of a regulatory submission – licensure verification supplement, Field Alert Reports, etc.

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Data Integrity Regulations

- US Code of Federal Regulations (21 CFR):
  - ✓ §211.68 – Any calculations used must be verified and data generated in an analysis must be backed up and the back up data must be exact and complete
  - ✓ §211.160(a) - Methods used must be documented and approved and data generated and transformed must meet the criterion of scientific soundness
  - ✓ §211.160(b), §211.63 – Instruments must be qualified and fit for purpose
  - ✓ §211.180(d) – records must be retained as original or true copies
  - ✓ §211.194(a) – Methods must be verified under actual conditions of use, Test data must be accurate and complete and follow procedures and Data and the reportable value must be checked by a second individual to ensure accuracy, completeness and conformance with procedures
  - ✓ § 211.194 (c) Reagents and reference solutions are prepared correctly with appropriate records
  - ✓ Part 11 Sec. 11.10 - *"Use of secure, computer generated, time stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information"*
- Submitting false data to the FDA can be deemed a criminal violation and can invoke FDA's Application Integrity Policy - *Title 18 U.S. Code-various sections*

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Data Integrity Regulations

- Directive 2003/94/EC for medicinal products for human use (*as interpreted via EudraLex The Rules Governing Medicinal Products in the European Union Volume 4 Good Manufacturing Practice Medicinal Products for Human and Veterinary Use (Chapter 4: Documentation*)
- Directive1999/93/EC (The European Parliament and of the Council of 13 December 1999 on a Community framework for electronic signatures)
- Eudralex Annex 11 Principle 9 Audit Trails
  - ✓ *Consideration should be given, based on a risk assessment, to building into the system the creation of a record of all GMP-relevant changes and deletions (a system generated "audit trail"). For change or deletion of GMP-relevant data the reason should be documented. Audit trails need to be available and convertible to a generally intelligible form and regularly reviewed*

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Regulatory Perspectives

Data integrity continues to be a major concern to FDA

- ✓ Generic Drug Scandal in late '80s and early '90s found some generic firms to have submitted falsified or inaccurate data to FDA, or to have paid bribes or illegal gratuities to FDA officials
- ✓ Criminal investigation of several firms/individuals has occurred
- ✓ As a result of the Generic Drug Enforcement Act (GDEA) of 1989, FDA's inspectional program was significantly revised to include more emphasis on data integrity.
- ✓ The drug approval process now includes pre-approval inspections to assure that a manufacturing establishment named in a drug application is capable of manufacturing a drug, and that all of the submitted data in an application is accurate and complete.

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Consequences of Data Integrity Violations

- USA – Recall, Warning or Untitled Letter, Import Alert, Injunction, Seizure, Application Integrity Policy Invocation

Reference: K. Takahashi, Senior Policy Advisory, FDA/CDER/Office of Compliance at ISPE Annual Meeting Nov. 2013

- Europe and RoW - Recalls, withdraw of products from the market, Rejection of data (+ withdrawal of approved applications), Sanctions, legal actions, fines and prison, 'Black-listed' (SFDA), Refusal to issue GMP certificate or revoke previously awarded one, Re-inspection, Seizure and Forfeiture

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When Do Data Integrity Issues Occur

- Data Integrity issues can occur at any time during the life cycle of a product to any company
  - Data may be unreliable due to poor documentation practices. A pattern of errors can raise question about the overall reliability of the data.
  - Data may be unreliable due to deliberate actions
- Data could also be unreliable for a variety of reasons including training, etc. In either case it leads to the same lack of trust and usability of the data.

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Why Data Integrity Issues Happen

- Computer systems are not secure
- Inadequate procedures
- Resource constraints
- Inventory demands
- Desire to meet metrics/goals
- Lack of training

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General Examples of Data Integrity Issues

- Not recording activities contemporaneously
- Human errors
- Fabricating data
  - ✓ Backdating
  - ✓ Copying existing data as new data
  - ✓ Reporting only passing or unrealistic values (data is too good)
  - ✓ Creating acceptable results without performing the task
- "Testing into compliance"
  - ✓ Re-running samples
  - ✓ Basing results on non-scientific rationale
- Discarding or altering data – not saving electronic or hard copy data
- Reported data is inaccurate and/or not supported by raw data
- Forging and/or unauthorized signatures
- Keeping and reporting un-official or private records
- Site does not actually manufacture the drug as described in the drug application

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Data Integrity Audit Techniques

Audit should involve combination of Top-Down & Bottom-Up techniques

- Evaluate whether the existing systems, controls, processes, and tools are robust enough to prevent data integrity issues, detect them if they occur, and mitigate quickly and effectively. (*Top-Down*)
- Look for any sign of pattern or practice of data integrity issues through review of executed batch records and registration files, to ensure the validity of data submitted to regulatory agencies and those used to release products. (*Bottom-Up*)

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Data Integrity Audit Techniques

Original Records are discarded

- Look for trends in discrepancies/investigations
- Documentation has no errors
- Evaluate intermediate document storage areas (bins for document corrections, document movement between departments)
- Look behind copiers, random drawers
- Look through shred bins

Falsifying Signatures

- Compare investigation/OOS list to lot release list Ensure no open investigations/OOS are in place for released batches
- If electronic release of batch, ensure transaction made by QA qualified individual
- Interview individuals. Ensure they acknowledge having performed the tasked they signed for
- Verify through facility access records
- Verify authenticity signatures on GXP entries

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Data Integrity Audit Techniques

Inadequate Resources for Operations

- If significantly more product has to be produced or samples tested than capacity allows, this may lead to skip testing or not report failing results
- Verify that during periods of vacation/illness personnel did not perform documented work
- Number of individuals to a work shift

Metric Driven Behaviors

- Look at risk reduction, discrepancy reduction goals and see if numbers achieved were due to significant process improvements or potentially attributable to a lack of reporting
- For metrics that drive for a quota for example 50 deviations/month, look for reporting volumes at the beginning of the month versus end of month. If all is equal, significant deltas in reporting volumes should be evaluated
- Look at LIMS samples processed. Cancelled LIMS samples without explanation should be further assessed if they were cancelled inappropriately to assure a clean LIMS invent
- Review lot release and inventory systems

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Data Integrity Audit Techniques

Inadequate Procedures

- Have an individual explain a process. Then review the SOP with them. Ensure the sequence in SOP can be followed & critical steps are not missed. Deviations and changes are raised in cases of misalignment (QC Raw Materials).

Data Alteration

- Compare records by area and / or by personnel; look for trends
- Verify times and dates of data recording
- If electronic, check audit trails, related validation, review of controls
- Look in lab and manufacturing for non-reported data results or processes that failed. Is the license or application being followed? Does the process have poor capabilities? Is the analytical method being followed?
- Regenerate computer trend graphic (e.g. autoclave cycle/HPLC chromatogram) and superimpose to graphic in validation document
- Verify cycle parameters in validation report match those identified in the computer system
- Compare raw data to CMC and records
- Perform a selected trace of reported results back to source data

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Points to Consider

- Is your Quality System robust enough to prevent, detect and mitigate data integrity issues
- Are your records accurate and protected
- Are you routinely reviewing audit trails
- Does your Raw data files support a conclusion that the data/information in the application is complete and enables an objective analysis by reflecting the full range of data/information about the component or finished product known to the establishment
- Are your internal audits checking for data integrity on a routine basis
- Are your auditors trained on techniques to detect data integrity issues

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Questions?