Preparing for Successful Data Integrity Audits

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Preparing for Successful Data Integrity Audits

- U.S. Food & Drug Administration and other regulatory agencies found major issues beginning in 2014

- Data Integrity has been a major concern for pharmaceutical and medical device companies since 2014
Preparing for Successful Data Integrity Audits

Session One
- General data integrity concepts

Session Two
- How to audit paper and electronic records for data integrity
- Data integrity focus of regulatory inspections
General Data Integrity Concepts

Data is Recorded...

Paper

Electronic Systems

October 12 - 13, 2017
General Data Integrity Concepts

**RAW DATA**
Original records and documentation, retained in the format in which they were originally generated (paper or electronic)

**DATA**
All original records, including source data, metadata, subsequent transformations and reports, generated or recorded at the time of the activity. Allows full and complete reconstruction and evaluation of the activity.
General Data Integrity Concepts

[ORIGINAL RECORD]

Data as the file or format in which it was originally generated, preserving the integrity (accuracy, completeness, content and meaning) of the record:

- original paper record of manual observation
- electronic raw data file from a computerized system
General Data Integrity Concepts

Which of these is an original paper record?

- Printout from pH Meter or balance
  - It depends:
    - With data storage
    - No data storage

- Photocopy of autoclave cycle report:
  - Autoclave does not store data
  - Report was originally printed on thermal paper

- Report printed from Ethylene Oxide monitoring system

- Printed chromatogram from automated system such as FTIR (Fourier Transform Infrared Spectroscopy), HPLC (High Performance Liquid Chromatography)
Data Integrity:
The extent to which all data are complete, consistent and accurate throughout the data lifecycle
General Data Integrity Concepts

Data Integrity = Good

Data Integrity Issue = Not Good
General Data Integrity Concepts

Mistake

Error is made: Acknowledge error so it can be addressed

Bad Practice

Action is taken that is not compliant with cGMP to save time, for instance

Intention

Or Fraud

Procedures and/or cGMPs are bypassed knowingly

Data Integrity Issue

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General Data Integrity Concepts

Prevent Integrity Issue Detect

Data
General Data Integrity Concepts

**ALCOA**

Data must be:
- **Attributable** to the person generating the data
- Legible
- Contemporaneous
- Original record
- Accurate

**ALCOA-Plus**

ALCOA, with additional emphasis on data being:
- Complete
- Consistent
- Enduring
- Available

October 12 - 13, 2017
# General Data Integrity Concepts

<table>
<thead>
<tr>
<th>Good Doc Practices Principle</th>
<th>Paper</th>
<th>Electronic</th>
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<tbody>
<tr>
<td><strong>Attributable</strong></td>
<td>• Initials/signature by person who performed activity</td>
<td>• Electronic signature (username + password)</td>
</tr>
<tr>
<td><strong>Legible</strong></td>
<td>• Indelible ink • No erasure or correction fluid/tape • Changes are corrected properly</td>
<td>• Data is visible in fields</td>
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<tr>
<td><strong>Contemporaneous</strong></td>
<td>• Recorded at time of activity • No pre- or post-dating</td>
<td>• Record is saved when data is entered • Time/date stamps • Synchronized time (for accuracy)</td>
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<tr>
<td><strong>Original</strong></td>
<td>• Paper form • No post-its or temporary method of recording then transcribing data</td>
<td>• Data generated by computerized system includes metadata • Not able to modify original data</td>
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<td><strong>Accurate</strong></td>
<td>• Data recorded is accurate • Calculations are checked • Second person verification</td>
<td>• Data transfers from original data system accurately (e.g., to LIMS, archival) • Calculations correct • Second person verification</td>
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General Data Integrity Concepts

- DI is not a new expectation of regulatory bodies.
- **Predicate rules:** 21 CFR 211, ICH Q7, 21 CFR Part 11, EudraLex Annex 11

Examples of predicate rules related to data integrity:

| $211.68$: | • Changes in records are made by authorized personnel  
• Backup data are exact and complete, and secure from alteration, inadvertent erasures, or loss |
| $211.160$ | • Laboratory activities are documented at the time of performance |
| $211.188$ | • Documentation that significant steps were accomplished including identification of person performing and supervising the steps |
| $211.194$ | • Laboratory records include all data secured in the course of each test |
| EudraLex Vol. 4, 4.9 | • Changes made to entry are signed and dated; alteration permits reading of original information |
| EudraLex Vol. 4, Annex 11 | • Audit trails (record of all GMP-related changes and deletions) need to be available and regularly reviewed |
# Data Integrity Requirements

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<thead>
<tr>
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## Data Integrity Requirements

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Data Integrity Focus of Regulatory Inspections
DI Focus of Regulatory Inspections

Primary Considerations for cGMP Enforcement:

• Is drug adulterated?
• Most important factor – is there risk to patient?
  – High risk: FDA takes quick action
    • Sub- or super-potent
    • Contamination
    • Sterility concerns
    • Other defects

- Paula R. Katz, CDER, India Pharmaceutical Forum

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2016 Warning Letters:

- 19 - Data Integrity
  - Lack of control over access to computerized systems
  - Non-contemporaneous record-keeping
  - Deletion, falsification, alteration, or other manipulation

54 warning letters
47 import alerts
4 untitled letters

2016 OMQ Enforcement Actions

- Paula R. Katz, CDER, India Pharmaceutical Forum
FDA concerns with data integrity:

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<th>Shared login accounts</th>
<th>Cannot identify a unique individual</th>
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<tbody>
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<td>System administrator role not independent</td>
<td>Assigned to personnel responsible for record content</td>
</tr>
<tr>
<td>cGMP record not complete</td>
<td>All electronic data generated to satisfy a CGMP requirement is not included</td>
</tr>
<tr>
<td>Testing into compliance</td>
<td>Actual samples were used during “system suitability,” test, or equilibration runs</td>
</tr>
</tbody>
</table>

- Paula R. Katz, CDER, PDA Data Integrity Workshop
FDA recommends audit trails that capture changes to critical data be reviewed:

- With each record
- Before final approval of the record
- History of finished product test results
- Sample run sequences
- Sample identification
- Critical process parameters

Regular review of audit trails should include, at a minimum, changes to:

- History of finished product test results
- Sample run sequences
- Sample identification
- Critical process parameters

- Paula R. Katz, CDER, PDA Data Integrity Workshop
DI Focus of Regulatory Inspections

Deadline for Audit Trails

- If no audit trailed system exists:
  - Paper based audit trail is permitted (if equivalent to integrated audit trail in Annex 11 of EudraLex) until a fully audit trailed system becomes available
  - Facilities should upgrade to an audit trailed system by the end of 2017 if equivalence cannot be demonstrated

- MHRA GMP Data Integrity Definitions and Guidance for Industry, March, 2015
Deadline for Unique Logins

• If a computerized system supports one or limited number of user logons:
  – Upgrade to computerized system that can provide the required number of unique logons by the end of 2017
  – Paper based traceability is permitted if no suitable alternative computerized system exists

- MHRA GMP Data Integrity Definitions and Guidance for Industry, March, 2015
DI Focus of Regulatory Inspections

• 2 kinds of data integrity problems
  – Top down, pervasive, dictated by management
  – Bottom up, isolated, one or a few operators or analysts

• If FDA finds DI issue in one place…
  – Assume data integrity is an issue everywhere, unless a credible audit determines otherwise

- Takahashi: Look Out for These Data Integrity Issues
Regulatory Focus for Inspections

When something doesn’t look right, take a tangent and zero in on it. Examples:

- Test results for one batch used to release other batches
  - Test file has same date and time as other tests
  - Too many tests run in the time available
- Audit trail disabled until passing test results were obtained
- Failing and passing batches of active pharmaceutical ingredient blended to produce passing results
  - Lab and management knew about this practice
- Created falsified training records that were requested during the inspection

- Takahashi: Look Out for These Data Integrity Issues
DI Focus of Regulatory Inspections

• Look for data that is too good
  – No complaints, deviations, or out-of-specification investigations
  – Handwritten data that looks too neat
DI Focus of Regulatory Inspections

26 Active Pharmaceutical Ingredient (API) FDA warning letters

• 12 focused primarily on data integrity concerns
• 4 focused secondarily on data integrity concerns
• Quality System records
  – Only 2 of 17 complaints in complaint log; complete list found on warehouse floor
  – Many production deviations in a GMP Anomalies folder that were not investigated or reported

- Bowman Cox, FDA GMP Warning Letters Review
API FDA warning letters

- Laboratory records and computerized systems
  - Unofficial test records and deleted unknown peaks in chromatograms – potential impurities
  - Reference standard tested instead of 12 month stability sample
  - Retested samples until in-specification results were reported
DI Focus of Regulatory Inspections

API FDA warning letters

- Laboratory records and computerized systems
  - Microbiologist did not record test results contemporaneously
  - QC worksheet completed after FDA investigators asked for it
  - Gas chromatograph clock set back to make it appear stability test was done months earlier; failing tests deleted
  - HPLC system configured to automatically delete aborted tests, and turn back clock for passing results

- Bowman Cox, FDA GMP Warning Letters Review
2 Drug Product FDA warning letters focused on data integrity concerns

- Laboratory records and computerized systems
  - Trial HPLC injections; data stored separately from reported test results
  - Administrator privileges given to analysts, who changed time and date settings then overwrote and deleted HPLC test data
  - Unreported gas chromatography results, including out of specification test results for a raw material
2 Drug Product FDA warning letters focused on data integrity concerns

- Other records
  - Batch record pages destroyed and replaced with backdated revised pages
  - Workers in production failed to record activities contemporaneously
  - Workers incinerated GMP documentation

- Bowman Cox, FDA GMP Warning Letters Review
FDA Warning Letters from FY2015

- Requirements approaching those of a consent decree
- Boilerplate text was included in warning letters for serious data integrity deficiencies

- Barbara W. Unger, Data Integrity: Surveying the Current Regulatory Landscape, Pharmaceutical Online
DI Focus of Regulatory Inspections

1. A comprehensive investigation into the extent of the inaccuracies in data records and reporting

   • A detailed investigation protocol and methodology
     o Summary of all systems to be covered by the assessment
     o A justification for any systems excluded

   • Interviews of current and former employees
     o Identify the nature, scope, and root cause of data inaccuracies
     o Interviews conducted by a qualified third party

   • Determine extent of data integrity deficiencies
     o Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies
     o Identify operations where data integrity lapses were discovered

   • A comprehensive retrospective evaluation of the nature of all data integrity deficiencies
     o Conducted by qualified third party
     o Specific expertise in the area where potential batches were identified

- Barbara W. Unger, Data Integrity: Surveying the Current Regulatory Landscape, Pharmaceutical Online
2. A current risk assessment of the potential effects of the observed failures on the quality of your drugs.

   • Your assessment should include:
     • Risks to patients caused by the release of drugs affected by a lapse of data integrity
     • Risks posed by ongoing operations

- Barbara W. Unger, Data Integrity: Surveying the Current Regulatory Landscape, Pharmaceutical Online
3. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include:

- A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including:
  - analytical data,
  - manufacturing records, and
  - all data submitted to FDA.

- A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment.
  - Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm.

- Barbara W. Unger, Data Integrity: Surveying the Current Regulatory Landscape, Pharmaceutical Online
3. Your management strategy should include:

- Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as:
  - notifying your customers,
  - recalling product,
  - conducting additional testing,
  - adding lots to your stability programs to assure stability,
  - drug application actions, and
  - enhanced complaint monitoring.

- Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company’s data.

- A status report for any of the above activities that are already underway or completed.

- Barbara W. Unger, Data Integrity: Surveying the Current Regulatory Landscape, Pharmaceutical Online
Completion of these activities will not happen quickly and will take a concerted effort on the part of the firms involved.
• Uncontrolled documentation was noted throughout production engineering notebooks with setup details and passwords, crib notes on the wall of the Goods In area, scraps of paper containing numbers of components brought onto line.

• Printouts of particle count data from HEP filter testing were not transferred from thermal paper to non-volatile media to ensure the integrity of the record throughout the retention period.
DI Observations - EU

- Following a software update, data was lost from an autoclave control system. The system backup was unable to recover lost data as the backup was only performed on a 3 monthly basis.

- The backup CD/DVD for the autoclave control system was not stored within a controlled environment to assure its integrity.

- Data from the integrity test was not backed up. The system was observed to overwrite previous data.

- Backups were permitted to be made on the same computer drive which failed to ensure that a separate copy was available following drive failure or corruption.
DI Observations - EU

- Access to files and the system clock on the hard drive was available to all users.

- The lock screen used a shared password. If a user had logged into the software behind the lock screen and another user opened the computer, they could perform actions under the initial user’s login.

- Users had more authorisation on the chromatography data system than was permitted according to the SOP.

- Access control systems were not considered GMP systems despite their intended purpose to control access to GMP areas.
DI Observations - EU

• HPLC software in the laboratory was not configured for GMP compliance:
  – Unique user passwords were not enforced
  – Users were permitted to:
    • Change the default audit trail
    • Change the default “require user comments”
    • Copy non-related projects
    • Use annotation tools
DI Observations - EU

• Control of dosimeter readings was deficient:
  – Dosimeters could be reread and individual thicknesses be input into the system if a variation of 6% was identified for a location; this did not result in a deviation to review the validity of previous acceptable results
  – New thickness readings had no second person verification to ensure accuracy of the data used
Additional Sources of Information

- **MHRA GMP Inspection Deficiency Data Trend 2016**

- **Current Expectations and Guidance, including Data Integrity and Compliance With CGMP**, Sarah Barkow, PhD, Team Lead, CDER/OC/OMQ Guidance & Policy, ISPE DI Workshop, June 5, 2016

Additional Sources of Information

  [https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM539554.pdf](https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM539554.pdf)

- **Takahashi: Look Out for These Data Integrity Issues**, Pink Sheet & Gold Sheet, by Bowman Cox (subscription required), Mar. 28, 2014

- **FDA GMP Warning Letters Review: API Supplier Warnings Surge on Data Integrity Concerns**, Pink Sheet, by Bowman Cox (subscription required), Apr. 26, 2017
Additional Sources of Information

• FDA GMP Warning Letters Review: Foreign Drug Product Firms Hit Hard on GMP Basics, Pink Sheet, by Bowman Cox (subscription required), Apr. 27, 2017

• Data Integrity: Surveying the Current Regulatory Landscape, Pharmaceutical Online, Barbara W. Unger, Aug. 4, 2016
Questions?