Data Integrity Requirements in a GxP Environment

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What is Data Integrity?

US FDA Definition

Data Integrity refers to the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA).

MHRA Definition

Data Integrity is the degree to which data are complete, consistent, accurate, trustworthy, reliable and that these characteristics of the data are maintained throughout the data life cycle. The data should be collected and maintained in a secure manner, so that they are attributable, legible, contemporaneously recorded, original and accurate (ALCOA). Assuring data integrity requires appropriate quality and risk management systems, including adherence to sound scientific principles and good documentation practices.

EMA Definition

Data Integrity enables good decision making by pharmaceutical manufacturers and regulatory authorities. It is a fundamental requirement of the pharmaceutical quality system described in EU GMP Chapter 1, applying equally to manual (paper) and electronic systems.

Why do we care about the integrity of the data?

- Data has varying importance to quality, safety and efficacy decisions.
- Data used to make decisions has to be reliable and accurate.
- It is critical throughout the cGMP data lifecycle, including the creation, modification, processing, maintenance, archival, retrieval, transmission, and disposition of data after the record's retention period ends.
- Speaks to the quality culture and ethics of the organization.
- Patient Safety and Product Quality!

Impact of Data integrity on GMP norms

- Increase focus by regulatory agencies.
- Validity of raw data used to preparing regulatory dossier crucial to product safety and efficacy.
- Added responsibility of management and Quality groups to ensure good data integrity.
- Added focus on security of electronic systems.
- Increased training and awareness on good Data Integrity practices.

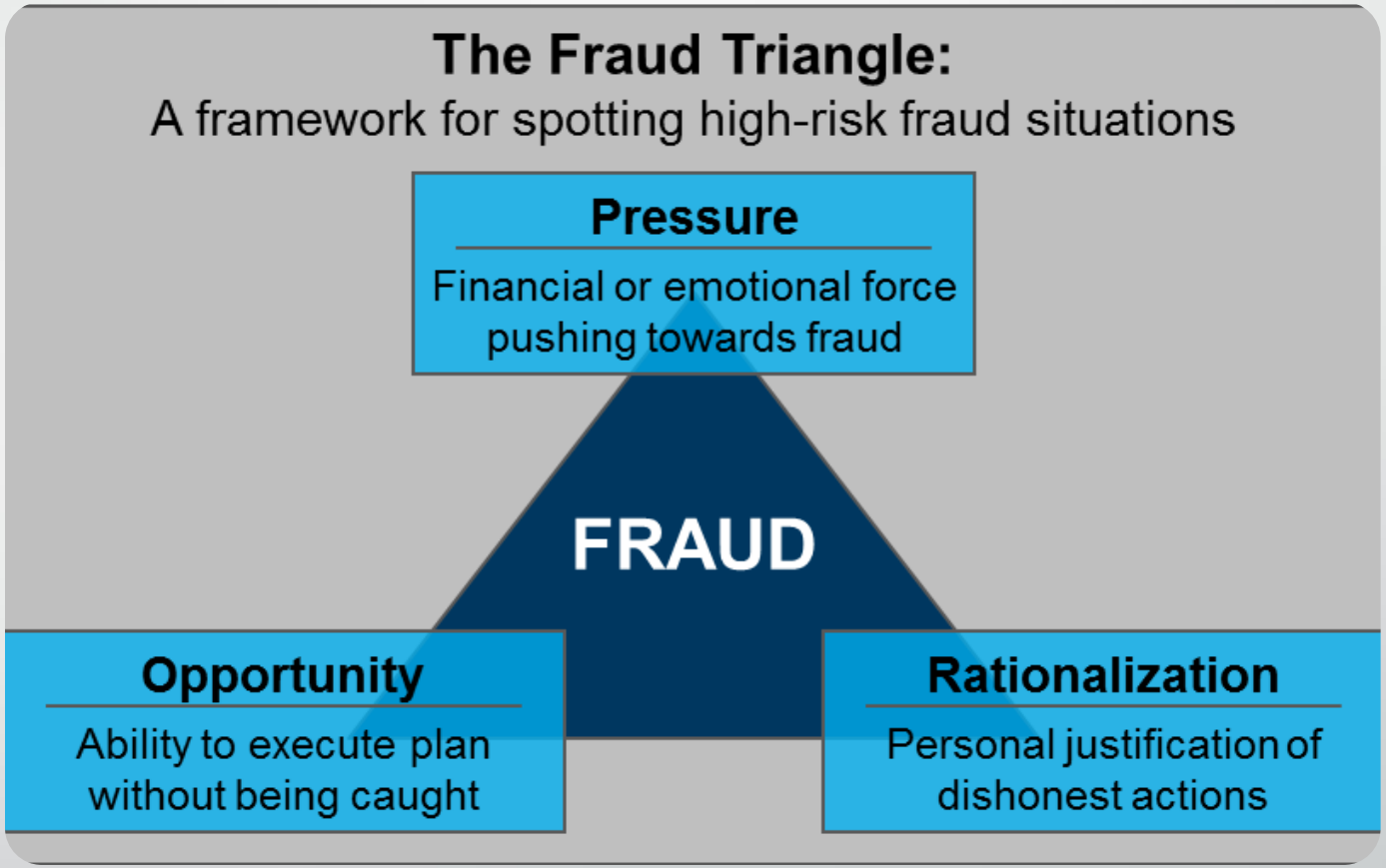
Ways of managing and retaining GMP records

- Good Document Control Practices.
- Implementing and enforcing error correction practices.
- Having an SOP on SOPs in place.
- Physical or logical (or technical) control over Master copies of Controlled Document, e.g., Batch Records, Laboratory Worksheets, DMFs, INDs, NDAs, and ANDAs.
- Maintaining GMP records during statutory retention period.

Maintaining data Integrity in laboratory and manufacturing operations

- SOP controls and mandates over documentation practices, laboratory reporting, deviation reporting.
- Quality System oversight.
- Eliminating or reducing the MOM factor (Motive (incentive/pressure), Opportunity and Means).
- Logical controls of GMP software including access level rules.
- Accurate date and time stamping.
- Audit Trails
- Quality Culture
- Enforcing Data Integrity "Code of Conduct."
- Internal Audit findings
- Data integrity training
- Whistleblower protection

THE FRAUD TRIANGLE



Source: Occupational Fraud and Abuse, by Joseph T. Wells, 1997

- It is the responsibility of management to ensure good data integrity practices are adhered to.

- Strong company management oversight is critical to achieve this end.

- Firms should have a data integrity monitoring program in place as part of their quality system. Breaches in data integrity should be detected before they result in any negative consequences.

Elements of a Data Integrity Monitoring Program

I. Manufacturing Operations

- Monitoring of documentation practices with respect to Batch Records and other controlled documents. Are they meeting ALCOA requirements?

- Adhering to Good Document Control Practices (issuance, retrieval, and archival).

- Stamping or watermarking controlled records when issued.

II. Laboratory Operations

a. Access control and defined user rights to electronic data management and instrument control systems. No generic user accounts are in use.

b. Standardize chromatography injection sequences for each product or sample type.

c. Details or specifics of on-going data integrity management program including scope, objective, responsibilities, procedure, and reporting.

d. File and project naming conventions for electronic data management systems and defined storage location for data files.

e. Policy on manual integration of chromatography peaks

f. Ensure all QC instrumentation generating and storing electronic data are Part 11 compliant including access control and audit trail. Prepare instrument replacement plan for non-compliant systems.

g. Ensure all electronic data files are stored in the file location specified by procedure. Data files should be stored on a network server if possible and not in any unauthorized locations, e.g. temp folders, USB drives, recycle bin, etc.

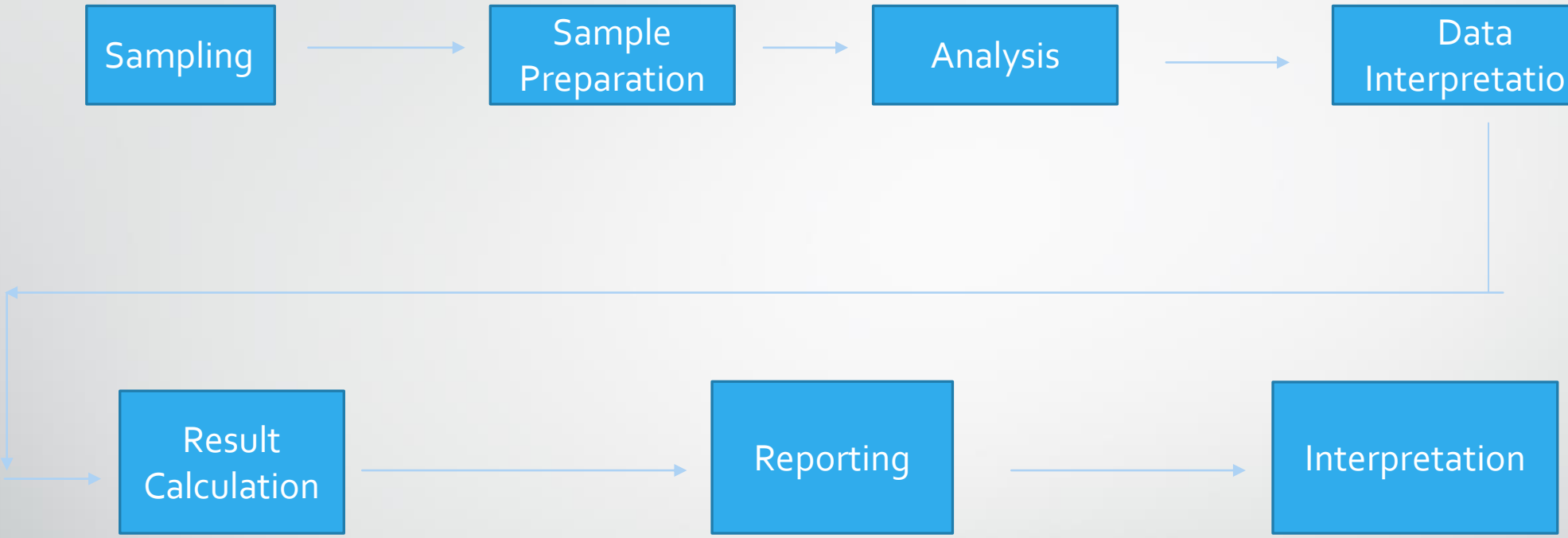
h. The electronic files are accessible only through the instrument's data management system interface.

i. Data integrity monitoring program should be administered by personnel independent from the QC laboratory (if possible). Review of raw data from each analytical instrument is performed to ensure the electronic data meets ALCOA+ principles and is free of intentional falsification. System and sample audit trail functionality and correctness is verified. The extent and quantity of raw data reviewed is based upon the sample testing load, risk assessment, and trends.

j. Review of audit trails for each critical record prior to batch release. Review should include changes to run sequences, changes to sample identification, changes to product test results, single injections, etc.

k. Electronic data is backed at defined intervals to secure storage media. The backup process is documented following Good Documentation Practices.

The Chromatographic Process



Each of these stages includes key items for ensuring data integrity.

Examples of GMP Issues Related to Data Integrity

- Repeated tests, trial runs, sample runs (testing into compliance).
- Changing integration parameters of chromatographic data to obtain passing results.
- Deletion/manipulation of electronic records.
- Altered data
- Turning off audit trail.
- Sharing username and password.
- Inadequate controls for access privileges.
- Inaccurate reporting of microbial limits, sterility, or endotoxin data results.
- Loss of data during changes to the system.
- Activities not recorded contemporaneously, pre or back dating.
- Records falsely indicating that an employee competed a manufacturing step.

Good documentation practices following ALCOA PRINCIPLES

- A = Attributable: traceable to a unique individual.
- L = Legible: readable, permanent, traceable changes.
- C = Contemporaneous: results recorded at the time they occur.
- O = Original: first capture of the data.
- A = Accurate: correct in all details. Assured through equipment/instrument qualification, calibration and maintenance, validation, and data review.

+ = Adds Complete, Consistent, Enduring, and Available.

Think of the Data Life Cycle: (1) Data Collection, (2) Data Processing, (3) Data Review, (4) Data Reporting, and (5) Data Retention. The goal of GDP practices is to ensure accurate and true reporting of data.

Workshop Scenario

Operator RST went home at 0700. Operator XYZ arrived at 0700 and noticed that temperature readings for the past 2 hours (0500 to 0700) were missing. He filled in the entries and signed with Employee RST's initials.

Is there an integrity issue here?

Time	Temperature (˚C)	Done By
0440	34.5	RST
0510		
0540		
0610		
0640		

Time	Temperature (˚C)	Done By
0440	34.5	RST
0510	34.8	RST
0540	35.0	RST
0610	34.2	RST
0640	34.8	RST
0710	34.9	XYZ
0740	34.3	XYZ

Where are Integrity Issues Found?

In the Pharmaceutical Industry

Where are integrity issues found?

1. **Laboratory**
2. **?**
3. **?**
4. **?…**

Where are integrity issues found?

1. Laboratory
2. Production
3. Maintenance
4. Personnel
5. Materials Storage
6. Suppliers
7. Validation
8. Data Storage

etc. … Basically Everywhere

How do Integrity Issues Happen?

Routine → Shortcuts

Told to do it

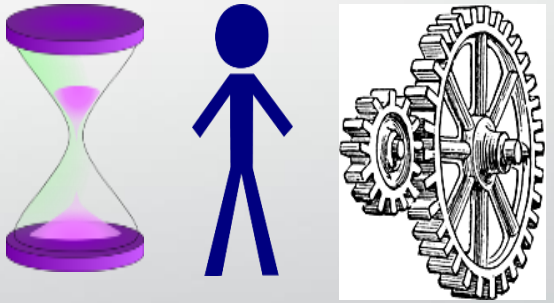
Instructions

Lack of training

Lack of resources

Cost savings

Lack of:



There are 10,000 ways to manipulate chromatography results. For example:

- Substitution
- Alter sample weight
- Dilution/Concentration
- Alter the Flow
- Change integration parameters

There are three main types of Analyst bias commonly encountered when reviewing electronic chromatography data:

1. Trial Sample Analysis
2. Deletion and Overwriting of Raw Data
3. Testing Into Compliance

Integrity Issues

Intentional

or

Unintentional

?

Just so you know…

Intentional versus Unintentional – same affect

No Excuses!

What factors can lead to non-compliance with Data Integrity standards?

- Insufficient or poor employee training.
- Failure not an option mentality.
- Product always meets specification.
- Poor quality culture or ethical standards.
- Cultural or language barriers.
- Disgruntled employee(s). Low pay, lack of advancement, etc.
- Poorly written SOPs or STPs.
- Poorly maintained instruments, equipment, or IT systems.
- Production goals over product quality and cGMP compliance.
- Manual operations.

Testing Into Compliance Case Study

Sorted by “Date Acquired”

Duplicate Sample Analysis

Sample Name	Vial	Injection	Date Aquired	Sample Set Name
Blank	1	1	5/5/2013 3:51	Xyl_Stb_Assay_05052013
Sys Suit	2	1	5/5/2013 4:01	Xyl_Stb_Assay_05052013
Sys Suit	2	2	5/5/2013 4:11	Xyl_Stb_Assay_05052013
Sys Suit	2	3	5/5/2013 4:21	Xyl_Stb_Assay_05052013
Sys Suit	2	4	5/5/2013 4:31	Xyl_Stb_Assay_05052013
Sys Suit	2	5	5/5/2013 4:41	Xyl_Stb_Assay_05052013
06L1001 Sample_1	3	1	5/5/2013 4:51	Xyl_Stb_Assay_05052013
06L1001 Sample_2	3	2	5/5/2013 5:01	Xyl_Stb_Assay_05052013
06L1002 Sample_1	4	1	5/5/2013 5:11	Xyl_Stb_Assay_05052013
06L1002 Sample_2	4	2	5/5/2013 5:21	Xyl_Stb_Assay_05052013
06L1003 Sample_1	5	1	5/5/2013 5:31	Xyl_Stb_Assay_05052013
06L1003 Sample_2	5	2	5/5/2013 5:41	Xyl_Stb_Assay_05052013
Bkt Std	2	1	5/5/2013 5:51	Xyl_Stb_Assay_05052013
06L1002 Sample_1	4	1	5/5/2013 6:01	Xyl_Stb_Assay_05052013
06L1002 Sample_2	4	2	5/5/2013 6:11	Xyl_Stb_Assay_05052013

Testing Into Compliance Case Study

Sample Name	Vial	Injection	Date Aquired	Assay Result
06L1002 Sample_1	4	1	5/5/2019 5:11	115%
06L1002 Sample_2	4	2	5/5/2019 5:21	117%
06L1002 Sample_1	4	1	5/5/2019 6:01	100%
06L1002 Sample_2	4	2	5/5/2019 6:11	100%

→ Not reported

→ Reported

- Compare results of the duplicate analysis
- Now begin the analyst interviews
  - Was the sample re-prepared or substituted?
    - Confirm through interviews and review of the QC raw data worksheets/attachments

What do our interviews tell us?

- It depends on the landscape
- This product cannot fail
- I cannot report failures to management
- We don’t have the resources to investigate
- Disgruntled with management and compensation

Regardless of their type, GxP records must be permanent, legible, and changes traceable.

PAPER RECORD

- No Pencil
- Indelible Ink
- No Opaque Correction Fluid or illegible handwriting.
- Changes with single-line cross-out that are initialed, dated, explained.
- Archive of Records

ELECTRONIC RECORD

- Enforce Saving
- No Over-writing
- No Deletion
- 'Hidden Fields' and 'Voided' Records must be visible
- No Obscuring with Data Annotation Tools
- Changes captured in 'audit trail'
- Back-up & Archival

Audit Trial Reviews

- Audit trail is a chronology of the "who, what, when and why" of a record.
- Audit trail feature must be enabled at all times.
- Chromatography Data Software (CDS) will include some or all of the following Audit Trails: System Level, Application Level, Method, Sequence, and Results.
- Always review the assignment of user rights in CDS, look for shared or generic accounts.
- Sequence audit trail will show aborted sequences, sample name changes, or sample set alterations. All must be justified in the comment section of the CDS and/or in an external report.
- Some CDS will allow for query reports in which aborted, repeated sequences or samples, and single injections are presented.
- The Method and Sequence Audit Trails must be reviewed prior to batch release. System audit trails can be reviewed less frequency as only the system administrator can typically invoke changes which will show up in this record, e.g. creating new account.

Closing Points

- Be skeptical when everything appears too perfect (the data or facility).
- Investigate thoroughly when adequate checks and balances are not in place.
- Always ask QA technician to demonstrate how to audit trail reviews are performed.
- Ensure there is adequate justification for aborted or repeated sequences or samples. All aborted or repeated analyses must be investigated and the root cause investigated.
- Review Quality Metrics (if available) . High rates of invalidated OOS test results or laboratory errors could be indicative of data integrity breaches.
- Always take time to personally review the raw laboratory data, particularly the chromatography sequences and project folders. Ask a lot of questions.
- It is not an easy job to uncover a case of intentional data falsification, especially when the guilty party is determined to cover their tracks.

Good technical resources:

- Data Integrity in the GxP Chromatography Laboratory, by Mark E. Newton and R.D. McDowal, LCGC Chromatography Online, 2018.
- PDA Technical Report No. 80, Data Integrity Management System for Pharmaceutical Laboratories.

Any Questions?