# Data Integrity

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## Agenda

- Introduction
- ANNEX 11, Computerized Systems
- Part 11, Electronic Records and Electronic Signatures - Scope and Application
- *FDA draft guidance: Data Integrity and Compliance with CGMP Q&A, 2016*
- *Draft PIC/S Guidance: Good Practices for Data Integrity in Regulated GMP/GDP Environments*
- Warning Letter case studies

# Introduction

## What are the inspectors looking for?

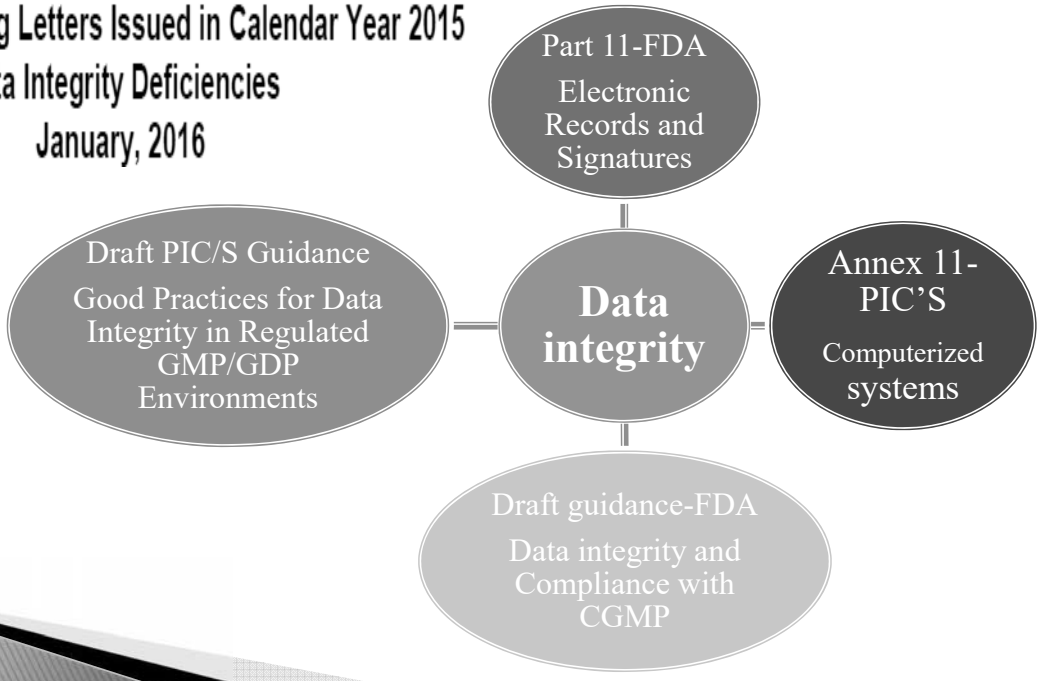
- Date Integrity : the assurance that the data supporting a product quality decision can be trusted.
- This is achieved when:
  - All of the data, raw date, and supporting metadata is present
  - Any and all changes to the data have been independently tracked and can be reviewed
  - For each data record, it is known exactly who did what, when and why.
- Regulatory agencies are using the term ALCOA

# ALCOA for Data Integrity

- ALCOA
  - Attributable to the person generating the data
    - Authentication, unique ID, access permissions
  - Legible and Permanent
    - Human readable, usable format
  - Contemporaneous
    - Recorded at the time of the event, audit trail
  - Original record (or "true copy")
    - Audit trail, record linking
  - Accurate
    - Reliable, calibrated

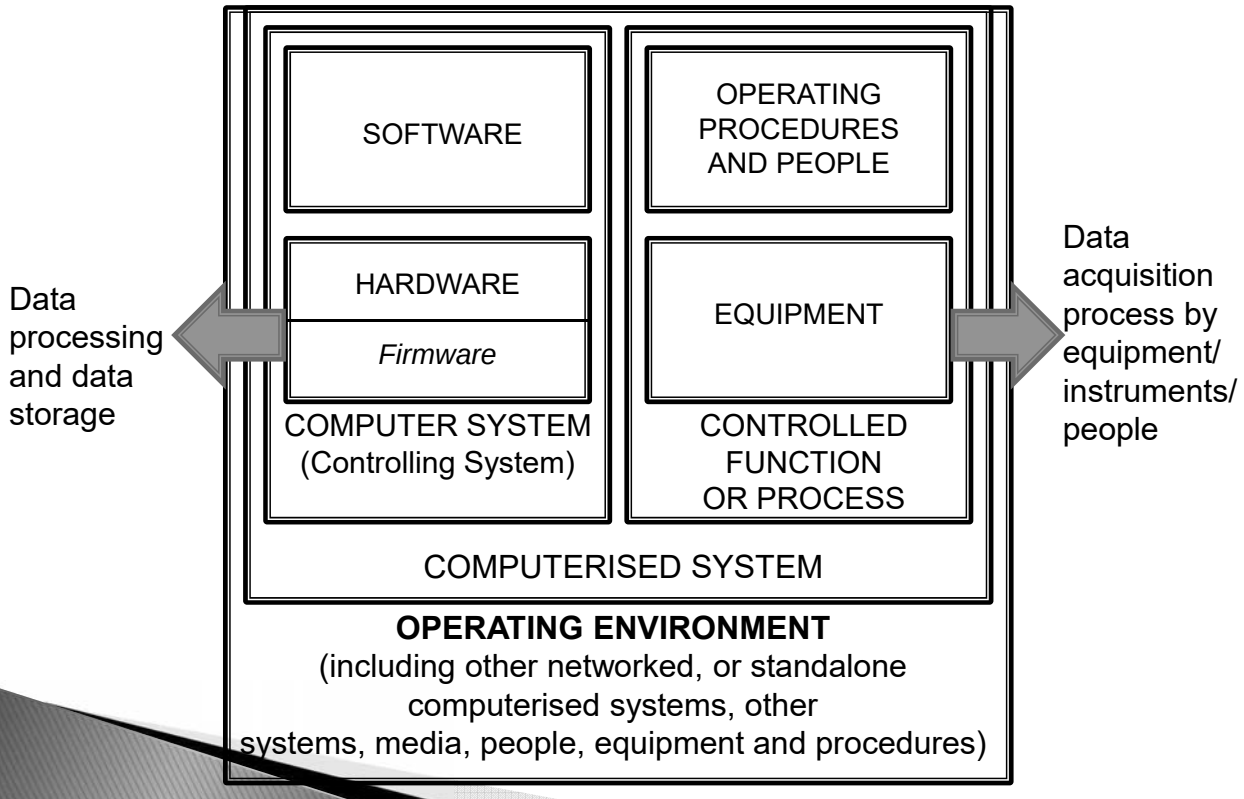
In recent years, FDA has increasingly observed CGMP violations involving data integrity during CGMP inspections.

**GMP Drug Warning Letters Issued in Calendar Year 2015**
**Data Integrity Deficiencies**
**January, 2016**



# ANNEX 11, Computerized Systems

## ANNEX 11, Computerized system



# ANNEX 11, Computerized Systems

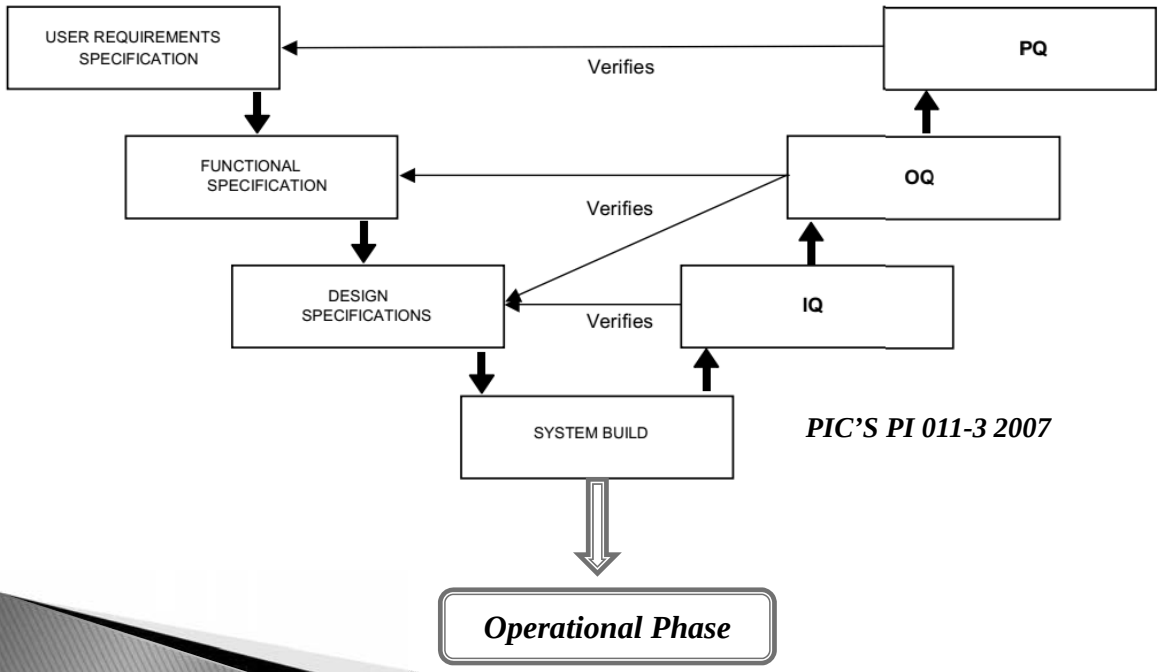
A computerized system is a set of software and hardware components which together fulfill certain function.

**Risk Management**

| Patient Safety | Data Integrity | Product Quality |
|---|---|---|
| Relies on the instrumentation correctly detecting impurities and measuring product concentration.<br>The data collected is accurate and reliable (data quality)<br><br>**Instrument Qualification and Method Validation** | Essential to any lab data system<br><br>**Computerized System Validation & Control** | Affected mainly by the manufacturing process and the raw material<br><br>Not typically impacted by lab activities.<br><br>**Equipment Qualification and Process Validation** |

# ANNEX 11, Computerized Systems

Figure 2 below maps the relationships between the key specification and qualification elements as the system is specified, designed, built and tested.




*PIC'S PI 011-3 2007*

## ANNEX 11, Computerized Systems _ Operational Phase

***Data:***

Appropriate built-in checks for the correct and secure entry and processing of data.

***Accuracy Checks :***

For critical data entered manually, there should be an additional check on the accuracy of the data.

***Data Storage :***

Secured by both physical and electronic means against damage.
Checked for accessibility, readability and accuracy.
Regular backups: Integrity and accuracy of backup date and the ability to restore the date should be checked

***Printouts***

clear printed copies of electronically stored data

***Audit Trails***

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.

## ANNEX 11, Computerized Systems _ Operational Phase

***Change and Configuration Management :***

Any changes to a computerised system including system configurations should only be made in a controlled manner in accordance with a defined procedure.

***Periodic Evaluation :***

- Periodically evaluated to confirm that they remain in a valid state and are compliant with GMP
- The current range of functionality, deviation records, incidents, problems, upgrade history, performance, reliability, security and validation status reports.

***Security :***

- Physical and/or logical controls should be in place to restrict access to computerised system to authorised persons.
- Management systems for data and for documents should be designed to record the identity of operators entering, changing, confirming or deleting data including date and time.

# ANNEX 11, Computerized Systems _ Operational Phase

***Incident Management***

All incidents, not only system failures and data errors, should be reported and assessed and the root cause should be identified.

***Electronic Signature :***

- The same impact as hand-written signatures
- Permanently linked to their respective record
- Include the time and date that they were applied

***Batch release :***

The system should allow only authorised Persons to certify the release of the batches and it should clearly identify and record the person releasing or certifying the batches.

***Business Continuity***

Ensure continuity of support for those processes in the event of a system breakdown (e.g. a manual or alternative system).

***Archiving***

The ability to retrieve the data should be ensured and tested

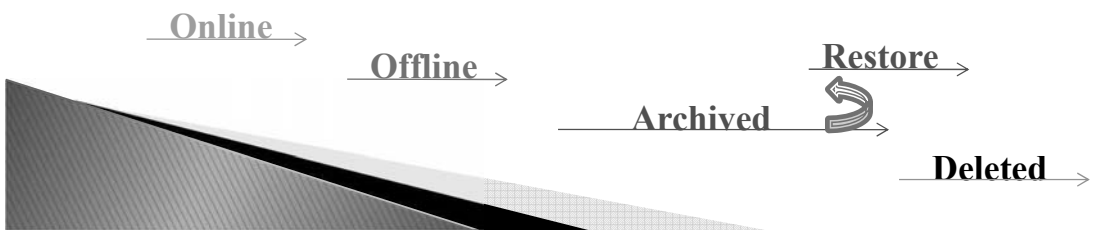
# Backup

1. Are designed for disaster recovery
2. Are of short-term value
3. Replace the **entire system** when restored
4. Often are stored on hard disk or tape
5. Are done (usually) on a timed-basis

# Archiving

1. Are designed for data and result storage
2. Are of long-term value
3. Contain just the **data** for a specific project/experiment or product
4. Are often stored on durable media such as DVD
5. Are done when data is complete

***Data Life Cycle***



# Part 11, Electronic Records and Electronic Signatures - Scope and Application

Part 11, Electronic Records and Electronic Signatures - Scope and Application

***Narrow interpretation of the scope of part 11:***

With respect to records required to be maintained under predicate rules or submitted to FDA, when persons choose to use records in electronic format in place of paper format, part 11 would apply.

On the other hand, when persons use computers to generate paper printouts of electronic records, and those paper records meet all the requirements of the applicable **predicate rules** and persons rely on the paper records to perform their regulated activities, FDA would generally not consider persons to be "using electronic records in lieu of paper records. In these instances, the use of computer systems in the generation of paper records would not trigger part 11.

**Predicate Rules:**

Any FDA regulation that requires companies to maintain certain records and submit information to the agency as part of compliance.

# Part 11, Electronic Records and Electronic Signatures - Scope and Application

***Definition of Part 11 Records:***

1. Records that are required to be maintained under predicate rule requirements and that are maintained in electronic format in place of paper format.
   - Document the decision under the predicate rule.
2. Records that are required to be maintained under predicate rules, that are maintained in electronic format in addition to paper format, and that are relied on to perform regulated activities.
   - Actual business practices may dictate whether you are using electronic records instead of paper records under § 11.2(a).
3. Records submitted to FDA, under predicate rules in electronic format.
   - A record that is not itself submitted, but is used in generating a submission, is not a part 11 record unless it is otherwise required to be maintained under a predicate rule and it is maintained in electronic format.
4. Electronic signatures that are intended to be the equivalent of handwritten signatures, initials, and other general signings required by predicate rules.

# FDA draft guidance: Data Integrity and Compliance with CGMP Q&A, 2016

## Data Integrity and Compliance with CGMP_draft guidance
QUESTIONS AND ANSWERS

- Please clarify the following terms as they relate to CGMP records.
  - *What is "data integrity"?*
  - *What is "metadata"?*
  - *What is an "audit trail"?*
  - *How does FDA use the terms "static" and "dynamic" as they relate to record formats?*
  - *How does FDA use the term "backup" in § 211.68(b)?*
  - *What are the "systems" in "computer or related systems" in § 211.68?*
- When is it permissible to exclude CGMP data from decision making?
- Does each workflow on our computer system need to be validated?
- How should access to CGMP computer systems be restricted?
- Why is FDA concerned with the use of shared login accounts for computer systems?
- How should blank forms be controlled?
- How often should audit trails be reviewed?
- Who should review audit trails?
- Can electronic copies be used as accurate reproductions of paper or electronic records?
- Is it acceptable to retain paper printouts or static records instead of original electronic records from stand-alone computerized laboratory instruments, such as an FT-IR instrument?

## Data Integrity and Compliance with CGMP_draft guidance
QUESTIONS AND ANSWERS

- Can electronic signatures be used instead of handwritten signatures for master production and control records?
- When does electronic data become a CGMP record?
- Why has the FDA cited use of actual samples during "system suitability" or test, prep, or equilibration runs in warning letters?
- Is it acceptable to only save the final results from reprocessed laboratory chromatography?
- Can an internal tip regarding a quality issue, such as potential data falsification, be handled informally outside of the documented CGMP quality system?
- Should personnel be trained in detecting data integrity issues as part of a routine CGMP training program?
- Is the FDA investigator allowed to look at my electronic records?
- How does FDA recommend data integrity problems identified during inspections, in warning letters, or in other regulatory actions be addressed?

# *What is "data integrity"?*

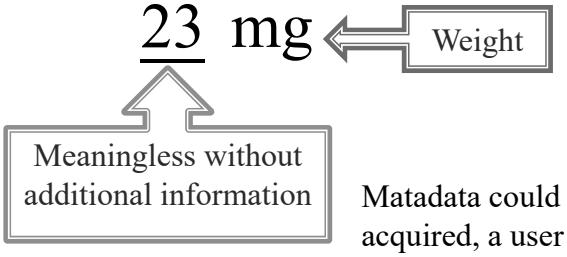
Data Integrity: The completeness, consistency and accuracy of data
ALCOA: Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate.

A ttributable: who acquired the data or performed an action?
L egible: can you read and understand the data entries?
C ontemporaneous: documented at the time of the activity
O riginal: first recorded observation
A ccurate: no errors or editing
\+ Complete/Consistent/Enduring/Available

* For attributable, see §§ 211.101(d), 211.122, 211.186, 211.188(b)(11), and 212.50(c)(10); for legible see §§ 211.180(e) and 212.110(b); for contemporaneously recorded (at the time of performance) see §§ 211.100(b) and 211.160(a); for original or a true copy see §§ 211.180 and 211.194(a); and for accurate see §§ 211.22(a), 211.68, 211.188, and 212.60(g).

# *What is "metadata"?*

Data should be maintained throughout the record's retention period with all associated **metadata** required to reconstruct the CGMP activity (e.g., §§ 211.188 and 211.194)
• Metadata is the contextual information required to understand data.

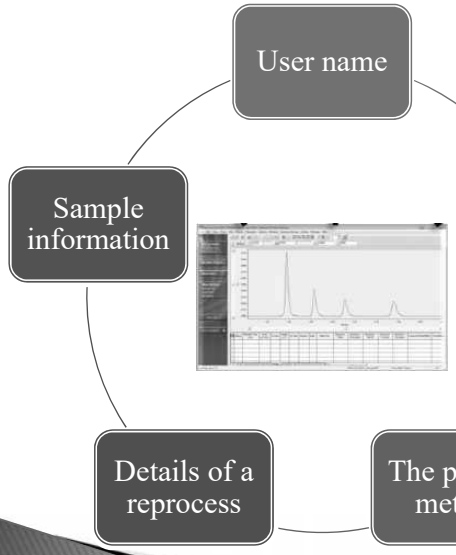



Matadata could include a date/time stamp for when the data were acquired, a user ID of the person who conducted the test or analysis that generated the data, the instrument ID used to acquire the data, audit trails, etc.

The relationships between data and their metadata should be preserved in a secure and traceable manner.

# *What is "audit trail"?*

Audit trail: A chronology of the "who, what, when, and why" of a record.




## Audit trail

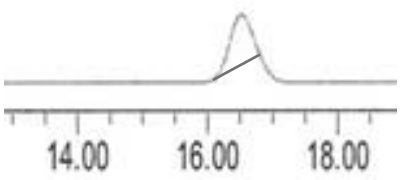
Secure, computer-generated, time-stamped electronic records.

Reconstruction of the course of events relating to the creation, modification, or deletion of an electronic record.

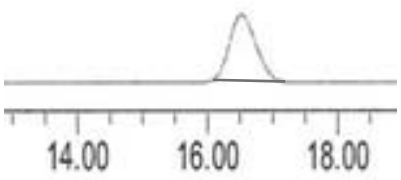
# *How does FDA use the terms "static" and "dynamic" as they relate to record formats?*

Static: Indicate a fixed-data document such as a paper record or an electronic image.
Dynamic: The record format allows interaction between the user and the record content

**Dynamic chromatographic**




Peak area: 100

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

A true copy of the original data that is maintained securely throughout the records retention period.-211.68(b)

**Backup File**

- Data (includes associated metadata )
- Original format or in a format compatible with the original format

Not the temporary backup copies during normal computer use for disaster recovery.
Ex: Recovery point. (Microsoft)


Data can be recovered at the different recovery points, but…
If the software can not work ?
If the file is deleted or broken?

## *What are the "systems" in "computer or related systems" in § 211.68?*

### *Systems:*

As people, machines, and methods organized to accomplish a set of specific functions.

### *Computer or related systems:*

Refer to computer hardware, software, peripheral devices, networks, cloud infrastructure, operators, and associated documents (e.g., user manuals and standard operating procedures).

## When is it permissible to exclude CGMP data from decision making?

**§§ 211.22, 212.70 and 211.180**
Any data created as part of a CGMP record must be evaluated by the quality unit as part of release criteria and maintained for CGMP purposes.

Electronic data generated to fulfill CGMP requirements should include relevant metadata.

**§§ 211.188, 212.192, 212.71(b) and the guidance for industry Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production.**

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

## Does each workflow on our computer system need to be validated?

**§§ 211.63, 211.68(b) and 211.110(a)**
An intended use of a computer system needs to be checked through validation.

Manufacturing Execution System (MES) → Qualify the computer system and ensure that it meets specification

Creation of an electronic master production and control record (MPCR)

***Such a workflow requires validation to for examples ensure that it contains the correct calculation.***

## How should access to CGMP computer systems be restricted?

**§§ 211.68(b)**
You must exercise appropriate controls to assure that changes to computerized MPCRs, or other records, or input of laboratory data into computerized records, can be made only by authorized personnel

FDA recommendation:

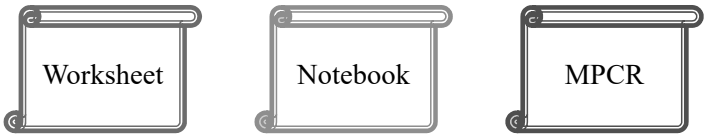
1. Restrict the ability to alter specification, process parameters or manufacturing or test method.
2. The system administrator role, including any rights to alter files and settings, be assigned to personnel independent from those responsible for the record content.
3. Maintain a list of authorized individuals and their access privileges for each CGMP computer system in use.

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

**§§ 211.68(b), 211.188(b)(11), 211.194(a)(7) and (8), and 212.50(c)(10)**
You must exercise appropriate controls to assure that only authorized personnel make changes to computerized MPCRs, or other records, or input laboratory data into computerized records, and you must implement documentation controls that ensure actions are attributable to a specific individual.

## How should blank forms be controlled?

**§§ 211.110, 211.160(a), 211.186, 212.20(d) and 212.60(g)**
There must be document controls in place to assure product quality.




Controlled by the quality unit or by another document control method.

- Number sets of blank forms
- Reconcile upon completion of all issued forms.
- Incomplete or erroneous forms should be kept as part of the permanent record along with written justification for their replacement

§§ 211.192, 211.194, 212.50(a), and 212.70(f)(1)(vi)

## How often should audit trails be reviewed?

Audit trails that capture changes to critical data be reviewed with each record and before final approval of the record.

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

Audit trails subject to regular review should include, but are not limited to, the following: the change history of finished product test results, changes to sample run sequences, changes to sample identification, and changes to critical process parameters.

## Who should review audit trails?

**§§ 211.22(a), 211.101(c), 211.194(a)(8), and 212.20(d)**
Personnel responsible for record review under CGMP should review the audit trails that capture changes to critical data associated with the record as they review the rest of the record

## Can electronic copies be used as accurate reproductions of paper or electronic records?

**Yes**

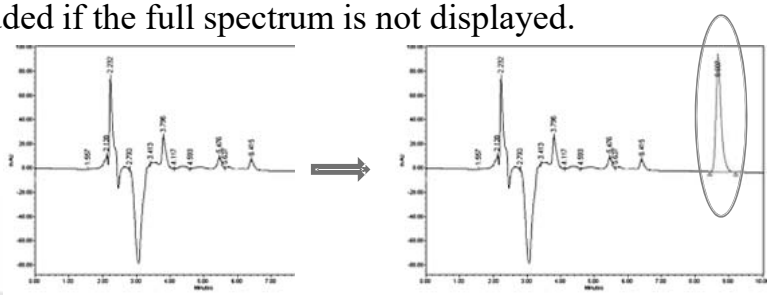
Electronic copies can be used as true copies of paper or electronic records, provided the copies preserve the content and meaning of the original data, which includes associated metadata and the static or dynamic nature of the original records.

## Is it acceptable to retain paper printouts or static records instead of original electronic records from stand-alone computerized laboratory instruments, such as an FT-IR instrument?

**§§ 211.68(b), 211.188, 211.194, 211.180 and 212.60**

A paper printout or static record may satisfy retention requirements if it is a complete copy of the original record.

A printout or static record does not preserve full the dynamic record. Contaminants may be excluded if the full spectrum is not displayed.



## Can electronic signatures be used instead of handwritten signatures for master production and control records?

**Yes**

**§§ 211.186 (a)**

Electronic signatures with the appropriate controls can be used instead of handwritten signatures or initials in any CGMP required record.

An electronic signature with the appropriate controls to securely link the signature with the associated record fulfills this requirement.

Part 11 electronic Record; Electronic Signatures _ Guidance for Industry

## When does electronic data become a CGMP record?

**§§ 211.100(b), 211.160(a), 211.180(d)**
When generated to satisfy a CGMP requirement, all data become a CGMP record.

It is not acceptable to record data on pieces of paper that will be discarded after the data are transcribed to a permanent laboratory notebook. Similarly, it is not acceptable to store date electronically in temporary memory, in a manner that allows for manipulation, before creating a permanent record.

## Why has the FDA cited use of actual samples during "system suitability" or test, prep, or equilibration runs in warning letters?

FDA prohibits sampling and testing with the goal of achieving a specific result or to overcome an unacceptable result
→ ***Testing into compliance, is not consistent with CGMP***

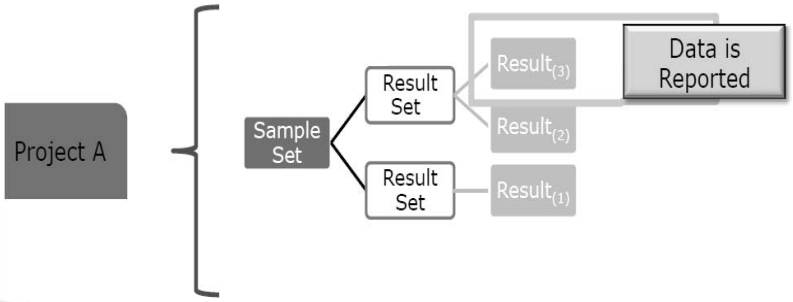
In some situations, use of actual samples to perform system suitability testing has been used as a means of testing into compliance. FDA would consider it a **violative practice** to use an actual sample in *test, prep, or equilibration runs as a means of disguising testing into compliance.*

USP:
system suitability tests should include replicate injections of a standard preparation or other standard solutions to determine if requirements for precision are satisfied.

**§§ 211.160, 211.60**
System suitability tests, including the identity of the preparation to be injected and the rationale for its selection, should be performed according to the firm's established written procedures and the approved application or applicable compendial monograph.

**§§ 211.160, 211.60, 211.165**
If an actual sample is to be used for system suitability testing, it should be a properly characterized secondary standard, written procedures should be established and followed, and the sample should be from **a different batch** than the sample(s) being tested.

**All data** should be included in the record that is retained and subject to review unless there is documented scientific justification for its exclusion




## Test Injection → System Readiness checks

| What? | How? | When? |
|---|---|---|
| Never Samples<br><br>Possibly standard<br><br>An independent solution which mimics real samples | Never delete them<br><br>How is it assessed visual check, reported or not, calculations performed<br><br>How do you proceed when it doesn't meet the criteria | Every run?<br><br>As part of sample set, as individual injection |

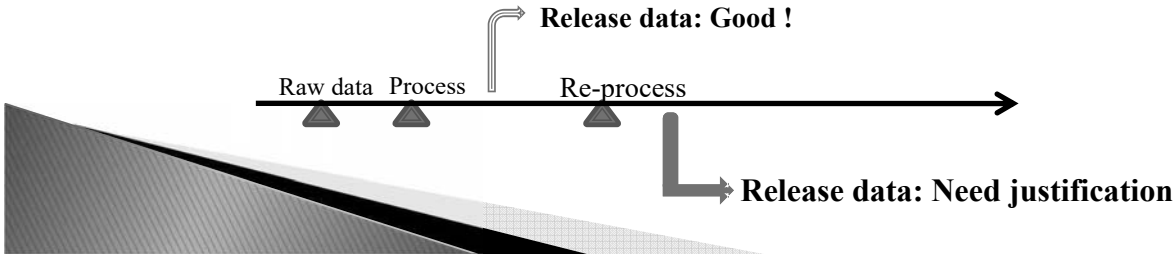
## Is it acceptable to only save the final results from reprocessed laboratory chromatography?

No

Analytical methods should be capable and stable.

**§§ 211.160(a), 211.160(b), 211.165(c), 211.194(a)(4) and 212.60(a)**
If chromatography is reprocessed, written procedures must be established and followed and each result retained for review.

FDA requires complete data in laboratory records, which includes raw data, graphs, charts, and spectra from laboratory instruments




## Can an internal tip regarding a quality issue, such as potential data falsification, be handled informally outside of the documented CGMP quality system?

No

**§§ 211.22(a), 211.125(c), 211.192, 211.198, 211.204, and 212.100**
Suspected or known falsification or alteration of records required under parts 210, 211, and 212 must be fully investigated under the CGMP quality system to determine the effect of the event on patient safety, product quality, and data reliability; to determine the root cause; and to ensure the necessary corrective actions are taken.

## Should personnel be trained in detecting data integrity issues as part of a routine CGMP training program?

**Yes**

Training personnel to detect data integrity issues is consistent with the personnel requirements under **§§ 211.25 and 212.10**, which state that personnel must have the education, training, and experience, or any combination thereof, to perform their assigned duties.

## Is the FDA investigator allowed to look at my electronic records?

**Yes**

**§§ 211.180(c), 211.110(a) and (b), section 704 of the FD&C 400**
All records required under CGMP are subject to FDA inspection. You must allow authorized inspection, review, and copying of records, which includes copying of electronic data.

## How does FDA recommend data integrity problems identified during inspections, in warning letters, or in other regulatory actions be addressed?

FDA encourages you to demonstrate that you have effectively remedied your problems by:

1. hiring a third party auditor,
2. determining the scope of the problem,
3. implementing a corrective action plan (globally), and
4. removing at all levels individuals responsible for problems from CGMP positions.

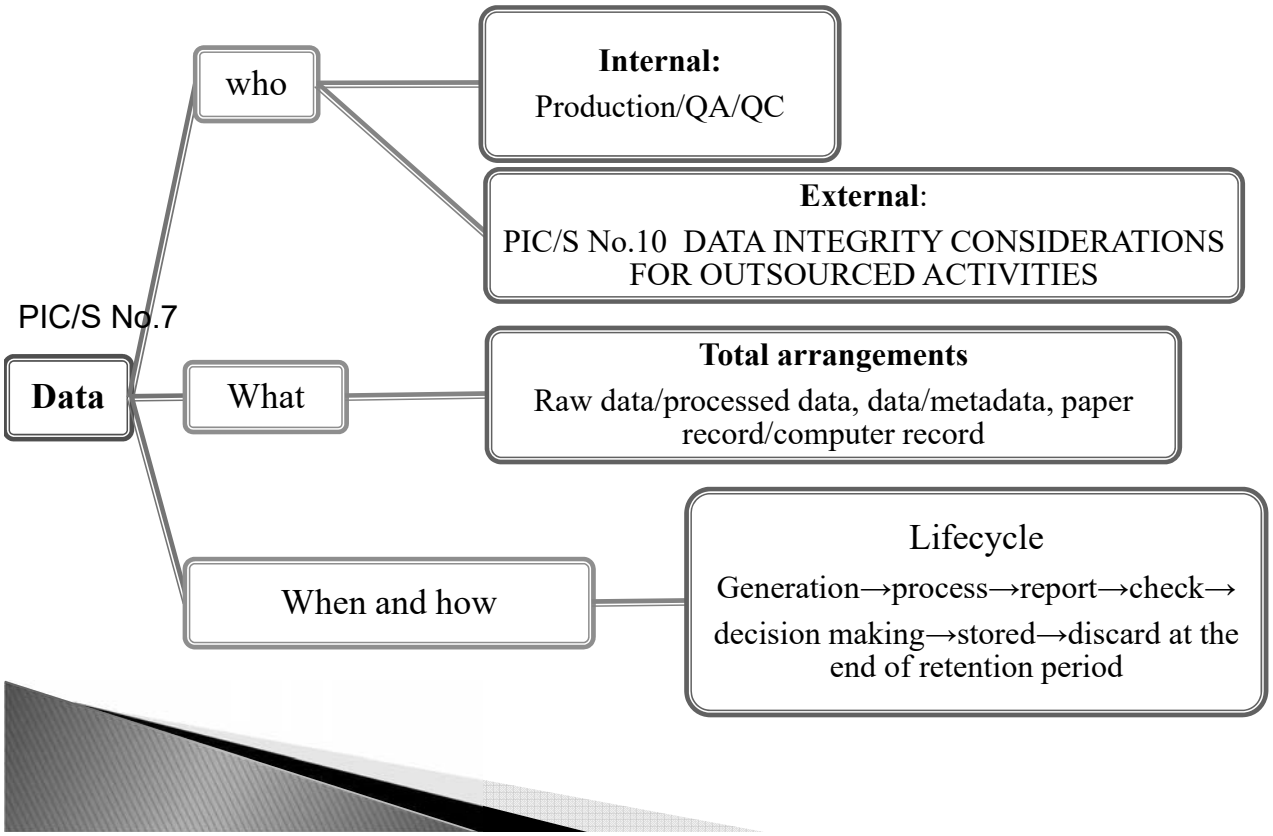
# Draft PIC/S Guidance Good Practices for Data Integrity in Regulated GMP/GDP Environments

# PIC/S Guidance: Good Practices for Data Integrity in Regulated GMP/GDP Environments

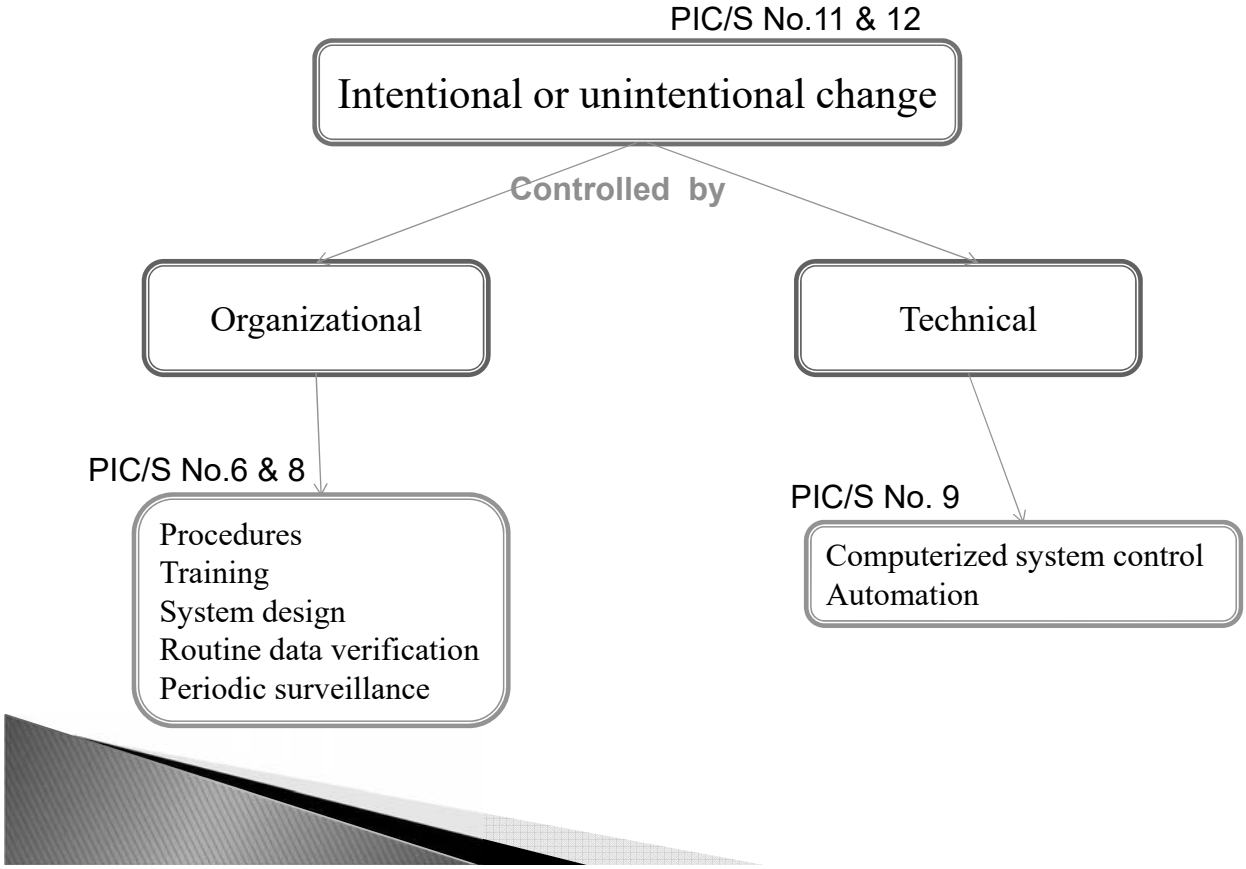
## Scope:

Apply to both on-site and remote (desktop) inspection of those sites performing manufacturing (GMP) and distribution (GDP) activity.

## *Data Governance System :*



## *Data Governance System :*




## *Data Governance System :*

### *Data criticality:*

- Data influences may differ in importance and the impact of the data to a decision may also vary.
  - ➢Data Influence: data for batch release vs warehouse cleaning record
  - ➢Product quality and safety: Assay v.s friability for an oral tablet

### *Data risk: risk assessment should consider*

- Process complexity
- Methods of generating, storing, and retiring data and their ability to ensure data accuracy, legibility, indelibility.
- Process consistency and degree of automation/human interaction
- Subjectivity of outcome/results (ie the process open-ended or well-defined?)
- The outcome of a comparison between electronic system data and manually recorded events could be indicative for malpractice

# Data Governance System :

## Data governance system review

- Should be assessed periodically as part of self-inspection (internal audit) or other periodic review processes.
- A wider review of control measures, including :
  - A check of continued personnel understanding of data integrity.
  - A review for consistency of reported data/outcomes against raw data entries.
  - A validated "exception report"
    - A validated search tool that identifies and documents predetermined "abnormal" data or actions.

# Organisational Influences On Successful Data Integrity Management

## General

An understanding of how behavior influences
(i) the incentive to amend, delete or falsify data and
(ii) the effectiveness of procedural controls

The influence of culture on organizational behavior

- 'open' : where hierarchy can be challenged by subordinates, and full reporting of a systemic or individual failure is a business expectation
- 'closed': where reporting failure or challenging a hierarchy is culturally more difficult

## Code of ethics and policies

## Quality culture

## *Organisational Influences On Successful Data Integrity Management*

### *Modernising the Pharmaceutical Quality Management System*

***Prevent*** → Automation, Training, Authorization…

***Detect*** → Audit trail, Data review, Self-inspection…

***Correct*** → Deviation, CAPA (interim measure, long-term measure)…

## *Organisational Influences On Successful Data Integrity Management*

### *Regular management review of quality metrics*

1. Head of Quality Unit has direct access to the highest level of management
2. Management can have an independent expert periodically verify systems and controls

### *Resource allocation*

- Appropriate resources to support and sustain good data integrity management such that the workload and pressures on those responsible for data generation and record keeping do not increase the likelihood of errors or the opportunity to deliberately compromise data integrity

### *Dealing with data integrity issues found internally*

- Deviation and CAPA

## *Specific DI (Data Integrity) Considerations for Paper-based Systems*

Procedures outlining good documentation practices and arrangements for
document control should be available within the QMS. These procedures should specify:

- How master documents and procedures are created, reviewed and approved for use
- Generation , distribution and control of templates used to record data (master , logs, etc.);
- Retrieval and disaster recovery processes regarding records.

## *Specific DI (Data Integrity) Considerations for Paper-based Systems*

- The process for generation of working copies of documents for routine use, with specific emphasis on ensuring copies of documents, e.g. SOPs and blank forms are issued and reconciled for use in a controlled and traceable manner.
- Guidance for the completion of paper based documents, specifying how individual operators are identified, data entry formats and amendments to documents are recorded.
- How completed documents are routinely reviewed for accuracy, authenticity and completeness;
- Processes for the filing, retrieval, retention, archival and disposal of records.
- How data integrity is maintained throughout the lifecycle of the data.

## *Specific DI (Data Integrity) Considerations for Computerised Systems*

1. Qualification and validation of computerised systems
2. System security for computerised systems
3. Audit trails for computerised systems
4. Data capture/entry for computerised systems
5. Review of data within computerised systems
6. Storage, archival and disposal of electronic data

ANNEX 11

## *Data integrity considerations for outsourced activities*

1. **Routine document verification**
   - Emphasis should be placed upon robust supplier and contractor qualification, using the principles of quality risk management.
2. **Quality agreement**
3. **Strategies for assessing data integrity in the supply chain**
   - The outcome of site audits, with focus on data governance measures
   - Comparison of analytical data reported by the contractor or supplier vs in-house data from analysis of the same material
   - Quality monitoring: Incentive for data falsification (eg raw materials which marginally comply with specification on a frequent basis)

## *Regulatory actions in response to data integrity findings*

**Remediation of Data Integrity Failure**

1. Resolved the immediate issues identified and assess the risk
2. A comprehensive investigation into the extent of the inaccuracies in data records and reporting.

**CAPA to be taken**

1. Interim measures:
   - Actions to protect patients and ensure product quality
   - Ex. Notify customers, recall, additional testing, adding lots to stability testing, enhanced complaint monitoring…etc
2. Long-term measures:
   - Any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources designed to ensure the data integrity

## *Regulatory actions in response to data integrity findings*

**Data integrity deficiencies**

- Data integrity failure resulting from bad practice
- Opportunity for failure (without evidence of actual failure) due to absence of the required data control measures

**Classification of deficiencies**

1. **Critica**l
   - Impact to product with risk to patient health.
     - ➢ Product failing to meet specification at release or within shelf life
     - ➢ Reporting of a 'desired' result rather than an actual out of specification result when reporting of QC tests, critical product or process parameters.
2. **Major**
   - ➢ Impact to product with no risk to patient health
   - ➢ No impact to product; evidence of widespread failure
3. **Other deficiency**
   - ➢ Limited evidence of failure

# Warning Letter case studies

# Warning Letters

## _Data Integrity deficiency

**GMP Drug Warning Letters Issued in Calendar Year 2015**
**Data Integrity Deficiencies**
**January, 2016**

**Data Integrity Associated Warning Letters Issued in CY 2015:**

| Date of WL Issue | Company | Product Type | Date of Inspection(s) | Approximate Interval inspection to WL | Country |
|---|---|---|---|---|---|
| Jan. 9, 2015 | Micro Labs Limited | Drug product | May 5-10 and May 12-13, 2014 | 8 months | India |
| Jan. 30, 2015 | Apotex Research Private Limited | Drug product | June 23-July 1, 2014 | 7 months | India |
| Feb. 27, 2015 | Novacyl Ltd | API | April 21-25, 2014 | 10 months | Thailand |
| Mar. 31, 2105 | Hospira Spa | Drug product | May 5-9 and 12-13, 2014 | 10 months | Italy |
| Apr. 6, 2015 | Yunnan Hande Bio-Tech Ltd | API | Apr. 14-17, 2014 | 12 months | China |
| May 27, 2015 | VUAB Pharma a.s. | API | June 9-13, 2014 | 12 months | Czech Republic |
| July 13, 2015 | Mahendra Chemicals | API | May 19-24, 2014 | 14 months | India |
| Aug. 16, 2015 | Mylan Laboratories Limited (3 sites) | Drug product | Aug 1-8, 2014<br>Sept 23-Oct 3, 2014<br>Feb. 6-13, 2015 | 6-12 months | India |

| Date | Company | Country | Text of Compliance | Import Alert |
|---|---|---|---|---|
| 9-Jan-15 | *Micro Labs Limited*<br><br>(drug product) | India | **1.Your firm failed 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)).**<br><br>Our inspection identified laboratory test records that you did not review and evaluate in making batch release decisions. These records contained uninvestigated, out of specification (OOS) data. You did not include the data described below when calculating test results that you used to release finished product. You also failed to identify, investigate, and determine the significance of the OOS results discussed below until our investigators identified the excluded records during our inspection.<br><br>a) During the inspection, your management admitted that employees in both of your Quality Control (QC) laboratories had frequently conducted unauthorized "trial" High Performance Liquid Chromatography (HPLC) injections prior to additional injections that were used in the reported test results. Although your management stated that this practice ended in February 2014, FDA investigators discovered evidence that this practice continues. The inspection found that the names assigned to each sequenced injection were often changed during testing, obscuring the traceability of repeated injections. The data from "trial" injections was not reviewed or considered in determining batch quality. For example,<br><br>1) For the related substances analysis of (b)(4) USP (b)(4) mg Tablets batch (b)(4) conducted on February 25, 2013, there were three sample injections of vial 1_8, all named "TEST," which were run prior to the reported sample injections. The "TEST" injection data was stored in the "Trial" folder located on a personal computer (PC) with no audit trail linked to the HPLC instrument.<br><br>During the inspection, the calculations that you performed using the target sample weight showed that the "TEST" injections were OOS ((b)(4) as compared to the specification of NMT (b)(4)) for the highest unknown impurity. | YES 9/19/14 |
| 31-Mar-15 | *Hospira Spa*<br><br>(drug product) | Italy | **4. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21CFR 211.194(a)).**<br><br>Our investigators identified your practice of performing trial sample injections for HPLC analyses. For example, trial injections of (b)(4) stability samples (lot (b)(4) and (b)(4)) were acquired in the "Test" folder prior to official testing. Immediately after the trial injections were completed, the official samples were analyzed. The trial injection raw data, captured in the back-up files, were deleted from the test folder.<br><br>You retested analytical samples without reporting original results in laboratory records. Because of this practice, you are unable to assure that all raw data generated is included and evaluated when you review analytical test results to determine whether your products conform with their established specifications and standards.<br><br>For example, (b)(4) lot #(b)(4) failed the content uniformity test, where sample #8 of (b)(4) resulted with a value (b)(4)%. Your firm proceeded to retest the sample on a different instrument without initiating an out-of-specification (OOS) investigation, as required by your chemistry laboratory investigation standard operating procedure, SOP QAG-097. These injections were not reported as part of the original data or included in your laboratory investigation report. Subsequently, the electronic raw data files were deleted. Moreover, there is no procedure describing the use of re-injections for standards or samples on a different system to verify an original result. | |
| 30-Jan-15 | *Apotex Research Private Limited*<br><br>(drug product) | India | **3. Your firm failed to establish and follow appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile (21 CFR 211.113(a)).**<br><br>On June 23, 2014, during the inspection of the QC Microbiology Laboratory, our investigators observed missing in-progress microbiological test plates for various finished drug products, in-process products, water, and media growth promotion samples. For example:<br><br>Finished drug product (b)(4) Tablets (b)(4)mg batches (b)(4) and (b)(4) microbial sample plates/tubes were placed in the incubators on June 19-20, 2014, as documented in your LIMS computer system. The plates should have been incubated for (b)(4) days, per your procedures. On June 23, 2014, no plates/tubes for this batch were observed in any of the incubation chambers. | |

| | | | |
|---|---|---|---|
| 5-Nov-15 | *Dr. Reddys Laboratories Limited*<br><br>(API and drug product) | India | **2. Failure to prevent unauthorized access or changes to data, and to provide adequate controls to prevent omission of data.**<br><br>During the inspection we found the following examples of uncontrolled access to electronic systems used to generate data in your Product Development Laboratory (PD Lab).<br><br>a. Your HPLC systems are configured so that no passwords are required to log in. Credentials are unverified. Anyone who accesses the system can use software administrator privileges, which means that there is no electronic or procedural control to prevent manipulation of data.<br><br>b. Your HPLC system had no access controls to prevent alteration or deletion |
| 28-Sept-15 | *Unimark remedies Limited*<br><br>API | India | ***3. Failure to maintain complete data derived from all testing, and to ensure compliance with established specifications and standards.***<br><br>Because you discarded necessary chromatographic information such as integration parameters and injection sequences from test records, you relied on incomplete records to evaluate the quality of your APIs and to determine whether your APIs conformed with established specifications and standards. For example:<br><br>a. During the inspection, the investigator found no procedures for manual integration or review of electronic and printed analytical data for **(b)(4)** stability samples. Electronic integration parameters were not saved or recorded manually. When the next samples were analyzed, the previous parameters were overwritten during the subsequent analyses.<br><br>b. We found that some analytical testing data was inadequately maintained and reviewed. |

# Summary of the Warning Letter

| Data Manipulation | Poor Lab Control | Incomplete Data Review |
|---|---|---|
| • Falsification of documents<br><br>• Discrepancies between electronic data and data reported on paper<br><br>• Falsified entries<br><br>• Unreported / unauthorized trial injections of samples.<br><br>• Raw data chromatogram files deleted<br><br>• Retesting samples until passing results obtained | • Insufficient management of data.<br><br>•No user requirements<br><br>•Shared password<br><br>• Failure in integrity and security of data.<br>• Unreported / unauthorized trial injections of samples.<br><br>• PC admin account used to change time back and overwrite failing results<br><br>• No system validation of electronic record generating systems | • OOS results marked as passed<br><br>•Weakness of QA department around data integrity.<br><br>• No procedure for audit trail<br><br>• Hide non conformities from QA |

# Reference


- Data Integrity and Compliance with CGMP-FDA draft guidance, 2016
- GMP Drug Warning Letters Issued in Calendar Year 2015, Data Integrity Deficiencies, January, 2016
- Part11, Electronic Records; Electronic Signatures – Scope and Application
- PIC'S: Annex 11 Computerized Systems
- PIC'S: Good Practices for Computerized Systems in Regulated "GXP" Environment.
- Draft PIC/S Guidance: Good Practices for Data Integrity in Regulated GMP/GDP Environments


# Thank you and Questions?