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ICH Q7 Principles and Data Integrity

A Robust Quality System:

The Key to Preventing and Detecting “Data Integrity Practices, and Operating in Sustainable Compliance with CGMPs”

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Carmelo Rosa, FDA





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Objectives

- Apply Q7 Principals to Data Integrity Practices**
- Explain Regulators Expectation**
- Distinction between a GMP deficiency versus a data integrity practice**
- Recent Examples of Data Integrity**


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Quality (Q) Management

1. Q is everyone's responsibility
2. Manufacturers should establish, document, and implement an effective system for managing quality
3. The system for managing quality should encompass the organizational structure, procedures, processes and resources, as well as activities to ensure confidence that the API will meet its intended specifications for quality and purity.


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Q Management

3. Not being aware of on-going data integrity practices does not exempt one from the responsibility .


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WL Language- API Site

SM informed FDA investigators that they were unaware of information generated at the XXX plant that may have an impact on the quality of API.

Your SM, at the local and corporate levels, is responsible for assuring that strict corporate standards, procedures, resources, and communication processes are in place to detect and prevent breaches in data integrity, and that such significant issues are identified, escalated, and addressed in a timely manner.


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Q- Management

4. All quality-related activities should be recorded at the time they are performed
5. Any deviation should be documented and explained


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Q Management


6. Critical deviations **should be investigated,** and **the investigation and its conclusion should be documented.**

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Common phrase found under the responsibility of the QU/Production in Q7 is: “MAKING SURE” (MS)


1. MS critical deviations are investigated, resolved, conclusions recorded

2. MS that quality-related complaints are investigated and resolved


3. MS that effective systems are used for maintaining and calibrating critical equipment

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One of the most common phrases found in Q7 is: “MAKING SURE” (MS)

4. MS that materials are appropriately tested and the results are reported


5. MS that there is stability data to support retest or expiry dates and storage conditions on APIs and/or intermediates, where appropriate

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One of the most common phrases found in Q7 is: “MAKING SURE” (MS)


6. MS that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded
7. MS that production facilities are clean and, when appropriate, disinfected
8. MS that the necessary calibrations are performed and records kept

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One of the most common phrases found in Q7 is: “MAKING SURE” (MS)


9. MS that the premises and equipment are maintained and records kept
10. MS that validation protocols and reports are reviewed and approved
11. MS that new and, when appropriate, modified facilities and equipment are qualified

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What is DI

Data is complete and trustworthy


Data is reliable, consistent and accurate

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Therefore,

Your inability to detect and prevent poor data integrity practices raises serious concerns about the lack of quality system effectiveness. It is imperative that the data generated and used to make manufacturing and quality decisions at your firm is trustworthy and reliable.

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Q7 Language to Ensure DI

1. Computerized systems should have sufficient controls to prevent unauthorized access or changes to data.
2. There should be controls to prevent omissions in data (e.g., system turned off and data not captured).
3. There should be a record of any data change made, the previous entry, who made the change, and when the change was made.




Key to Prevent & Detect DI

1. Is the data reliable, trustworthy and verifiable.
2. Was the data generated following GMPs ?
3. Is the data traceable and/or referenced to original raw data and reviewed by a reliable quality structure ?
4. Are the appropriate controls in place to ensure that all data is reported?



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Key to Prevent & Detect DI

5. How long in a process can an employee go w/o direct oversight?
6. How do you know all the data is available?
7. DO you have mechanisms to ensure the data is authentic, retrievable?


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Key to Prevent & Detect DI

8. Where critical data are being entered manually, there should be an additional check on the accuracy of the entry. This can be done by a second operator or by the system itself.

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Key to Prevent & Detect DI

9. An SOP regarding retaining all appropriate documents.

10. Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays



Key DI Topics


1. Who-When-What- How:

Is Data collected ?

Is Data processed?


Is Data reviewed?

Is Data reported?



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How do we Know there is a DI Situation?


1. Intent to deceive VS a mistake ?

Ex.
Failure to Protect Computerized Data from authorize changes or access

Is this a DI issue, a GMP issue, or both?


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2. DI problem, GMP or Both ?

“Your QC Chemist admitted that, under the direction of a senior colleague, he had recorded false visual examination data in the logbooks for reserve samples...Your firm’s failure to prevent, detect, and rectify the falsification of your GMP documentation is concerning.”


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DI problem, GMP or Both ?

Failure to document the mixing time in your Batch Production Record?

Torn Batch Production Record were found in a trash can, and when examined, batches had been found to failed the blend uniformity test?


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DI, GMP or Both?

“Out-of-specification or undesirable results were ignored and not investigated”

Samples were retested without a record of the reason for the retest or an investigation. Only passing results were considered valid, and were used to release batches of APis intended for US distribution.


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DI, GMP or Both ?

Unacceptable practices in the management of electronic data were also noted.

The management of electronic data permitted unauthorized changes, as digital computer folders and files could be easily altered or deleted.


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So, if Q7 is Clear, What's Happening?

1. Superficial or ineffective controls
2. NO checks and balance
3. Management lacking expertise or competency to detect the problems
4. Audit trail manipulation-NO true security
5. Accuracy, authenticity and integrity is assumed and not verified
6. Poor security management, no Back UP-Archive


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What's Happening ?

7. Are users prevented from deleting electronic records from within the software or outside the software application?
8. Can the user alter the time/date stamp for the system?
9. Does the system have computer-generated audit trails in place to track changes and deletions of critical data?


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What's Happening ?


10. Are user rights restricted to ensure users cannot turn on/off the computer-generated audit trails?
11. Is someone from management verifying the electronic records/files for possible deletions or alterations.

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DI Examples


1. Electronically stored HPLC (high performance liquid chromatography) data was not a part of the official test records .
2. Missing or No Records Available
3. Performing “trial” sample analysis for HPLC analyses prior to acquiring the official sample result

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DI Examples

4. ...our investigator noticed that the “trial” related to...rendered an...(OOS) result for the X&Y assay. It appears that...did not pass the trial analysis but met specifications when the official sample was tested shortly thereafter.
5. ...our investigator noted some of the “trial injection” data was not kept on HPLC drives because you deleted them.

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DI Examples

6. Your firm deleted multiple HPLC data files acquired in 2013 allegedly to clear hard drive space w/o creating back-ups.
7. Your management confirmed there is no audit trail


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DI Examples


8. Top site management admitted both, testing and manufacturing operations that occurred outside of the quality system, but assuming no responsibility. Usual Response by firms:
 - It was 1 or 2 employees cutting corners
 - This has never happened before, isolated event
 - Management not aware of these practices
 - Quality is not compromised

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DI Examples

9. API failing impurity specifications was mixed with other API batches to make an API batch that would pass the test. Management claimed not being aware of such practice
10. Instrumentation and records had been removed from the site expressly to avoid their becoming a part of the inspection.


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DI Examples


11. Selection of only passing results from HPLC and GC (gas chromatography) data, while failing test results are disregarded, ignored, and more concerning, not investigated. This practice was noted during the testing of raw materials, finished drug release and stability studies.

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DI Examples


12. Undesirable electronic raw data related to GC testing were found in the PC “Recycle Bin”.
13. Partially destroyed hardcopy records of equipment maintenance and instrumentation calibration data were found, as well as 5,000 deleted HPLC data files.

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DI Examples

14. Indiscriminate retesting of raw materials, intermediate drug products, and finished API in order to produce acceptable test results.
15. Failures were not reported or investigated to find the cause.


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Concluding Remarks

1. We need to know the difference between falsification and poor/bad GMPs.
2. Existing systems should be able to ensure data integrity , traceability and reliability.
3. Companies who outsource operations should have systems in place to verify and compare the data generated by their contractor


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Concluding Remarks

4. Once DI Practices are found, known or uncovered, A CHANGE TO AN SOP OR FIRING AN EMPLOYEE IS NOT ENOUGH!!!!
5. QRM approaches to prevent, detect and control potential risk are essential
6. If it looks too good to be true, it probably is not true, so keep your eyes WIDE opened

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Our kids assume the drugs they take will make them feel better!!!!



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