Data Integrity, Data Analysis and Monitoring
Contents

• Regulatory requirements and guidelines
• ALCOA
• Data Integrity for computer, paper and hybrid systems
• Control of meta-data
• Data integrity strategies for compliance
• Checking for Data Integrity issues in practice
Directive 2003 / 94/ EC – Article 9

“The manufacturer shall establish and maintain a **documentation system** based upon specifications, manufacturing formulae and processing and packaging instructions, procedures and records covering the various manufacturing operations performed. Documents shall be **clear, free from error and kept up to date**. Pre-established procedures for general manufacturing operations and conditions shall be kept available, together with specific documents for the manufacture of each batch. That set of documents shall **enable the history of the manufacture of each batch ... to be traced**”
Directive 2003 / 94/ EC – Article 9

“For a medicinal product, the batch documentation shall be retained for at least one year after the expiry date of the batches to which it relates or at least five years after the (QP) certification ... whichever is the longer period”
Directive 2003 / 94/ EC – Article 9

“When electronic, photographic or other data processing systems are used instead of written documents, the manufacturer shall first validate the systems by showing that the data will be appropriately stored during the anticipated period of storage. Data stored by those systems shall be made readily available in legible form and shall be provided to the competent authorities at their request. The electronically stored data shall be protected, by methods such as duplication or back-up and transfer on to another storage system, against loss or damage of data, and audit trails shall be maintained”
So what is Data Integrity?

“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 (or a true copy) and accurate.”

MHRA GXP Data Integrity Guidance and Definitions; Revision 1: March 2018
Data Integrity in EU GMP

1. Pharmaceutical Quality System  New 2013
2. Personnel  New 2014
3. Premises & equipment  New 2015
4. Documentation  New 2011
5. Production  New 2015
6. Quality Control  New 2014
7. Outsourced activities  New 2013
9. Self inspection
Data Integrity in EU GMP

1. Pharmaceutical Quality System
2. Personnel
3. Premises & equipment
4. **Documentation**
5. Production
6. Quality Control
7. Outsourced activities
8. Complaints, Defects & Product Recalls
9. Self inspection
Data Integrity in EU GMP

1. Pharmaceutical Quality System
2. Personnel
3. Premises & equipment
4. **Documentation** *(New 2011)*
5. Production
6. Quality Control
7. Outsourced activities
8. Complaints, Defects & Product Recalls
9. Self inspection

- Updated *slightly* to cover the increasing use of computer systems
- Computer systems to be validated and controlled
Data Integrity in EU GMP Annexes

1. Sterile manufacturing
2. Biological products
3. Radiopharmaceuticals
4. Veterinary medicinal products
5. Immunological veterinary products
6. Medicinal gases
7. Herbal medicinal products
8. Sampling of starting materials
9. Liquids, creams & ointments
10. Metered dose inhalers
Data Integrity in EU GMP Annexes

11. Computerised systems
12. Use of ionizing radiation
13. Investigational medicinal products
14. Products derived from blood
15. Qualification and validation
16. Certification by a QP
17. Parametric release
18. Withdrawn
19. Reference samples
20. Withdrawn
21. Importation of medicinal products
Data Integrity in EU GMP Annexes

11. Computerised systems

12. Use of ionizing radiation

• Only makes a passing reference to Data Integrity:

1. Risk Management:

Risk management should be applied throughout the lifecycle of the computerised system taking into account patient safety, data integrity and product quality. As part of a risk management system, decisions on the extent of validation and data integrity controls should be based on a justified and documented risk assessment of the computerised system.
Remember – GMP are guidelines

“It is recognised that there are acceptable methods, other than those described in the Guide, which are capable of achieving the principles of Quality Assurance. The guide is not intended to place any restraint upon the development of any new concepts or technologies which have been validated and which provide a level of Quality Assurance at least equivalent to those set out in this guide”
So what is Data Integrity?

Data Integrity – is not actually mentioned in EU or USA GMP
Where does it apply?

- Paper based systems
- Computer based systems
- Hybrid systems
- Don’t forget the *meta data*
What is Meta Data?

• Take a simple analysis trace

mV signal

What Does it mean?
What is Meta Data?

• Take a simple analysis trace
Data Integrity TODAY
Data Integrity TODAY

- System might delete data when memory starts to run out
- You need to know this and have a way of keeping the data elsewhere
| A | Attributable to the person generating the data |
| L | Legible and permanent |
| C | Contemporaneous |
| O | Original record (or certified true copy) |
| A | Accurate |
Data Integrity – ALCOA +

<table>
<thead>
<tr>
<th>A</th>
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**Complete**: the data must be whole; a complete set

**Consistent**: the data must be self-consistent

**Enduring**: durable; lasting throughout the data lifecycle

**Available**: readily available for review or inspection purposes
Spreadsheets

• Are useful, simple and cheap to use
  – Often first created by an individual
• Potential problems:
  – No audit trail for:
    • When data was added
    • Changes (overwriting of data)
    • Who altered any data
Spreadsheets

• Potential problems:
  – The accuracy of calculations
    • Plus altering them
  – The saving of data
    • Often on a general server with access to a whole group of people
    • Can it be deleted?
    • Is data archived in the same way as paper-based records?
Primary Records and True Copies

• Batch records are never totally computerised
• Paper forms and records used for certain activities
  – Line clearance sheets
  – Sterilisation charts
  – Printouts
• These are Primary Records
  – You may keep these
  – You may scan or copy these
  – Both
Primary Records and True Copies

• Copy or scan is a True Copy
  – Only if an exact copy

• Need to control what you do with these
  – Especially if not stored with the computer-based record
Reporting DI issues

• Incorporate data integrity assessment and Reporting into self-inspection program
• Ensure a system is in place to record data integrity issues (e.g. CAPA)
  – Data integrity issues
    • Have had a problem
  – Data integrity weaknesses
    • An issue – but no evidence of a problem
Reprocessing of events

• Does anything look strange here?

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<th>Filename</th>
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<td>Volt.@100 inj acc</td>
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<td>120215-009.rst</td>
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Avoid “Testing into Compliance”
Data Integrity strategy

• It starts at the top - Management Led
• Have a Policy on Data Integrity
• Know what systems you have
• Know where you have weaknesses
  – Plan to deal with these
Data Integrity strategy

• Train personnel in DI
• An open approach for reporting DI concerns
• Look for DI issues during Internal Audits
• Look for DI issues during External Audits
• Look for DI issues with any new projects
References

- EU GMP Directives and Guidelines:
- Many regulatory authorities have produced Data Integrity Guidance documents:
  - FDA:
  - EMA:
  - PICS:
  - WHO:
  - MHRA (UK):