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
8. Complaints, Defects & Product Recalls	New 2015
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

Data Integrity in EU GMP

1. Pharmaceutical Quality System
2. Personnel
3. Premises & equipment
4. **Documentation** **New 2011**

- Updated *slightly* to cover the increasing use of computer systems
- Computer systems to be validated and controlled

8. Complaints, Defects & Product Recalls
9. Self inspection

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.*

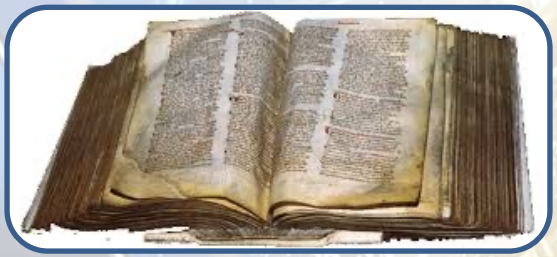
Remember – GMP are guidelines

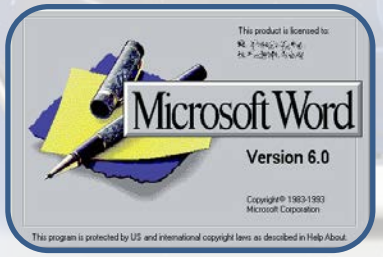
*"It is recognised that there are **acceptable methods**, **other than those described in the Guide**, **which are capable of achieving the principles of Quality Assurance**. The guide **is not intended to place any restraint** upon the development of any **new concepts or technologies** which have been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

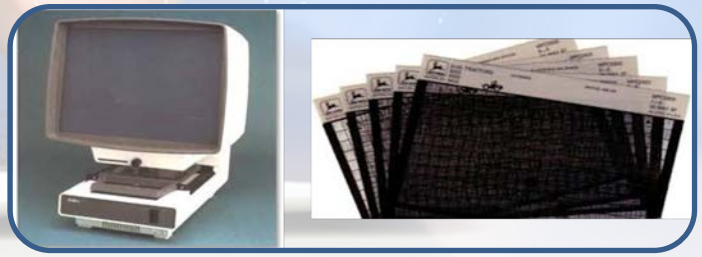
So what is Data Integrity?

Data Integrity – is not actually mentioned in EU or USA GMP

Data Integrity BACKGROUND







Where does it apply?

- Paper based systems
- Computer based systems
- Hybrid systems
- Don’t forget the **meta data**

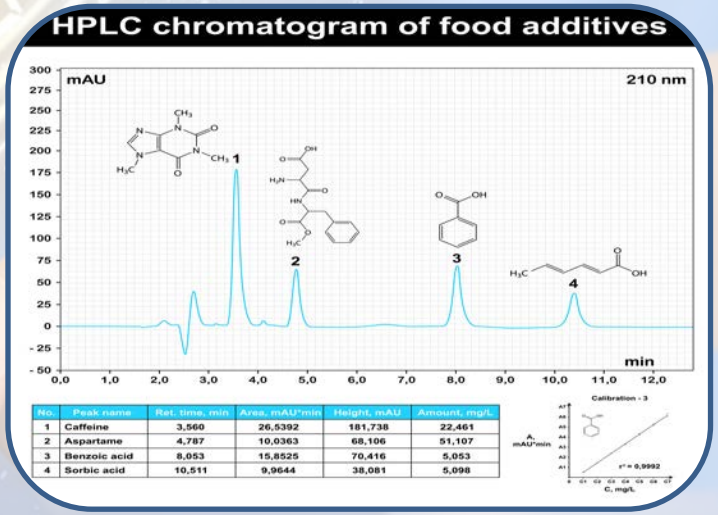
What is Meta Data?

- Take a simple analysis trace

What is Meta Data?

- Take a simple analysis trace

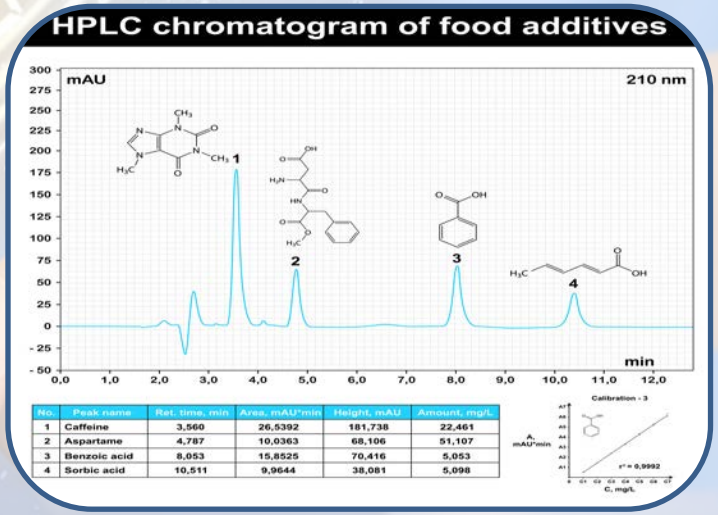
Data Integrity TODAY



No.	Peak name	Ret. time, min	Area, mAU*min	Height, mAU	Amount, mg/L
1	Caffeine	3,560	26,5392	181,738	22,461
2	Aspartame	4,787	10,0363	68,106	51,107
3	Benzoic acid	8,053	15,8525	70,416	5,053
4	Sorbic acid	10,511	9,9644	38,081	5,098

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



No.	Peak name	Ret. time, min	Area, mAU*min	Height, mAU	Amount, mg/L
1	Caffeine	3,560	26,5392	181,738	22,461
2	Aspartame	4,787	10,0363	68,106	51,107
3	Benzoic acid	8,053	15,8525	70,416	5,053
4	Sorbic acid	10,511	9,9644	38,081	5,098

Data Integrity

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 +

A	Attributable to the person generating the data
L	Legible and permanent
C	Contemporaneous
O	Original record (or certified true copy)
A	Accurate

Complete: the data must be whole; a complete set

Consistent: the data must be self-consistent

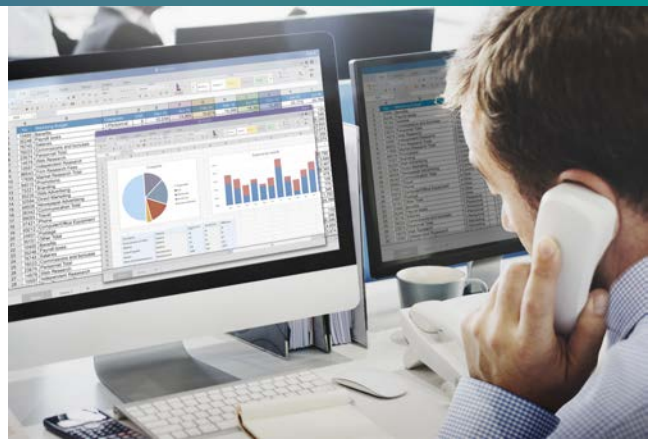
Enduring: durable; lasting throughout the data lifecycle

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 people
    - Can it be deleted?
    - Is data archived in the same way as paper-based records?

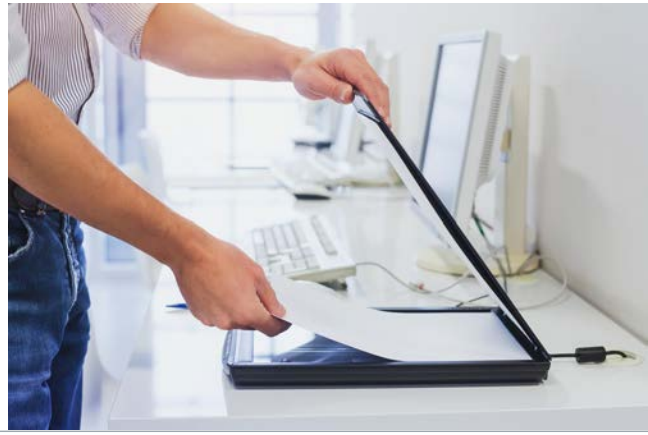
Primary Records *and* True Copies

- 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?

Sample name	Acquisition time	Filename
Volt.@100 Run 1	14:12:19	120215.003.rst
Volt.@100 Run 2	14:18:10	120215-004.rst
Volt.@100 Run 5	14:29:19	120215-007.rst
Volt.@100 Run 5	14:36:07	120215-007-20110809-173718.rst
Volt.@100 Run 6	14:39:58	120215-008.rst
Volt.@100 inj acc	14:43:58	120215-009.rst

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:
- https://ec.europa.eu/health/documents/eudralex/vol-4_en
- Many regulatory authorities have produced Data Integrity Guidance documents:
- FDA:
- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/data-integrity-and-compliance-drug-cgmp-questions-and-answers-guidance-industry
- EMA:
- https://www.ema.europa.eu/en/news/data-integrity-key-public-health-protection
- PICS:
- https://picscheme.org/en/news?itemid=33
- WHO:
- https://www.who.int/medicines/news/emp-data-integrity-guide/en/
- MHRA (UK):
- https://www.gov.uk/government/publications/guidance-on-gxp-data-integrity