Data Integrity: Success by Design

Fat-finger, Falsification and Fraud

Presented by Trevor Schoerie

30 July 2015

PDA Parenteral Drug Association Australia Chapter

The 3 Fs of data integrity

System design failures and design controls

Fat Finger	An inadvertent mistake made by an operator during the course of their work that can be made either on **paper** or **electronically**.
Falsification	An **individual** who deliberately writes or enters data or results with the intention to deceive.
Fraud	Collusion between **two or more individuals** who deliberately write or enter data or results with the intention to deceive.

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World's biggest medicines recall

The suspension follows audits of the company's manufacturing premises, which revealed widespread and serious deficiencies and failures in the company's manufacturing and quality control procedures, including the **systematic and deliberate manipulation** of quality control test **data**.

- 219 products **immediately** recalled
- 1650 export products **cancelled**

'The **Australian** public should not forget how bad the manufacturing practices were at **<the company>** which prompted what may be the world's biggest medicines recall.'

Source
https://www.tga.gov.au/product-recall/pan-pharmaceuticals-limited-regulatory-action-product-recall-information
https://www.tga.gov.au/media-release/tga-reminds-australians-potential-danger-pan-pharmaceuticals

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The Rogue Analyst

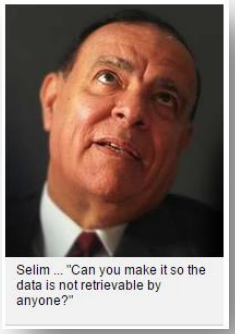
…… that he believed "**a rogue analyst**" had manipulated the test results, but "the defendant tried to downplay the seriousness of the matter".

Giving evidence, the former IT manager said:

"The MD said to me, 'What is happening with the computer? Is there any data still on it?' to which I replied, 'No, there is no data still on it, I've reformatted the computer," he told the court.

The MD then asked him whether a computer expert would be able to retrieve the data if they were to access the computer.

"Can you make it so the data is not retrievable by anyone?"



http://www.smh.com.au/news/business/drug-recall-tests-manipulated-court-told/2005/07/18/1121538910545.html

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A horse called Jim

A German scientist, **Emil von Behring** discovered that diphtheria antitoxin present in certain animals' blood could be made into a serum and injected into humans. His development of serum therapy against the disease earned him the first Nobel Prize in Medicine in 1901.

Jim was retired from milk cart duties and enlisted into the production of serum. Unfortunately, Jim contracted tetanus between the 25th Aug. and 30th Sept. 1901 and was put down.

Tragically, blood drawn on the 30th Sept was **mislabelled**, the 24th Aug and released, it resulted in the death of 12 children.

In the late 19th century diphtheria was one of the world's most feared childhood diseases. Children infected with diphtheria had a 10 to 15% chance of dying from the disease

This incident and a similar Smallpox vaccine incident lead to the passage of the Biologicals Controls of 1902, which established the Center Biologics Evaluation and Research and later the formation of the **FDA** in 1906.

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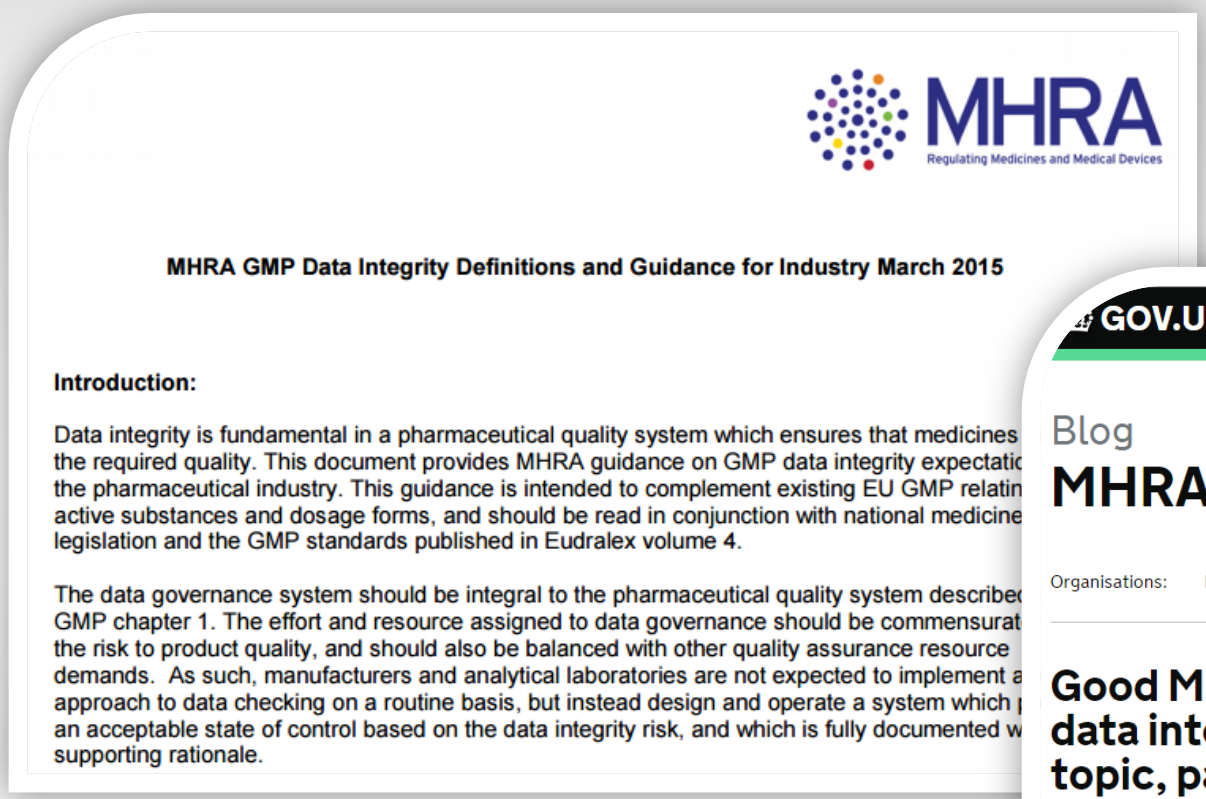
MHRA – Data Integrity Definitions and Guidance for Industry & Blog



MHRA

Regulating Medicines and Medical Devices

MHRA GMP Data Integrity Definitions and Guidance for Industry March 2015

Introduction:

Data integrity is fundamental in a pharmaceutical quality system which ensures that medicines
the required quality. This document provides MHRA guidance on GMP data integrity expectatio
the pharmaceutical industry. This guidance is intended to complement existing EU GMP relatin
active substances and dosage forms, and should be read in conjunction with national medicine
legislation and the GMP standards published in Eudralex volume 4.

The data governance system should be integral to the pharmaceutical quality system describe
GMP chapter 1. The effort and resource assigned to data governance should be commensurat
the risk to product quality, and should also be balanced with other quality assurance resource
demands. As such, manufacturers and analytical laboratories are not expected to implement a
approach to data checking on a routine basis, but instead design and operate a system which
an acceptable state of control based on the data integrity risk, and which is fully documented w
supporting rationale.

GOV.UK

Blog

MHRA Inspectorate

Organisations: Medicines and Healthcare products Regulatory Agency

Good Manufacturing Practice (GMP) data integrity: a new look at an old topic, part 1

David Churchward, 25 June 2015 — Compliance matters

Data integrity is fundamental in a pharmaceutical quality system which ensures that medicines are of the required quality.

A robust data governance approach will ensure that data is complete, consistent and accurate, irrespective of the format in which data is generated, used or retained.

"a new look at an old topic"

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Misconception

"There is a general misconception that data integrity failures only result from **acts of deliberate fraud**.

…. majority of issues relate to –

- bad practice,
- poor organisational behaviour and
- weak systems,

which create opportunities for data to be manipulated.

….. some basic behavioural, procedural and technical steps to significantly improve their systems."

MHRA – David Churchward

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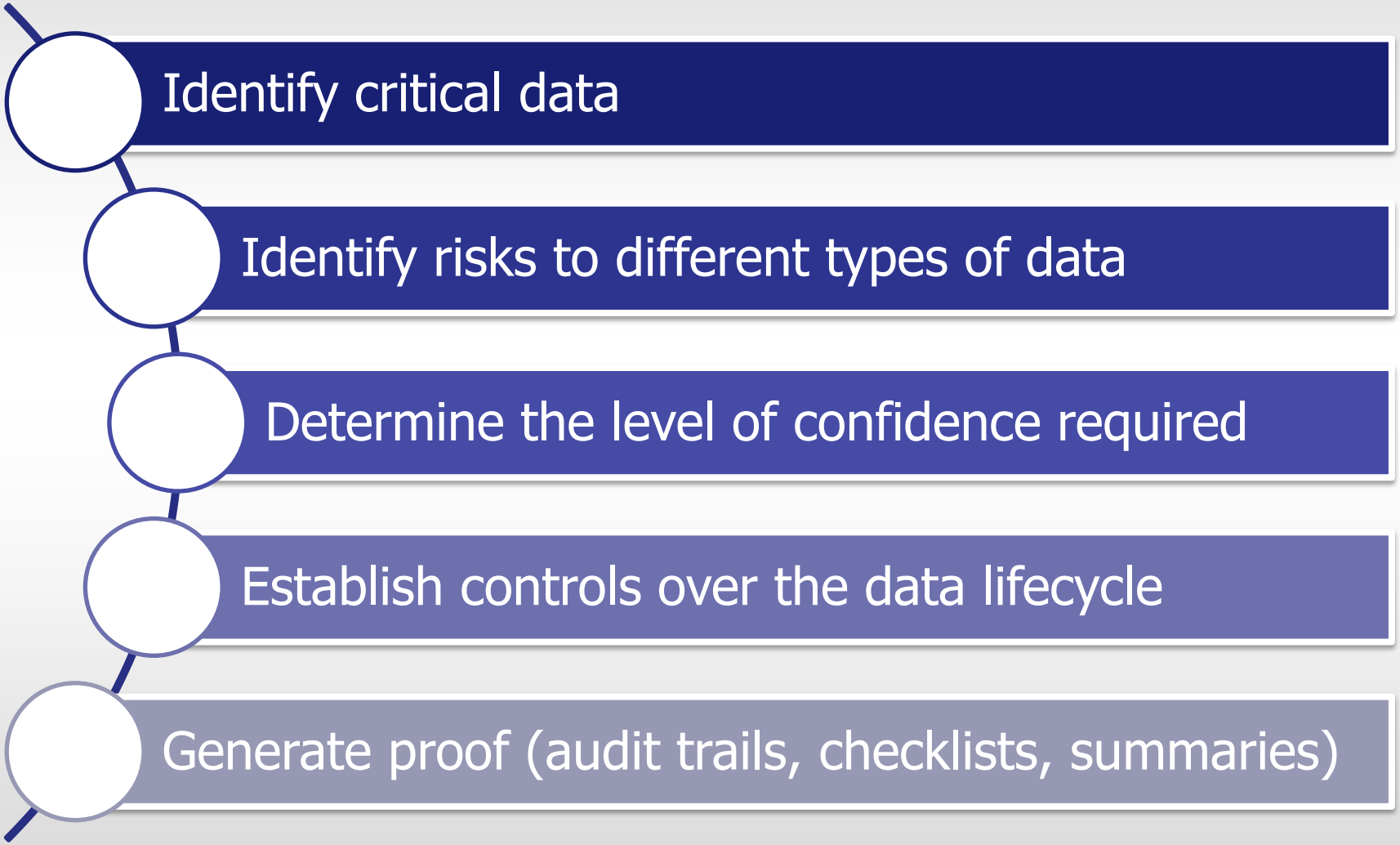
Design Controls for Data



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Identify critical data
CFR Part 11, Scope and Application

Three critical data criteria –

1. **Predicate rules -** e.g. approved, reviewed and verified - *in place of paper format*
2. **Submitted to the inspector -** *in addition to paper format, and that are relied on to perform regulated activities*
3. **Regulatory submission -**

helped us determine critical steps or data.

New FDA Draft Request for Quality Metrics – July '15
"in lieu of inspection"

APR data, cPk, lot acceptance rate, OOS rate, Complaint rate, CAPA effectiveness,

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FDA Part 11 – Design controls

- limiting system access to authorized individuals
- use of operational system checks
- use of authority checks
- use of device checks
- determination that persons who develop, maintain, or use electronic systems have the education, training, and experience to perform their assigned tasks
- establishment of and adherence to written policies that hold individuals accountable for actions initiated under their electronic signatures
- appropriate controls over systems documentation
- controls for open systems corresponding to controls for closed systems bulleted above (§ 145 11.30)
- requirements related to electronic signatures

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PIC/S Chapter 4

CHAPTER 4

DOCUMENTATION

PRINCIPLE

Good documentation constitutes an essential part of the quality assurance system and is key to operating in compliance with GMP requirements. The various types of documents and media used should be fully defined in the manufacturer's Quality Management System. Documentation may exist in a variety of forms, including paper-based, electronic or photographic media. The main objective of the system of documentation utilised must be to establish, control, monitor and record all activities which directly or indirectly impact on all aspects of the quality of medicinal products. The Quality Management System should include sufficient instructional detail to facilitate a common understanding of the requirements, in addition to providing for sufficient recording of the various processes and evaluation of any observations, so that ongoing application of the requirements may be demonstrated.

control, monitor and record

accuracy, integrity

Suitable controls should be implemented to ensure the accuracy, integrity, availability and legibility of documents. Instruction documents should be free from errors and available in writing. The term 'written' means recorded, or documented on media from which data may be rendered in a human readable form.

availability, legibility

PIC/S Guide to Good Manufacturing Practice for Medicinal Products PE 009-11

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Data integrity PIC/S GMPs

What type of data would you classify as critical?

Manual entry of critical data should be checked by a second person or managed as part of or a validated system

§4.20, 4.21,

c) Identification (initials) of the operator(s) who performed each significant step of the process and, where appropriate, the name of any person who checked these operations;

§6.17

g) initials of the persons who verified the testing and the calculations, where appropriate;

h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

But "Significant Step" data?

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Definitions

approved, reviewed and verified

Verified	Witnessed	Checked
Approved	Authorised	Performed
	Prepared	

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Technical Design Controls

1. System complexity / inherent data risk
2. User access, permissions
3. Transactional windows
4. Data structure and location
   - Dynamic vs static, hosted
   - File structure
   - Audit trails and metadata
5. Validation vs functional verification

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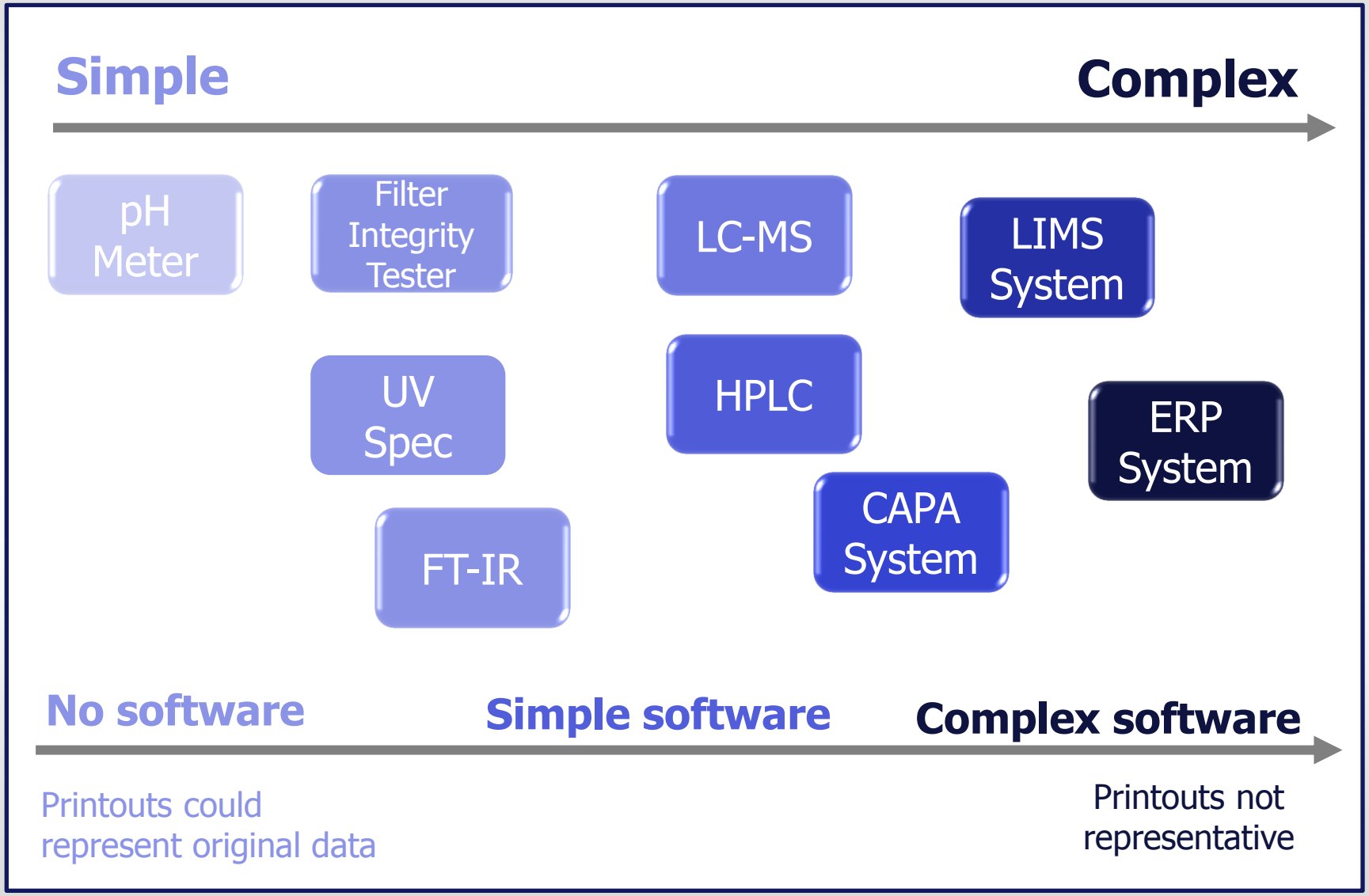
1. System complexity

Data criticality and inherent integrity risk



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2. User Access

System access
Individual logins (always)

User/group permissions
Appropriate to an individuals roles
No IT Department?
Independence of roles
PQS / QMS visibility

Watch recently the departed (CC)

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3. Transactional window

Data entry window, idle log off

No	Added raw material?	Performed by	Checked by
1	Ensure room and vessel is …..		
2	Add 100 litres purified water Start the stirrer Add 0.3kg catalyst Add 2kg buffer Add 30kg lactose		
3	Record the time: _____am/pm		

No	Added raw material?	Performed by	Checked by
1	Ensure room and vessel is …..		
2	Add 100 litres purified water		
3	Start the stirrer		
4	Add 0.3kg catalyst		
5	Add 2kg buffer		
6	Add 30kg lactose		
7	Record the time: _____am/pm		

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4. Data structure and location

- Dynamic, i.e. mirrored, DC, backed up?
- Business continuation planning?
- Data only or real process information
- Can be restored? With Audit trail and metadata?
- If hosted,
  - who else can see it?
  - Service Level Agreement?
  - Can company and other parties inspect?

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Just data vs process information, i.e. importance of metadata?

Date		TIC601	HIC601
20/07/2015		22.00	69.80
21/07/2015		23.00	68.30
22/07/2015		24.00	66.50
23/07/2015		25.00	62.10
24/07/2015		25.00	63.60
27/07/2015		25.00	80.90
28/07/2015		22.00	65.40
29/07/2015		21.00	53.80
30/07/2015		20.00	55.10

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Meta data vs just data?

Date	Location As per WI023/1	Temp. < 25°C	% RH <75%	Operator	Date/time
20/07/2015	Top rack	22.00	69.80	TS	20Jul15 06:07:28GMT
21/07/2015	Top rack	23.00	68.30	TS	21Jul15 06:09:26GMT
22/07/2015	Top rack	24.00	66.50	TS	22Jul15 06:14:15GMT
23/07/2015	Bottom rack	25.00	62.10	TS	23Jul15 06:06:78GMT
24/07/2015	Top rack	25.00	63.60	TS	24Jul15 07:01:25GMT
27/07/2015	Top rack	25.00	80.90	TS	27Jul15 06:11:55GMT
27/07/2015	Top rack	25.00	72.30	TS	27Jul15 06:15:12GMT *notation/deviation….
28/07/2015	Top rack	22.00	65.40	TS	28Jul15 06:23:25GMT
29/07/2015	Bottom rack	21.00	53.80	TS	29Jul15 06:07:10GMT
30/07/2015	Top rack	20.00	55.10	TS	30Jul15 06:04:30GMT

Available through the audit trail.

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Ditto, blank and brackets

Date	Location As per WI023/1	Temp. < 25°C	% RH <75%	Operator	Remarks
20/07/2015	Top rack	22.00	69.80	TS	
21/07/2015	Top rack	23.00	68.30	"	
22/07/2015	Top rack	24.00	66.50	"	
23/07/2015	Bottom rack	25.00	62.10	"	
24/07/2015	Top rack	25.00	63.60	"	
27/07/2015	Top rack	25.00	75.90		
28/07/2015	Top rack	22.00	65.40		
29/07/2015	Bottom rack	21.00	53.80	TS	
30/07/2015	Top rack	20.00	55.10		

Left blank?

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5. Functional verification vs validation?

Determined by system complexity

- Raw data includes equipment printouts, original workbook and logbook entries, readings transcribed by an operator from an electronic display, or a hand worked calculation, an observation etc.
- Raw data is a type of record but there is also an inference that the original 'result' is used further to derive a final result.
- Information captured within a batch record is raw data if it can’t be sourced from a validated electronic system.

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MHRA GMP Data Integrity Definitions & Guidance for Industry, March 2015 and Blog

Compliment	PQS	Risk	Expectation	Design
Intended to **compliment** existing EU GMP	The "data governance system" integral to the PQS	Effort and resource assigned to governance should be commensurate with the risk to product quality	Not expected to implement a forensic approach	Design and operate a system that provides an acceptable state of control based on data integrity risk

Data integrity requirements apply equally to manual (paper) and electronic data

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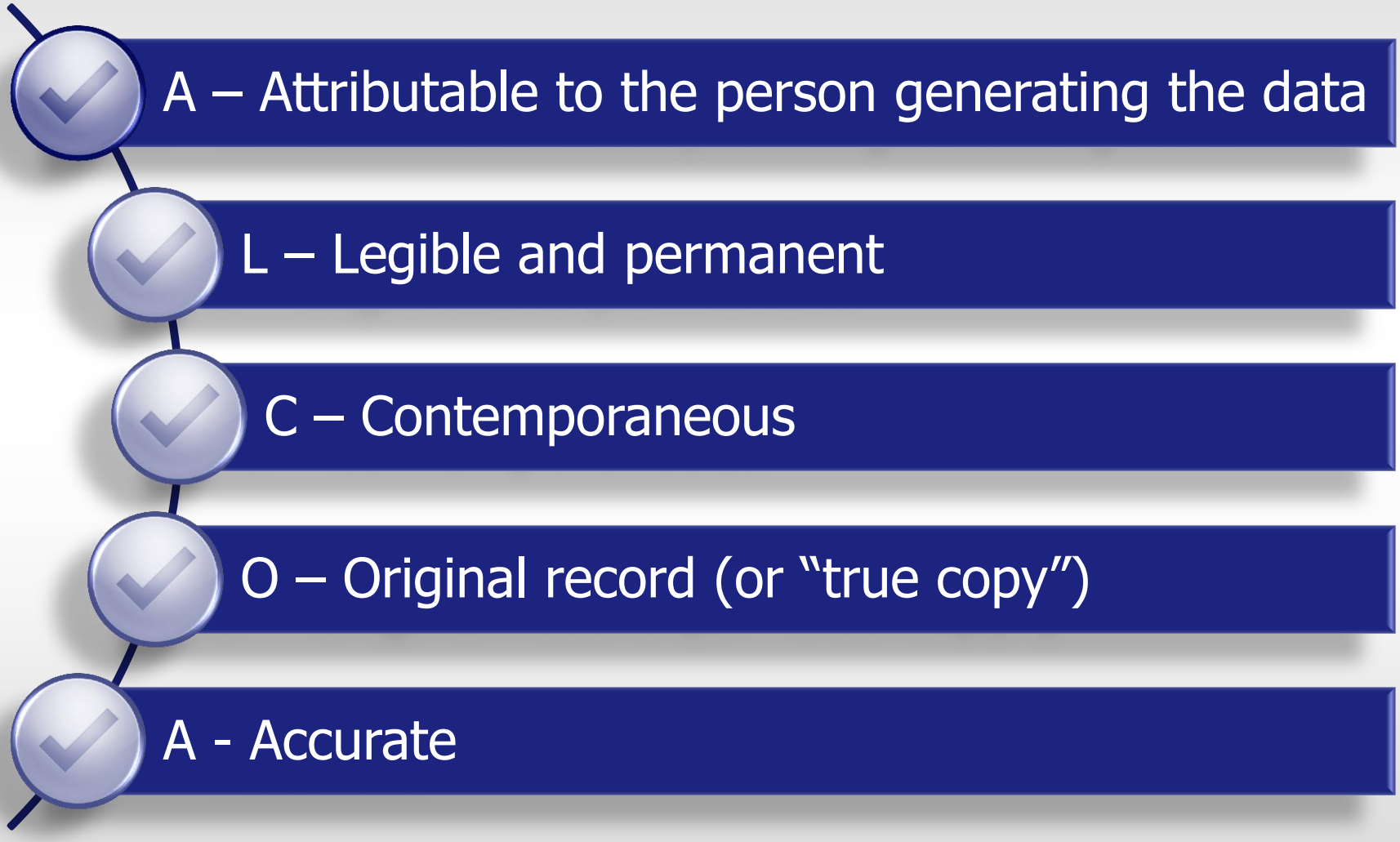
Data must be:



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Design DI into your systems

Paper based

Attributable	Legible/ Permanent	Contemporaneous	Original	Accurate
Initials & Signature registers	Control of blank forms, pen policy/white out	Documents available in right place at right time, +- time limits	Verified 'true copies', scans	Reflective of the observation data checking

Electronic

Attributable	Legible/ Permanent	Contemporaneous	Original	Accurate
Active directory, e-sig, audit trails, metadata	Data annotation tools, audit trail	System clock, sync., transaction window	Meta data, data about the data that permits reconstruction	Data capture, manual data entry

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Take home message

- It's a big old problem
- Identify critical data
- Its not just the labs
- Its not just IT systems
- Culture –
  - awareness and education

….. some basic behavioural, procedural and technical steps to significantly improve their systems.

MHRA – David Churchward

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Thank you for your time.

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