Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Current Trends in Data Quality and Integrity Issues in Inspections and Risk Based Approach to Investigations; EU perspective

Mark Birse / Richard Andrews, MHRA

“Data Integrity has no relationship with product quality”

CEO of multinational API supplier

Top 10 Most cited deficiency groups 2016

Ranking	Groups	Critical	Major	Others
1	Quality System	38	449	772
2	Sterility Assurance	34	190	162
3	Production	20	191	543
4	Complaints and Recall	11	80	110
5	Qualification/Validation	10	123	232
6	Premises & Equipment	9	113	464
7	Computerised Systems	9	44	120
8	Personnel	8	42	150
9	Documentation	2	166	646
10	Quality Control	2	42	192

2016 Deficiencies:

Non-contemporaneous recording was noted during placebo manufacture as the date completed for the process step on the batch production record had already been entered before that process step had actually been completed.

Deficiency:

EU GMP

- Ch. 4; 4.8

Guidance given:

MHRA GXP Guide

- Section 6. Data life cycle
- Section 2. Raw data
- Section 12. Computer system transactions

2016 Deficiencies:

A photocopy of a batch sheet page related to pallet stacking pattern seen in the trash container outside the bottle packing line was indication of an unacceptable practice of uncontrolled photocopying of pages of the batch record during use.

Deficiency:

EU GMP

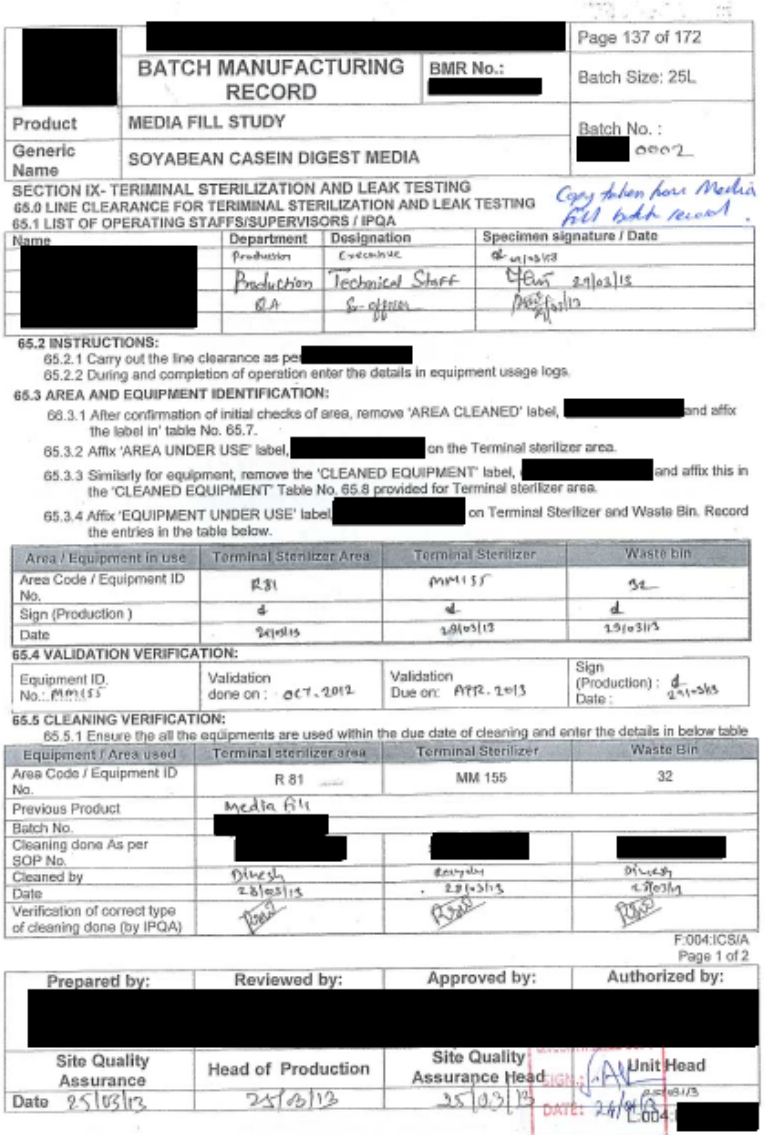
- Ch. 4; 4.2 & 4.10

Guidance given:

MHRA GXP Guide

- Section 1. Data
- Section 11.2 True copy
- Section 17, data retention

Falsification of records



[redacted] | Page 137 of 172

BATCH MANUFACTURING RECORD | BMR No.: [redacted] | Batch Size: 25L

Product: MEDIA FILL STUDY | Batch No. : [redacted] 0002

Generic Name: SOYABEAN CASEIN DIGEST MEDIA

SECTION IX- TERIMINAL STERILIZATION AND LEAK TESTING

65.0 LINE CLEARANCE FOR TERIMINAL STERILIZATION AND LEAK TESTING

65.1 LIST OF OPERATING STAFFS/SUPERVISORS / IPQA

Copy taken from Media Fill batch record.

Name	Department	Designation	Specimen signature / Date
[redacted]	Production	Executive	29/03/13
	Production	Technical Staff	29/03/13
	QA	Sr. officer	29/03/13

65.2 INSTRUCTIONS:

65.2.1 Carry out the line clearance as per [redacted]

65.2.2 During and completion of operation enter the details in equipment usage logs.

65.3 AREA AND EQUIPMENT IDENTIFICATION:

65.3.1 After confirmation of initial checks of area, remove 'AREA CLEANED' label, [redacted] and affix the label in' table No. 65.7.

65.3.2 Affix 'AREA UNDER USE' label, [redacted] on the Terminal sterilizer area.

65.3.3 Similarly for equipment, remove the 'CLEANED EQUIPMENT' label, [redacted] and affix this in the 'CLEANED EQUIPMENT' Table No. 65.8 provided for Terminal sterilizer area.

65.3.4 Affix 'EQUIPMENT UNDER USE' label [redacted] on Terminal Sterilizer and Waste Bin. Record the entries in the table below.

Area / Equipment in use	Terminal Sterilizer Area	Terminal Sterilizer	Waste bin
Area Code / Equipment ID No.	R 81	MM155	32
Sign (Production)			
Date	29/03/13	29/03/13	29/03/13

65.4 VALIDATION VERIFICATION:

Equipment ID. No.: MM155	Validation done on : OCT. 2012	Validation Due on: APR. 2013	Sign (Production) : Date : 29/03/13

65.5 CLEANING VERIFICATION:

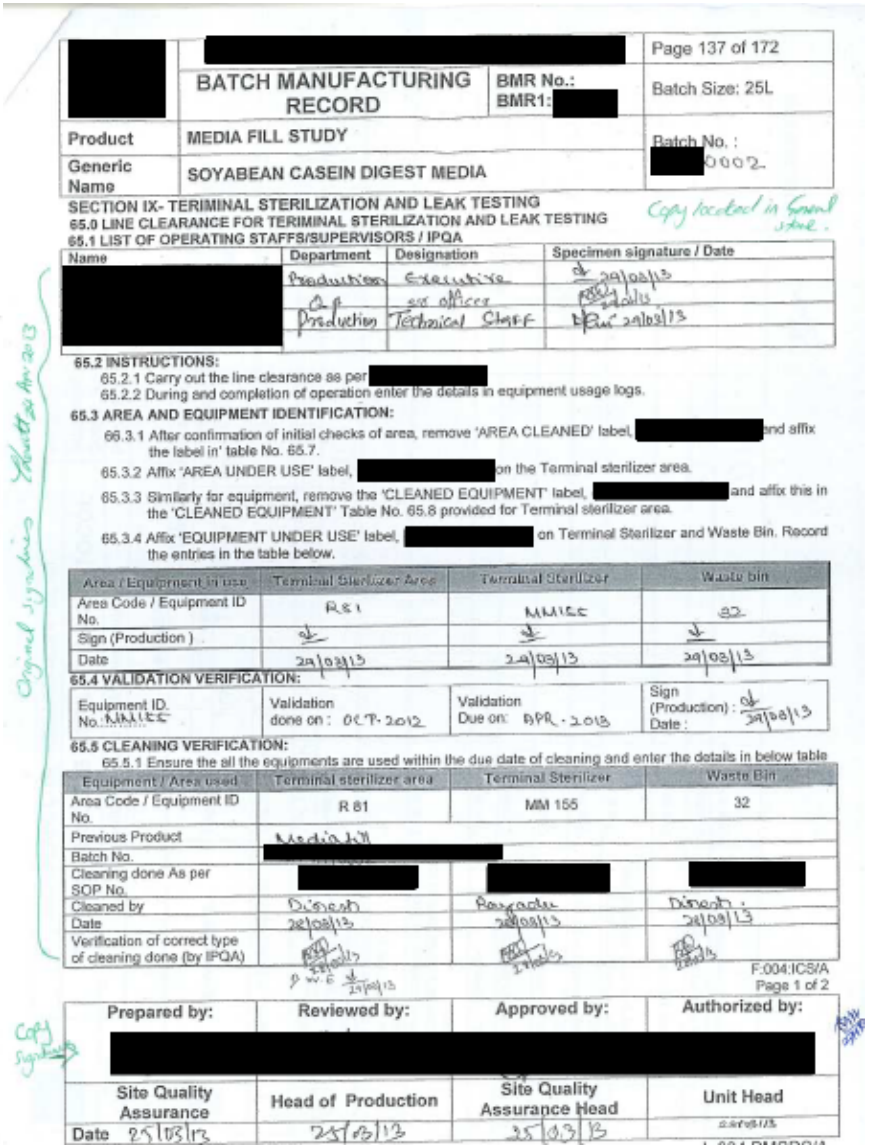
65.5.1 Ensure the all the equipments are used within the due date of cleaning and enter the details in below table

Equipment / Area used	Terminal sterilizer area	Terminal Sterilizer	Waste Bin
Area Code / Equipment ID No.	R 81	MM 155	32
Previous Product	Media fill		
Batch No.	[redacted]	[redacted]	[redacted]
Cleaning done As per SOP No.			
Cleaned by	Dinesh	Ranjeet	Dinesh
Date	28/03/13	28/03/13	28/03/13
Verification of correct type of cleaning done (by IPQA)			

F:004:ICS/A

Page 1 of 2

Prepared by:	Reviewed by:	Approved by:	Authorized by:
[redacted]			
Site Quality Assurance	Head of Production	Site Quality Assurance Head	Unit Head
Date 25/03/13	25/03/13	25/03/13	



[redacted] | Page 137 of 172

BATCH MANUFACTURING RECORD | BMR No.: BMR1: [redacted] | Batch Size: 25L

Product: MEDIA FILL STUDY | Batch No. : [redacted] 0002

Generic Name: SOYABEAN CASEIN DIGEST MEDIA

SECTION IX- TERIMINAL STERILIZATION AND LEAK TESTING

65.0 LINE CLEARANCE FOR TERIMINAL STERILIZATION AND LEAK TESTING

65.1 LIST OF OPERATING STAFFS/SUPERVISORS / IPQA

Copy located in General store.

Name	Department	Designation	Specimen signature / Date
[redacted]	Production	Executive	29/03/13
	QA	Sr. officer	29/03/13
	Production	Technical Staff	29/03/13

65.2 INSTRUCTIONS:

65.2.1 Carry out the line clearance as per [redacted]

65.2.2 During and completion of operation enter the details in equipment usage logs.

65.3 AREA AND EQUIPMENT IDENTIFICATION:

65.3.1 After confirmation of initial checks of area, remove 'AREA CLEANED' label, [redacted] and affix the label in' table No. 65.7.

65.3.2 Affix 'AREA UNDER USE' label, [redacted] on the Terminal sterilizer area.

65.3.3 Similarly for equipment, remove the 'CLEANED EQUIPMENT' label, [redacted] and affix this in the 'CLEANED EQUIPMENT' Table No. 65.8 provided for Terminal sterilizer area.

65.3.4 Affix 'EQUIPMENT UNDER USE' label, [redacted] on Terminal Sterilizer and Waste Bin. Record the entries in the table below.

Area / Equipment in use	Terminal Sterilizer Area	Terminal Sterilizer	Waste bin
Area Code / Equipment ID No.	R 81	MM155	32
Sign (Production)			
Date	29/03/13	29/03/13	29/03/13

65.4 VALIDATION VERIFICATION:

Equipment ID. No.: MM155	Validation done on : OCT. 2012	Validation Due on: APR. 2013	Sign (Production) : Date : 29/03/13

65.5 CLEANING VERIFICATION:

65.5.1 Ensure the all the equipments are used within the due date of cleaning and enter the details in below table

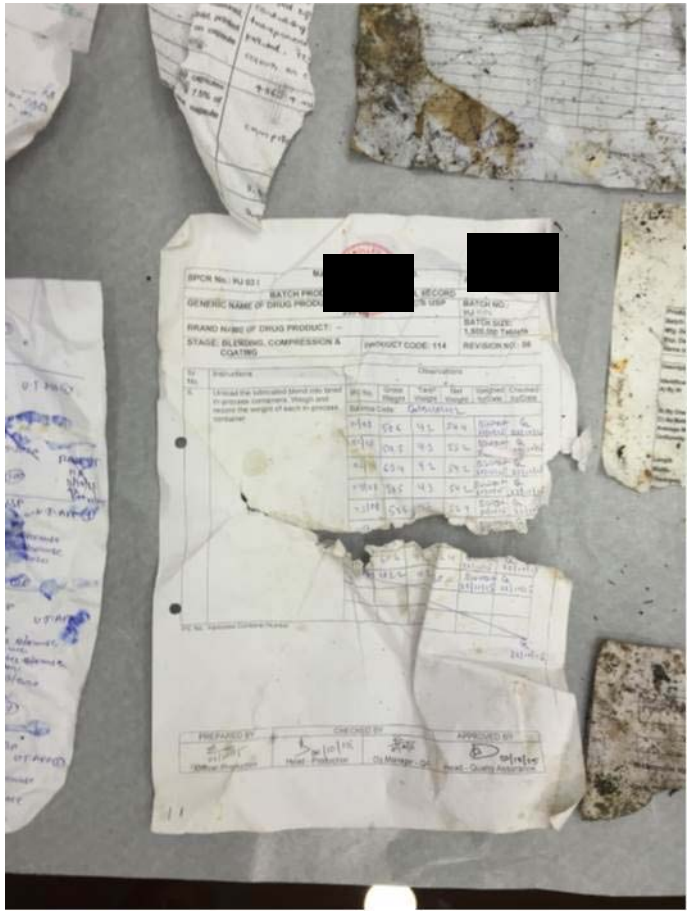
Equipment / Area used	Terminal sterilizer area	Terminal Sterilizer	Waste Bin
Area Code / Equipment ID No.	R 81	MM 155	32
Previous Product	Media fill		
Batch No.	[redacted]	[redacted]	[redacted]
Cleaning done As per SOP No.			
Cleaned by	Dinesh	Ranjeet	Dinesh
Date	28/03/13	28/03/13	28/03/13
Verification of correct type of cleaning done (by IPQA)			

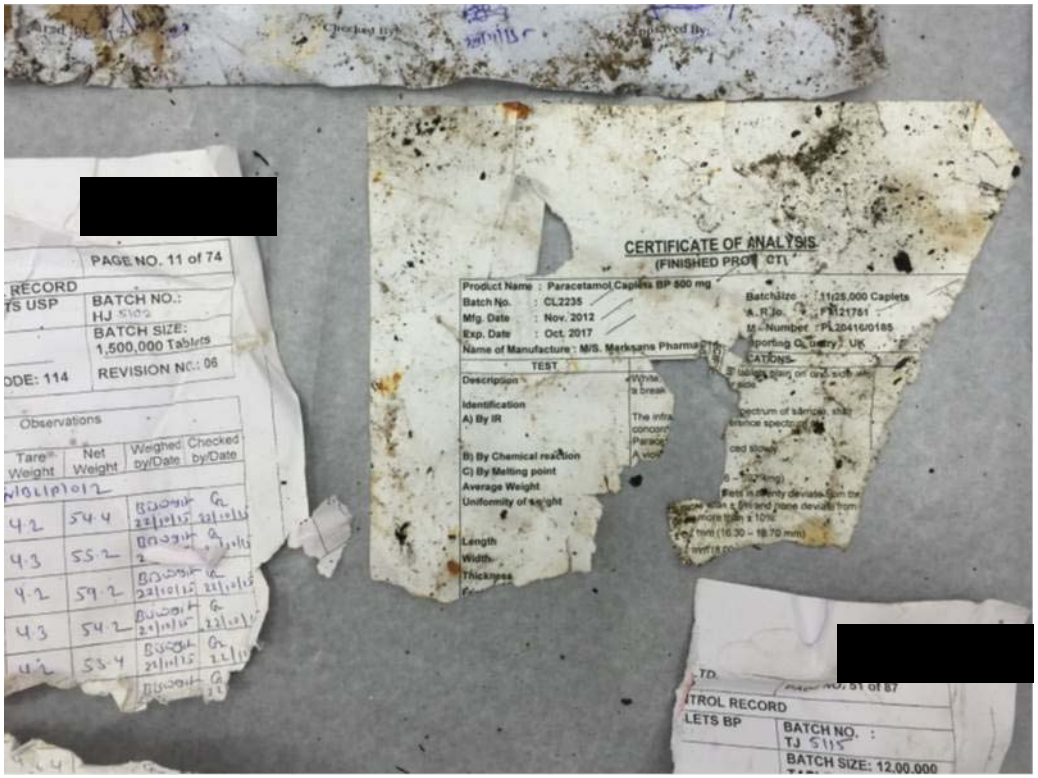
F:004:ICS/A

Page 1 of 2

Prepared by:	Reviewed by:	Approved by:	Authorized by:
[redacted]			
Site Quality Assurance	Head of Production	Site Quality Assurance Head	Unit Head
Date 25/03/13	25/03/13	25/03/13	

Destruction of records





2016 Deficiencies:

Uncontrolled documentation was noted throughout: production engineering notebooks with set up details and passwords, crib notes on the wall of the goods in area, scraps of paper containing numbers of components brought onto line.

Deficiency:

EU GMP

- Ch. 4; 4.1, 4.2, 4.3, 4.4, 4.6, 4.18, 4.19 d),
- Annex 11; 12.1

Guidance given:

MHRA GXP Guide

- Designing systems to assure data quality and integrity
- Section 16 Computerised system user access

2016 Deficiencies:

Printouts of particle count data from HEPA filter testing were not transferred from thermal paper to non-volatile media to ensure the integrity of the record

Deficiency:

EU GMP

- Ch. 4; 4.1
- Annex 11; 7.1

Guidance given:

MHRA GXP Guide

- Section 11. Original record / True copy
- Section 11.2 True copy
- Section 17. Data retention

2016 Deficiencies:

Data integrity assessments were focused on system compliance and failed to consider the impact of business processes on the integrity of data, for example manual transfer of data between electronic systems.

Deficiency:

EU GMP

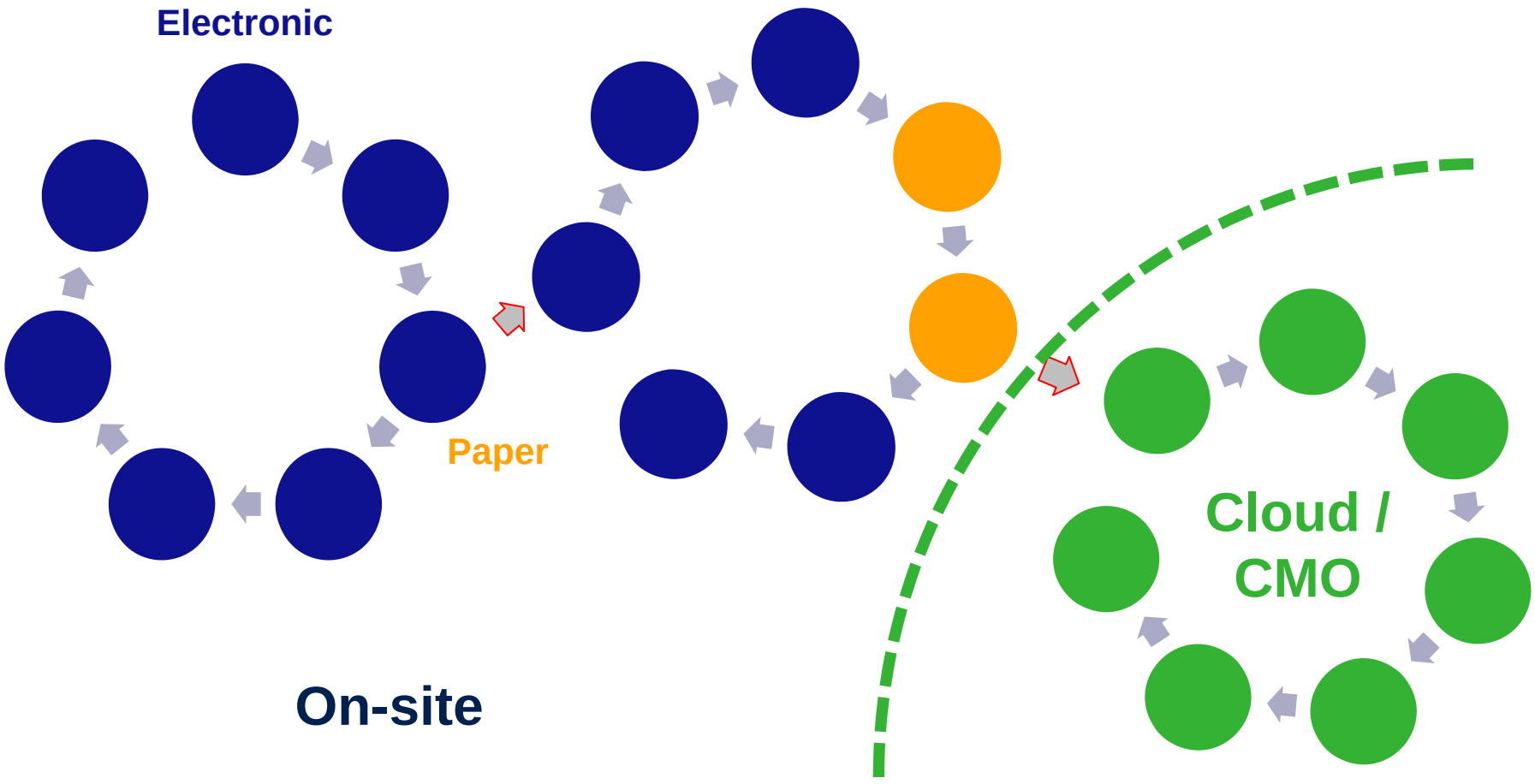
- Ch. 4; principle
- Annex 11; 4.8, 6

Guidance given:

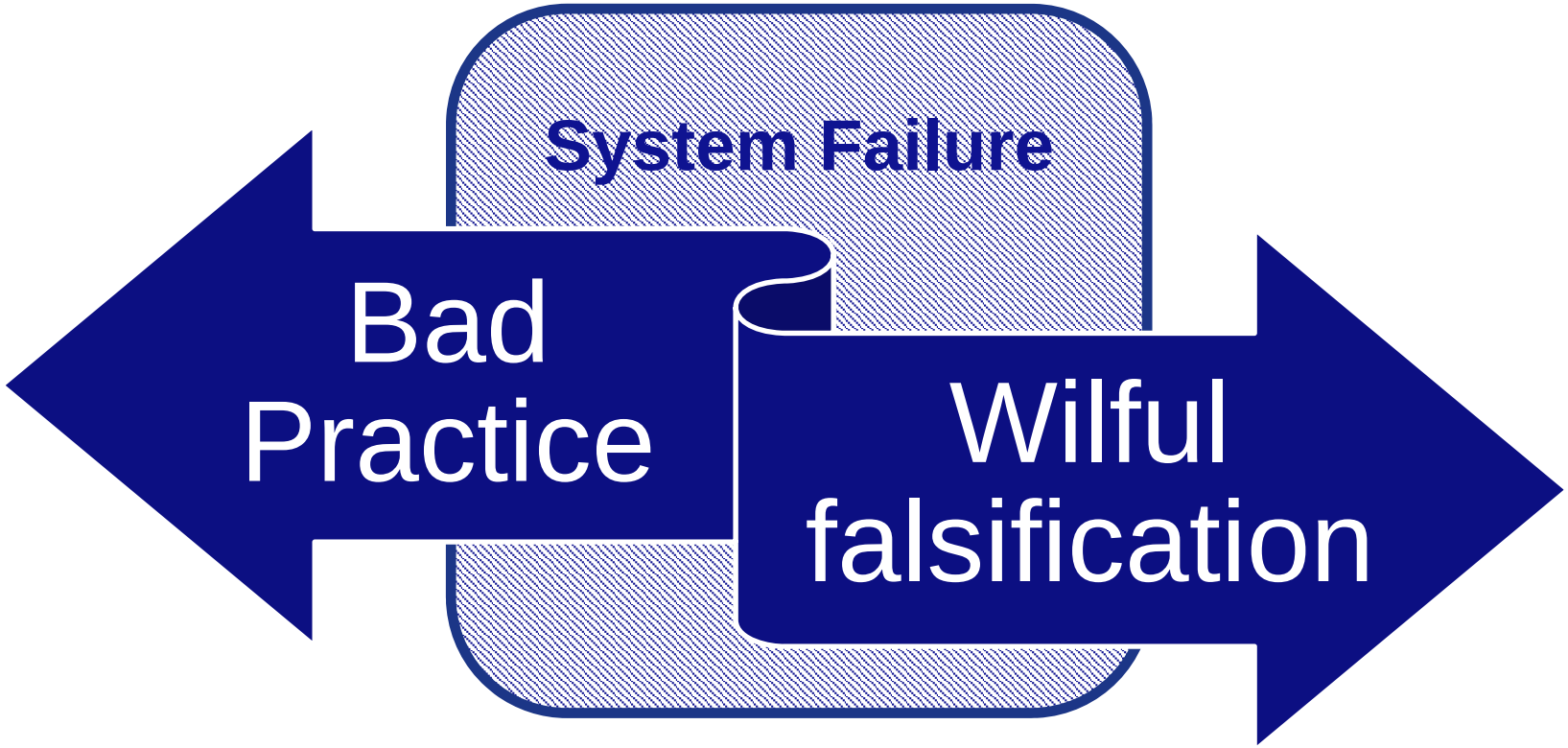
MHRA GXP Guide

- Section 7. Data Transfer/ migration
- Section 17. Data Retention

Data lifecycle mapping



Inspection experience: spectrum of issues



12

Inspections: deficiency examples

- Organisational culture:
  - Pressures leading to incentive to falsify data
  - Analytical output exceeding capacity
  - Manufacture to unapproved formula (falsified BMR)

- Business process risks
  - Administrator access to operating system for data users
  - Storage of data in ‘temporary memory’; undetected data manipulation prior to permanent storage and audit trail
  - Regulatory submission data generated under (less rigid) R&D control systems.

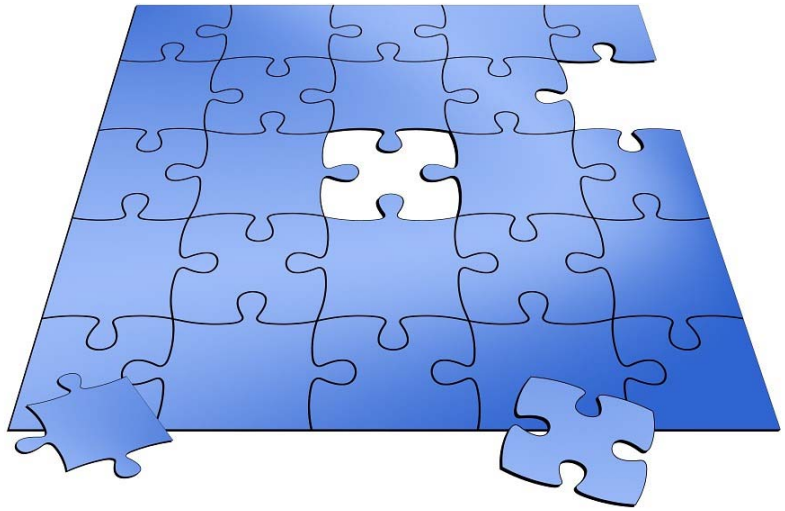
Inspections: deficiency examples

- Data Generation
  - Non-contemporaneous recording
  - Unreported ‘trial’ analytical runs
  - Data manipulation outside boundary of computerised system
  - Reprocessing data to achieve ‘in-specification’ result
  - Falsifying / duplicating / deleting records

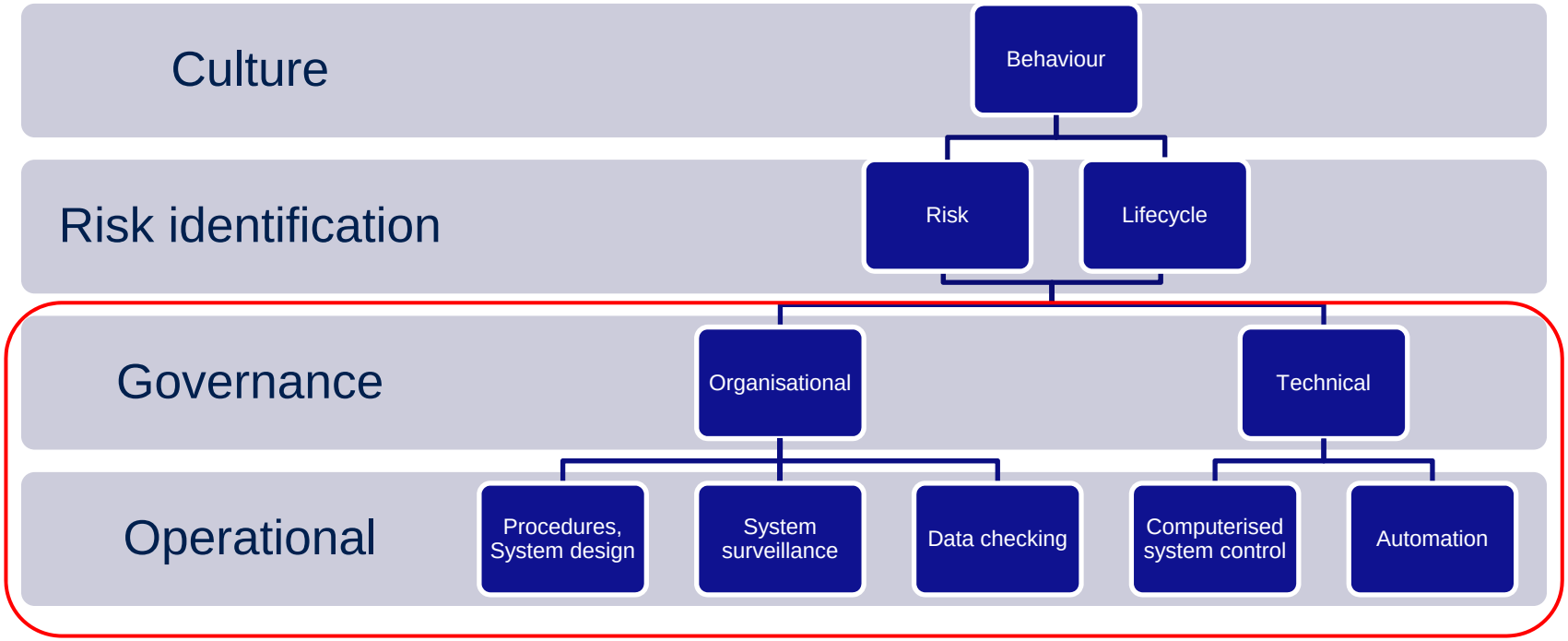
- Data verification
  - Use of printouts from electronic systems as ‘raw data’
  - Failure to verify relevant raw data and metadata.

- Pre-inspection compliance report
- Increased stakeholder awareness
- Implementation of guidance – varying effectiveness

What's been missing?



Data Integrity: Risk reducing strategies



GMPs; Data Integrity Guidance documents

Organisational Culture

“Data Integrity has no relationship with product quality”

CEO of multinational API supplier

Organisational Culture

Can a global policy really work?

Organisational Culture

- Open culture
  - Hierarchy can be challenged
  - Failure reporting is a business expectation
- Personnel empowerment
  - Understanding importance of reliable data
  - “My actions impact the patient and our organisation”

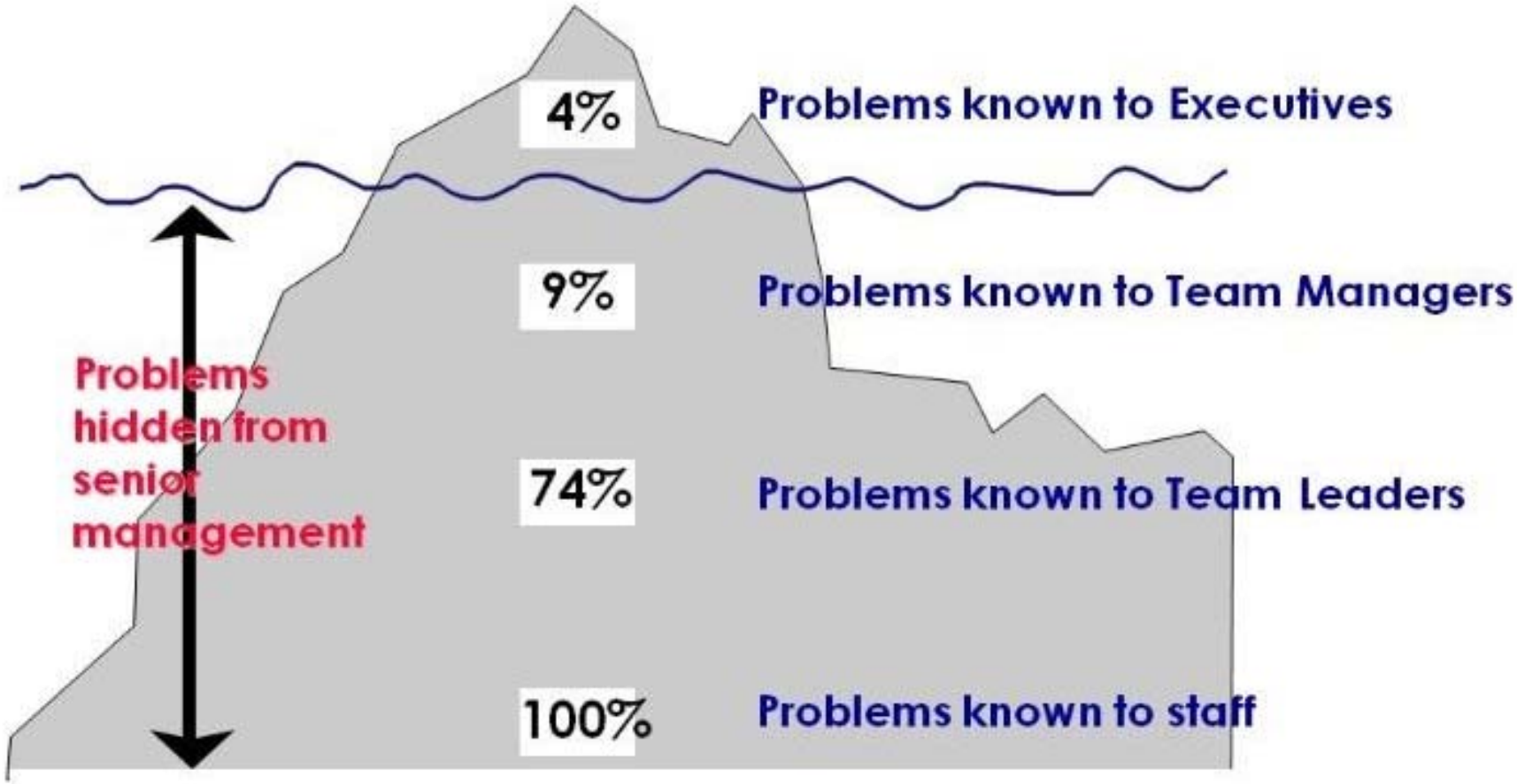
Organisational Culture

- Closed culture (rule-based)
  - Reporting failure/challenging hierarchy is more difficult
- Alternative ways to achieve similar results
  - Oversight and secondary review
  - Anonymous escalation to senior management

Organisational Culture

- Systems
  - Good documentation practice – include e-data
  - Define data checks
  - Performance indicators
    - Company and Personnel
- Training
  - Awareness training
  - Visibility from process to the patient
  - Understanding technical aspects

The Iceberg of Ignorance



Adapted from
"Quality Improvement and TQC Management at Calsonic in Japan and Overseas"
Sydney Yoshida

Lewin's (heuristic) equation 1943:

$$B=f(P,E)$$

Where B is behaviour, P is Person, and E is the environment.

Environment = Culture, processes, procedures, policy etc.

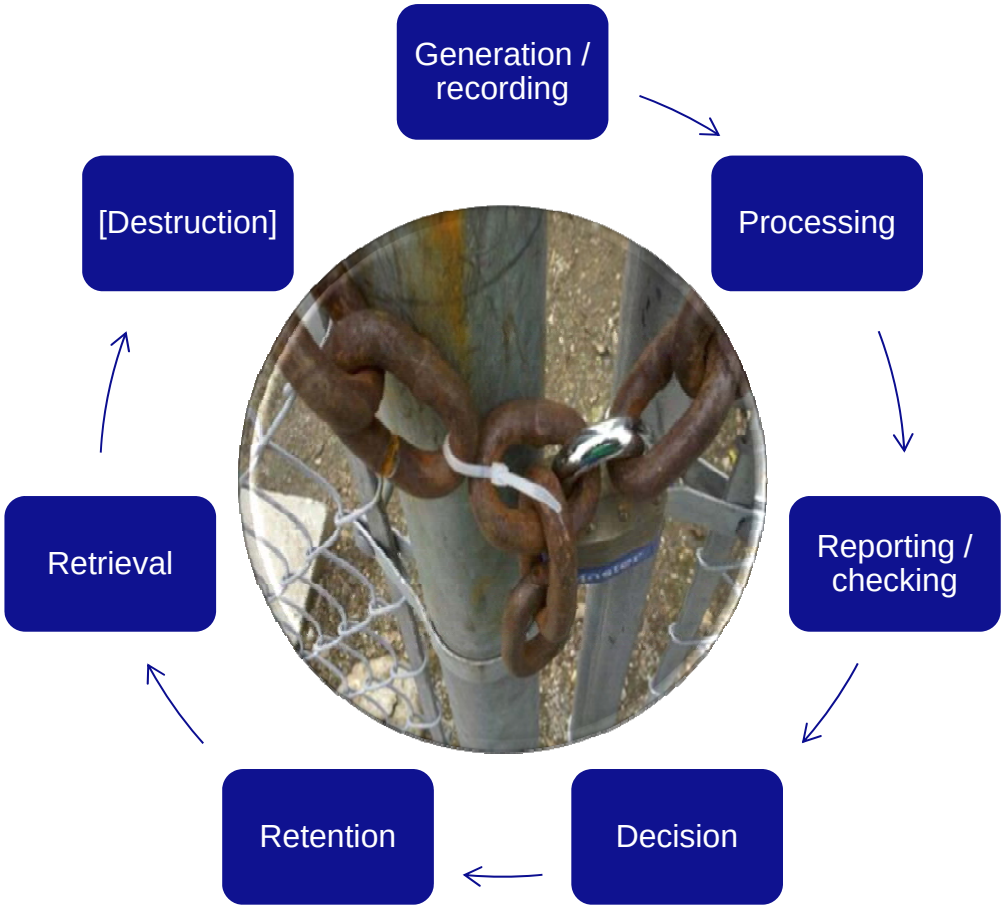
In short the PQS should be the driving force

Chapter 1; 1.1

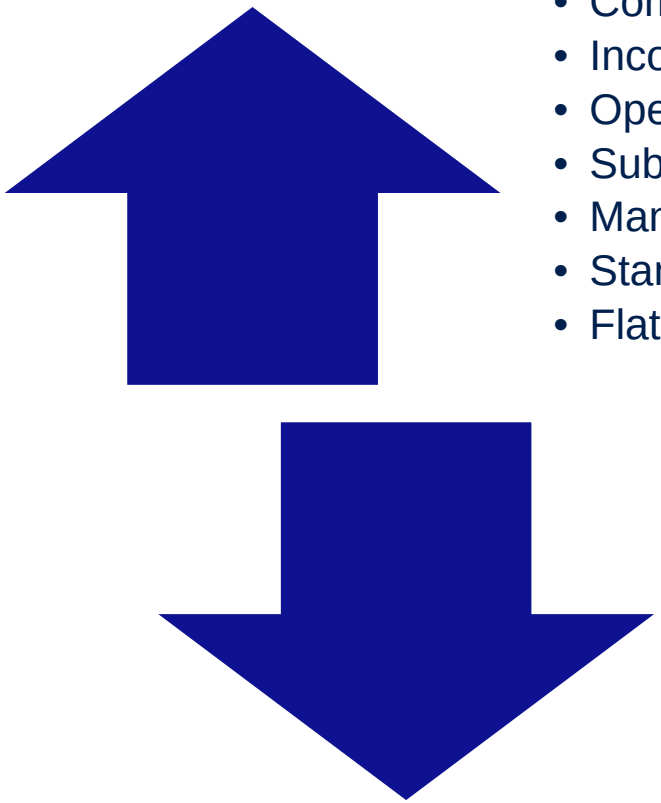
1.1 Quality Management is a wide-ranging concept, which covers all matters, which individually or collectively influence the quality of a product. It is the sum total of the organised arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended use. Quality Management therefore incorporates Good Manufacturing Practice.

Business process, Data lifecycle, Risk

Data Lifecycle



Assessing Data Integrity Risk: Business Process and System Level

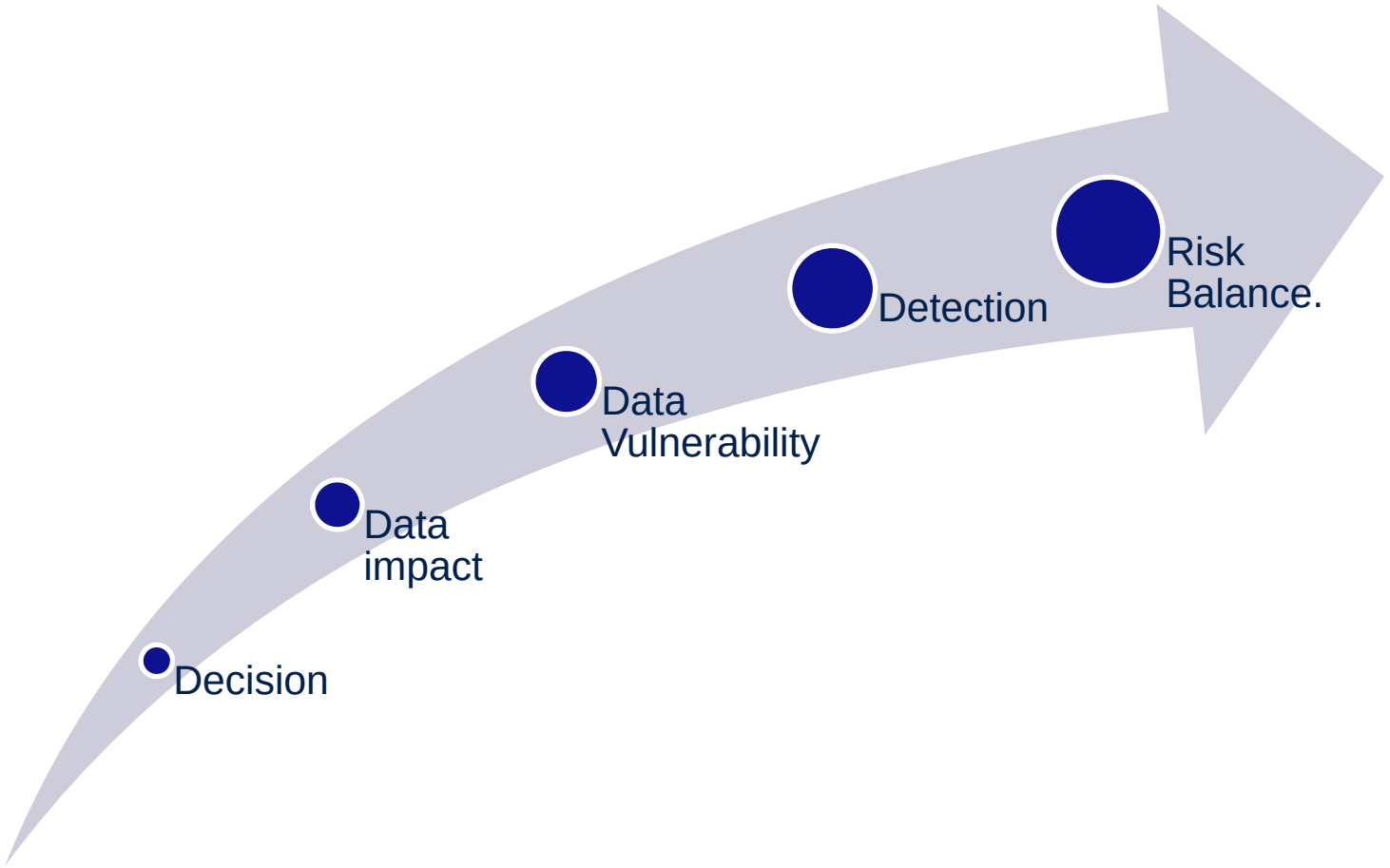


- Complex
- Inconsistent
- Open-ended
- Subjective
- Manual process or human interface
- Stand-alone computerised system*
- Flat file*

- Simple
- Consistent
- Well defined
- Objective
- Automated
- Networked computerised system*
- Relational database.*

* System Level

Risk Based Review



Data review

Estimate: For every 1 hour creating data, it takes up to 3 hours to review all the data and metadata

M Rutherford;
ISPE Copenhagen 4-5 Oct 2016

Data review

- Need a defined, structured approach to data review
- “Review all the data” may lead to falsification of review process
- Do not rely on reverse checking (from result backwards to data) – miss unreported testing/processes
- Who owns the data?
  - IT?
  - Cloud provider?
  - Operational group e.g. QC, manufacturing?

Critical thinking:

Are my control measures effective?

Case study – inspection findings

- Partially completed production documents
  - Blend uniformity spreadsheets partially completed. Different versions in batch record
  - In-process testing data (out of specification) unreported

- Lack of control over analytical data
  - Not all GMP analytical data was reported or reviewed
  - Twenty two QC analysts had access to the separate R&D Empower HPLC server. Data on this server was not reviewed or reconciled.

Case study – inspection findings

- A QC analyst had generated GMP data using the R&D Empower server without authorisation
  - The processing method audit trail showed four amendments including inhibiting the integration of peaks.
  - Data from five of seven HPLC sample sets were not processed
  - Only selected chromatograms were reported from the processed data
- Chromatograms were printed from a preview screen and not saved. The processing methods were not referenced or reviewed for their suitability
- **Printed copies from electronic systems were believed to be ‘raw data’.**

Case study – inspection findings

Stand-alone analytical equipment:

- Analysts could delete or change data
  - No review of user privileges
  - Users had a shared administrator-level logon for PC
  - Local hard drive storage. No audit trails
  - Access to change date/time for print-outs
- No check of data processing (peak threshold, report presentation)
- **Printed copies from electronic systems were believed to be ‘raw data’.**

First print-out from computerised system is not ‘raw data’

- Treating any printout as raw data risks blind spots in data review
  - Over-reliance on perceived control measures
  - Human interaction with what data is presented
  - Human interaction with how data is presented
- No ability for the data verifier to interact with the data
- Summary reports don’t tell the whole story
  - Includes data from a ‘validated system’

Segregation of duties and system configuration

- Who has access to create, amend or verify data?
- Vendor ‘standard configuration’ may not be appropriate for business process segregation
- Has the operating system been considered?
  - Inadequate OS control undermines application controls
  - Inappropriate reliance on perceived controls

Bioequivalence Case Study

Facility did not fully document volunteer records:

- Could not be verified if volunteers existed
- Could not be verified if volunteers attended the facility

Clinic records did not accurately record study conduct:

- Specific procedures could not be attributed to volunteers or staff
- No controls over data resulting in the possibility to overwrite or commit fraud

Bioequivalence Case Study

Laboratory records did not accurately record study conduct:

- Instrument audit trails missing (deleted?)
- Failure to follow DI guidance documents
- Inspectors unable to verify conduct of analysis

Inspection Outcome:

The bioequivalence study could not be verified:

- Missing source data
- Activities could not be reconstructed
- Data was unreliable
- Study was rejected

What are your weaknesses?

- Pharmaceutical Quality System
  - Good documentation practice – do they include e-data?
  - What data checks are defined?
  - Performance indicators – what do they drive?
    - Company and Personnel
    - Training
      - Awareness training
      - Visibility from process to the patient
      - Understanding technical aspects

Summary

- Despite Data integrity guidance being widely available deficiencies are still being identified during inspections
- Effective implementation requires understanding of:
  - Organisational behaviour
  - Business process
  - Data lifecycle
  - Data risk
  - Critical thinking

Let’s not forget ‘why’……

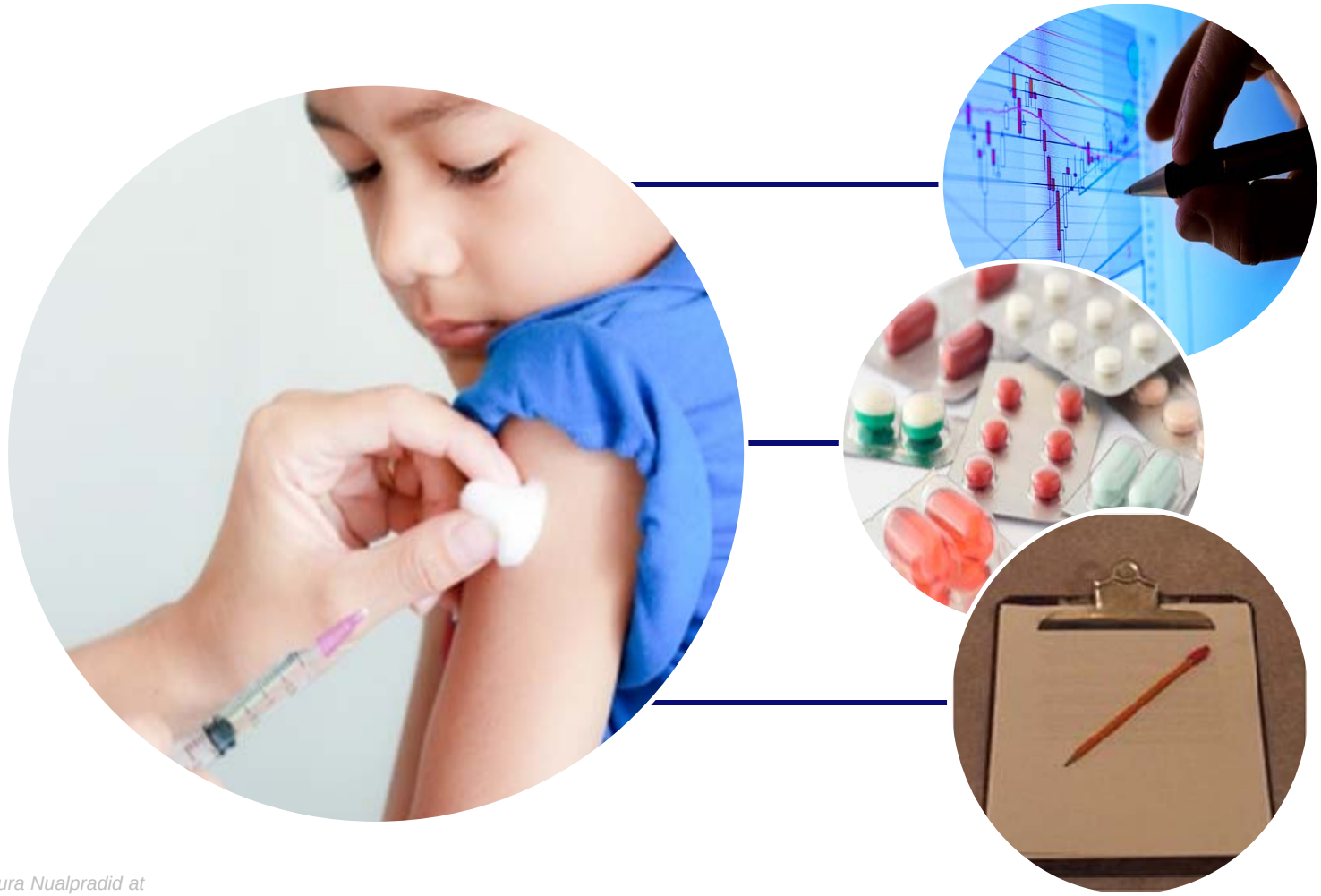


Image courtesy of Sura Nualpradid at FreeDigitalPhotos.net

Published guidance

MHRA Data Integrity Guidance:

https://www.gov.uk/government/publications/good-manufacturing-practice-data-integrity-definitions

MHRA Data Integrity Blog:

https://mhrainspectorate.blog.gov.uk

WHO consultation on good data management practices:

http://www.who.int/entity/medicines/areas/quality_safety/quality_assurance/Guidance-on-good-data-management-practices_QAS15-624_16092015.pdf?ua=1