MHRA GMP Data Integrity Definitions and Guidance for Industry January 2015

Initial Review and Critique – March 2015

Bob McDowall

R.D.McDowall Ltd

Thanks to Mark Newton, Lorrie Schuessler & Chris Burgess

Overview

- MHRA expectations for data integrity December 2013
- MHRA Guidance on data integrity January 2015
  - Introduction
  - Establishing data criticality & inherent integrity risk
  - Designing systems to assure data quality & integrity
  - Data integrity definitions and expectations
- Question:
  - One country of 28 EU member states – impact?

Introduction

Setting Expectations

- *Data integrity is fundamental in a pharmaceutical quality system which ensures that medicines are of the required quality*.
  - Guidance compliments EU GMP
  - Data governance integral within the company's PQS and EU GMP Chapter 1
  - *The effort and resource assigned to data governance should be commensurate with the risk to product quality, and should also be balanced with other quality assurance resource demands.*
  - *… manufacturers and analytical laboratories are not expected to implement a forensic approach to data checking, but instead design and operate a system which provides an acceptable state of control based on the data integrity risk, and which is fully documented with supporting rationale*.

Data Integrity Definitions

- Data Integrity: The extent to which all data are complete, consistent and accurate throughout the **data lifecycle**.
  - MHRA 2015

- Data Integrity: The degree to which a collection of data are complete, consistent and accurate.
  - FDA Glossary of Computer Systems Software Development Terminology (1995)
- Integrity: Data, information and software are accurate and complete and have not been improperly modified
  - FDA Guidance on Content of Premarket Submissions for Management of Cybersecurity in Medical Devices (Oct 2014)
- Integrity: The degree to which a system or component prevents unauthorized access to, or modification of, computer programs or data.
  - IEEE Standard 610 (Glossary)

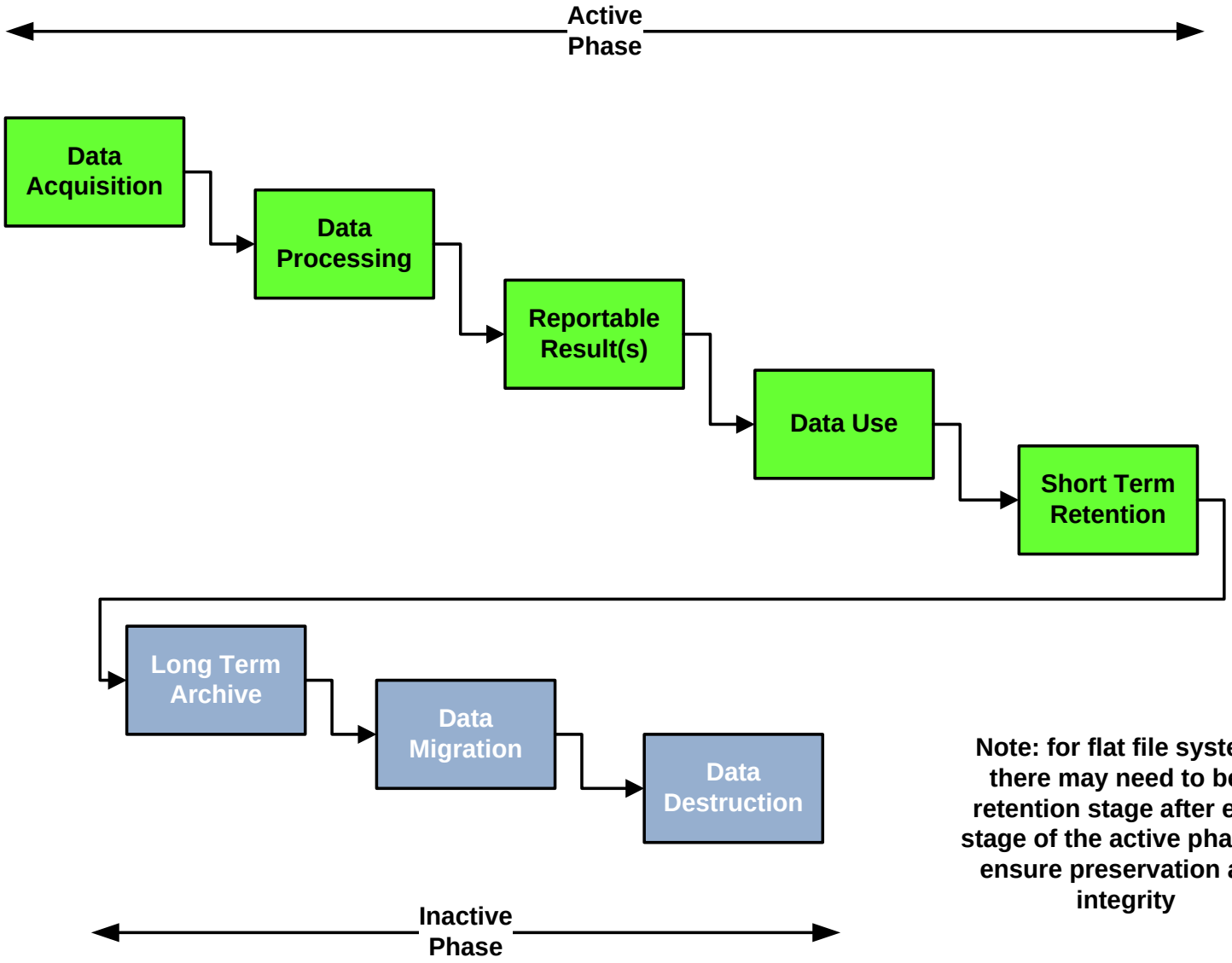
Criteria for Data Integrity

- Attributable — Who acquired the data or performed an action and when?
- Legible — Can you read the data file / any written entries?
- Contemporaneous — Documented at the time of the activity.
- Original — Written printout or observation or a certified copy thereof.
- Accurate — No errors or editing without documented amendments.
- Complete — All data including any repeat or reanalysis performed on the sample.
- Consistent — All elements of the analysis such as the sequence of events follow on and are date or time stamped in the expected sequence.
- Enduring — Not recorded on the back of envelopes, cigarette packets, Post-It notes but in laboratory notebooks or electronic media
- Available — Can be accessed for review and audit or inspection over the lifetime of the record.

Data Life Cycle

- All phases in the life of the data (including raw data) from initial generation and recording through processing (including transformation or migration), use, data retention, archive / retrieval and destruction.
  - Applicable to paper, hybrid and electronic records
  - ALCOA+ principles apply throughout the life cycle
  - Access for trending up to 2 years after generation
    Note: Arbitrary & prescriptive time period
  - Retention for up to 30 years in some cases e.g. supporting an MA

Data Life Cycle



Note: for flat file systems there may need to be a retention stage after each stage of the active phase to ensure preservation and integrity

Applies to All Record Types

- Data integrity requirements apply equally to manual (paper) and electronic data.
  - Implicitly this also includes hybrid systems
  - Also see definition of true copy (p7) and paper audit trails (p11)
- Inconsistency:
  - MHRA guidance does not refer to homogeneous and hybrid systems as mentioned in EU GMP Chapter 4

Return to Paper? No Way!

- Manufacturers and analytical laboratories should be aware that **revert**ing from automated / computerised **to** manual / **paper-based systems will not in itself remove the need for data integrity controls**.
  - Contravention of Annex 11 Principle – new system with lower quality
  - No time sequence enforcement
- This may also constitute a failure to comply with Article 23 of Directive 2001/83/EC, which requires an authorisation holder to take account of scientific and technical progress and enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.
  - Equivalent to the FDA's "c" in the cGMPs

Establishing Data Criticality & Inherent Integrity Risk

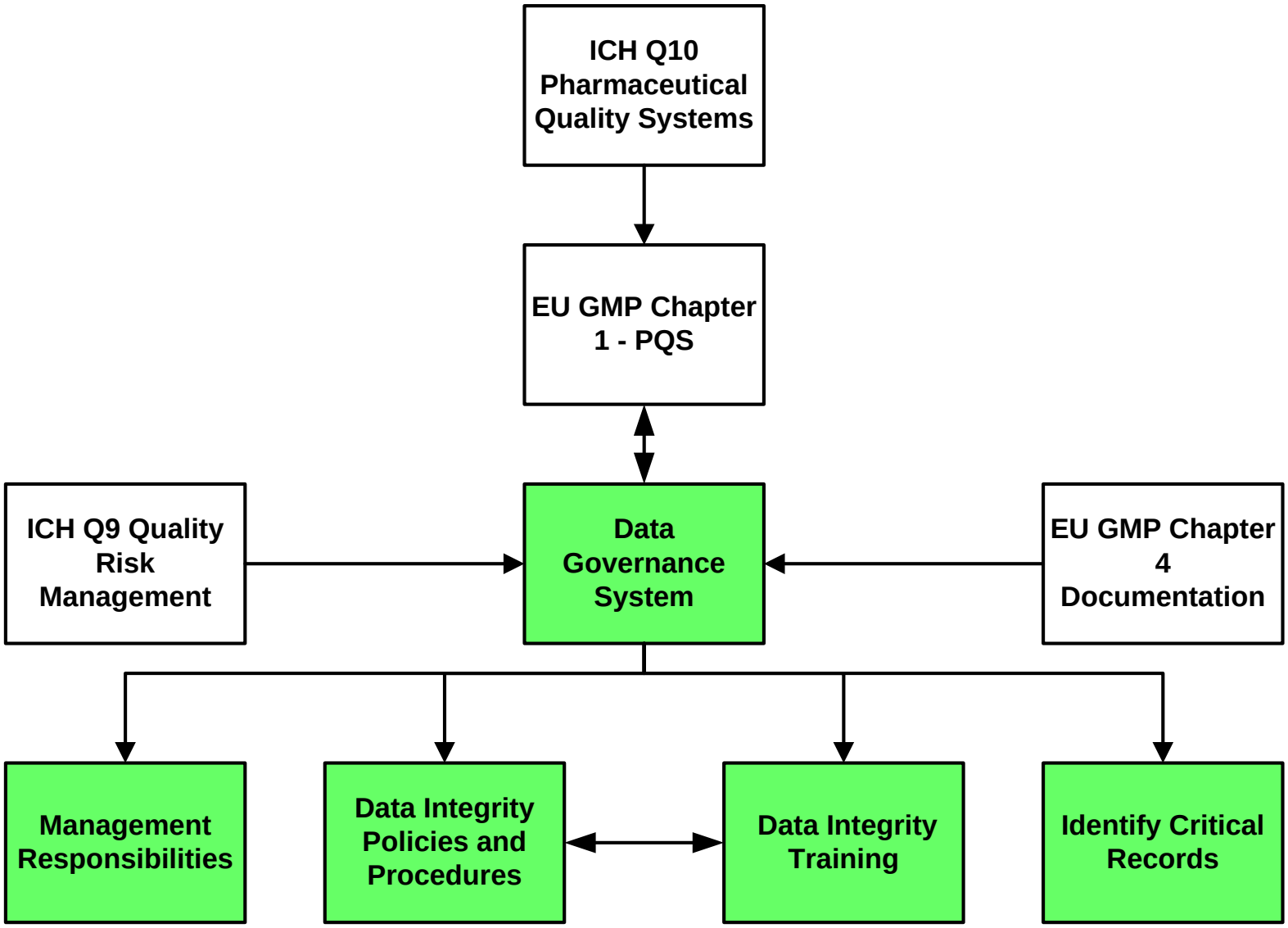
Data Governance Definition

- The sum total of arrangements to ensure that data, irrespective of the format in which it is generated, is recorded, processed, retained and used to ensure a complete, consistent and accurate record throughout the data lifecycle.

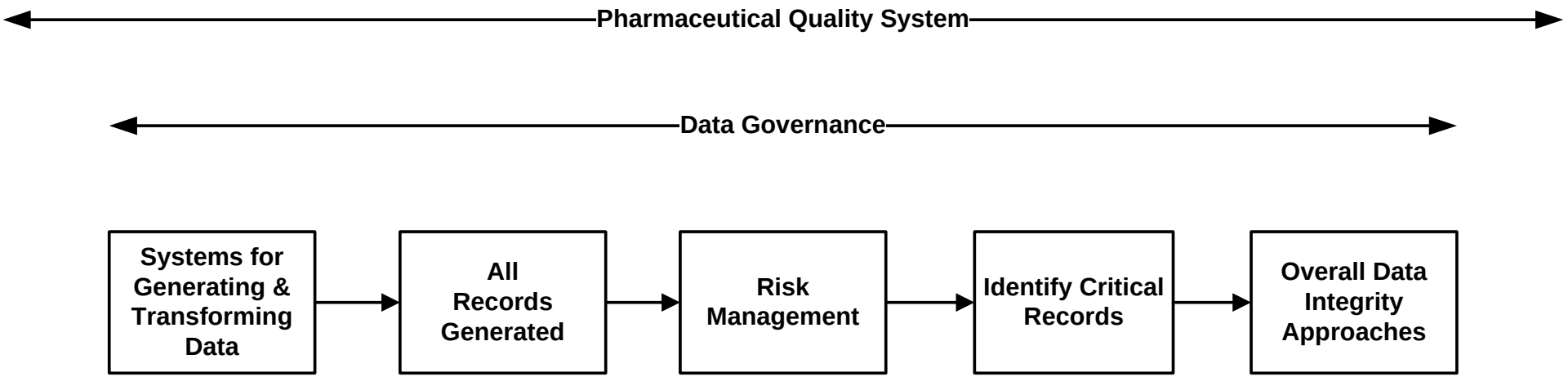
Data Governance Expectation

- Data governance should address **data ownership** throughout the lifecycle, and **consider the design, operation and monitoring of processes / systems** in order to comply with the **principles of data integrity** including **control over intentional and unintentional changes to information**.
- Data Governance systems should include **staff training in the importance of data integrity principles** and the creation of a working environment that encourages an **open reporting culture for errors, omissions and aberrant results**.
- **Senior management is responsible** for the implementation of systems and procedures to minimise the **potential risk to data integrity**, and for identifying the residual risk, using the principles of ICH Q9. Contract Givers should perform a similar review as part of their vendor assurance programme

Data Governance System



Data Integrity Approaches

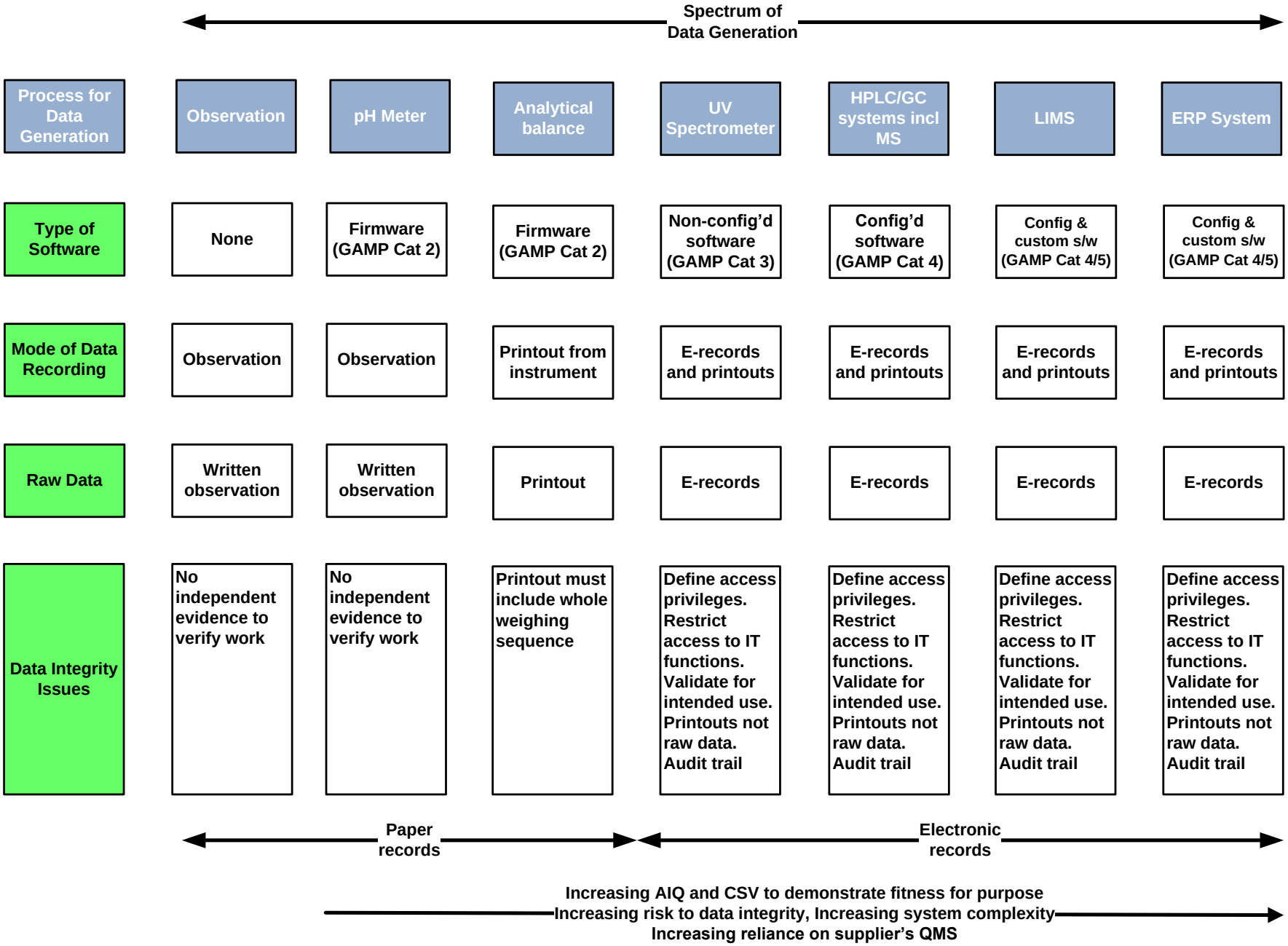


Note: System can apply to paper, hybrid or electronic data generation & manipulation

Designing Systems to Assure Data Quality & Integrity

Designing Systems to Ensure Data Integrity

- Poorly written section
  - (Restrict) *Access to clocks for recording timed events*
  - *Accessibility of batch records at locations where activities take place so that ad hoc data recording and later transcription to official records is not necessary*
  - *Control over blank paper templates for data recording* (FDA Guide to Inspection of QC Labs 1993)
  - *User access rights which prevent (or audit trail) data amendments*
  - *Automated data capture or printers attached to equipment such as balances*
  - *Proximity of printers to relevant activities*
  - *Access to sampling points (e.g. for water systems)*
  - *Access to raw data for staff performing data checking activities*.


Spectrum of Data Generation
Process for Data Generation
Observation
pH Meter
Analytical balance
UV Spectrometer
HPLC/GC systems incl MS
LIMS
ERP System
Type of Software
None
Firmware (GAMP Cat 2)
Firmware (GAMP Cat 2)
Non-config'd software (GAMP Cat 3)
Config'd software (GAMP Cat 4)
Config & custom s/w (GAMP Cat 4/5)
Config & custom s/w (GAMP Cat 4/5)
Mode of Data Recording
Observation
Observation
Printout from instrument
E-records and printouts
E-records and printouts
E-records and printouts
E-records and printouts
Raw Data
Written observation
Written observation
Printout
E-records
E-records
E-records
E-records
Data Integrity Issues
No independent evidence to verify work
No independent evidence to verify work
Printout must include whole weighing sequence
Define access privileges. Restrict access to IT functions. Validate for intended use. Printouts not raw data. Audit trail
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Paper records
Electronic records
Increasing AIQ and CSV to demonstrate fitness for purpose
Increasing risk to data integrity, Increasing system complexity
Increasing reliance on supplier's QMS

Use of Scribes to Record Data?

- Don't… work electronically!
  - More manual processes = lower quality and more mistakes
  - No technical controls to enforce integrity
- *The use of scribes to record activity on behalf of another operator should be considered '**exceptional**', and only take place where:*
  - *The act of recording places the product or activity at risk e.g. documenting line interventions by sterile operators.*
  - *To accommodate cultural or staff literacy / language limitations, for instance where an activity is performed by an operator, but witnessed and recorded by a Supervisor or Officer.*
  - Question: real time verification of observation?

Use of Scribes to Record Data?

- *The use of scribes to record activity on behalf of another operator should be considered '**exceptional**', and only take place where:*
  - *Continued….*
  - *In both situations, the supervisory **recording must be contemporaneous with the task being performed**, and must identify both the person performing the observed task and the person completing the record.*
  - *The **person performing the observed task should countersign the record wherever possible**, although it is accepted that this countersigning step will be retrospective. The process for supervisory (scribe) documentation completion should be **described in an approved procedure, which should also specify the activities to which the process applies**.*
  - Human error rates considered?
- **Note: there is no equivalent FDA position on this approach**

Data Integrity Definitions and Expectations

An surfeit of “data” and no diagrams

MHRA Data Integrity Guidance: 19 Definitions

- Data
- Raw data
- Metadata
- Data integrity
- Data governance
- Data life cycle
- Primary Record
- Original Record / True Copy
- Computer system transaction
- Audit trail
- Data review
- Computerised system user access / system admin roles
- Data retention
- Archive
- Backup
- File structure
- Flat files
- Relational database
- Validation for intended purpose

Focus on 5 MHRA Definitions

- Data
- Metadata
- Raw Data
- Primary Record
- Original Record / True Copy
  - Guidance document only presents a list of definitions and leaves to the reader to connect them
  - Relationship to OOS guidance?

Definition: Raw Data

- Original records and documentation, retained in the format in which they were originally generated (i.e. paper or electronic), or as a 'true copy'.
  - Raw data must be contemporaneously and accurately recorded by permanent means.
  - In the case of basic electronic equipment which does not store electronic data, or provides only a printed data output (e.g. balance or pH meter), the printout constitutes the raw data.
- Raw data must:
  - Be legible and accessible throughout the data lifecycle.
  - Permit the full reconstruction of the activities resulting in the generation of the data

Definition: Metadata

- Metadata is data that describe the attributes of other data, and provide context and meaning. Typically, these are data that describe the structure, data elements, inter-relationships and other characteristics of data. It also permits data to be attributable to an individual.
  - Contextual data putting an observation into context
  - Applies to manual observations as well as hybrid and electronic systems

Definition: Data

- Information derived or obtained from raw data (e.g. a reported analytical result)
  - This definition is wrong and confusing
  - This is NOT data it is information!
  - Inconsistent with MHRA's own guidance (PPT) on OOS which talks about results
- Expectation (ALCOA):
  - A: attributable to the person generating the data
  - L: legible and permanent
  - C: contemporaneous
  - O: original (or 'true copy')
  - A - accurate
  - Not good enough should include the four additional parameters of ALCOA+!
  - ALOCA+ must be applicable throughout analytical process

Definition: Primary Record

- The record which takes primacy in cases where data collected or retained concurrently by more than one method fail to concur.
  - Data – wrong term under MHRA
  - In situations where the same information is recorded concurrently by more than one system, the data owner should define which system generates and retains the primary record, in case of discrepancy.
  - The 'primary record' attribute should be defined in the quality system, and should not be changed on a case by case basis.
  - Not a term in EU GMP
  - When is a primary record NOT the original record?
  - How do you get into a situation where Primary Record comes into lay

Definition: Original Record

- Original record: Data as the file or format in which it was originally generated, preserving the integrity (accuracy, completeness, content and meaning) of the record, e.g. original paper record of manual observation, or electronic raw data file from a computerised system
  - Original records must preserve the integrity (accuracy, completeness, content and meaning) of the record.
  - Are these raw data?

Definition: True Copy

- True Copy: An exact copy of an original record, which may be retained in the same or different format in which it was originally generated, e.g. a paper copy of a paper record, an electronic scan of a paper record, or a paper record of electronically generated data
  - Exact (true) copies of original records may be retained in place of the original record (e.g. scan of a paper record), provided that a documented system is in place to verify and record the integrity of the copy.

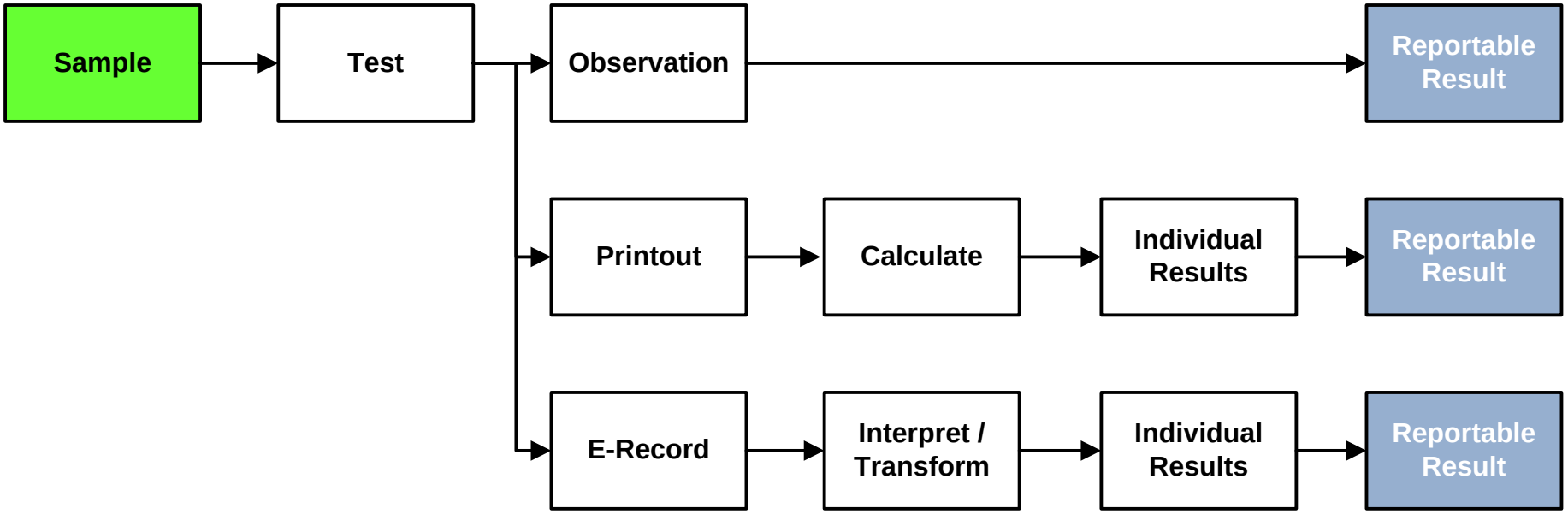
True Copies: Conversion to PDF or Paper?

- It is conceivable for raw data generated by electronic means to be retained in an acceptable paper or pdf format.
  - However, the data retention process must be shown to include verified copies of all raw data, metadata, relevant audit trail and result files, software / system configuration settings specific to each analytical run*, and all data processing runs (including methods and audit trails) necessary for reconstruction of a given raw data set.
  - It would also require a documented means to verify that the printed records were an accurate representation. This approach is likely to be onerous in its administration to enable a GMP compliant record.
  - * computerised system configuration settings should be defined, tested and 'locked' as part of computer system validation. Only those variable settings which relate to an analytical run would be considered as electronic raw data.
- **Don't be stupid**

Where are the Data?

- MHRA document does not provide sufficient information or figures to link the definitions together
- Slides that follow are for:
  - Manual observation to paper record e.g. colour or odour test
  - Printout from an analytical balance
  - Chromatographic analysis with a CDS configured for electronic working

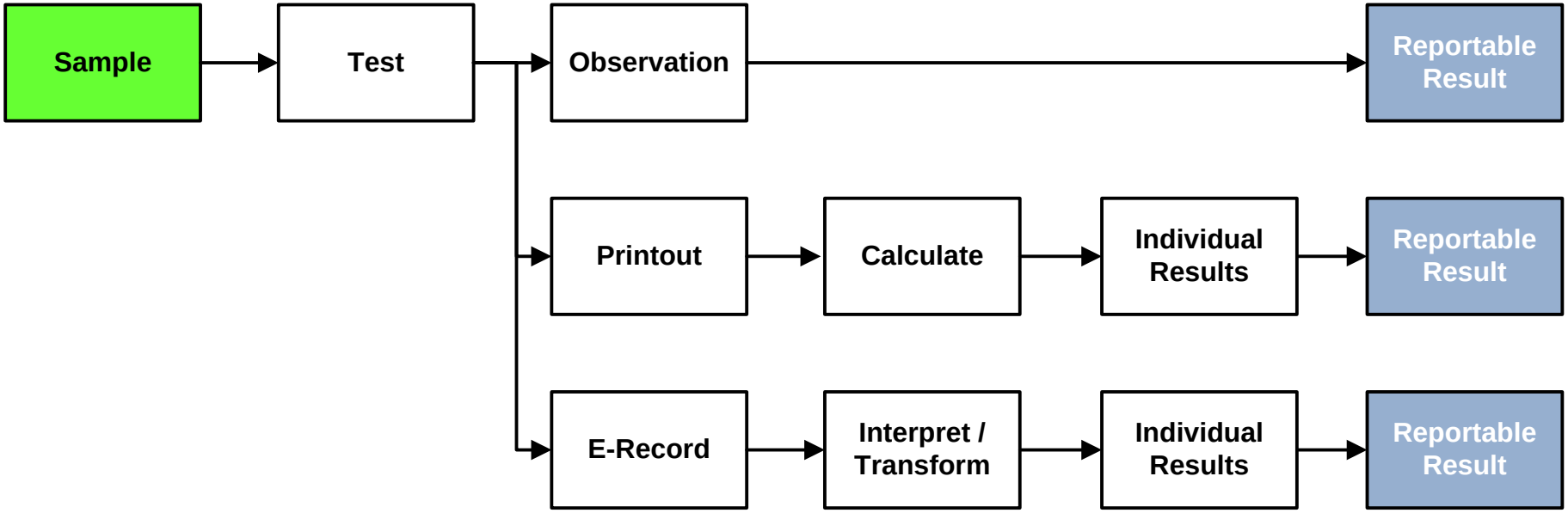
Where Are The Records?



For a Test with an Observation:

- Raw Data (also Original Record) = observation / written record
- Metadata = written information for the analysis
- Information = reportable result

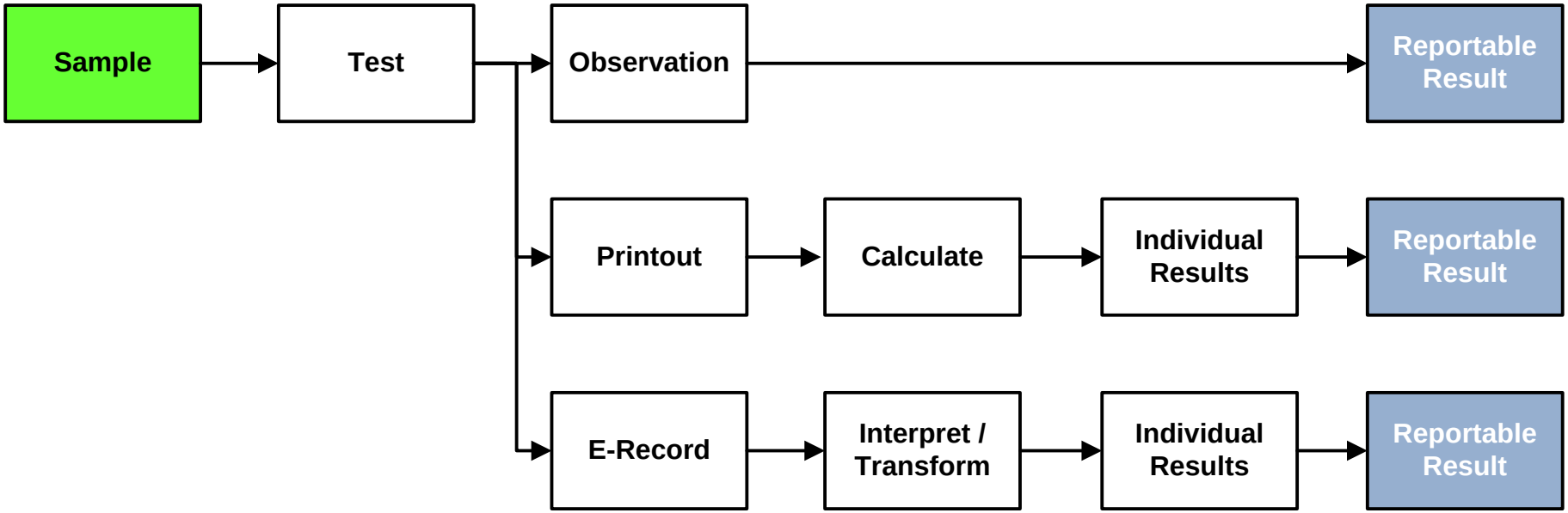
Where Are The Records?



For a Test with a Printout:

- Raw Data (also Original Record) = printout
- Metadata = written information for the analysis
- Further record generation = entry into Excel for calculations with e-record and printout, that to generate individual results
- Information = reportable result

Where Are The Records?



For a Test generating Electronic Records:

- Raw Data (also Original Record) = electronic records of the test
  Plus either electronically signed records or signed paper printout
- Metadata = contextual data in the CDS system of the analysis
- Data and metadata of the transformed / interpreted data (manual integration, calculations, dilutions etc) with associated electronic signatures within CDS
- Information = reportable result

Initial Conclusions

- It is a good document but not that good
- Good:
  - It exists and is risk based
  - Explains data governance system in more detail than web site
  - Identifies responsibilities of data owners and senior management
  - Examples good e.g. problems with flat files and ways to remediate, EBRS contemporaneous example for batch records, reviews of audit trail documented

Initial Conclusions

- It is a good document but not that good
- Bad:
  - Fails in many definitions
    e.g. Confuses data with information – wrong!
  - Vague – shopping list of definitions which need linking together: diagram to link concepts
  - Revision of some terms to look at data and information
  - Section on design controls poorly written
  - Congruence required with MHRA OOS guidance(s)