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U.S. FOOD & DRUG ADMINISTRATION

Overview of Data Integrity

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MHRA

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Learning Objectives

- To understand
  - Why Data Integrity is a fundamental requirement
  - How to approach data integrity based on risk; related to criticality of the data
  - How organisational culture can affect Data Integrity
  - How lack of control of Data Integrity can lead to findings on inspection

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Data Integrity

- Has **always** been at the heart of what we do
- Decisions made are based on data
- Fundamental requirement of any GXP Quality System
- The extent to which activities, events, actions, processes etc. can be reconstructed and traceable with respect to knowing who did what, when and why has always been a key objective of any regulatory inspection and or assessment.
- It’s not new!

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Data Integrity – past & present

- Changes to the way regulatory data is generated
- Developments in technology
- Automation of systems
- Complexity – use of vendors

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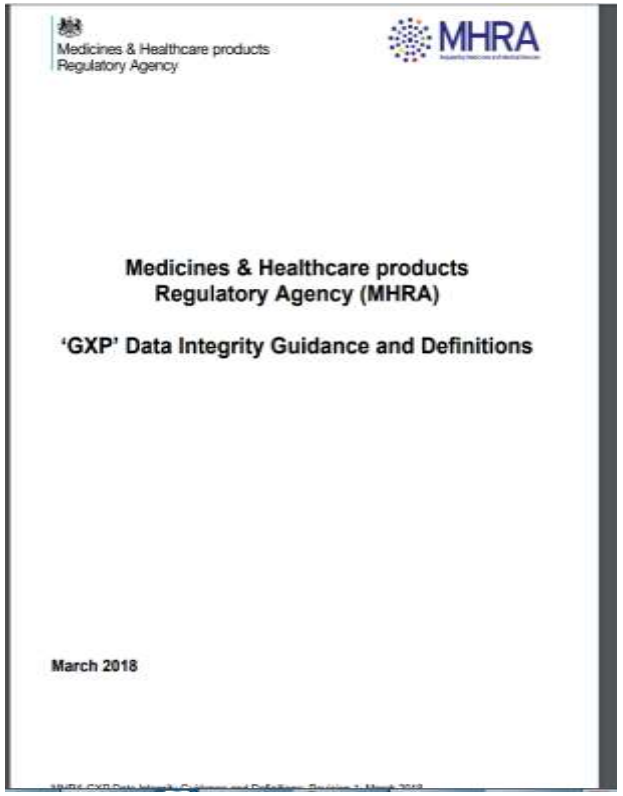
Guidance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Medicines & Healthcare products Regulatory Agency (MHRA)

'GXP' Data Integrity Guidance and Definitions

March 2018


PIC/S

PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PI 041-1 (Draft 2)
16 August 2016

DRAFT PIC/S GUIDANCE

GOOD PRACTICES FOR DATA MANAGEMENT AND INTEGRITY IN REGULATED GMP/GDP ENVIRONMENTS

DRAFT

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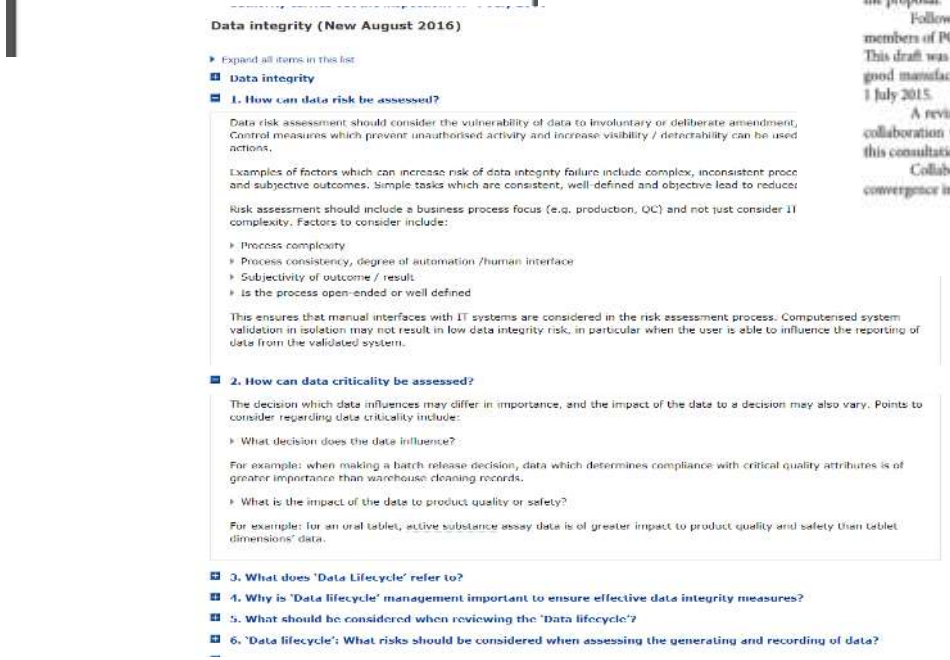
Data integrity (New August 2016)

Expand all items in this list

Data integrity

1. How can data risk be assessed?

Data risk assessment should consider the vulnerability of data to involuntary or deliberate amendment. Control measures which prevent unauthorised activity and increase visibility / detectability can be used actions.

Examples of factors which can increase risk of data integrity failure include complex, inconsistent proce and subjective outcomes. Simple tasks which are consistent, well-defined and objective lead to reduce

Risk assessment should include a business process focus (e.g. production, QC) and not just consider IT complexity. Factors to consider include:

- Process complexity
- Process consistency, degree of automation /human interface
- Subjectivity of outcome / result
- Is the process open-ended or well defined

This ensures that manual interfaces with IT systems are considered in the risk assessment process. Computerised system validation in isolation may not result in low data integrity risk, in particular when the user is able to influence the reporting of data from the validated system.

2. How can data criticality be assessed?

The decision which data influences may differ in importance, and the impact of the data to a decision may also vary. Points to consider regarding data criticality include:

- What decision does the data influence?

For example: when making a batch release decision, data which determines compliance with critical quality attributes is of greater importance than warehouse cleaning records.

- What is the impact of the data to product quality or safety?

For example: for an oral tablet, active substance assay data is of greater impact to product quality and safety than tablet dimensions' data.

3. What does 'Data Lifecycle' refer to?

4. Why is 'Data lifecycle' management important to ensure effective data integrity measures?

5. What should be considered when reviewing the 'Data lifecycle'?

6. 'Data lifecycle': What risks should be considered when assessing the generating and recording of data?


Annex 5

Guidance on good data and record management practices

Background

During an informal consultation on inspection, good manufacturing practices and risk management guidance in medicines' manufacturing held by the World Health Organization (WHO) in Geneva in April 2014, a proposal for new guidance on good data management was discussed and its development recommended. The participants included national inspectors and specialists in the various agenda topics, as well as staff of the Prequalification Team (PQT)–Inspections.

The WHO Expert Committee on Specifications for Pharmaceutical Preparations received feedback from this informal consultation during its forty-ninth meeting in October 2014. A concept paper was received from PQT-Inspections describing the proposed structure of a new guidance document, which was discussed in detail. The concept paper consolidated existing normative principles and gave some illustrative examples of their implementation. In the Appendix to the concept paper, extracts from existing good practices and guidance documents were combined to illustrate the current relevant guidance on assuring the reliability of data and related GXP (good (anything) practice) matters. In view of the increasing number of observations made during inspections that relate to data management practices, the Committee endorsed the proposal.

Following this endorsement, a draft document was prepared by members of PQT–Inspection and a drafting group, including national inspectors. This draft was discussed at a consultation on data management, bioequivalence, good manufacturing practices and medicines' inspection held from 29 June to 1 July 2015.

A revised draft document was subsequently prepared by the authors in collaboration with the drafting group, based on the feedback received during this consultation, and the subsequent WHO workshop on data management.

Collaboration is being sought with other organizations towards future convergence in this area.

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Guidance

- International convergence in data integrity guidance
  - WHO, MHRA
  - EMA Q&As,
  - Draft USFDA, CFDA, PIC/S

  – Cooperation between international regulators
  - Shared / common training
  - Exchange of information
  - Joint inspections

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Guidance

- Guidance promotes risk based approach to data management
  - Data risk, criticality and lifecycle
  - Applicable to both electronic and paper records
  - Mapping of data processes (lifecycle)
  - Identifying data with greatest GxP impact
  - Risk based control and review of data
    - most effective and efficient

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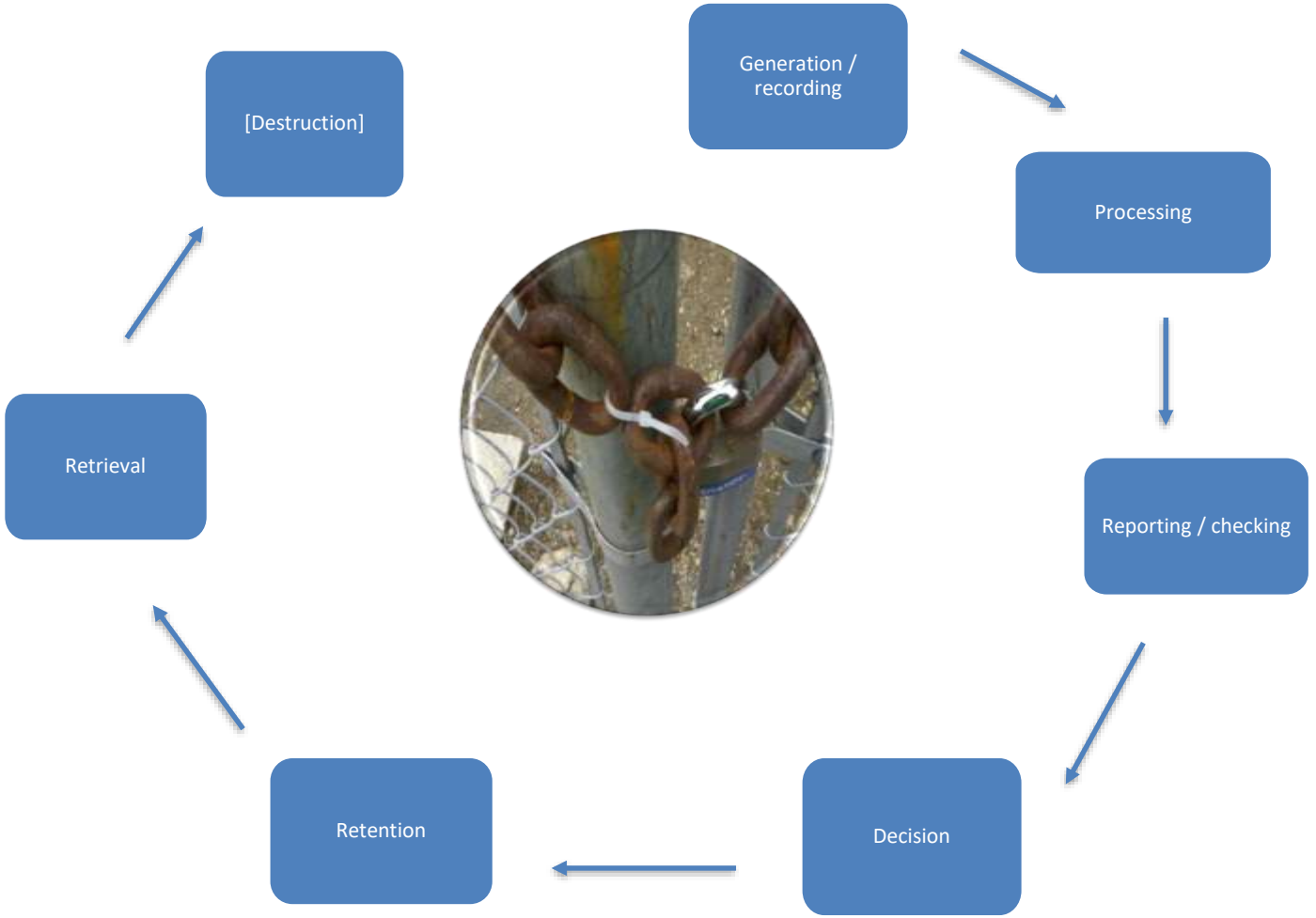
DI GxP Guidance – Data lifecycle



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Data Integrity

Data Integrity applies to systems that involve manual processes and paper as well as computerised systems

People are part of that process; management culture also has an influence

Data Integrity Control:

- Risk-based – related to criticality of the data, potential impact
- Data Review (integrity of a data set)
- Periodic system review/Audit (effectiveness of control)

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Data Integrity

Organisations are expected to implement, design and operate a fully documented system that provides an acceptable state of control based on the data integrity risk with supporting rationale

Fit for purpose – consider people as well as the computerised system

Needs to encourage compliance

- Ease of use of forms
- Appropriate user access rights (prevent unauthorised edits)
- Physical layout – encourage performance of tasks (equipment, space and time)

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Data Governance

The arrangements to ensure that data, irrespective of the format in which they are generated, are recorded, processed, retained and used to ensure the record throughout the data lifecycle

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Data Governance

- Applies to the entire lifecycle – should address ownership and accountability
- Includes monitoring and control of processes/systems (intentional and unintentional changes)
- Staff training – people are part of the process
- Culture – working environment that encourages reporting of errors
- Identify and minimise risk to data integrity

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Data Governance

- Contract Givers should ensure that data ownership, governance and accessibility are included in any contract/technical agreement with a third party.
- Data governance systems should also ensure that data are readily available and directly accessible on request from national competent authorities.
- Electronic data should be available in human-readable form.

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Culture

- Understand that ‘it can happen here’
- Leadership
    - Communicating realistic expectations
  - Reporting mechanisms
  - Proportionate investigation of errors and data integrity failure

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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”

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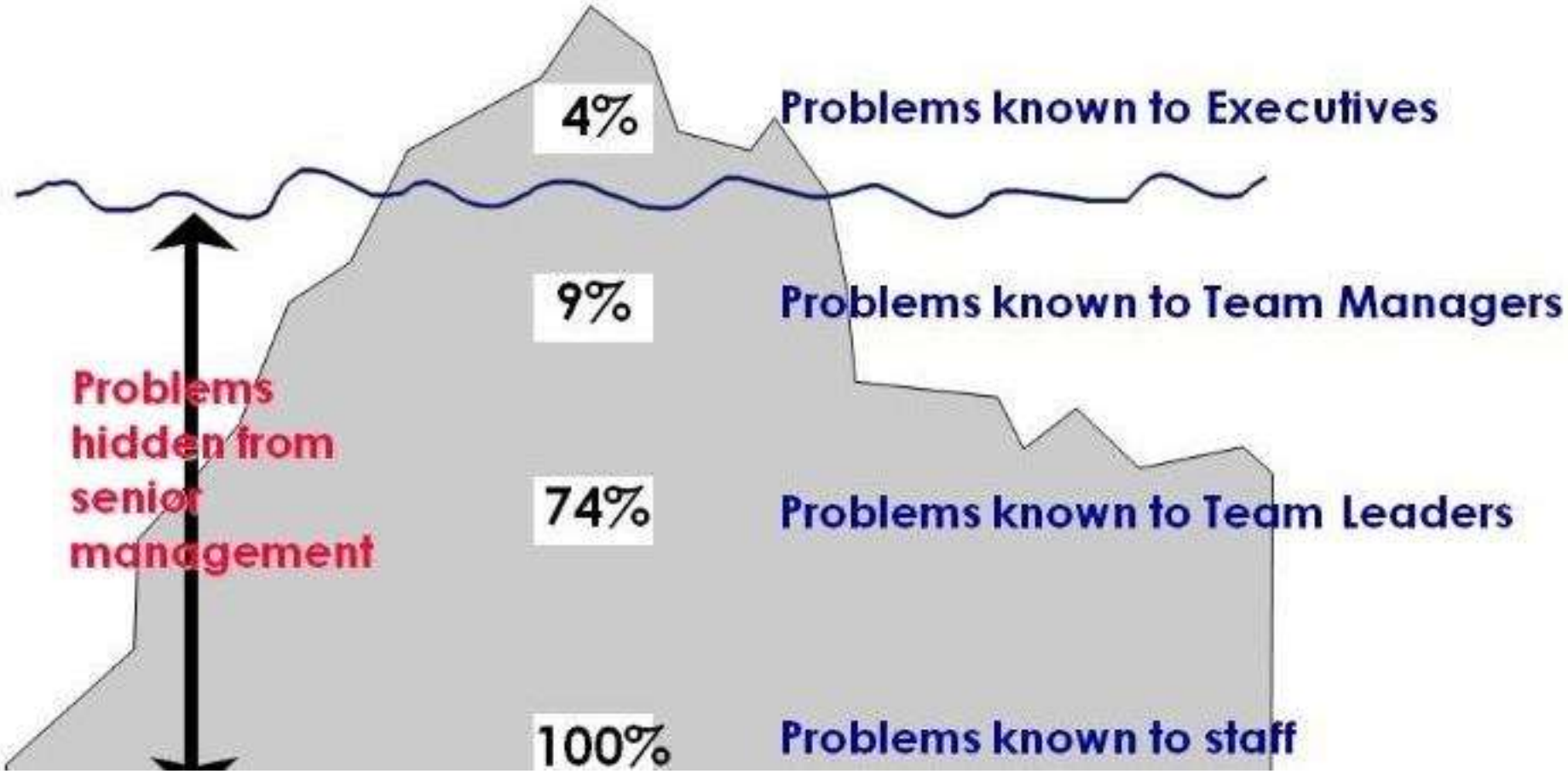
Culture

- 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


4%
Problems known to Executives
9%
Problems known to Team Managers
Problems hidden from senior management
74%
Problems known to Team Leaders
100%
Problems known to staff

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Data Integrity – Common Findings

- Several hundred changes made to subject-reported e-diary data across six trials, sometime months after event to ensure ‘best-fit’ of IMP administration vs. planned administration schedule
- Changes requested by sponsor’s data management and investigator site staff
- Changes made in study databases with no support from source data i.e. no contemporaneous record of the discussion between the investigator site staff and the subject/caregiver documenting the reason to support why changes were needed and/or confirming patient approval of change
- Identified via review of the audit trail of the system.

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Data Integrity – Common Findings

- Documentation in TMF showed eCRF database was unlocked on 25 Nov 2013 and re-locked on 4 Dec 2013
- The reason documented for unlocking the database (signed 25 Nov 2013) was **"randomisation number for patient 10122 to be updated to R017"** following QC check that showed patient 20 and 22 both had the randomisation number "R018".
- Review of the audit trial showed that 20 data point changes to the R0 numbers were made on 29 Nov 2013 and a further change to the eligibility criteria status of "Y" to "N" on 2 Dec 2013 all by the PI. None of the R0 changes made on 29 Nov 2013 involved a change of value of "R018" to "R017" as per the reason approved.
- **No documentation to demonstrate that these changes had been authorised and why were randomisation numbers being amended post un-blinding the trial?**

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Data Integrity Common Findings

An eHR was used in a clinical trial – this was an 'off the shelf product' and had not been configured with clinical trials in mind:

- Records were created in the system, but had to be manually locked to save changes and create an audit trail. If edited while unlocked this was not captured in the audit trail; patient notes remained unlocked for months.
- There was no requirement for site staff to lock records when entered
- The audit trail only showed that a record had been created, locked or unlocked, but did not show what had been added, edited into the system
- The clinical trial started in Feb 2012, however the audit trial for the eHR only showed data from Jan 2013

Access to audit trail has not always been possible. Required to demonstrate investigator review of laboratory results as no paper copy signed/dated as "all electronic".

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Further Guidance and Information

MHRA Data Integrity

https://www.gov.uk/government/publications/guidance-on-gxp-data-integrity

MHRA Blogs – TMF, ePRO, Data Integrity

https://mhrainspectorate.blog.gov.uk/

EMA Q&A on contracts with eSystems Vendors

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000016.jsp

EMA DI

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp&mid=WC0b01ac05800296ca#section16

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Challenge Questions

1. True or False? Organisations that report data integrity issues are viewed as less compliant by the regulators.

   ANSWER: False

2. Data Integrity applies to which of the following?

   a) Electronic Systems
   b) Paper-based systems
   c) People and processes
   d) All of the above

   ANSWER: d)