



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

## EMA's Guidance on Data Integrity

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Indian Pharmaceutical Alliance Annual Congress

Mumbai, India

Presented by Brendan Cuddy on 23 – 24 February 2017

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An agency of the European Union



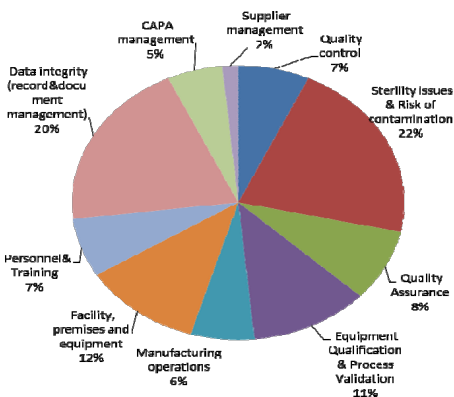


## Contents

- EU Requirements for Data Integrity
- Implications of Data Integrity Failure.
- Conclusions



## Analysis of Critical / Major Deficiencies in SNC's India Manufacturers 2013 – 2016



- Record keeping: data integrity.
- Contamination and Cross contamination issues (sterility assurance)
- Quality Assurance and Control Systems
- Equipment qualification & process validation
- Loss of traceability for raw materials
- Facility Maintenance



## Examples of Data Integrity findings in Statements of Non-Compliance

1. The control of electronic data and laboratory systems was not adequately robust and could not assure data traceability or security.
2. Several documents were found within a pile of rubble on the other side of a wall. These included an original batch repacking record which should have been placed under retention and a large number of purchase orders dated from 2013 for active substances, ...Moreover, due to the severe lack of transparency of the company regarding its manufacturing activities, there is no assurance as regards to the origin of every batch of active substances claimed to have been manufactured by the company

.....Consequently, it is considered that the identified risks are applicable to all active substances manufactured at the site”.



## EU Requirements for Data Integrity

- Data integrity is a fundamental requirement of the pharmaceutical quality system described in EU GMP chapter 1 of [Eudralex volume 4](#).
- [New guidance](#) developed by EU GMP Inspectors Working Group for stakeholders on measures that ensure data integrity and minimise risks at all stages of the data lifecycle in pharmaceutical quality systems has been published in August 2016.
- The guidance is aligned GMP guidance published by the [Pharmaceutical Inspection Co-operation Scheme](#) (PIC/S) and in conjunction with medicines legislation and the GMP standards published in [Eudralex volume 4](#).
- Should be read in conjunction with national guidance, medicines legislation and the GMP standards published in [Eudralex volume 4](#)



## EU Requirements for Data Integrity

- Guidance available on EMA website, in the Q&A on GMP inspections:

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q\\_and\\_a/q\\_and\\_a\\_detail\\_000027.jsp&mid=WC0b01ac05800296ca%20-%20section16](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp&mid=WC0b01ac05800296ca%20-%20section16)

The screenshot shows the EMA website interface. On the left is a navigation menu with categories like 'Pre-authorisation', 'Post-opinion', 'What we publish', etc. The main content area is titled 'Questions and answers: Good manufacturing practice'. Below the title, there is a description: 'This page lists the European Medicines Agency's answers to frequently asked questions, as discussed and agreed by the Good Manufacturing Practice (GMP) / Good Distribution Practice (GDP) Inspectors Working Group.' There is also a 'Code' section with sub-points for human and veterinary medicines, and a 'Table of contents' link. On the right side, the 'Data integrity (NEW August 2016)' section is expanded, showing a list of seven questions related to data risk, criticality, lifecycle, and management. A 'Back to top' link is visible at the bottom right of the content area.

Pre-authorisation  
Post-opinion  
Post-authorisation  
What we publish  
Product information  
Scientific advice and protocol assistance  
Support for early access  
Adaptive pathways

Home ▶ Human regulatory ▶ Inspections ▶ GMP/GDP compliance ▶ Q&A

### Questions and answers: Good manufacturing practice

Email Print Help

This page lists the European Medicines Agency's answers to frequently asked questions, as discussed and agreed by the Good Manufacturing Practice (GMP) / Good Distribution Practice (GDP) Inspectors Working Group.

Further questions and answers are published as the need arises. Individual questions and answers may be removed when relevant GMP guidelines are updated.

**Code**

- ▶ H: applicable to human medicines
- ▶ V: applicable to veterinary medicines

**Table of contents**

### Data integrity (NEW August 2016)

Expand all items in this list

- Data integrity**
- 1. How can data risk be assessed?
- 2. How can data criticality be assessed?
- 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?
- 7. 'Data lifecycle': What risks should be considered when assessing the processing data into usable information?
- 8. 'Data lifecycle': What risks should be considered when checking the completeness and accuracy of reported data?

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## EU requirements for Data Integrity

The main regulatory expectation for data integrity is to comply with the requirement of ALCOA (Attributable, Legible, Contemporaneous, Original, Accurate) principles and EU expectations can be found here for API and FP.

- Chapter 4 (Part I): Documentation
- Chapter 6 (Part I): Quality control
- Chapter 5 (Part II): Process equipment (computerized system)
- Chapter 6 (Part II): Documentation and records
- Annex 11 (Part III): Computerised Systems



## EU GMP Guide & Data Integrity Traceability Matrix

	<b>Basic Requirements for Medicinal Products (Part I): Chapter 4<sup>(1)</sup> / Chapter 6<sup>(2)</sup></b> [4.20, c & f], [4.21, c & i], [4.29, e]	<b>Basic Requirements for Active Substances used as Starting Materials (Part II) : Chapter 5<sup>(3)</sup> / Chapter 6<sup>(4)</sup></b>	<b>Annex 11 (Computerised System)</b>
<b>Attributable</b> (data can be assigned to the individual performing the task)		[6.14], [6.18], [6.52]	[2], [12.4], [15]
<b>Legible</b> (data can be read by eye or electronically and retained in a permanent format)	[4.1], [4.2], [4.7], [4.8], [4.9], [4.10]	[5.43] [6.11], [6.14], [6.15], [6.50]	[7.1], [9], [10], [17]
<b>Contemporaneous</b> (data is created at the time the activity is performed)	[4.8]	[6.14]	[12.4], [14]
<b>Original</b> (data is in the same format as it was initially generated, or as a 'verified copy', which retains content and meaning)	[4.9], [4.27], [Paragraph "Record"]	[6.14], [6.15], [6.16]	[8.2], [9]
<b>Accurate</b> (data is true / reflective of the activity or measurement performed)	[4.1], [6.17]	[5.40], [5.45], [6.6]	[Paragraph "Principles"],[5], [6], [10], [11]





## EU requirements for Data Integrity

- No requirement for a specific procedure, however it may be beneficial to provide a summary document which outlines the organisations total approach to data governance.
- A compliant pharmaceutical quality system generates and assesses a significant amount of data. While all data has an overall influence on GMP compliance, different data will have different levels of impact to product quality.
- A quality-risk management (ICH Q9) approach to data integrity can be achieved by considering data risk and data criticality at each stage in the Data lifecycle. The effort applied to control measures should be commensurate with this data risk and criticality assessment.
- The approach to risk identification, mitigation, review and communication should be iterative, and integrated into the pharmaceutical quality system. This should provide senior management supervision and permit a balance between data integrity and general GMP priorities in line with the principles of ICH Q9 & Q10



## Data Risk Assessment

- Should consider the vulnerability of data to involuntary or deliberate amendment, deletion or recreation. Control measures which prevent unauthorised activity and increase visibility / detectability can be used as risk mitigating actions.
- Risk assessment should include a business process focus (e.g. production, QC) and not just consider IT system functionality or complexity. 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.



## Data Criticality

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



## Life Cycle Approach

- 'Data lifecycle' refers to how data is generated, processed, reported, checked, used for decision-making, stored and finally discarded at the end of the retention period.
- Data may cross boundaries within organisations and between organisations.
- Therefore important to understand the lifecycle elements for each type of data or record, and ensure controls which are proportionate to data criticality and risk at all stages.



## Life Cycle Approach

EU Q&A covers;

- Assessing the generation and recording of data;
- Assessing the processing of data into usable information;
- Risks to be considered when checking the completeness and accuracy of reported data and processed information;
- Risks to be considered when data (or results) are used to make a decision
- Risks to be considered when retaining or retrieving data.
- Risks to be considered when retiring or disposing of data



## Reviewing Data

- In the case of data generated from an electronic system, electronic data is the original record which must be reviewed and evaluated prior to making batch release decisions and other decisions relating to GMP related activities (e.g. approval of stability results, analytical method validation etc.).
- In the event that the review is based solely on printouts there is potential for records to be excluded from the review process which may contain un-investigated out of specification data or other data anomalies.
- The review of the raw electronic data should mitigate risk and enable detection of data deletion, amendment, duplication, reusing and fabrication which are common data integrity failures.
- The principles of quality risk management may be applied during the review of electronic data and review by exception is permitted, when scientifically justified.



## Third Party Contractors

- Data integrity requirements should be incorporated into the company's contractor/vendor qualification/assurance program and associated procedures.
- In addition to having their own data governance systems, companies outsourcing activities should verify the adequacy of comparable systems at the contract acceptor. The contract acceptor should apply equivalent levels of control to those applied by the contract giver.
- Formal assessment of the contract acceptors competency and compliance in this regard should be conducted in the first instance prior to the approval of a contractor, and thereafter verified on a periodic basis at an appropriate frequency based on risk.



## Supply Chain

All actors in the supply chain play an important part in overall data integrity and assurance of product quality.

Data governance systems should be implemented from the manufacture of starting materials right through to the delivery of medicinal products to persons authorised or entitled to supply medicinal products to the public.

Relative responsibilities and boundaries should be documented in the contracts between the relevant parties. Final responsibility of ensuring compliance throughout the supply chain rests with batch certifying QP



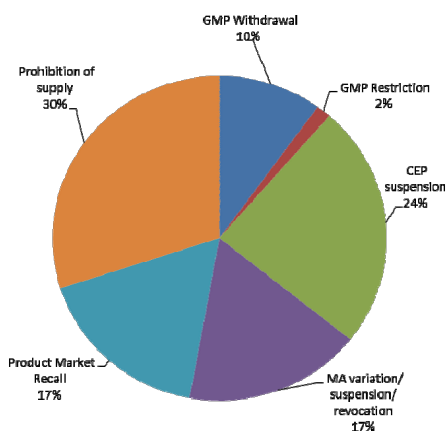


## Next Steps for EU Guidance

- Review of GMP Q&A's for development of possible "GxP" guidance covering GCP and PhVig activities;
- Possible future review of EU GMP Guide to establish if revisions needed.



## Actions as a result of GMP SNC's for India Manufacturers 2013 – 2016



- In case of serious deficiencies/critical findings actions may need to be taken by Inspectorate and EU authorities. These actions may include:
  - Prohibition of supply
  - Batches withdrawn from the EU market
  - Refusal of the granting of a Marketing Authorisation
  - Variation of Marketing Authorisation(s)
  - Suspension of Marketing Authorisation(s)
  - Revocation of Marketing Authorisation(s)
  - Action v CEP (API's)



## What kinds of CAPA's have we seen?

- Introduction of technological and/or procedural safeguards.
- Changes to business processes
- Changes in workforce and management
- Significant financial investment
- None of the above on their own are sufficient.
- There has to be evidence of significant cultural initiatives at management level and in the workforce and that these are working.



## Importance of Quality Culture

- Responsibility of senior management.
  - A quality culture together with
  - implementation of organisational and technical measures
  - data integrity risk is assessed, mitigated and communicated in accordance with the principles of quality risk management.
- Participation and commitment by staff at all levels within the company, by the company's suppliers and by its distributors.
- The effort and resource assigned to data integrity measures should be commensurate with the risk to product quality, and balanced with other quality assurance resource demands.



## Conclusions

Data integrity enables good decision-making by pharmaceutical manufacturers and regulatory authorities.

Data integrity issues can be seen on a continuum ranging from bad practice through to deliberate malpractice and falsification.

Data integrity issues are corrosive to good science and to the trust that underpins the acceptance and use of medicinal products:

- Regulator and regulated industry;
- Regulator and healthcare provider and patient;
- Regulated industry and healthcare provider and patient;
- Regulated industry and investors.

Once lost, trust can not be easily restored, and there are no standard CAPA's to heal breaches of trust.



# Thank you for your attention

## Further information

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