Data Integrity and Good Documentation Practices in Manufacturing

Indian Pharmaceutical Alliance

Advanced GMP Workshops 2017

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Summary

• European Medicines Agency and the EU Network

• Basics of data integrity

• Good Documentation Practices

• Common data integrity issues and case study
1. EMA – EU Network

- 28 EU member states + 3 EEA members states (~500 million citizens)
- European Commission & Decentralised Agency (EMA)
- ≈ 50 National Regulatory Authorities
- 4,500 European experts
- EMA is a technical, scientific and administrative secretariat
- EMA role for GMP:
  - Co-ordination of verification of GMP Compliance
  - Co-ordination of Market Surveillance
  - Experience with training of assessors, inspectors, coordination of inspections and evaluation processes
  - GMDP Inspectors Working Group
Data Quality and Integrity in Manufacturing (1)

- 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:
  - Assessment of risks to data integrity in the collection, processing, and storage of data.
  - Risk management measures at various stages of the data lifecycle.
  - Design and control of both electronic and paper-based documentation systems.
  - Measures to ensure data integrity for activities contracted out to another company.

Data Integrity - EMA
Data Quality and Integrity in Manufacturing (2)

• The guidance is aligned with 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.

Data Integrity - EMA

PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PI 041-1 (Draft 2)
10 August 2016

DRAFT PIC/S GUIDANCE

GOOD PRACTICES FOR DATA MANAGEMENT AND INTEGRITY IN REGULATED GMP/GDP ENVIRONMENTS
EU requirements for Data Integrity

- No requirement for a specific procedure, however it may be beneficial to provide a summary document which outlines the organisation's 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
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 (computerised system)
- Chapter 6 (Part II): Documentation and records
- Annex 11 (Part III): Computerised Systems
## Data Quality and Integrity in Manufacturing (4)

### EU GMP Guide & Data Integrity

#### Traceability Matrix

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Basic Requirements for Medicinal Products (Part I): Chapter 4(1) / Chapter 6(2)</th>
<th>Basic Requirements for Active Substances used as Starting Materials (Part II): Chapter 5(3) / Chapter 6(4)</th>
<th>Annex 11 (Computerised System)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attributable</td>
<td>[4.20, c &amp; f], [4.21, c &amp; i], [4.29, e]</td>
<td>[6.14], [6.18], [6.52]</td>
<td>[2], [12.4], [15]</td>
</tr>
<tr>
<td>Legible</td>
<td>[4.1], [4.2], [4.7], [4.8], [4.9], [4.10]</td>
<td>[5.43] [6.11], [6.14], [6.15], [6.50]</td>
<td>[7.1], [9], [10], [17]</td>
</tr>
<tr>
<td>Contemporaneous</td>
<td>[4.8]</td>
<td>[6.14]</td>
<td>[12.4], [14]</td>
</tr>
<tr>
<td>Original</td>
<td>[4.9], [4.27], [Paragraph &quot;Record&quot;]</td>
<td>[6.14], [6.15], [6.16]</td>
<td>[8.2], [9]</td>
</tr>
<tr>
<td>Accurate</td>
<td>[4.1], [6.17]</td>
<td>[5.40], [5.45], [6.6]</td>
<td>[Paragraph &quot;Principles&quot;],[5], [6], [10], [11]</td>
</tr>
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7 Data Integrity - EMA
EU Q&A on Data Integrity (Aug 2016)

- 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.
Data Quality and Integrity in Manufacturing (5)

- 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
Good Documentation Practices
Good Documentation Practices
Data Quality and Integrity in Manufacturing

• 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
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?
• 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
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 parts of 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
Good Documentation Practices

- 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
### 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 experts 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 draft paper resulted from PQT-Inspections describing the proposal for a future guidance document, which was discussed in detail. The concept paper was submitted to the Committee to illustrate existing existing data management principles and give the illustrative context of their implementation. In the Appendix, the concept paper includes an overview of existing data practices and guidance documents were continued to illustrate the most relevant guidance on ensuring the reliability and accuracy of data and related QM (good (anything) practice) matters. In view of the increasing number of observations made during inspections that related to data management practices, the Committee endorsed the proposal.

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**Appendix**

- **Appendix 1**: Expectations and examples of special risk management considerations for the implementation of ALCOA (plus) principles in paper-based and electronic systems

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These principles require that documentation has the characteristics of being attributable, legible, contemporaneously recorded, original and accurate (sometimes referred to as ALCOA).
WHO – Annex 5: guidance on good data and record management practices

9.2 **Attributable.** Attributable means information is captured in the record so that it is uniquely identified as executed by the originator of the data (e.g. a person or a computer system).

9.3 **Legible, traceable and permanent.** The terms legible and traceable and permanent refer to the requirements that data are readable, understandable, and allow a clear picture of the sequencing of steps or events in the record so that all GXP activities conducted can be fully reconstructed by the people reviewing these records at any point during the records retention period set by the applicable GXP.

9.4 **Contemporaneous.** Contemporaneous data are data recorded at the time they are generated or observed.

9.5 **Original.** Original data include the first or source capture of data or information and all subsequent data required to fully reconstruct the conduct of the GXP activity. The GXP requirements for original data include the following:

- original data should be reviewed;
- original data and/or true and verified copies that preserve the content and meaning of the original data should be retained;
- as such, original records should be complete, enduring and readily retrievable and readable throughout the records retention period.

9.6 **Accurate.** The term “accurate” means data are correct, truthful, complete, valid and reliable.

9.7 Implicit in the above-listed requirements for ALCOA are that the records should be complete, consistent, enduring and available (to emphasize these requirements, this is sometimes referred to as ALCOA-plus).

9.8 Further guidance to aid understanding as to how these requirements apply in each case and the special risk considerations that may need to be taken into account during implementation are provided in Appendix 1.
Common data integrity issues with a case study
Summary of GMP inspections performed by EU inspectorates (1)

2013-2016 Outcome of EU Inspections

Source: EudraGMDP data 13th January 2017
Summary of GMP inspections performed by EU inspectorates (2)

2013-2016 Outcome of EU Inspections India

Source: EudraGMDP data 13th January 2017
GMP deficiencies

2013 – 2016 India

- GMP Statements of Non-Compliance (SNC) include several critical or major deficiencies
- The reported deficiencies were grouped in the following categories:
  1. Data integrity (documentation and records)
  2. Contamination and Cross contamination issues (sterility assurance)
  3. Quality Assurance System
  4. Quality Control System
  5. Equipment qualification & process validation
  6. Premise, facilities and equipment
  7. Personnel & Training
  8. CAPA management
  9. Supplier management
  10. Manufacturing operations

Source: EudraGMDP data 13th January 2017
Due to a GMP Non-Compliance Statement, one or more actions can be taken at EU level:

**GMP certificate and EDQM Certificate of Suitability with Ph. Eur.**
- GMP certificate withdrawal
- GMP certificate restriction
- CEP suspension/withdrawal

**Market action**
- Prohibition of supply
- Batches withdrawn from the EU market

**Action on Product Marketing Authorisation (MA)**
- Variation of MA
- Suspension of MA
- Revocation of MA
- Rejection of MA application

2013 – 2016 India

- GMP Withdrawal: 24%
- GMP Restriction: 17%
- CEP Suspension: 17%
- Prohibition of Supply: 17%
- Batches withdrawn from the EU market: 2%

n=31 GMP Non-Compliance Statements

Source: EudraGMDP data 13th January 2017
What is the impact of GMP non-compliance?

- Following the issue of GMP Non-Compliance Statement the average re-inspection interval is ~ 1 year
- Following the issue of GMP Non-Compliance Statement there will be an impact on Product Marketing Authorisation (MA) which may take several months and maybe years to resolve
- Where a shortage occurs, the median time to resupply is 7 MONTHS

Impact on product availability and Public Health!
Examples of Data Integrity findings in Indian Statements of Non-Compliance (SNC)

1. The control of electronic data and laboratory systems was not adequately robust and could not assure data traceability or security.

2. Core principles of the management of electronic documentation was found not considered (or disregarded)

3. 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
Examples of Data Integrity findings in Indian SNCs

4. The batch packaging records were not completed and don’t refer the number of de-blistered and visually inspected blisters as well as the amount of rejected and approved tablets.

5. The traceability tools for testing are systematically and intentionally non-operative (e.g. no raw data, no column logbooks, deleted files from HPLCs, no audit trails in HPLC systems, no network system for R&D HPLCs).

6. The first critical deficiency was cited with regards to data integrity. E.g. Login details for the QA Manager were shared with a delegate. Employees have administrator rights to GMP related softwares (HPLC, stability chambers datasoft system). Controlled documents were found torn in a bin where used clothes are disposed-of. Records were not adequately stored to ensure their preservation and facilitate retrieval.
Data integrity and Quality Culture

• Regulators rely on data to evaluate the quality, safety and efficacy of medicines and to monitor benefit-risk balance

• Controlling of data records helps ensure that the data generated are accurate and consistent to support good decision-making by both pharmaceutical manufacturers and regulatory authorities

• Quality culture supports any organizational and technical measures to ensure data integrity

• The importance of data integrity to quality assurance and public health protection should be included in personnel training programmes

• It is expected that any risks to data integrity are assessed, mitigated and communicated in accordance with the principles of quality risk management
How do you improve quality culture

**Prepared**
- Are you **proactive** in picking up on evidence of a developing problem or only reacting after the problem has become significant?
- Can you **detect** signs of increasing risk especially if production pressure is increasing?
- How do you get top management to **engage**?
- How do you **encourage** staff to take ownership for quality and good behaviour

**Transparent**
- Do you identify and monitor vulnerabilities?
- To what extent is information about quality / compliance problems shared within your organisation?
- Shared within your supply network?
- Shared with regulators?
- How do you encourage staff dealing with suppliers to focus on the aspects that really matter, as opposed to price?

**Flexible**
- How do you adapt to change, disruptions and opportunities?
- Is your supply chain resilient and robust?
- Can you invest in quality at those times when it appears to be unaffordable?
Conclusions

• Data integrity / Integrity important – difficult to implement and quantify

• Good Documentation Practices – simply necessary in todays business environment

• Data integrity issues not new and likely to continue unless the culture is solid
Thank you for your attention

Further information

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