EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Data Integrity and Good Documentation Practices in Manufacturing

Indian Pharmaceutical Alliance

Advanced GMP Workshops 2017

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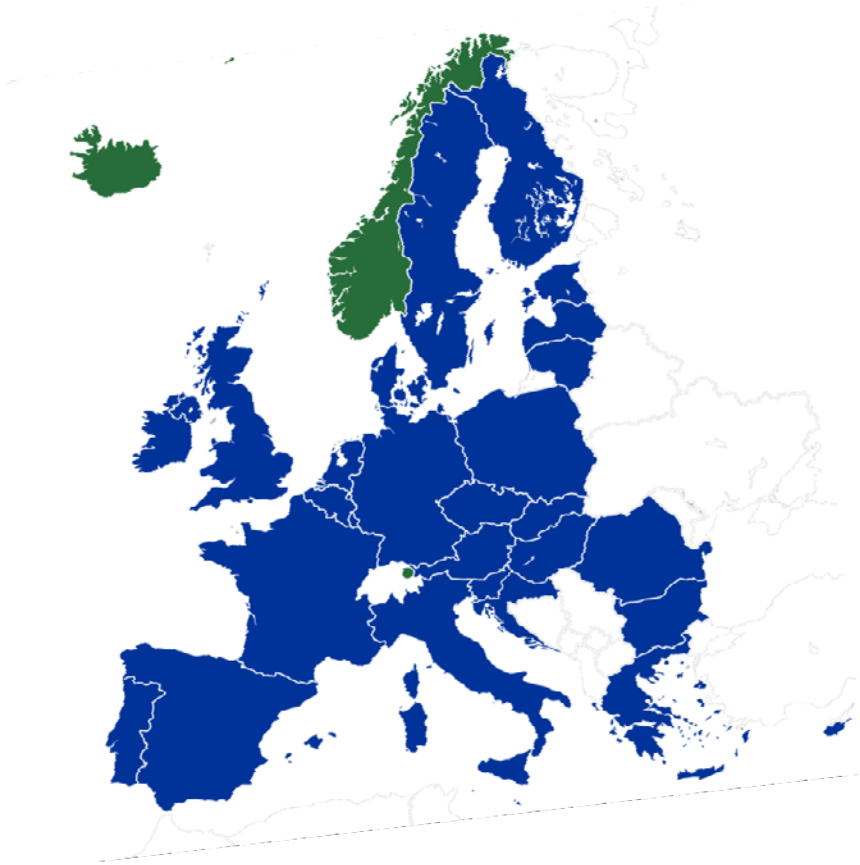
EUROPEAN MEDICINES AGENCY

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



PUBLIC HEALTH

European Commission > DG Health and Food Safety > Public health > Vol 4: GMP Human & Veterinary

VOL 4: GMP HUMAN & VETERINARY

All topics

EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines

Volume 4 of "The rules governing medicinal products in the European Union" contains guidance for the interpretation of the principles and guidelines of good manufacturing practices for medicinal products for human and veterinary use laid down in Commission Directives 91/356/EEC, as amended by Directive 2003/94/EC, and 91/412/EEC respectively.

Introduction

- Introduction (07/02/2011)
- Commission Directive 2003/94/EC, of 8 October 2003, laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use.
  Replacement of Commission Directive 91/356/EC of 13 June 1991 to cover good manufacturing practice of investigational medicinal products.
- Commission Directive 91/412/EEC of 23 July 1991 laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products.

Part I - Basic Requirements for Medicinal Products

- Chapter 1 - Pharmaceutical Quality System (Into operation since 31 January 2013)
- Chapter 2 - Personnel (Into operation since 16 February 2014)
- Chapter 3 - Premise and Equipment (Into operation since 1 March 2015)
  - See transitional arrangement for toxicological evaluation on page 1 of Chapter 3
  - Previous version
- Chapter 4 - Documentation (January 2011)
- Chapter 5 - Production (Into operation since 1 March 2015)
  - See transitional arrangement for toxicological evaluation on pages 1-2 of Chapter 5
  - Previous version
- Chapter 6 - Quality Control (Into operation since 1 October 2014)
- Chapter 7 - Outsourced activities (Into operation since 31 January 2013)
- Chapter 8 - Complaints and Product Recall (Into operation since 1 March 2015)
- Chapter 9 - Self Inspection

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Data integrity (NEW August 2016)

Back to top

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 and processed information?
- 9. 'Data lifecycle': What risks should be considered when data (or results) are used to make a decision?
- 10. 'Data lifecycle': What risks should be considered when retaining and retrieving data to protect it from loss or unauthorised amendment?
- 11. 'Data lifecycle': What risks should be considered when retiring or disposal of data in a controlled manner at the end of its life?
- 12. Is it required by the EU GMP to implement a specific procedure for data integrity?
- 13. How are the data integrity expectations (ALCOA) for the pharmaceutical industry prescribed in the existing EU GMP relating to active substances and dosage forms published in Eudralex volume 4?
- 14. How should the company design and control their paper documentation system to prevent the unauthorised re-creation of GMP data?
- 15. What controls should be in place to ensure original electronic data is preserved?
- 16. Why is it important to review electronic data?
- 17. Is a risk-based review of electronic data acceptable?
- 18. What are the expectations for the self-inspection program related to data integrity?
- 19. What are my company's responsibilities relating to data integrity for GMP activities contracted out to another company?
- 20. How can a recipient (contract giver) build confidence in the validity of documents such as Certificate of Analysis (CoA) provided by a supplier (contract acceptor)?
- 21. What are the expectations in relation to contract calibration service providers who conduct calibrations on-site and/or off-site? Are audits of these companies premises required?
- 22. What is expected of my company in the event that one of my approved contractors (e.g. active substance manufacturer, finished product manufacturer, quality control laboratory etc.) is issued with a warning letter/statement of non-compliance concerning data integrity, from a regulatory authority?
- 23. Where does my company's responsibility begin and end in relation to data integrity aspects of the supply chain for medicinal products?

Data g (2)

- The guid Co-operation Scheme ds published in Eudralex
- Should b the GMP standarc

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 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 Quality and Integrity in Manufacturing (3)

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

	Basic Requirements for Medicinal Products (Part I): Chapter 4[1] / Chapter 6[2]	**Basic Requirements for Active Substances used as Starting Materials (Part II) : Chapter 5[3] / Chapter 6[4]**	**Annex 11 (Computerised System)**
Attributable (data can be assigned to the individual performing the task)	[4.20, c & f], [4.21, c & i], [4.29, e]	[6.14], [6.18], [6.52]	[2], [12.4], [15]
Legible (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]
Contemporaneous (data is created at the time the activity is performed)	[4.8]	[6.14]	[12.4], [14]
Original (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]
Accurate (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]

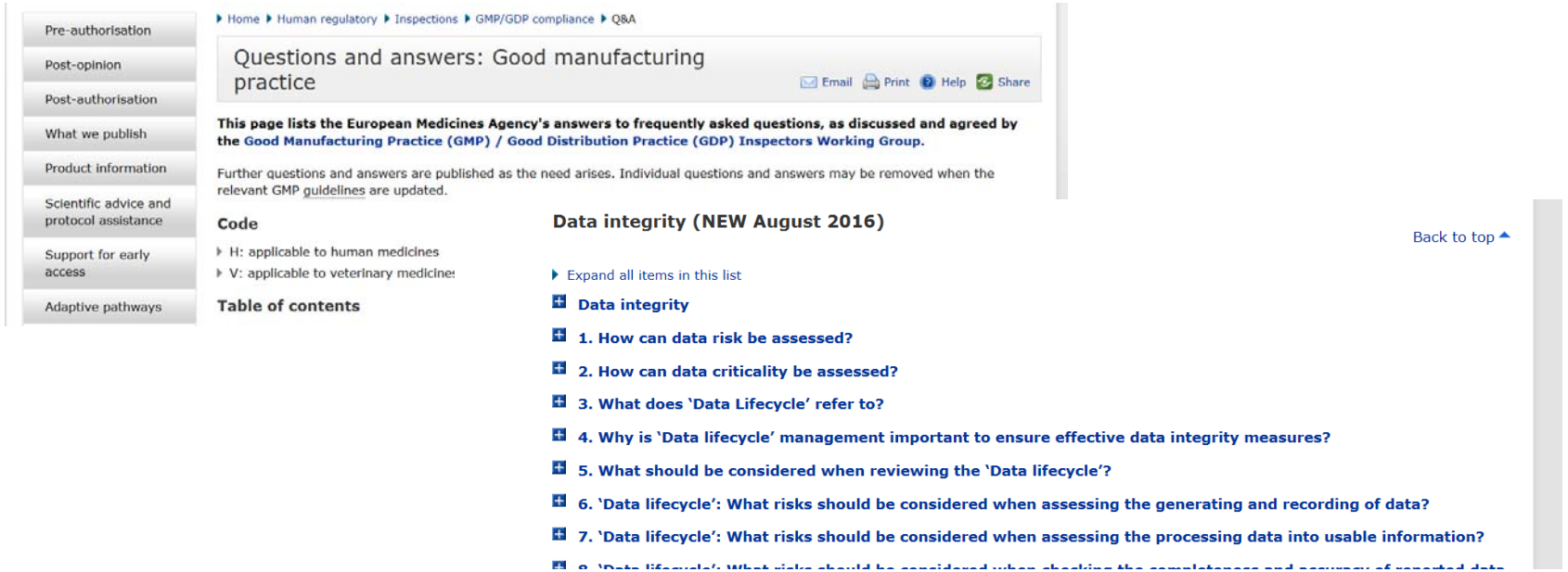
EU Q&A on Data Integrity (Aug 2016)

- 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:

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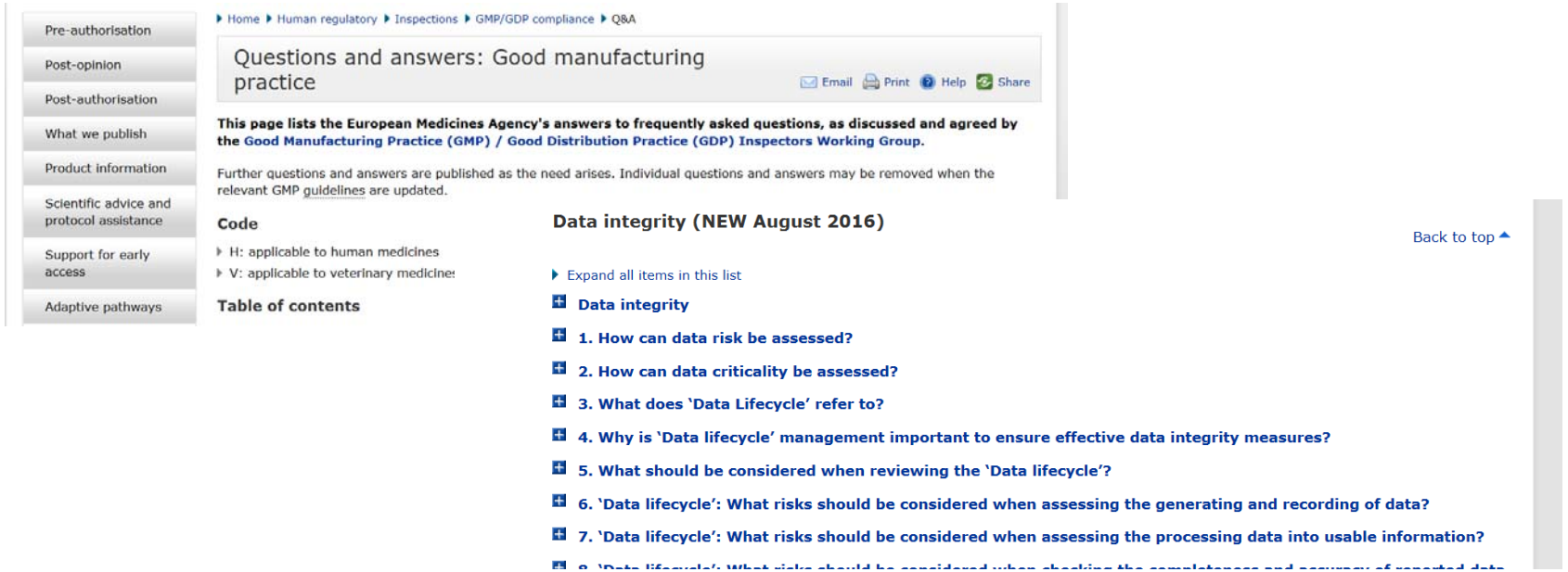


Data Risk Assessment

- 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.

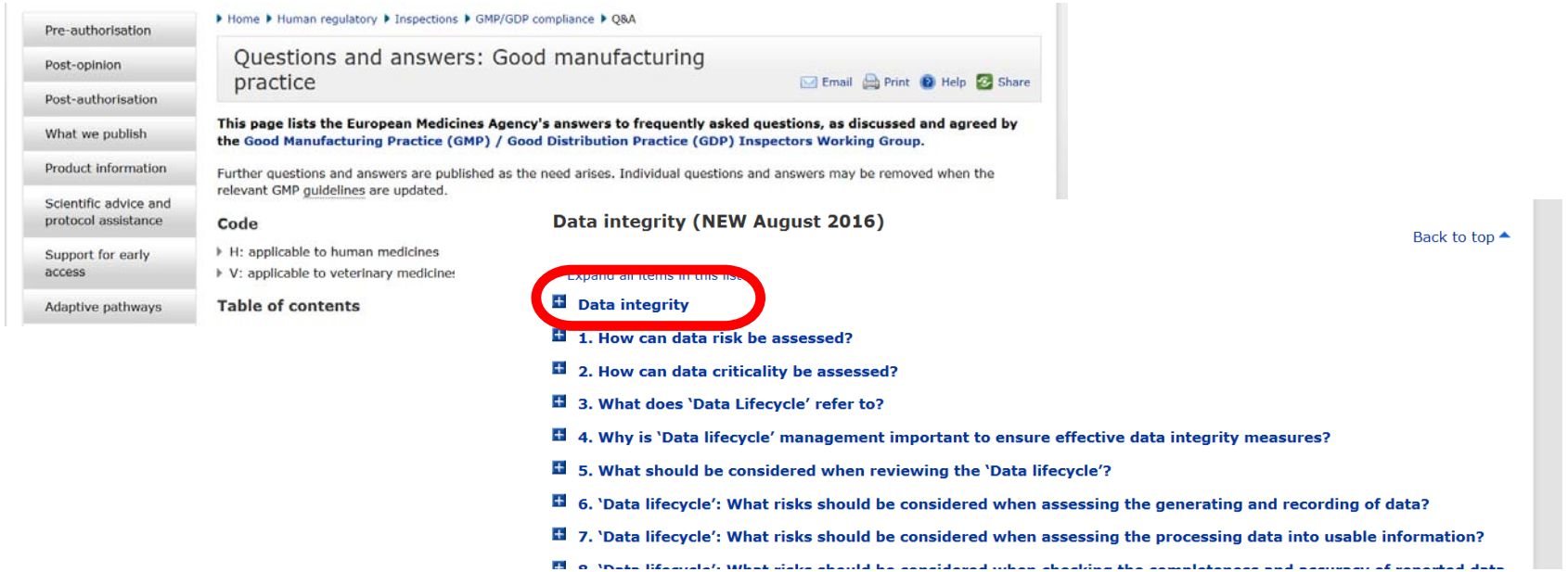
Supply Chain

- 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



WHO – Annex 5: guidance on good data and record management practices

http://www.who.int/medicines/publications/ph

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 concept paper was received from PQT–Inspections describing the proposed structure of a new guidance document, which was discussed in detail. The concept paper also indicated existing relevant principles and gave some illustrative examples of their implementation. In the Appendix to the concept paper, extracts from existing guidance and practices and guidance documents were compiled 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.

WHO Expert Committee on Specifications for Pharmaceutical Preparations Fiftieth report

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.

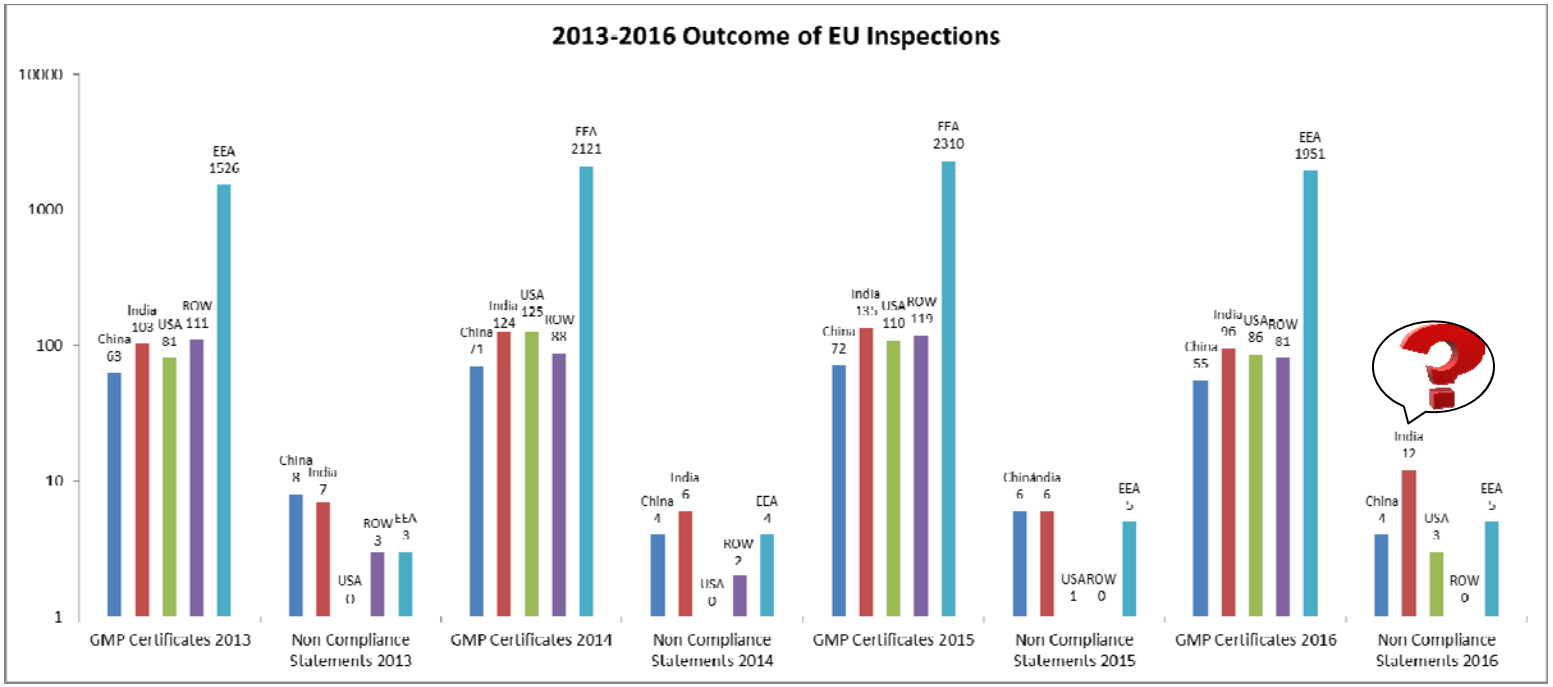
9.6 **Accurate.** The term "accurate" means data are correct, truthful, complete, valid and reliable.

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.

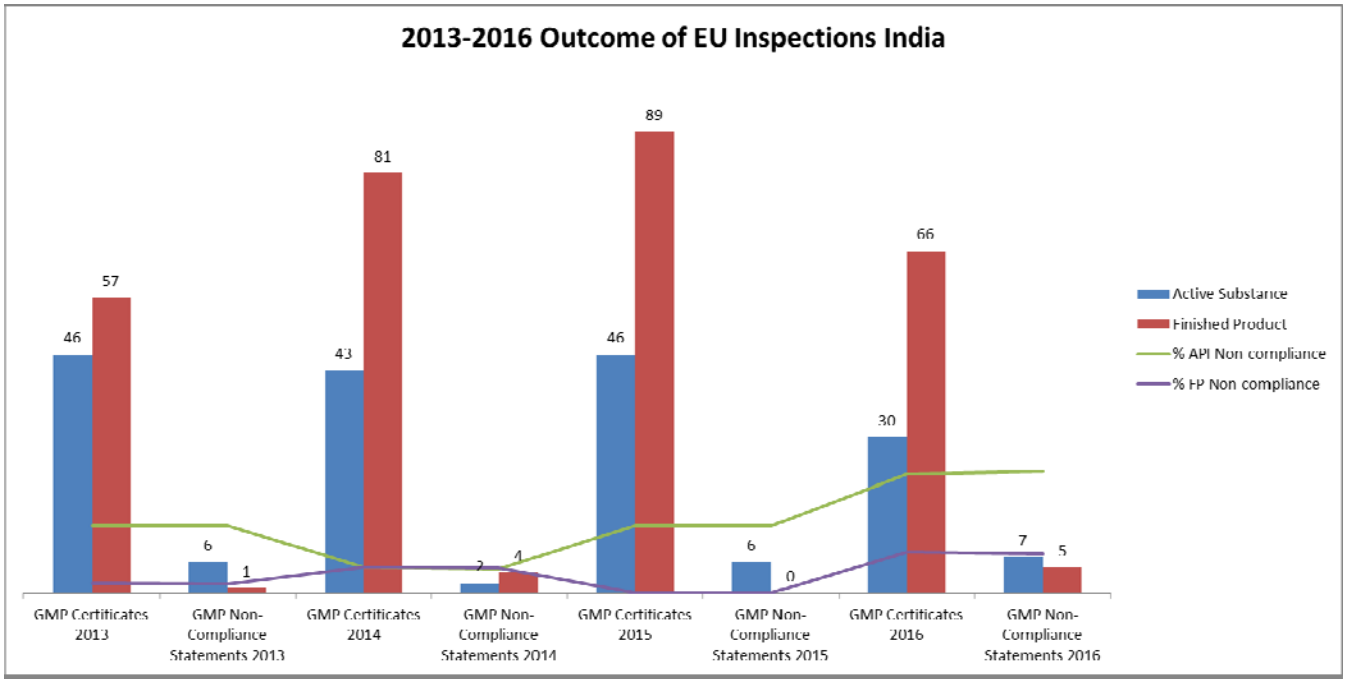
Common data integrity issues with a case study

Summary of GMP inspections performed by EU inspectorates (1)



Source: EudraGMDP data 13th January 2017

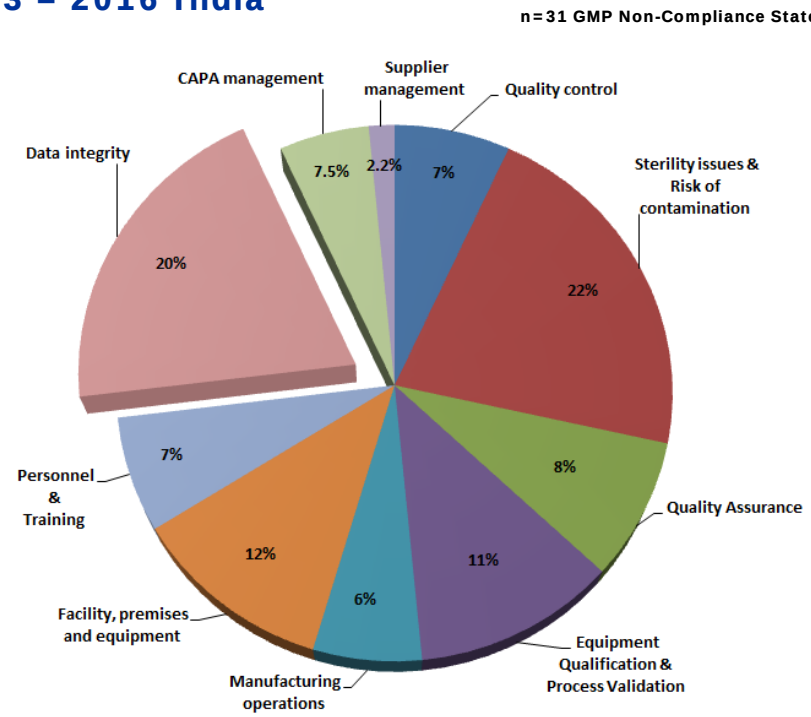
Summary of GMP inspections performed by EU inspectorates (2)



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

Actions following GMP Non-Compliance

2013 – 2016 India

- 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.

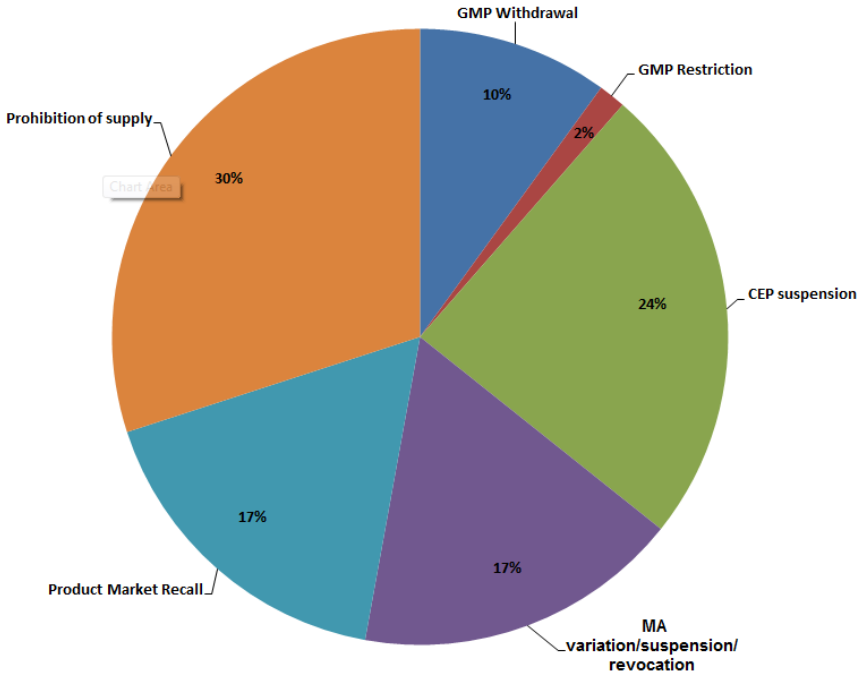
- GMP certificate withdrawal
- GMP certificate restriction
- CEP suspension/withdrawal

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



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

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Thank you for your attention

Further information

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