 Remediation, Resolution and Outcomes

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Contents

1. EMA – EU Network

2. Remediation and Resolution

3. Quality Risk Management

4. Outcomes

5. Case Management
1. EMA – EU Network
**EMA – EU Network**

- 28 EU member states + 3 EEA member 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

Remediation, Resolution and Outcomes
2. Remediation and Resolution
Key steps to investigation

1. Identify the Root-Cause

2. Assign Corrective and Preventive Actions (CAPAs)

3. Implement CAPAs

4. Conduct CAPA effectiveness check
Root Cause Analysis

• Critical step to any remediation action

• True root cause must be identified, and where this is not possible the most likely root cause
  • Where human error is suspected this needs to be formally justified, and process/procedures/systems are not overlooked

• Analysis needs to be based on science
  • Use the available knowledge and experience with the product, process and systems

• Cross functional effort that includes appropriately trained staff
Corrective and Preventive Actions

- Adequate CAPAs to ensure process is brought into compliance and prevent non-compliance in the future

- What is an adequate CAPA?
  - Must address the root cause that was previously identified
  - Must be scientifically sound and be based on the available knowledge of the product
  - Need to be effective and ensure that they do not adversely affect the product
  - Need to be linked to the protection of patient and be proportionate with the risk

- CAPAs should be verified and internally approved before being implemented

Remediation, Resolution and Outcomes
CAPA Implementation and Effectiveness Check

- CAPA implementation should be monitored and assessed to ensure they are fit for purpose
- It is important to define from the beginning how the effectiveness check will be performed:
  - When will it be performed?
  - Who is responsible?
  - What will be measured and how effectiveness will be verified?
  - How will it be documented?
- The effectiveness check needs to be documented
- Complaints/defects should be reviewed periodically for trends that indicate recurring issues

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CAPAs Common issues

- Defined CAPAs never implemented
- CAPAs not adequate to address the issue and to prevent reoccurrence
  - Root cause not identified correctly
  - CAPA does not mitigate the risk
- CAPAs not based on scientific argumentation or not using all the information / knowledge related to product / process
- Effectiveness checks not performed or do not take into consideration all available data
- Deadline for conducting effectiveness check not appropriate to identified issue
- Effectiveness check not appropriately implemented

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3. Quality Risk Management
What is QRM?

- ICH Q9 - QRM an important tool to support decisions regarding the degree of investigation and action taken
- Supports a scientific and practical approach to decision making
- Ensure risk is adequately reviewed and addressed
- The basic QRM principles
  1. *the evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient*
  2. *the level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk*
Communication

- Critical step for quality risk management
- Ensure that there is an efficient communication within the organisation but also outside the organisation
  - Partners/Clients
  - Regulatory Authorities
- In case of quality defects with impact to product pre- and post incident communication with regulatory authorities is required to determine:
  - Extent of the problem (nature, severity, impact)
  - Risk to patient
  - CAPAs
  - Required immediate market actions
- Communicate as soon as possible

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Issues noted during EEA Inspections

- Increasing use of risk assessment and QRM activities by industry
- Four key problems noted during inspections about risk assessment and QRM
  - **Lack of good science** (historical data, modelling data, preventive controls, assumptions regarding severity and detection not supported by data)
  - **Lack of rigour in applying the methodology** (using risk questions that are too high level, or not specific for the objective, focusing on too many failure modes and only treating them superficially or subjectively)
  - **Poor management of knowledge** (overlooking or ignoring existing and sometimes key knowledge during risk assessments)
  - **Overuse of formal risk assessments** (many issues managed through the formal risk assessments, sometimes formal but flawed risk assessments provide a sense of security in decision making)

4. Outcomes
What is the impact of poor investigations?

- Impact on product quality and productivity loss
- Regulatory Actions
  1. Market Recalls
  2. Prohibition of supply
  3. Inspections
  4. Action on product Marketing Authorisation
- Can lead to shortages
  - Where a shortage occurs, the median time to resupply is **7 MONTHS**

**Impact on product availability and Public Health!**

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Quality Defects and Recalls

2014-2017 Quality Defects and Recalls for EMA Centrally Authorised Products

Remediation, Resolution and Outcomes
GMP inspections performed by EU inspectorates in India

2014-2017 Outcome of EEA GMP Inspections India

Remediation, Resolution and Outcomes

Source: EudraGMDP data 9th January 2018
GMP deficiencies
2014 – 2017 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

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Source: EudraGMDP data 13th January 2018
5. Case management
Case Management

**Hypothetical case**

OOS result for an unknown impurity for a product (A) solution for injection.

**Root Cause**

- Manufacturer investigation: contamination with another API
- Root cause: *exceptional manufacture of a development batch of product B* using the same equipment
- Extent of problem: 1 batch of product A impacted by contamination

**Proposed CAPAs:**

1. Recall of impacted batch
2. Revalidation of cleaning procedure

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Case Management

**Quality defect case assessment**

- Root cause investigation was not substantiated and supported with scientific data
- Risk assessment very focused on event not on system
- Concerns for other batches being impacted
- Request follow-up inspection and additional testing

**For cause inspection**

- Another product routinely manufactured on the dedicated equipment as Product A
- Other batches of product were contaminated

**Regulatory Action**

- Recall all batches on the market based on risk assessment to patient
- Non-Compliance for the manufacturing site

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Case Management

**Key learnings**

1. Site was not respecting own risk assessment for reducing risk of cross-contamination

2. Root cause investigation did consider the real issue

3. Impact on other batches and products was not considered

4. CAPAs were inappropriate
   - did not address the real root cause
   - not proportionate to the risk and did not protect patient safety

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Key Messages

- Identifying the **correct root cause** is important in defining good CAPAs.
- CAPAs should be based on knowledge of the process/product.
- CAPAs need to be linked to the protection of patient and be proportionate with the risk.
- CAPAs should be verified before implementation.
- CAPAs should be monitored and assessed to ensure they are fit for purpose.
Thank you for your attention

Further information

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GMP inspections performed by EU inspectorates in India

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Source: EudraGMDP data 9th January 2018
Summary of GMP inspections performed by EU inspectorates

2017 Outcome of EEA GMP Inspections India per State

Source: EudraGMDP data 9th January 2018