EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Remediation, Resolution and Outcomes

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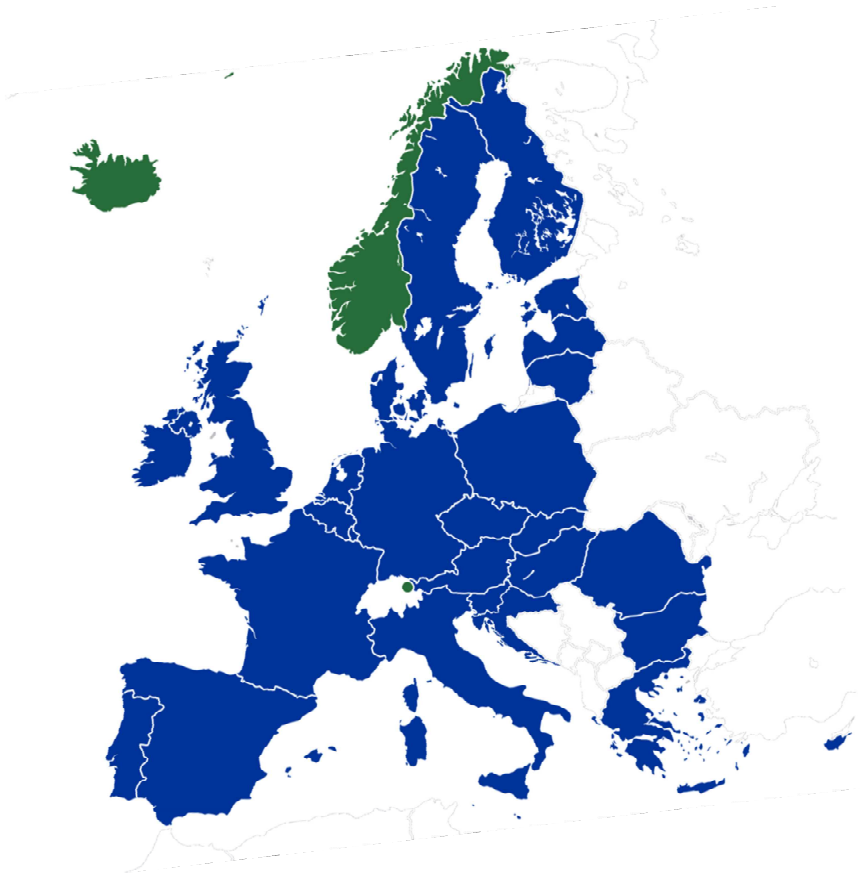
Presented by Andrei Spinei
Manufacturing and Quality Compliance, European Medicines Agency

Contents

1. EMA – EU Network

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



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

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

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

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*

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)

Source: Kevin O'Donnell "QRM in the GMP Environment: Ten Years On—Are Medicines Any Safer Now? A Regulators Perspective", QUALITY RISK MANAGEMENT, Journal of Validation Technology 2016.

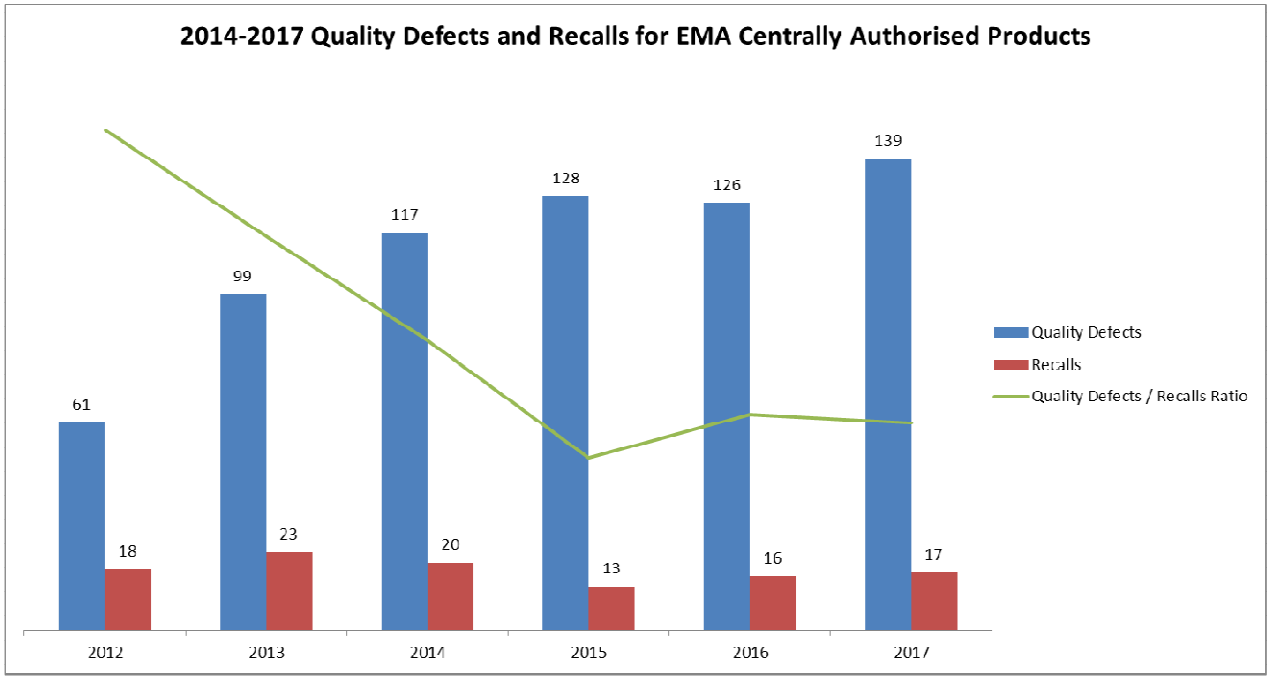
4. Outcomes

What is the impact of poor investigations?

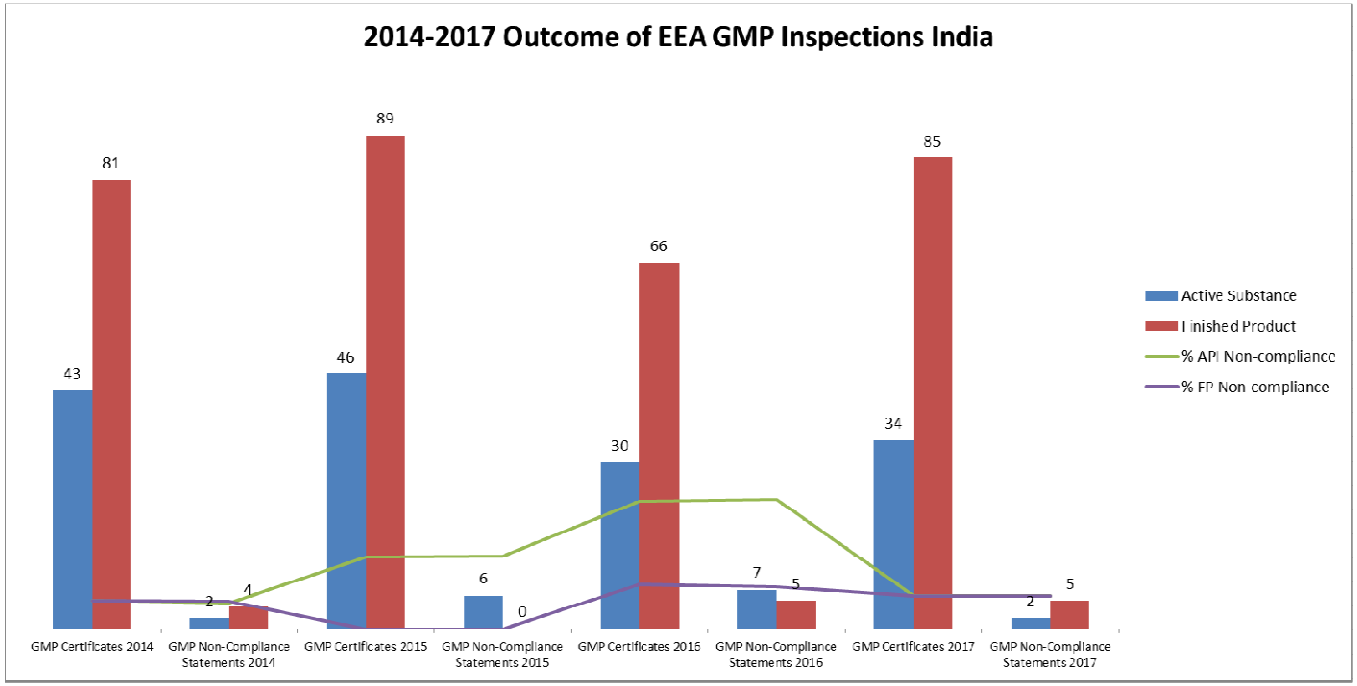
- Impact on product quality and productivity loss
- Regulatory Actions
    1. Market Recalls
    2. Prohibition of supply
    3. Inspections
    4. Action on product Marketing Authorisation
- Can lead to shortages
    - Where a shortage occurs, the median time to resupply is **7 MONTHS**

Impact on product availability and Public Health!

Quality Defects and Recalls



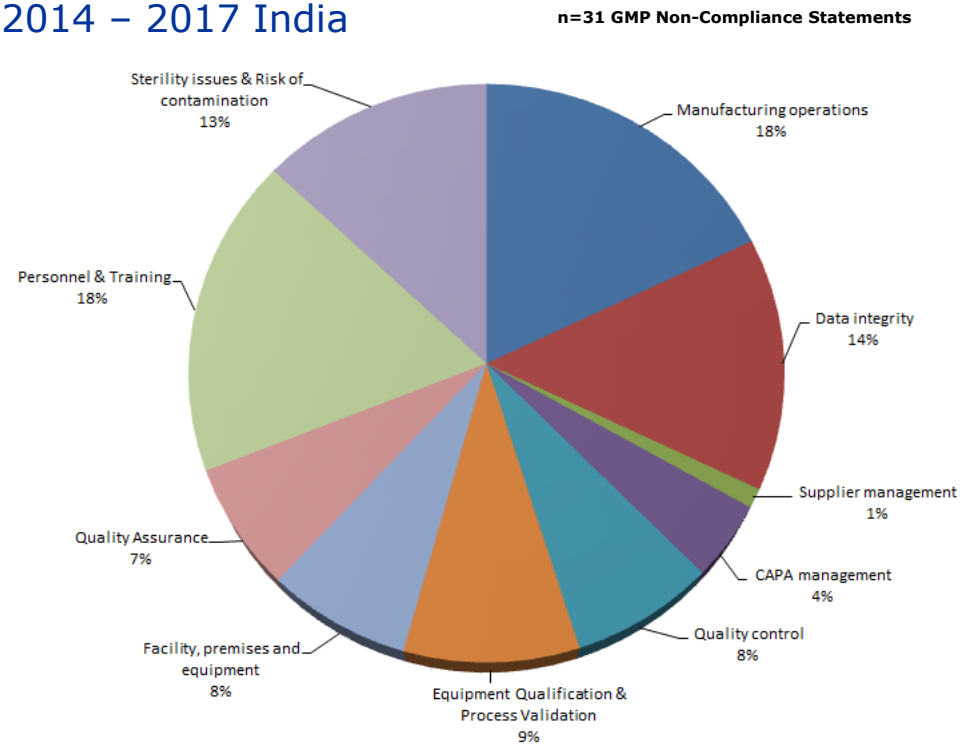
GMP inspections performed by EU inspectorates in India



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**

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

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

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

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

EUROPEAN MEDICINES AGENCY

Thank you for your attention

Further information

[andrei.spinei@ema.europa.eu]

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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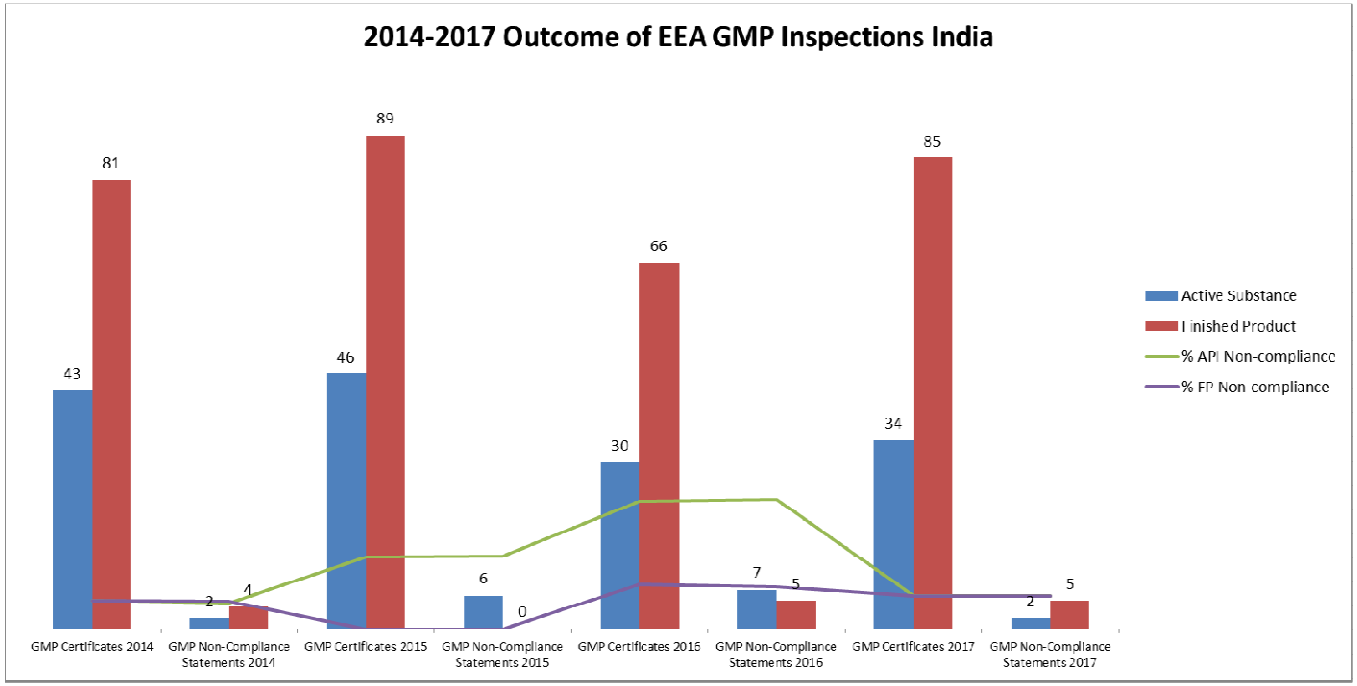
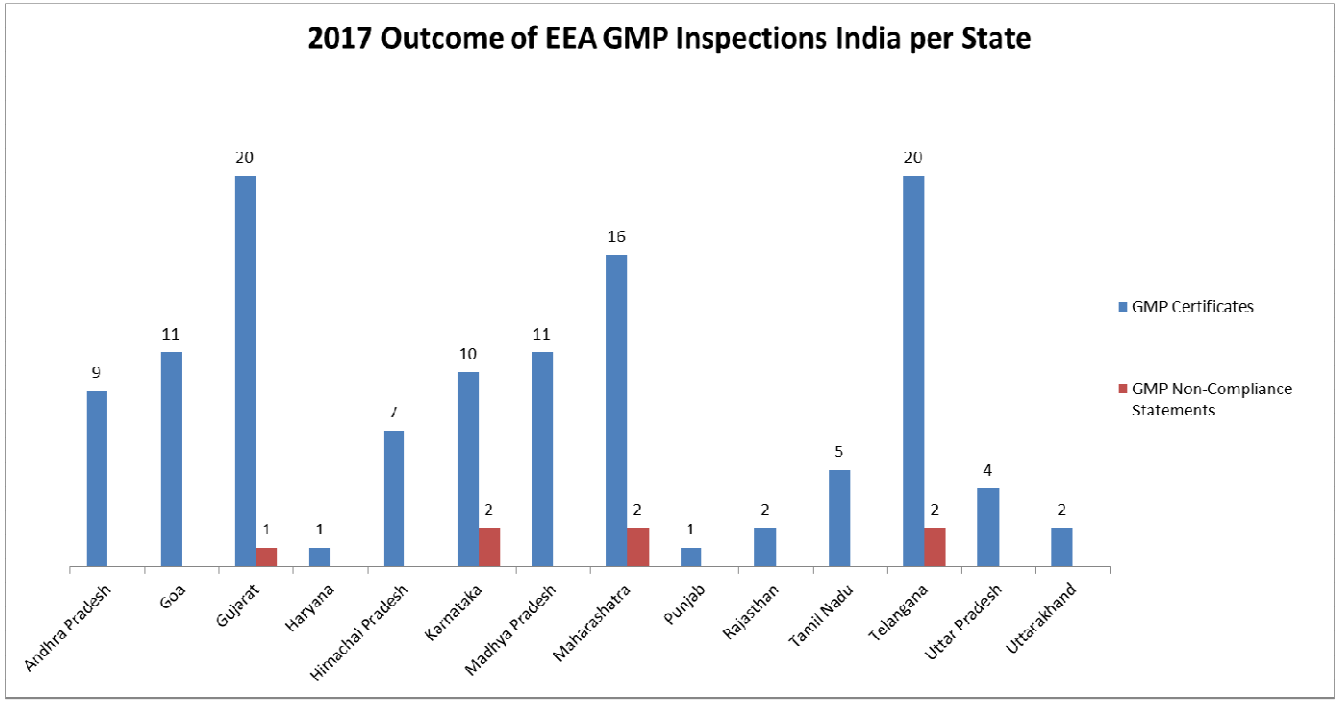


Source: EudraGMDP data 9th January 2018

Summary of GMP inspections performed by EU inspectorates



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