Most Common Deficiencies Found by EDQM

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Overview

• Fact & Figures
• Main deficiencies
• Conclusion
Inspection figures in 2016

- 40 sites covered by EDQM inspections
  (India 22, China 13, elsewhere 5)
  - 7 non-compliances, all with critical findings

- 39 sites covered by exchange of information (mainly inspections by EEA)
  - 6 cases, CEPs suspended or manufacturing site removed from CEP (statements of GMP non-compliance issued by EEA inspectorates)
  - 2 cases, CEPs withdrawn (refusal of inspection)
General Compliance Trends

- Inspected sites found non compliant:
  - 2013: 38%
  - 2014: 12%
  - 2015: 18%
  - 2016: 18%

- The high proportion of non compliant sites is seen as a result of the ability of EDQM to identify sites with higher risk of non-compliance and to focus on them.
  - In 2016, out of 7 non-compliances,
    - 3 were repeated history of NC leading to CEP withdrawal
    - 5 were already inspected and found compliant
Distribution of deficiencies from 2006 to 2015 (2016 data not yet available)

* - Quality management,
- Personnel,
- Documentation,
- Validation,
- Change control,
- Complaints and recalls
- Contract manufacturers

The distribution of the deficiencies is rather stable throughout the years.
Main GMP deficiencies

Insufficient quality system renders operations not reliable as evidenced by:

- Annual Quality Review:
  - Not a quality tool for companies
  - Not all batches reflected
  - Trends not detected and investigated

- Quality Risk Management:
  - Practically absent or poorly implemented
Main GMP deficiencies

• Personnel:
  ✓ No/insufficient training given to upper management with regard to GMP related matters
  ✓ No assessment of training’s efficiency or limited value

• Change control:
  ✓ Not a deep-rooted practice / Underreported
  ✓ Impact of change not properly assessed
Main GMP deficiencies

• Deviation management:
  ✓ Not a deep-rooted practice / Underreported
  ✓ Deviations not investigated in depth (e.g. no root cause for « black particles »)
  ✓ No proper CAPA (e.g. «training of related personnel»)
  ✓ Accumulation of minor deviations not treated as a major issue (or at least considered globally)
Main GMP deficiencies

- Documentation practices:
  - Rewriting documents (partly or completely)
  - Not recording operation at the time of performance
  - Improper recording of documents: loose sheets instead of bound and numbered pages
  - Falsification

DOES THE RECORDING DOCUMENT REALLY REFLECT WHAT HAPPENED??
WHAT ABOUT TRACEABILITY ???
Main GMP deficiencies

• Validation of processes:
  ✓ Critical process parameters not based on scientific rationale
  ✓ Blending or micronisation not always addressed

• Poor cleaning validation (lack of scientific understanding)

• Qualification of equipment:
  ✓ Lack of appropriate user requirement specifications
  ✓ Weakness of water systems
Main GMP deficiencies

- Process equipment / Buildings and facilities:
  ✓ Improper design, cleaning schedule and maintenance schedule cause risks of contamination and/or cross-contamination

  ✓ Computerised systems:
    o No management of access level causes risk of loss of traceability
    o Lack of sufficient controls to prevent manipulation of data
Main GMP deficiencies

- Materials management:
  - Risk of loss of traceability
  - Insufficient key starting material vendor approval
  - Improper storage
Main GMP deficiencies

- Laboratory controls:
  - Lack or insufficient review of audit trail
  - No management of access levels to the software causing risk of loss of traceability
  - Unreliable analytical results/data integrity concerns
  - Fraudulent practices: pretesting, deleting OOS results
Main GMP deficiencies

• Laboratory controls:
  ✓ Unreliable microbiological results
  ✓ Insufficient qualification and maintenance of equipment
  ✓ Chemical reference standards: lack of the Ph. Eur. CRS, insufficient establishment of secondary standards
  ✓ Lack of proper monitoring of the so-called potable water
Falsification – Fraud – Data integrity

- Falsified documents: Rewriting to cover OOS, deviations, incorrect or unapproved procedures
- Falsified layouts/premises: Hiding unacceptable parts of the facility, covering doors
- Falsified raw data: Presenting acceptable results in place of the actual (OOS) ones
  - Pretesting in “unofficial” laboratory equipment to select acceptable batches for the “official” testing
  - Deleting OOS results and replacing by “correct” ones

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Conclusions

• The EDQM has demonstrated its ability to detect non-compliances and take necessary actions through its inspection programme.

• Quality related issues constitute the main reasons for non-compliances during GMP inspections.

• API manufacturers should endorse their responsibilities and remain committed to quality.

• Finished products manufacturers must improve their ability to select GMP compliant API suppliers and audit/monitor them accordingly.
Thank you!

Questions / Suggestions?