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Most Common Deficiencies Found by EDQM

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Overview

- Fact & Figures
- Main deficiencies
- Conclusion

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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  - **2 cases, CEPs withdrawn** (refusal of inspection)

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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

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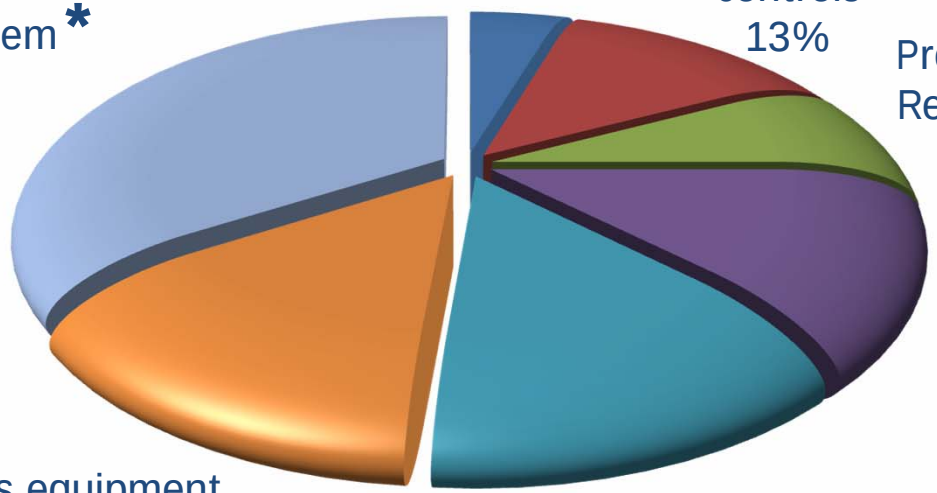
Distribution of deficiencies from 2006 to 2015 (2016 data not yet available)



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

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

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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

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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

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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)

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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 ???

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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

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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

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Main GMP deficiencies

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

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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

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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

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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?