THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)
Major compliance findings at API manufacturers and trends - Impact on future inspections and risk based inspections

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Overview

• EDQM Inspection Programme
• How does the procedure work
• Inspection facts & figures
• Perspectives - Conclusion
EDQM Inspection programme

• In application of EU Directives 2001/82/EC and 2001/83/EC on Compilation of Community Procedures as amended, EDQM was given a mandate by the European Commission to establish an annual programme for inspections

• In accordance with the EU guidance published by EMA (EMA/EMA/385898/2013 as amended, Compilation of community procedures on inspections and exchange of information)

• Selection of sites eligible to be inspected by EDQM according to a risk-based approach
Risk-based selection of the sites

• **Request from the assessors:** inconsistencies in the data, suspicion of data manipulation

• **Re-inspection:** depending on the compliance level after initial inspection, or after CEP suspension when requested

• **API related criteria:** physico-chemical properties, therapeutic use, sterile etc.

• **Company related criteria:** information from other authorities (i.e. from inspection) or other suspicions

• **Regulatory environment of the manufacturing site**

• **Several triggers involved**
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How does the procedure work

• Inspection performed by team composed of one EDQM inspector and one inspector from an EU/EEA/MRA authority (joint inspections can also be performed, e.g. with WHO, TGA, USFDA, PMDA)

• According to the inspection results the Company is quoted as compliant, borderline or non compliant

• Borderline status is only provisional: after assessment of the corrective and Preventive action plan (CAPA), the outcome is turned to compliant or non-compliant

• Companies found compliant may be re-inspected/ re-evaluated within 2-5 years depending on the numbers and classification of deficiencies found.
Negative Outcome

• In case of critical/major deficiencies to the GMP and/or the CEP dossier (failure in the declarations and commitments):
  – all CEP(s) of the site suspended or withdrawn
  – manufacturer removed if more than one involved in CEP
  – on-going CEP application(s) rejected

• Suspension/Withdrawal/Application rejection is:
  – recommended by the inspectors
  – discussed within the Certification Department
  – endorsed by the EDQM Ad Hoc Committee

• Holder and manufacturer notified and given a possibility of hearing within 14 days from notification.
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Inspection figures in 2018

- 36 sites covered by EDQM inspections
- 4 non-compliances, all with critical findings
- 46 sites covered by exchange of information (mainly inspections by EEA inspectorates)
Most frequent types of deficiencies: Quality related matters

- Quality Unit overview of activities: insufficient or even absent

- Quality Risk Management
  - Frequently absent or poorly implemented
  - Risk management principles not applied or adequately considered (e.g. deviations, change control, storage conditions)

- Annual quality review
  - Not a quality tool for companies
  - Not all batches reflected (especially the “non-CEP” grade, even though manufactured by same process)
  - Trends not detected and investigated
Most frequent types of deficiencies: Quality related matters

Deviation management/ Complaint management
• Not a deep-rooted practice / Underreported
• Anomalies not investigated in depth (e.g. no root cause assigned)
• No proper CAPA (e.g. « training of related personnel »)
• Accumulation of minor or repeated deviations not treated as a major issue

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 /opened after the initiation of the change
• Impact of change not properly assessed
Most frequent types of deficiencies: Quality related matters

- **Documentation practices**
  - Rewriting documents
  - Not recording operation at the time of performance
  - Insufficient control of electronic documents
  - Documentation control (weaknesses of QA oversight in issuance, distribution, removal)
  - Unavailability of documents (e.g. batch records)
  - Falsification in order to demonstrate acceptable, expected or presentable results, values or dates

- **Validation of processes**
  - Pharmaceutical development/technology transfer
  - Processes as blending, or micronisation, or recovery not properly addressed
  - Poor cleaning validation: Lack of scientific understanding including sound knowledge of different approaches
Most frequent types of deficiencies: Buildings and equipment

- Improper design, cleaning schedule and maintenance schedule causing risks of contamination and/or cross-contamination

- Computerised systems
  - Lack of appropriate user requirement specifications
  - Insufficient knowledge on how to validate computerised systems
  - No or insufficient management of access levels causing risk of loss of traceability
  - Lack of sufficient controls to prevent data manipulation
  - Lack of IT staff
  - IT staff without knowledge of GMP requirements

- Qualification of equipment
  - Lack of appropriate user requirement specifications
  - Weakness of water systems qualification
Most frequent types of 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: manipulation, pretesting, deleting OOS results
- Poor OOS investigation, inefficient root-cause determination, “easy” invalidation
- 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 potable water
- Lack of proper rationale for having loose specification for recycled solvents
Most frequent types of deficiencies

**Materials management**

- Risk of loss of traceability
- Insufficient key starting material vendor approval/management
- Lack of understanding the different concept/GMP requirements when qualifying suppliers (i.e. CMOs) of intermediates
- Improper storage
- Recycling of solvents/catalysts/reagents without reviewing the possibility of generation/accumulation of non-expected substances
- Insufficient R&D supervision when designing/amending/transferring processes

**Sub-contracted activities**

- No or insufficient review and/or acceptance (e.g. equipment/instrument calibration, computerised systems validation)
- No or insufficient technical agreement
General Compliance Trends

- Inspected sites found non compliant: Mean rate 2009-2018 = 18%
  - 2013: 41%
  - 2014: 12%
  - 2015: 18%
  - 2016: 18%
  - 2017: 7%
  - 2018: 11%

- High level of NC observed in the early years
- Since 2014, NC is relatively stable and low
Distribution of deficiencies from 2006 to 2018

Quality related matters:
- Quality management
- Personnel
- Documentation
- Validation
- Change control
- Complaints and recalls
- Contract manufacturers

- Compliance to CEP dossier & EP 4%
- Laboratory controls (11) 13%
- Production & IPC, Rejection & reuse of materials (8, 14) 7%
- Buildings & equipment (4 & 5) 26%
- Materials management, Storage, distribution, Packaging (7, 10, 9, 17) 14%
- Quality related matters (1, 2, 3, 6, 12, 13, 15, 16) 36%
Distribution of deficiencies from 2006 to 2018 (percentages)

- Compliance to CEP dossier & EP
- Laboratory controls (11)
- Production & IPC, Rejection & reuse of materials (8, 14)
- Buildings & equipment (4 & 5)
- Materials management, Storage, distribution, Packaging (7,10, 9, 17)
- Quality related matters (1, 2, 3,6, 12,13,15,16)

- 2006
- 2007
- 2008
- 2009
- 2010
- 2011
- 2012
- 2013
- 2014
- 2015
- 2016
- 2017
- 2018
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

![Pie charts showing critical and major deficiencies with numbers](chart.png)
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Perspectives

• Further development of the risk-based approach when elaborating the programme

• Continual reinforcement of collaboration and sharing of information with EU and International Inspectorates

• Optimisation of use of inspection resources by:
  ✓ International API Inspection Programme (EMA) - increasing number of contributors expected
  ✓ GMDP Inspector working group (EMA)
  ✓ Committee of officials of PIC Scheme (PIC/S)
  ✓ Confidentiality agreements
  ✓ Performance of distant GMP assessment
Conclusions

• Quality systems and data integrity related issues constitute the main non-compliances

• Recovery of solvent/catalyst/reagent is under increased scrutiny

• API manufacturers and their suppliers should endorse their responsibilities and be supportive to customers

• Finished products manufacturers should improve their ability to select GMP compliant API suppliers and audit/monitor them accordingly
Thank you for your attention

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