The EDQM Inspection Programme

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Overview:

• EDQM Inspection Programme in the frame of Certification Procedure
• How does the procedure work
• Inspection facts & figures
• Main GMP deficiencies
• Perspectives - Conclusion
EDQM Inspection programme

• Mandate given to EDQM by the European Commission to establish an annual programme for inspections (based on EU Directives 2001/82/EC and 2001/83/EC on Compilation of Community Procedures on inspections and exchange of information as amended)
• Inspections performed inside and outside Europe

EDQM Inspection programme

• Integral part of the Certification Procedure
• Involving manufacturing sites and brokers/distributors holding CEP(s)
• Performed before or after the CEP is granted
• Aim: to verify the compliance with
  ✓ submitted CEP dossier
  ✓ EU GMP Part II & any applicable annex such as 1 for sterile substances, 11 for computerised systems etc.
  ✓ Ph. Eur. in general
The EDQM inspection programme

- Drafted in accordance with the EU Compilation of community procedures
- Risk-based approach for the selection of sites eligible to be inspected by EDQM
- Circulation of draft programme to the EU/EEA Member States and presentation to the GMP/GDP Inspectors Working Group at EMA for discussion
- Adoption by the CEP Steering Committee & circulated to EU/EEA Member States

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, sterility etc.
- **Company related criteria**: information from other authorities (i.e. from inspection) or other suspicions
- **Regulatory environment of the manufacturing site**
- **Several triggers involved**
How does the procedure work

- Inspection team: one inspector from EDQM and one from an EU/EEA/MRA authority (or from WHO, USFDA in case of joint inspection)
- Initial inspection report: issued within 6 weeks.
- Company’s reply to the deficiencies (CAPA): within one month after the report - should be fully documented and reflect actual measures in place
- Request for revision of CEP in case of discrepancies to the dossier

Inspection Outcome

- Company quoted as **compliant, borderline** or **non compliant** according to the inspection results
- Borderline status is provisional: assessment of CAPA
  - -> upgrade to compliant
  - -> or downgrade to non-compliant
- Compliant companies may be reinspected / reevaluated within 2-5 years (depending on the numbers and classification of deficiencies found)
Positive Outcome

- If inspection conclusion positive
  + satisfactory evaluation of the submitted CAPA
  + any expected CEP revision submitted:
    Attestation of inspection delivered by EDQM, stating
    the compliance with the CEP and with GMP.
- GMP Certificate should be issued by the EEA
  participating Inspectorate via the EUDRA GMDP
  database (public information).

Negative Outcome

- In case of critical/major deficiencies to the GMP and/or
  the CEP dossier (failure in the declarations and commitments):
  actions taken against the validity of CEPs
- Possibility of hearing given to holder and manufacturer
- Information about suspension/withdrawal published on
  the EDQM websites (CEP database and Certification webpage)
- Ph.Eur. Member States, International partners, EMA,
  EU Commission and local Inspectorate informed
- Statement of GMP non-compliance issued by the EEA
  Inspectorate (public in EudraGMDP)
Actions on validity of CEPs

- **Suspension**: temporary cancellation for 2 years
  - Company requested to apply for a re-inspection to demonstrate GMP and CEP compliance and have the CEP restored

- **Withdrawal**: definite cancellation
  - When no corrective actions are deemed possible
  - For extensive cases of falsification of data
  - After repeated non-compliance
  - New dossier to be submitted + successful re-inspection if the company still interested in having a CEP

- **Removal of manufacturer**: if >1 involved in CEP

- **Rejection of on-going CEP application(s)**

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**Inspection facts & figures**

Participation of inspectorates in EDQM inspections

- TGA: 4 joint inspections
- WHO: 4 joint inspections
- USFDA: 8 joint inspections
Inspection figures in 2016

79 sites covered in 2016 by both EDQM inspections & exchange of information

- 40 EDQM inspections, 7 of which non-compliances, all with critical findings:
  1. concealment of the original manufacturer and use of non-compliant suppliers
  2. critical status of QA system
  3. overall critical risk from findings on lack of CAPA implementation, documentation & computerised systems validation
  4. critical findings regarding e-data integrity & OOS investigation
  5. overall critical risk from findings on falsification of training records and product & material management
  6. overall critical risk from findings on e-data integrity, staff qualification, equipment qualification & calibration etc.
  7. overall critical risk from findings on compliance of computerised systems, e-data integrity & insufficient production documentation
Inspection figures in 2016

79 sites covered in 2016 by both EDQM inspections
& exchange of information

• 39 sites covered by exchange of information (mainly inspections by EEA inspectorates)
  ➢ In 6 cases: suspension of CEPs or removal of the manufacturing site (statements of GMP non-compliance issued by EEA inspectorates)
  ➢ In 2 cases: withdrawal of CEPs because of refusal of inspection

General Compliance Trends

➢ Inspected sites found non compliant:
  • Mean rate 2009-2016: 29%
    • 2013: 38%
    • 2014: 12%
    • 2015: 18%
    • 2016: 18%
  ➢ High proportion of non compliant sites seen as a result of the ability of EDQM to identify sites with higher risk of non-compliance and to focus on them
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 (especially the “non-CEP” grade, even though manufactured by same process)
  ✓ Trends not detected and investigated

• Quality Risk Management:
  ✓ Frequent absence or poorly implemented
Main GMP deficiencies

• Deviation & OOS management:
  ✓ Not a deep-rooted practice / Underreported
  ✓ Not investigated in depth
  ✓ No proper CAPA (e.g. «training of related personnel»)
  ✓ Accumulation of minor deviations not treated as a major issue
  ✓ Frequent invalidation of OOS without a valid justification

• 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 or opened after the initiation of the change
  ✓ Impact of change not properly assessed
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
  ✓ Insufficient control of electronic documents
  ✓ Documentation control (weaknesses in issuance, distribution, removal)
  ✓ Falsification

Main question rising: DOES THE RECORDING DOCUMENT REALLY REFLECT WHAT HAPPENED???

Main GMP deficiencies

• Validation of processes:
  ✓ Critical process parameters not based on scientific rationale
  ✓ Processes as 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 Lack of appropriate user requirement specifications
    o Insufficient validation
    o No management of access level causing risk of loss of traceability
    o Lack of sufficient controls to prevent manipulation of data

• 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
  ✓ Unreliable microbiological results
  ✓ Insufficient qualification and maintenance of equipment
Main GMP deficiencies

- Laboratory controls:
  - Chemical reference standards: lack of the Ph. Eur. CRS, insufficient establishment of secondary standards
  - Lack of proper monitoring of the potable water

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

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
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 globally by participation in international platforms

Conclusions

• The EDQM has demonstrated its ability to detect non-compliances and take necessary actions through its inspection programme
• Quality systems and data integrity-related issues constitute the main reasons for non-compliances during EDQM inspections
• Worldwide collaboration is a must
Conclusions

• 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!
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