The EDQM Inspection Programme

Prague, 20 September 2017

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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

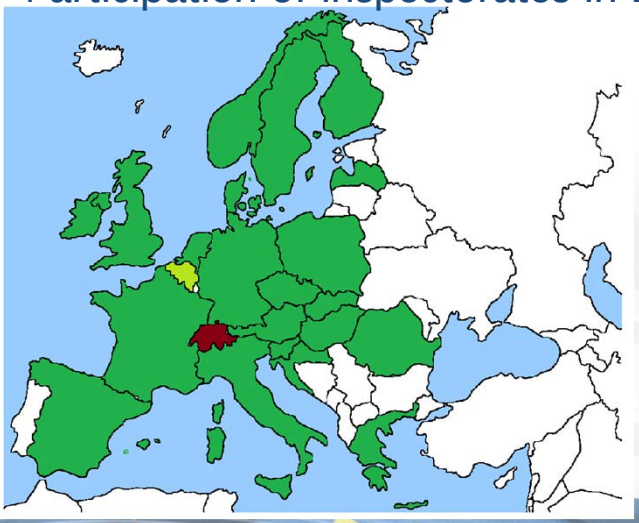
- In case of critical/major deficiencies to the GMP and/or the CEP dossier (failure in the declarations and commitments): actions taken against the validity of CEPs
- Possibility of hearing given to holder and manufacturer
- Information about suspension/withdrawal published on the EDQM websites (CEP 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)

Inspection facts & figures

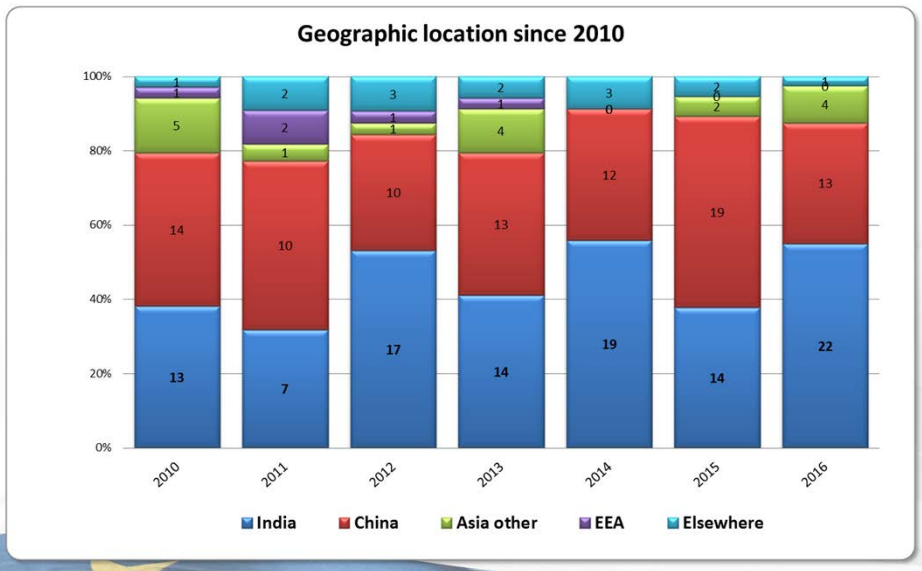
Participation of inspectorates in EDQM inspections

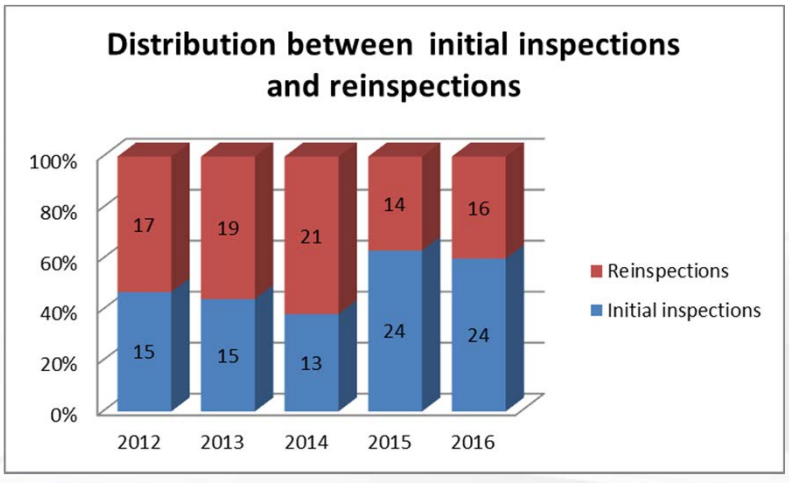


TGA:
4 joint inspections

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

Inspection figures in 2016

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

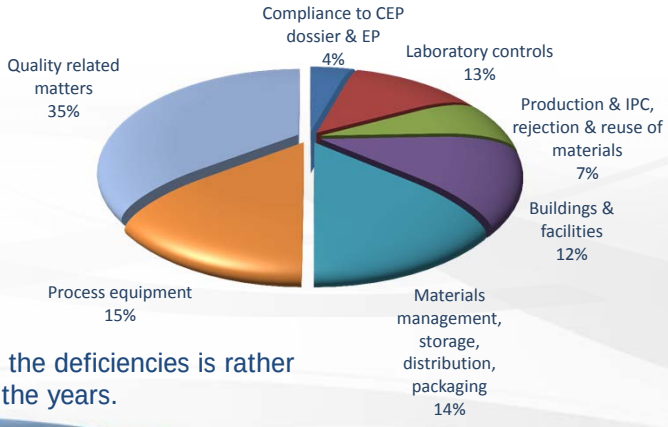
- 39 sites covered by exchange of information (mainly inspections by EEA inspectorates)
  - In 6 cases: suspension of CEPs or removal of the manufacturing site (statements of GMP non-compliance issued by EEA inspectorates)
  - In 2 cases: withdrawal of CEPs because of refusal of inspection

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

Distribution of deficiencies from 2006 to 2016

Quality related matters: 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 (especially the "non-CEP" grade, even though manufactured by same process)
  - ✓ Trends not detected and investigated
- Quality Risk Management:
  - ✓ Frequenty absent 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

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 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

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
  - ✓ 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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