THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

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GMP inspections of manufacturers in the framework of the Certification of Suitability (CEP) procedure

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Overview

- **The EDQM procedure for Certification of Suitability and the EDQM Inspection Programme**
- **How does an inspection procedure work**
- **Inspection facts & figures**

The CEP procedure

- CEP = Certificate of Suitability to the monographs of the European Pharmacopoeia
- Provides centralised assessment of the quality of a source of pharmaceutical substance (mainly APIs):
  - Compliance with European regulatory requirements with regards quality
  - Demonstrates that the substance is suitably controlled by the Ph. Eur. monograph, with additional tests if needed
  - Ensures that all possible impurities are suitably controlled
- Provides easier management of marketing applications and their variations – A CEP replaces main part of 3.2.S of CTD

  ➔ Saving of resources/costs
- CEPs are increasingly accepted by regulatory authorities worldwide

The EDQM Inspection programme

- Integral part of the CEP procedure
- For sites of manufacture of APIs involved in CEP applications
  - Inspections take place mainly in Asia

- Aim: to verify the compliance with:
  - EU GMP Part II (equivalent to ICH Q7) & any applicable annex (eg. Annex 1 for sterile substances, 11 for computerised systems etc.)
  - Submitted CEP dossier and Ph. Eur. in general
- Selection of sites eligible to be inspected by EDQM according to a **risk-based approach** (in line with EU guidance on GMP inspections)
  - Not all sites are inspected
  - Inspection may be performed before or after the CEP is granted

The EDQM inspection programme (2)

- EDQM establishes an annual inspection programme:
  - ✓On-site inspections carried out with official inspectors from European Member States
  - ✓Use of information obtained from inspectorates (eg. Inspection reports)
  - ✓Distant assessment (paper evaluation in the frame of the re-inspection programme)
- Inspection resources worldwide are limited and API manufacturers having CEPs supply generally the global markets ➔ Optimisation of use of inspection resources by exchange of information:
  - ✓ International API Inspection Programme
  - ✓ PIC Scheme (PIC/S)
  - ✓ Confidentiality agreements

Risk-based selection of the sites

- Request from the assessors: inconsistencies in the data, suspicion of data manipulation
- API related criteria: physico-chemical properties, therapeutic use, sterile etc.
- Company related criteria: information from other authorities (i.e. from inspections), regulatory environment of the manufacturing site, activities on the manufacturing site
- Re-inspection: depending on the compliance level after initial inspection, or after CEP suspension when requested
- Several triggers involved

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How does an inspection procedure work

- Inspection performed by team composed of one EDQM inspector and one inspector from an EU/EEA/MRA authority (joint inspections may also be performed, e.g. with WHO, TGA, USFDA, PMDA)
- Inspection lasts generally 3 days
  - Inspectors may take samples for analysis by OMCLs
- An (initial) inspection report is issued within 6 weeks after the inspection
- Immediate actions regarding the validity of the CEPs are taken in case of major or critical deficiencies.

How does an inspection procedure work (2)

- The company should reply to the deficiencies found with a CAPA (to be fully documented and reflect actual measures in place)
- Discrepancies with the CEP dossier should be specifically addressed and managed by the revision process at EDQM
- The CAPA is reviewed and the final report is issued

Inspection outcomes

- According to the inspection results, the Company is quoted as GMP compliant, “borderline” or non compliant
- Borderline status is only provisional: after assessment of the Corrective And Preventive Action plan (CAPA), the outcome is upgraded to compliant or downgraded to non-compliant

Positive outcome

- In case of positive conclusion of the inspection combined with a satisfactory evaluation of the submitted CAPA (and the CEP dossier is up-to-date), an inspection attestation is delivered by EDQM, stating compliance with the CEP and with GMP.
- A GMP Certificate is issued by the EU/EEA/MRA participating Inspectorate via the EUDRAGMDP database (public information): http://eudragmdp.ema.europa.eu/inspections/gmpc/index.do
- The company becomes candidate for re-inspection. It 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 GMP and/or the CEP dossier:
  - Actions are taken by EDQM on the CEPs/CEP applications:
    - ✓CEP(s) of the site are suspended or withdrawn
    - ✓site removed from the list if more than one involved in a CEP dossier
    - ✓on-going CEP application(s) rejected
  - A Statement of Non-Compliance is issued by the EU/EEA/MRA participating Inspectorate via the EUDRAGMDP database (public information)

Negative Outcome (2)

- Decisions to take actions on CEPs/CEP applications:
  - recommended by the inspectors
  - discussed within the EDQM Certification Department
  - decided by the EDQM Ad Hoc Committee
- Holder and manufacturer are notified of the decision
- Public information (EDQM website: http://www.edqm.eu/en/actions-ceps and on the CEP database) + information to international partners

Suspension of CEPs

- CEPs are suspended for a period of 2 years
- Company is requested to apply within this timeframe for a re-inspection
- Based on a valid justification, the company may ask for an extension of this period
- Lifting the suspension can only be done after an inspection demonstrating GMP and CEP compliance, as well as full implementation of the CAPA

Suspension vs withdrawal of CEPs

- **Suspension**: A temporary cancellation
  - CEP can be restored
- **Withdrawal**: A definite cancellation, decided:
  - When no corrective actions are deemed possible
  - For extensive cases of falsification of data
  - After repeated non-compliance

  If the company is still interested in having a CEP ➔ new dossier to be submitted + successful re-inspection

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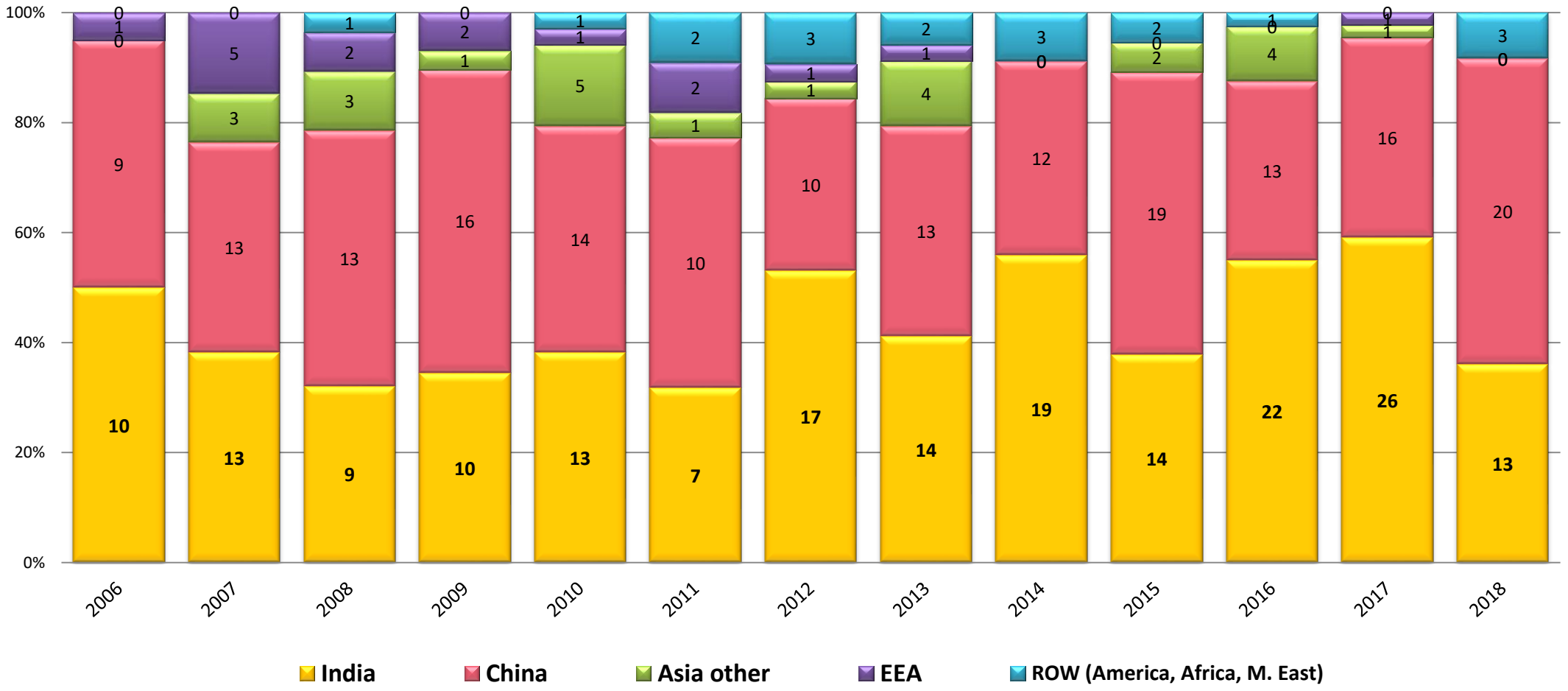
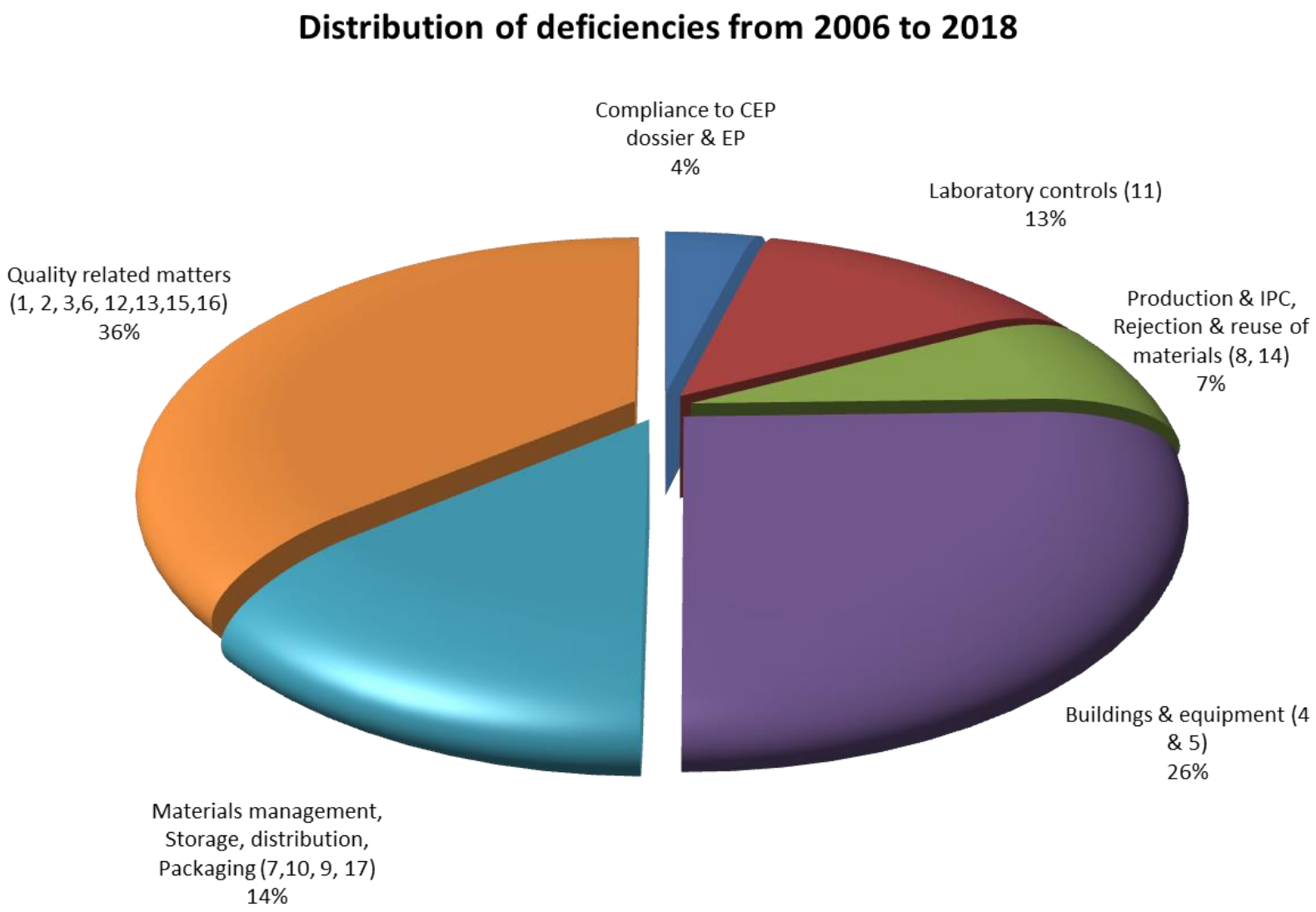
Inspection figures

- About 1200 manufacturers are involved in CEP applications
- 70 sites covered every year by the inspection programme:
  - # 50% on-site inspections
  - # 50% exchange of information + distant assessment
- 1/3 of on-sites inspections are re-inspections
- Rate of non-compliance is 10-20% ➔ ability of the EDQM to detect sites with risk of non-compliance
- In 2018:
  - 36 on-site inspections ➔4 non-compliances (all with critical findings)
  - 46 sites covered by exchange of information (mainly inspections by EEA inspectorates) + distant assessment ➔1 Statement of GMP non-compliance

Geographical location of EDQM inspections 2006-2018



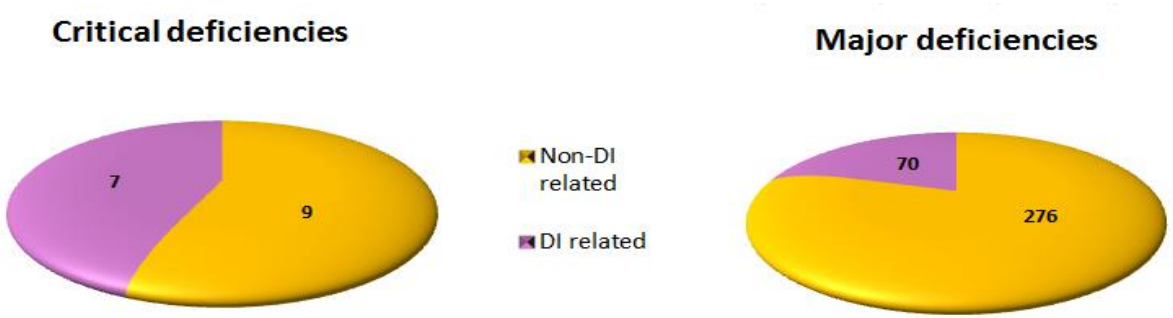
Quality related matters: Quality management, Personnel, Documentation, Validation, Change control, Complaints and recalls, Contract manufacturers



Falsification – Fraud – Data integrity

A hot topic !

- 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



Conclusion

- The EDQM inspection programme for API manufacturers is running efficiently (balance between on-site inspections and exchange of information)
  - For >50% of the CEP sites, the GMP status is known
  - The rate of non-compliance is 10-20%
- API manufacturers and their suppliers should endorse their responsibilities and be supportive to customers
- Medicinal 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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