

# 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
- Perspectives - Conclusion



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## EDQM Inspection programme

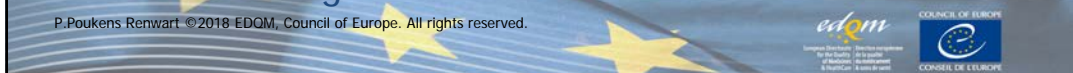
- In application of EU Directives 2001/82/EC and 2001/83/EC on Compilation of Community Procedures as amended, EDQM was given a mandate by the European Commission to establish an annual programme for inspections
- Inspections performed inside and outside Europe



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## EDQM Inspection programme

- Integral part of the Certification Procedure
- Involving manufacturing sites and brokers/distributors holding CEP(s)
- Inspection may be 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



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## Drafting of the programme



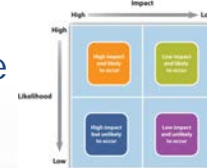
- Prepared in accordance with the EU guidance published by EMA (EMA/EMA/385898/2013 as amended, Compilation of Union procedures on inspections and exchange of information)
- Selection of sites eligible to be inspected by EDQM
- According to a risk-based approach

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## 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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## Adoption of the programme

- The draft programme is circulated to the EU/EEA Member States for comments and presented to the GMP/GDP Inspectors Working Group at EMA for information & expression of interest.
- The programme is finally adopted by the CEP Steering Committee.
- The final programme is circulated to all EEA Member State Competent Authorities (comments welcome at any time).

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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)
- An inspection report is issued within 6 weeks.
- Immediate actions regarding the validity of the CEPs are taken in case of major or critical deficiencies.

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## Inspection Outcome

- 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, the outcome is upgraded to compliant or downgraded to non-compliant.
- Companies found compliant may be re-inspected/ re-evaluated within 2-5 years depending on the numbers and classification of deficiencies found.



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## Inspection follow-up



- The company should reply to the deficiencies found within one month from the receipt of the inspection report.
- The replies (Corrective and Preventive Action Plan – CAPA) should be fully documented and reflect actual measures in place.
- Discrepancies with the Certification dossier are specifically addressed and managed by the revision process at EDQM.

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## Positive Outcome



- In case of positive conclusion of the inspection combined with a satisfactory evaluation of the submitted CAPA, and if any expected application for CEP revision has been submitted, an inspection attestation is delivered by EDQM, stating the compliance with the CEP and with GMP.
- A GMP Certificate should be issued by the EEA participating Inspectorate via the EUDRA GMDP database (public information Directives 2001/83/EC and 2001/82/EC as amended).

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## Negative Outcome



- In case of critical/major deficiencies to the GMP and/or the CEP dossier (failure in the declarations and commitments):
  - CEP(s) 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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## Negative Outcome

When the decision is confirmed:

- Information about suspension/withdrawal is published on the EDQM website (CEP database and Certification webpages):

CEP Suspensions		
a) As a result of an inspection of the manufacturing site(s)		
Date	Substance name	CEP Number

- Ph. Eur. Member States, International partners, EMA, EU Commission and local Inspectorate are informed.
- Statement of GMP non-compliance is issued by the EEA Inspectorate (public in EudraGMDP).

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## Suspension of the 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 the full implementation of the CAPA.

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## Suspension vs withdrawal: what's the difference ?

- **Suspension:** A temporary cancellation
  - CEP can be restored
- **Withdrawal:** A definite cancellation
  - 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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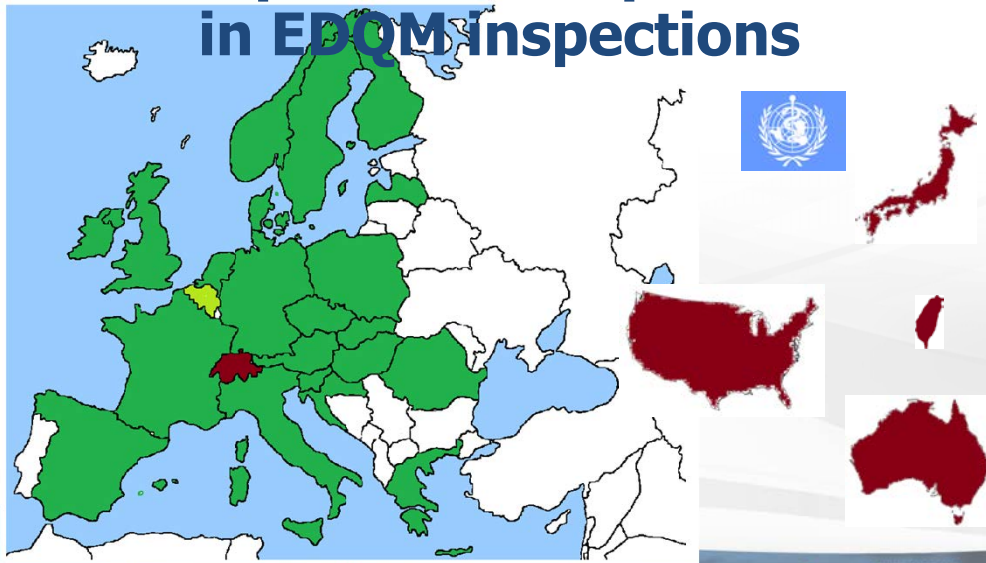
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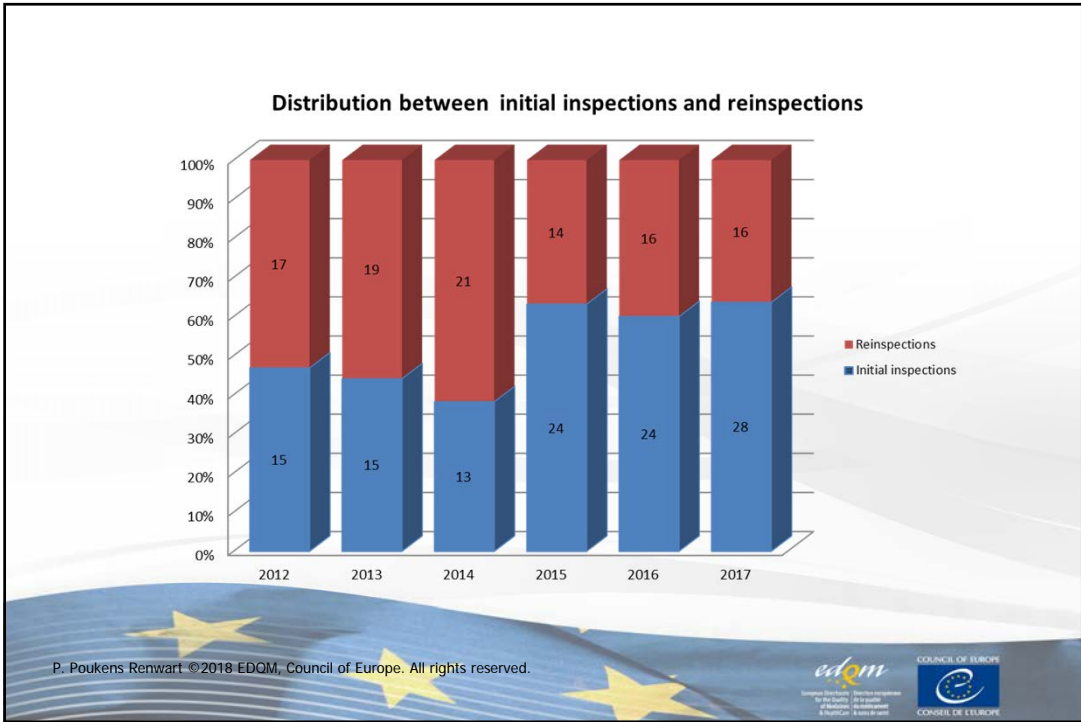
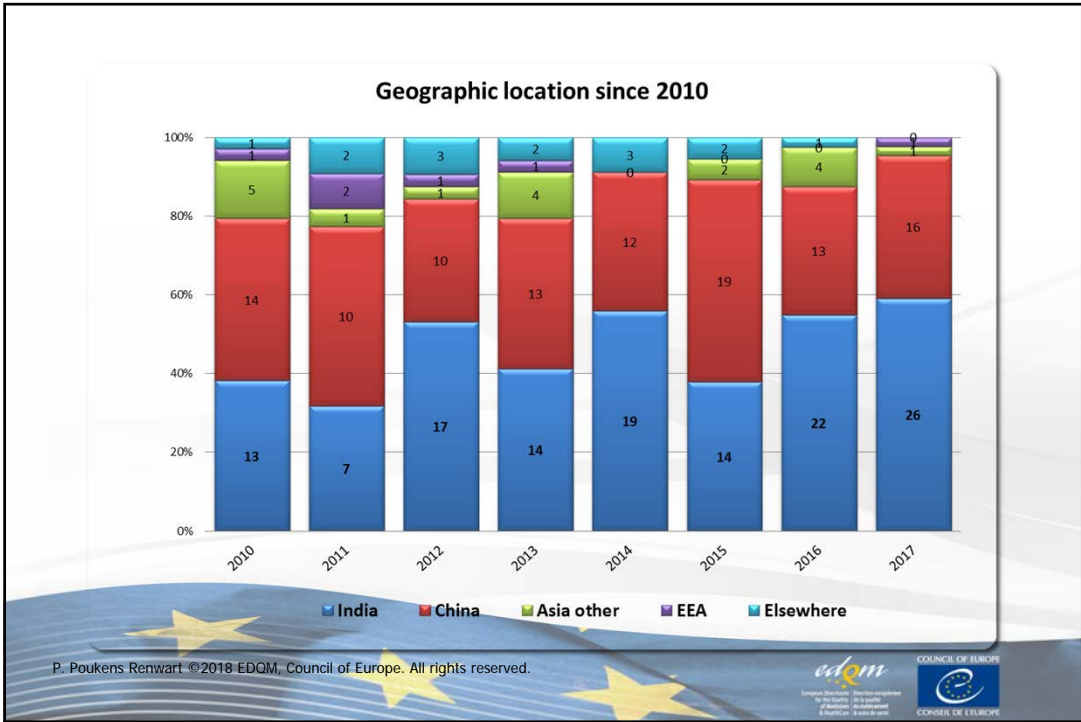


## Participation of inspectorates in EDQM inspections



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## Inspection figures in 2017

- 44 sites covered by EDQM inspections
- 3 non-compliances, all with critical findings:
  - a) quality management system found weak and incapable to allow consistent delivery of products with appropriate quality attributes (inadequate deviation management, unavailability of batch records, material storage management & starting material specifications not under control, failure to ensure recording and reporting of all analytical results, inappropriate qualification of computerised systems etc.)

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## Inspection figures in 2017

- b) overall critical risk resulting from findings on inadequacies of quality management system and of controls to limit contamination & cross contamination risks, lack of suitability and integrity of analytical tests, insufficient validation of cleaning methods
- c) overall critical risk resulting from inadequate management of quality events, insufficient qualification of personnel, manipulation of in-process test results, QC practices not ensuring data integrity

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## Inspection figures in 2017

- 37 sites covered by exchange of information (mainly inspections by EEA inspectorates), of which:
  - 2 statements of GMP non-compliance issued by EEA inspectorates were taken into account and led to actions on the site-related CEPs
  - 8 sites subject to a desktop GMP assessment for re-inspections

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## General Compliance Trends

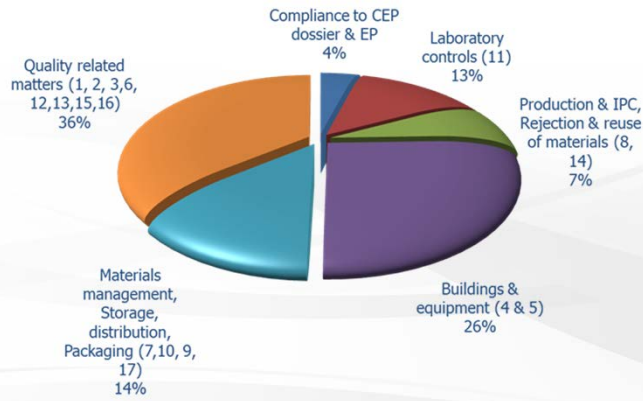
- Inspected sites found non-compliant:
  - 2013: 38%
  - 2014: 12%
  - 2015: 18%
  - 2016: 18%
  - 2017: 5%
- Ability of EDQM to identify sites with higher risk of non-compliance and to focus on them.

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## Distribution of deficiencies from 2006 to 2017

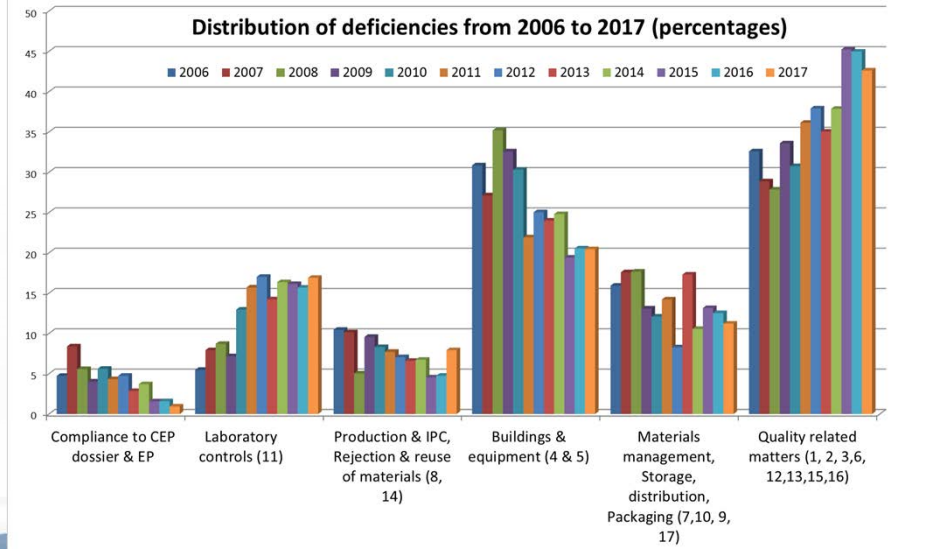
**Quality related matters:** Quality management, Personnel, Documentation, Validation, Change control, Complaints and recalls, Contract manufacturers



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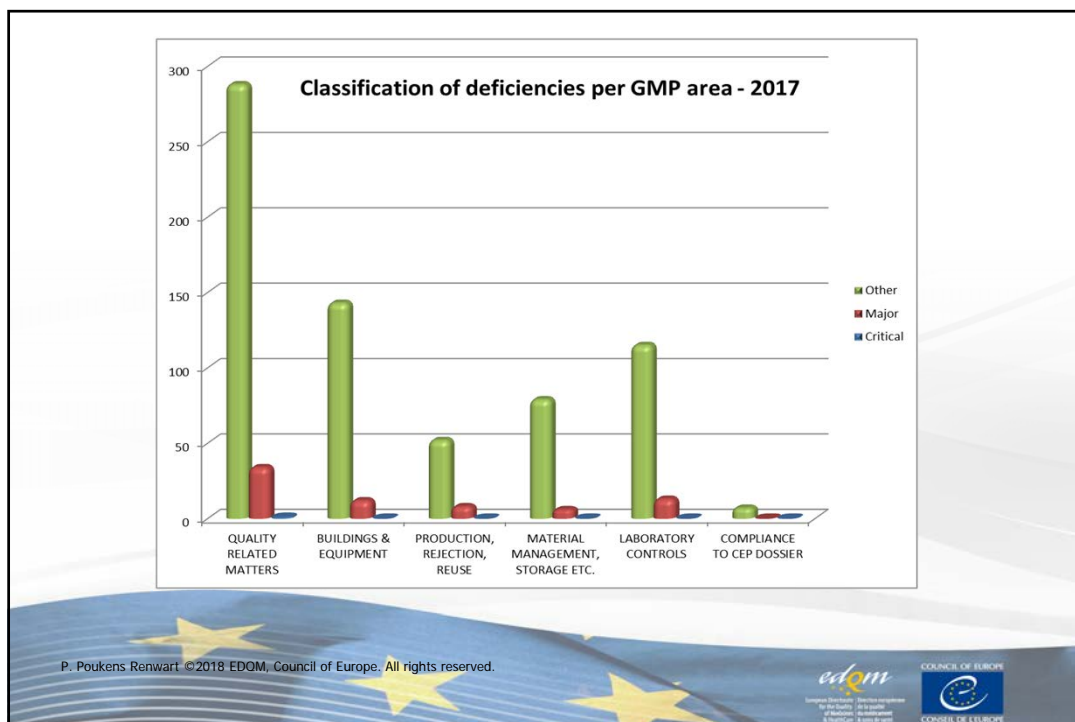
### Distribution of deficiencies from 2006 to 2017 (percentages)



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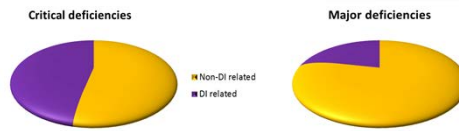
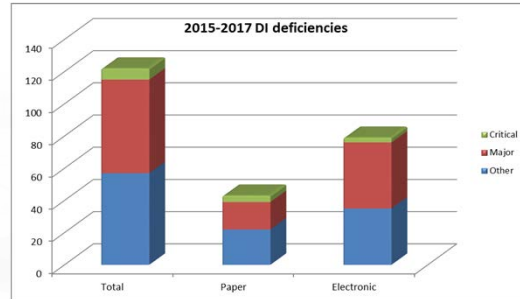
## Falsification – Fraud – Data integrity

- 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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# Deficiencies related to Data Integrity



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## Perspectives

- Need to further develop the risk-based approach when elaborating the programme
- Continual 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

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## 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.

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## 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.

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This presentation has been prepared  
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