

# How to benefit from EDQM inspections in the context of the certification procedure ?

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## Overview:

- Council of Europe, European Union and EDQM
  - EDQM Inspection Programme in the frame of Certification Procedure
  - How does the procedure work
  - Inspection facts & figures
  - Perspectives - Conclusion

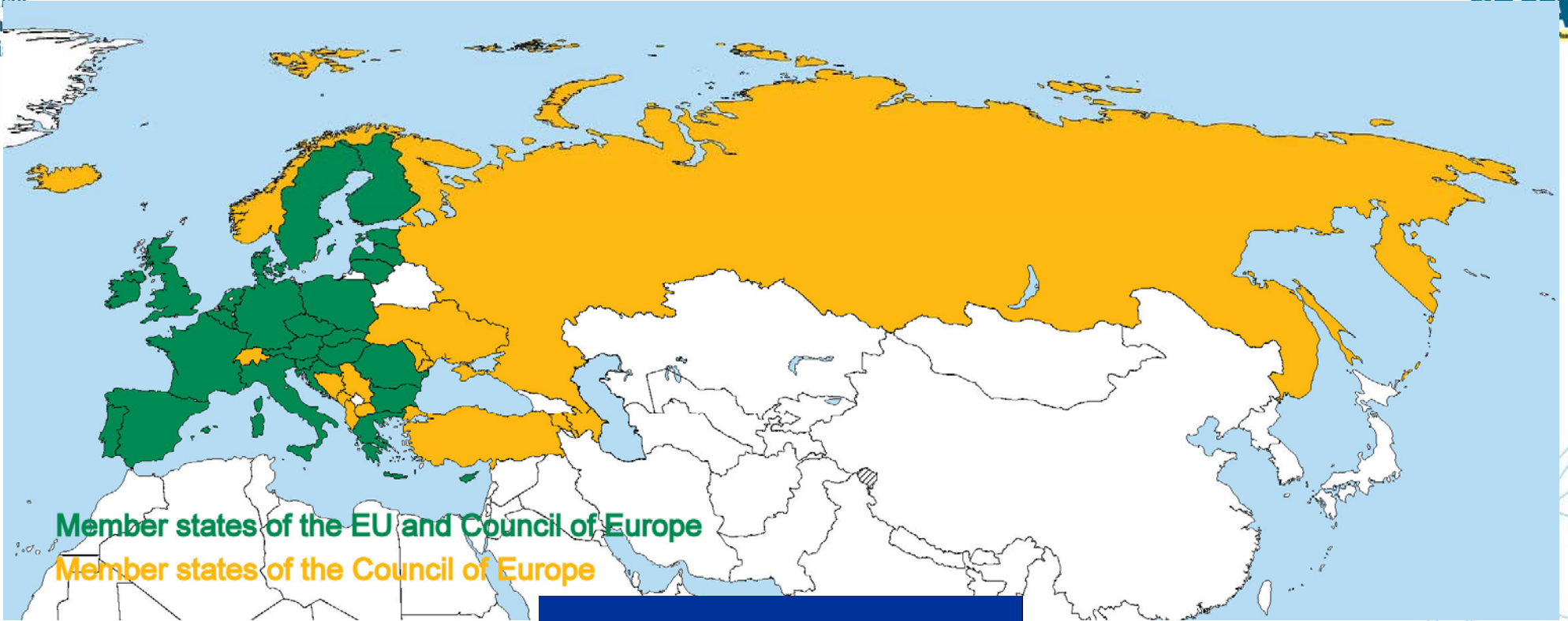
## The Council of Europe

- Founded in 1949
- Development of European common and democratic principles:
  - Democracy
  - Rule of law
  - Human rights
- 47 Member States

COUNCIL OF EUROPE



CONSEIL DE L'EUROPE



Member states of the EU and Council of Europe

Member states of the Council of Europe

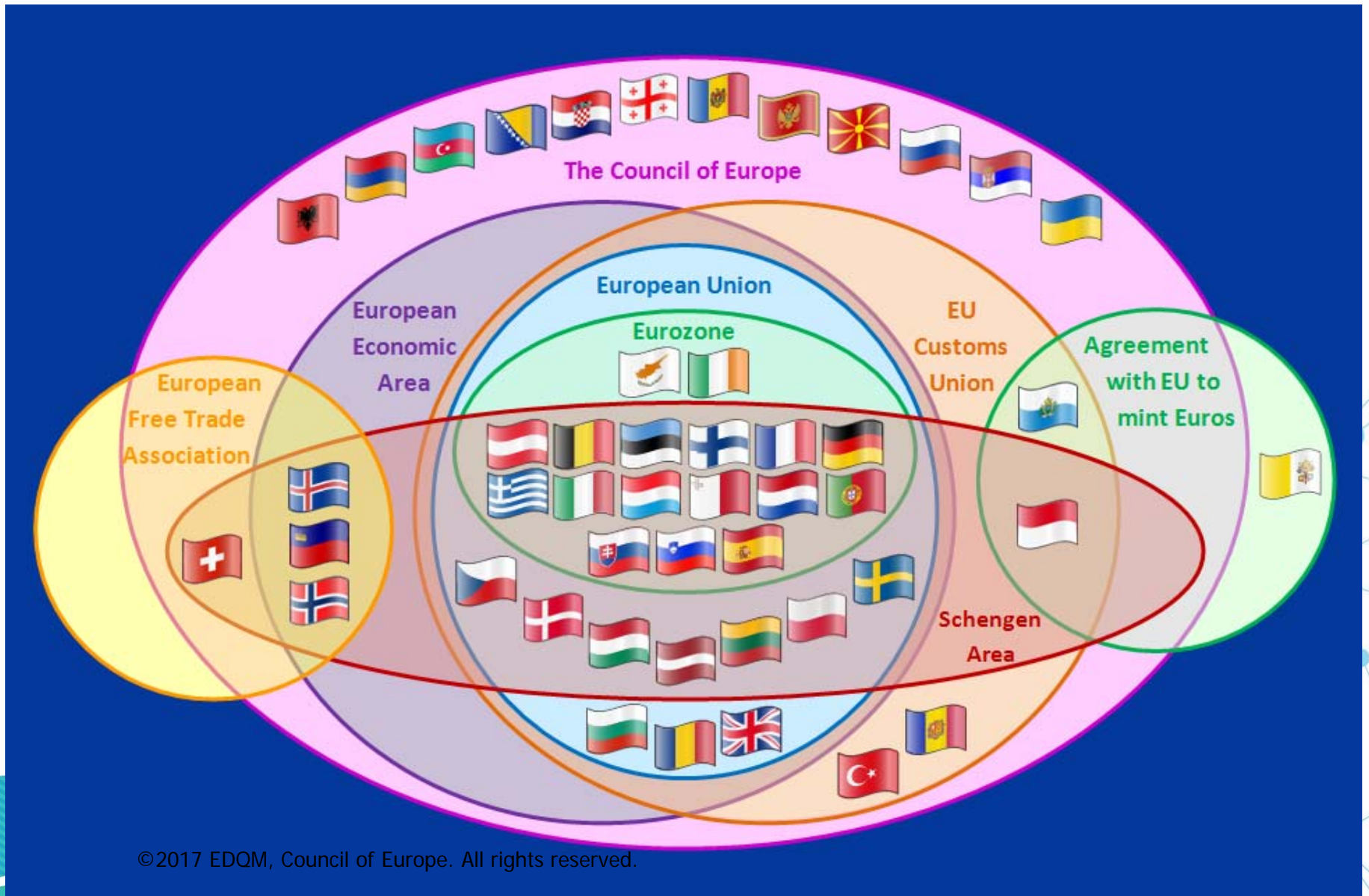


## The European Union

- ... a political and economic community of 28 Member States;
- ... traces its origins to the European Coal and Steel Community formed among 6 countries in 1951 and the Treaty of Rome in 1957;
- ... current legal framework based on the Maastricht Treaty (1993);
- ... comprises a single market created by a system of laws which apply in all Member States.



# European institutions/agreements/treaties/zones

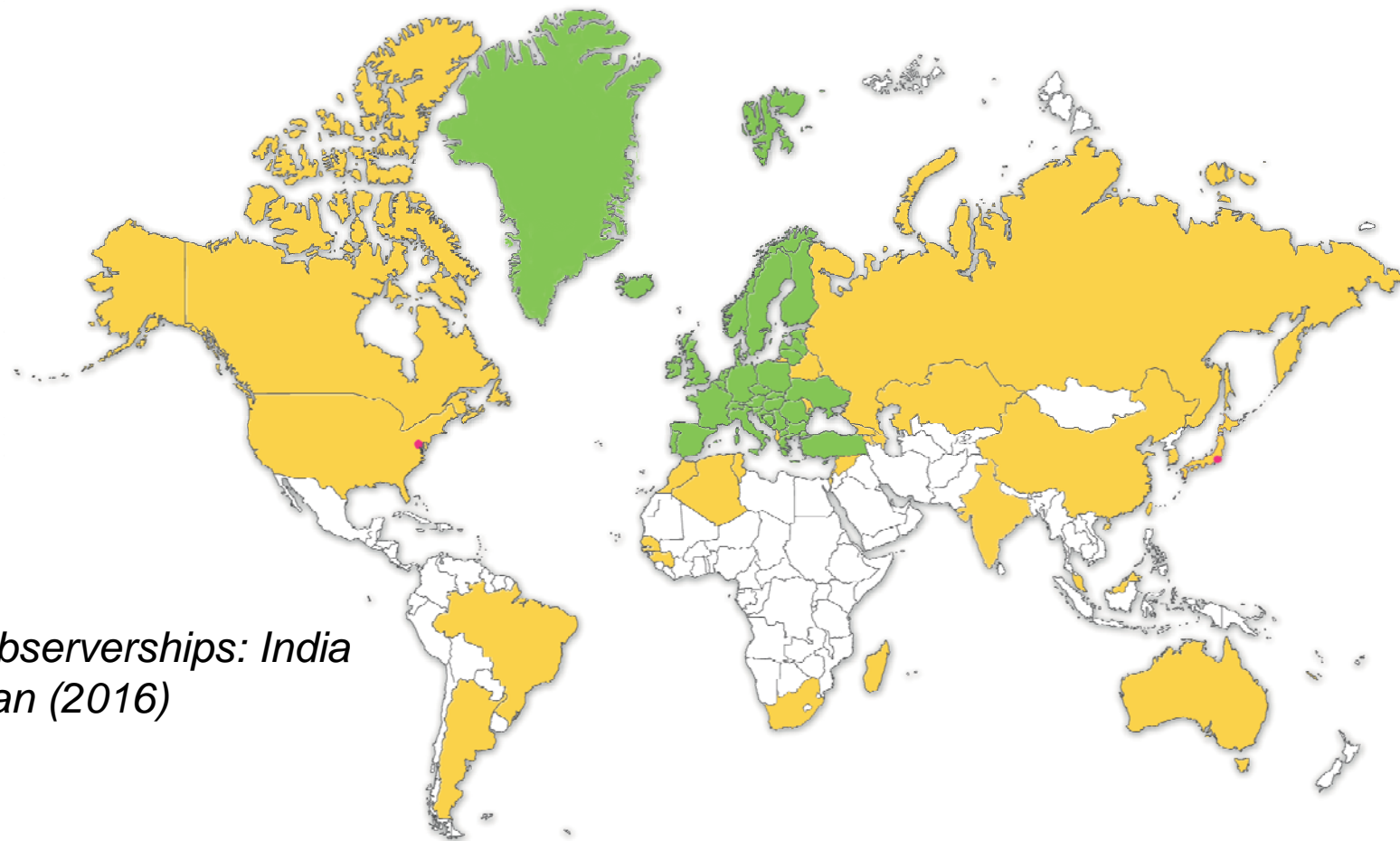


## The EDQM

- A Council of Europe Directorate
- 1964: Activities based on an International Convention from the Council of Europe to promote free movement of medicines in Europe
- Mandatory status reinforced in 1975 in the EU Regulations (Directives) (applicable to all EU Member States)
- 1994: EU ratified the Ph. Eur. Convention



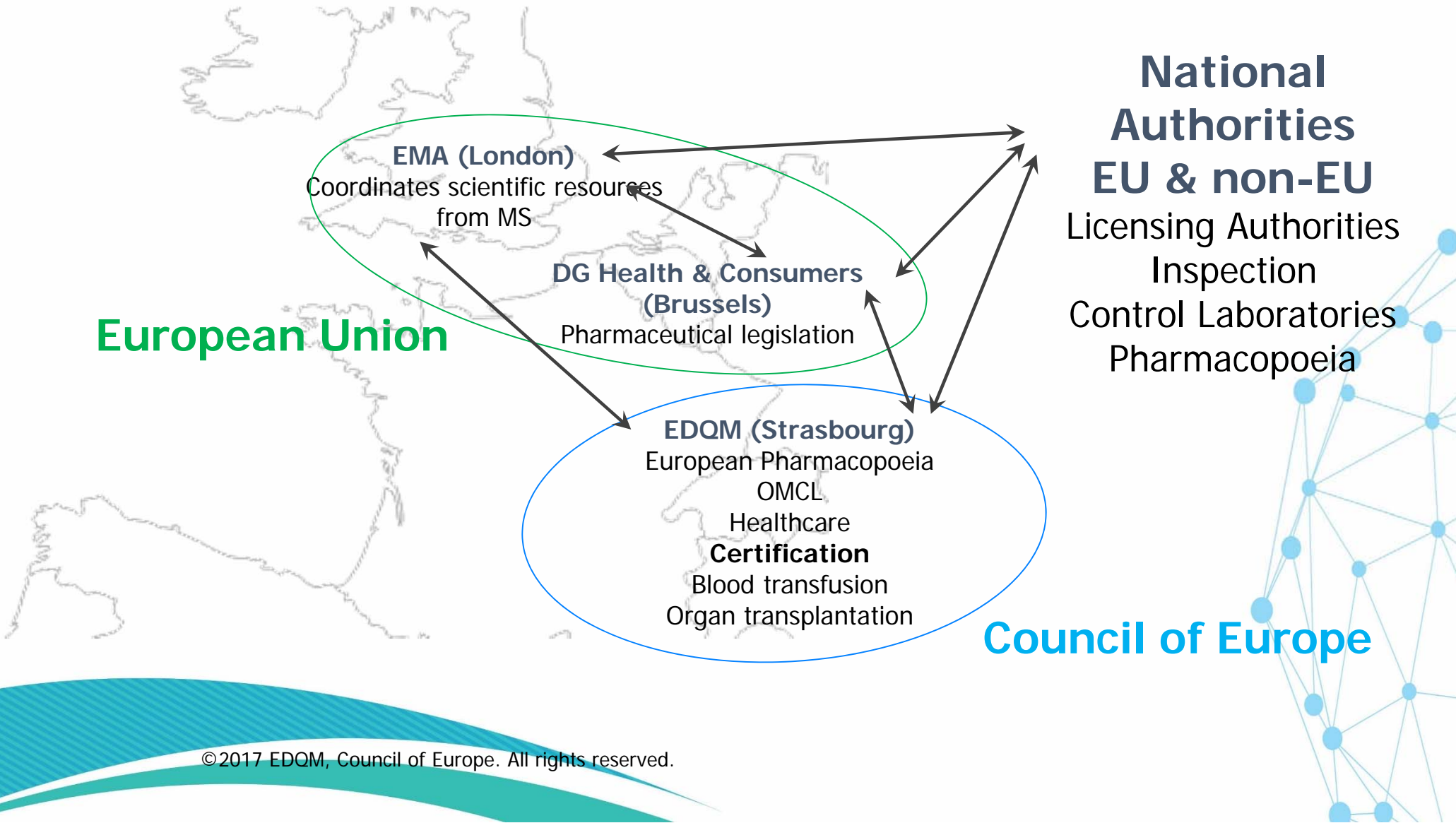
# Ph. Eur. Members (green) and observers (yellow)



*Last observerships: India  
& Japan (2016)*



# European interactions



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## Certification of Suitability

- Marketing Authorisation applicant in EU required to demonstrate that:
  - The active substance used complies with the Ph. Eur. monograph(s)
  - The Ph. Eur. monograph is able to control the quality of this active substances (impurity profile)



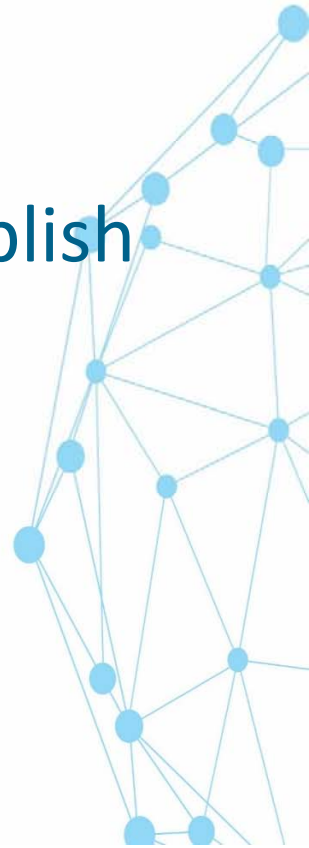
## Certification of Suitability

- 1994: EDQM initiated the procedure for Certification of Substances for which there is a monograph in the European Pharmacopoeia
- **CEP: Certificate-European-Pharmacopoeia**
- Also known as “COS” (“Certificate of Suitability”)
- Applications evaluated by assessors nominated by their national licensing authorities
- (currently: 103 from 24 countries)



## EDQM Inspection programme

- Integral part of the Certification Procedure
- In application of EU Directives 2001/82/EC and 2001/83/EC as amended, EDQM was given a mandate by the European Commission to establish an annual programme for inspections.



# EDQM Inspection programme

- Performed before or after a CEP is granted
- Mostly outside Europe (EU authorities are responsible of sites on their own soil)
- Covering manufacturing sites and brokers/distributors holding or having applied for CEP(s).

# EDQM Inspection programme

- Aim: to verify the compliance with
- Submitted CEP dossier
- EU GMP Part II
- EU GMP Annexes (e.g. Annex 1 for sterile substances, Annex 7 for substances of herbal origin)
- Implementation of CAPA (in case of re-inspection)
- Ph. Eur. in general

## Selection of the sites

- Performed 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)
- As per European legislation, a systematic inspection is not required. Instead, a risk-based approach is applied for the surveillance of manufacturers (reminder: it is the responsibility of the QP of the holder of the manufacturing authorization to ensure they only use GMP-compliant material)



## 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

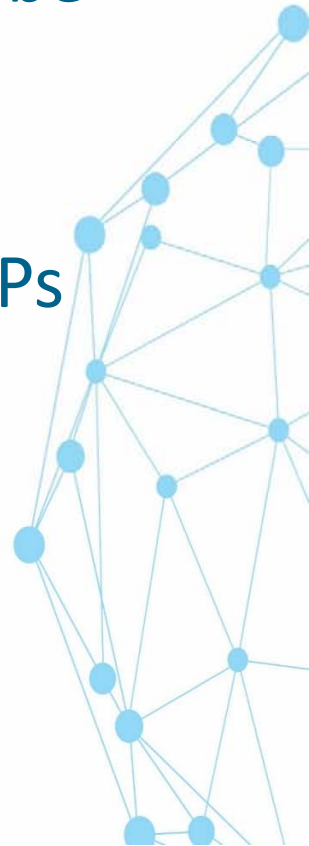


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## How does the procedure work

- Inspection performed by team composed of an EDQM inspector and an inspector coming from an EU/EEA/MRA authority (joint inspections can also be performed 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.



## 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 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.



## Inspection follow-up

- The company must 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 DCEP.



## 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).



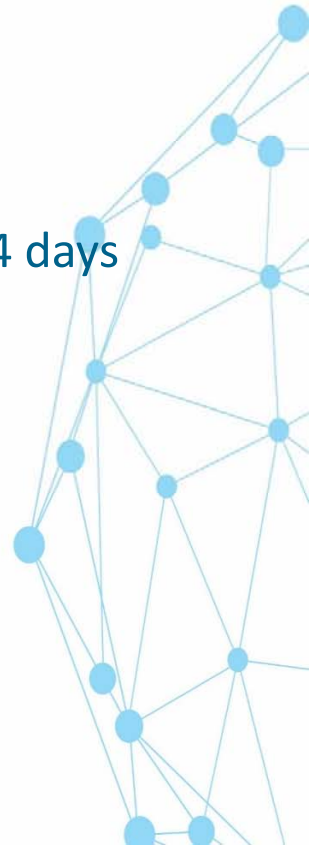
## Negative Outcome

- In case of critical/major GMP deficiencies or in case of major discrepancies compared to the dossier (failure in the declarations and commitments)
  - CEP(s) suspended or withdrawn
  - On-going CEP application(s) rejected



# Negative Outcome

- Suspension/Withdrawal/Application rejection is
  - recommended by the inspectors
  - discussed within the Certification Division
  - endorsed by an Ad Hoc Committee
- Holder and manufacturer notified and given a possibility of hearing within 14 days from notification.





## Negative Outcome

After the period for managing a hearing if any, or after 14 days :

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

**Actions taken by the EDQM**  
*The EDQM announces the suspension of the following CEPs :*

- As a result of an inspection of the manufacturing sites:

Date	Substance name	CEP Number
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- As failure to commitments of willingness to be inspected (refusal of inspection, reconstruction/restoration of sites to achieve GMP level, temporary closure of a site...) and/or to operate according to EU GMP:

## Negative Outcome

- 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).



## 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.



## 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 (e.g. extensive cases of falsification of data, repeated non-compliance)
  - A new dossier to be submitted if the company is still interested in having a CEP



## Restoration of the suspended CEPs

- It can only be done after an inspection has demonstrated GMP and CEP compliance as well as the full implementation of the CAPA.
- Final decision to restore the CEP(s) is also taken by the Ad Hoc Committee upon the inspectors' recommendation.



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## Inspection figures in 2016

- 40 sites covered by EDQM inspections (India 22, China 13, elsewhere 5)
- 7 non-compliances, all with critical findings
- 39 sites covered by exchange of information (mainly inspections by EEA inspectorates)
  - In 6 cases, CEPs were suspended or the manufacturing site was removed (statements of GMP non-compliance issued by EEA inspectorates)
  - In 2 cases, CEPs were withdrawn because of refusal of inspection



## General Compliance Trends

- Inspected sites found non compliant:
  - 2013: 38%
  - 2014: 12%
  - 2015: 18%
  - 2016: 17,5%
- The high proportion of non compliant sites is seen as a result of the ability of EDQM to identify sites with higher risk of non-compliance and to focus on them.





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## Perspectives

- Continual reinforcement of collaboration and sharing of information with EU and International Inspectorates
- Aim: optimisation of inspection resources by
- Programme for exchange of information on API (EMA): increasing number of contributors expected
- Committee of officials of PIC Scheme (PIC/S)
- Confidentiality agreements
- Performance of distant GMP assessment

## Conclusions

- The **EDQM** has demonstrated its **ability to detect non-compliances** and take necessary actions through its inspection programme.
- **Quality related issues** constitute the main reasons for non-compliances during GMP inspections.
- **API manufacturers** should endorse their **responsibilities** and remain committed to quality.
- **Finished products manufacturers** must improve their **ability to select GMP compliant API suppliers** and **audit/monitor** them accordingly.



Thank you!  
Questions / Suggestions?