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

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# General overview of the CEP procedure

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Module 5: Fundamentals of the CEP Procedure (Live Webinar)
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# Summary

- Background & legal framework
- The CEP procedure
- Comparison between CEP and ASMF procedures
- How to apply for a CEP
- Evaluation of applications and granting of CEPs
- Key figures
- Information available on EDQM website

# EU legislation and Certificates of Suitability

- EU Directives 2001/83/EC (human) states that for active substances:
  - They should comply with the Ph. Eur monograph if there is one
  - Directive 2001/83/EC amended by 2003/63/EC: In cases where a specification contained in a European Pharmacopeia monograph might be insufficient to ensure the quality of the substance (new impurities), the competent authorities may request more appropriate specifications from the marketing authorisation holder

...“where the active substance is the subject of a monograph of the Ph. Eur, the applicant can apply for a certificate of suitability that, where granted by the EDQM, shall be presented in the relevant section of the CTD Module. Those certificates of suitability ...are deemed to replace the relevant data of the corresponding sections described in the Module...”

# Governing document for the Certification procedure

**Resolution AP-CSP (07) 1** adopted by the Public Health Committee of the Council of Europe

- Describes the process for the procedure
- Available on the EDQM website (www.edqm.eu)

# Scope of the CEP procedure

- Substances described in monographs in the Ph. Eur. (Active substances, excipients, herbal drugs / herbal preparations)
  → “Chemical” or “Herbal” CEP

- Products with risk of TSE (SM, intermediates, reagents,..)
  → “TSE” CEP

- Open to any manufacturer of pharmaceutical substances regardless of geographical origin

# Out of Scope of the CEP Procedure

- Substances not included in Ph. Eur. (except TSE CEP)
- Substances which do not comply with the Definition section of the monograph, if applicable
- Biologicals and products extracted from animal tissues
- Human tissues derivatives, blood derivatives, vaccines
- Finished products

# The CEP procedure

- CEP = Certificate of Suitability to the monographs of the European Pharmacopoeia
- Managed by EDQM
- Official implementation in 1994
- An international platform for:
  - Assessment of the quality of substances for pharmaceutical use (mainly APIs), with reference to monographs of the Ph. Eur.
  - Source of information to update Ph. Eur. monographs
  - Centralised assessment
  - Facilitates management of MAAs and variations
  - Coordination and conduct of GMP inspections of API manufacturers

**Optimise time and resources!**

# Types of CEP

- To demonstrate that the quality of a substance is controlled by the Ph. Eur. monograph and additional tests if needed
  - “Chemical CEP”
  - “Herbal CEP”

- To guarantee compliance with the general monograph on Products with TSE risk
  - “TSE CEP”


A CEP **does not** replace a certificate of analysis.

A CEP **does not** replace the QP declaration.

A CEP **is not** a GMP certificate.

# CEP and ASMF procedures

- According to EU **NfG « Summary of requirements for active substances in the quality part of the dossier »**, the applicant can choose the way to provide data on the quality of an active substance:
  - ➢Certificate of suitability
  - ➢Active substance Master File (ASMF)
  - ➢Full details of manufacture in marketing authorisation application

- The data to be submitted are the same, regardless of the route selected

**CEPs are not mandatory, but generally avoid any subsequent reassessment**

# Comparison between CEP & ASMF procedures

| | CEP procedure | ASMF system |
|---|---|---|
| Scope | pharmacopoeial substances only<br>-> active substances or excipients<br>-> any substance for TSE CEP | active substances only<br>-> new or pharmacopoeial |
| Dossier | Content identical (CTD 3.2.S)<br>Full dossier sent directly by the manufacturer to EDQM<br>(will be the holder of the CEP) | Content identical (CTD 3.2.S)<br>Full dossier sent by API manufacturer to Competent Authorities<br>AP sent by API manufacturer to marketing authorisation applicant or holder of medicinal product |
| Additional data | Holders commitments | Letter of access (to be sent by API manufacturer) |
| Link with a medicinal product | Independent from marketing authorisation applications | In the context of a specific marketing authorisation application or variation for medicinal products |

# Comparison between CEP & ASMF procedures

| | CEP procedure | ASMF system |
|---|---|---|
| Evaluation | Single evaluation centralised at EDQM by assessors nominated by Competent Authorities / Certification Steering Committee | Assessment of ASMF by each competent authority in the context of assessing a specific marketing authorisation application or variation for medicinal products |
| | Principles identical:<br>Assessment against ICH/EU guidelines for quality + Ph. Eur monograph + EDQM specific guidance | Principles identical:<br>Assessment against ICH/EU guidelines for quality + Ph. Eur monograph if applicable |

# Comparison between CEP & ASMF procedures

| | CEP procedure | ASMF system |
|---|---|---|
| Deliverable | Certificate including annexes (additional tests to be performed) granted to manufacturer who supplies a copy to customers (users of the API) | A Marketing Authorisation for the medicinal product using this particular API |
| Variations | Changes to the CEP dossier centralised at EDQM<br>Submission of revised CEPs according to EU Variations regulation | Submission of changes to marketing authorisation applications, according to EU Variations regulation |
| Use | Ph. Eur member states & others (Australia, Canada, New Zealand, Tunisia, Morocco, Singapore, South Africa, Saudi Arabia, etc) | EU/EEA member states + Australia + Canada |

# EU ASMF worksharing

- Annex 7 of the CEP application form foresees sharing EDQM reports with:
  - National Competent Authorities of the Ph. Eur. member states
  - EMA including all CHMP and CVMP Members and their experts
  - Competent Authorities of countries with whom EDQM has a Memorandum of Understanding and/or Confidentiality Agreement in place
- ASMF reports may also be made available for EDQM (see NfG ASMF procedure CHMP/QWP/227/02 Rev 3 corr).
- Goal: improved efficiency & harmonisation
- When ASMF already registered: may speed up the process

# How to apply for a CEP

- Application form (for new application) available on the website. It contains tables to be filled in, statements and declarations to be signed
- Quality Overall Summary
- Fees:

| | NEW APPLICATIONS | |
|---|---|---|
| CEP 028 | Simple chemical certificate | 5000 € |
| CEP 027 | Simple TSE or herbal certificate | 3000 € |
| CEP 026 | Double certificate (chemical + TSE)* | 8000 € |
| CEP 025 | Certificate for chemical purity and sterility | 8000 € |
| CEP 024 | Certificate for chemical purity and sterility + TSE** | 9000 € |
| * In the case of TSE supported by a CEP the fees are only 5000 €.<br>** In the case of TSE supported by a CEP the fees are only 8000 €. | | |


**Updated application forms in force from *1 June 2023***

- EMA SPOR/OMS ORG_ID and LOC_ID for all companies involved must be provided
- Updated Holder's Commitment
- For Sister Files a template for comparative table is now added

# How to apply for a CEP

- When the product is already covered by an ASMF this information should be shared as it can speed up the evaluation :

**3. History of the substance**

In order to take into account commercialisation history and quality assessments already performed for this source of substance, please provide key information regarding approved/marketed medicinal products and/or accepted ASMFs/DMFs within the European Union, EEA, Switzerland, the UK, Australia, or Canada containing **the substance manufactured by your company according to the manufacturing process presented in this CEP dossier**.

**3.2 List of accepted ASMFs/DMFs**

Please provide information concerning ASMFs/DMFs which have been accepted **after October 2012**.

| Country of registration | ASMF/DMF registration number | Latest ASMF/DMF holder's version | Approval date |
|---|---|---|---|
| | | | |

# How to apply for a CEP

- Dossier in English (preferably) or French

- Content in compliance with:
  - Content of the Dossier for Chemical CEP: comparable to ASMF or 3.2.S of CTD
  - For TSE risk CEP: requirements from Ph. Eur. general text, 5.2.8 and Content of the dossier for TSE risk
  - Content of the dossier for herbal drugs/herbal drug preparations
  - Help for preparation of a dossier for sterile substance : PA/PH/Exp.CEP/T (06) 13 1R

- Electronic submissions of any applications (NDOS/Rev/Renewal) in eCTD only
  - via CESP, register for a CESP account on the Heads of Medicines Agencies website

# Responsibilities of the CEP holder

*See EDQM document PA/PH/CEP (21) 57*

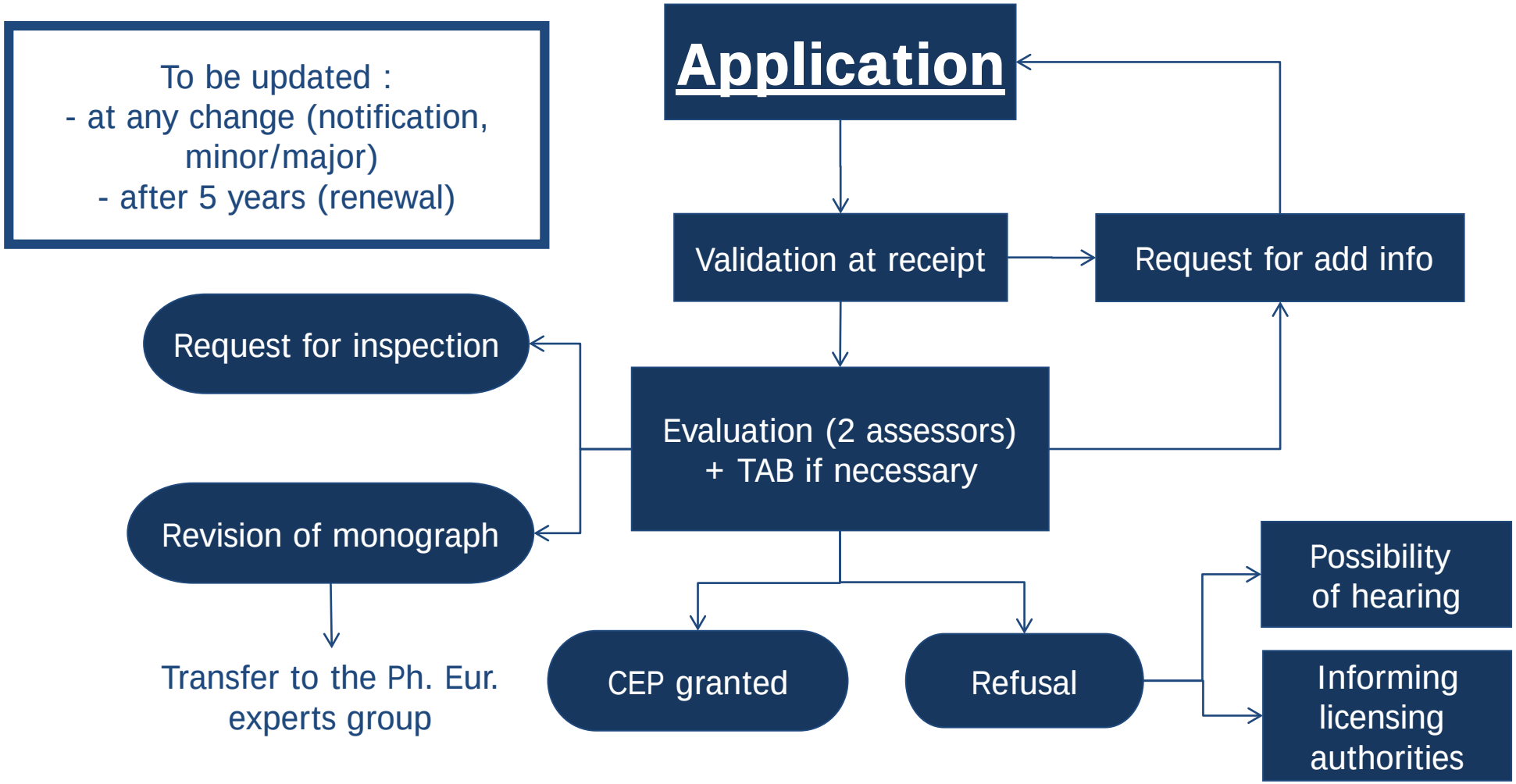
Obligation to inform MAH of any change in API manufacturing activities and information described in part 3.2.S of the CTD (quality agreements in place should specify whether the implementation needs pre-approval by the MAH acc. to criticality of change).

CEP holders shall also provide sufficient information towards MAHs in order to enable them to fulfil their respective legal responsibilities.

- Provide the MAH with the most recent version of the CEP in a timely manner
- Share any pivotal information which is not on the CEP but needed to guarantee quality, safety and efficacy of the medicines (e.g RoS, risks for nitrosamines, elemental impurities, etc.)
- Notify without delay when the CEP is suspended, withdrawn or expired, together with the reasons behind ⇒ an impact on MAA and require immediate actions by the MAH.

CEP holder responsibilities are taken into account, regardless of which stage of the manufacture/supply chain of an API during GMP/CEP inspections

# How it works



# Who performs the evaluation?

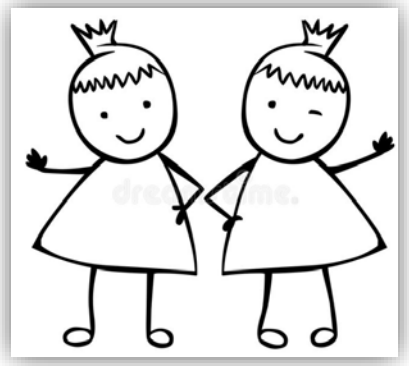
- ✓ Assessors are proposed by National Competent Authorities and appointed by Steering Committee
- ✓ EDQM assessors also appointed by the Steering Committee
- ✓ New application assessed by 2 assessors: 1 from EDQM and 1 from NCA from Ph. Eur. member states and beyond
- ✓ About 100 assessors from authorities from 25 countries, including Canada, Australia
  - Skilled in the relevant domain (chemical evaluation, TSE risk, herbal products, toxicologists)
  - Come regularly to EDQM premises for the evaluation of dossiers
  - Procedure for remote evaluations introduced in 2020 (due to Covid-19 pandemic)

**A great and successful example of international cooperation!**

# Sister files

- A company holding a CEP may wish to apply for another CEP for the same substance ⇒ sister file

- Policy document available on the EDQM website : 'Sister files' procedure.

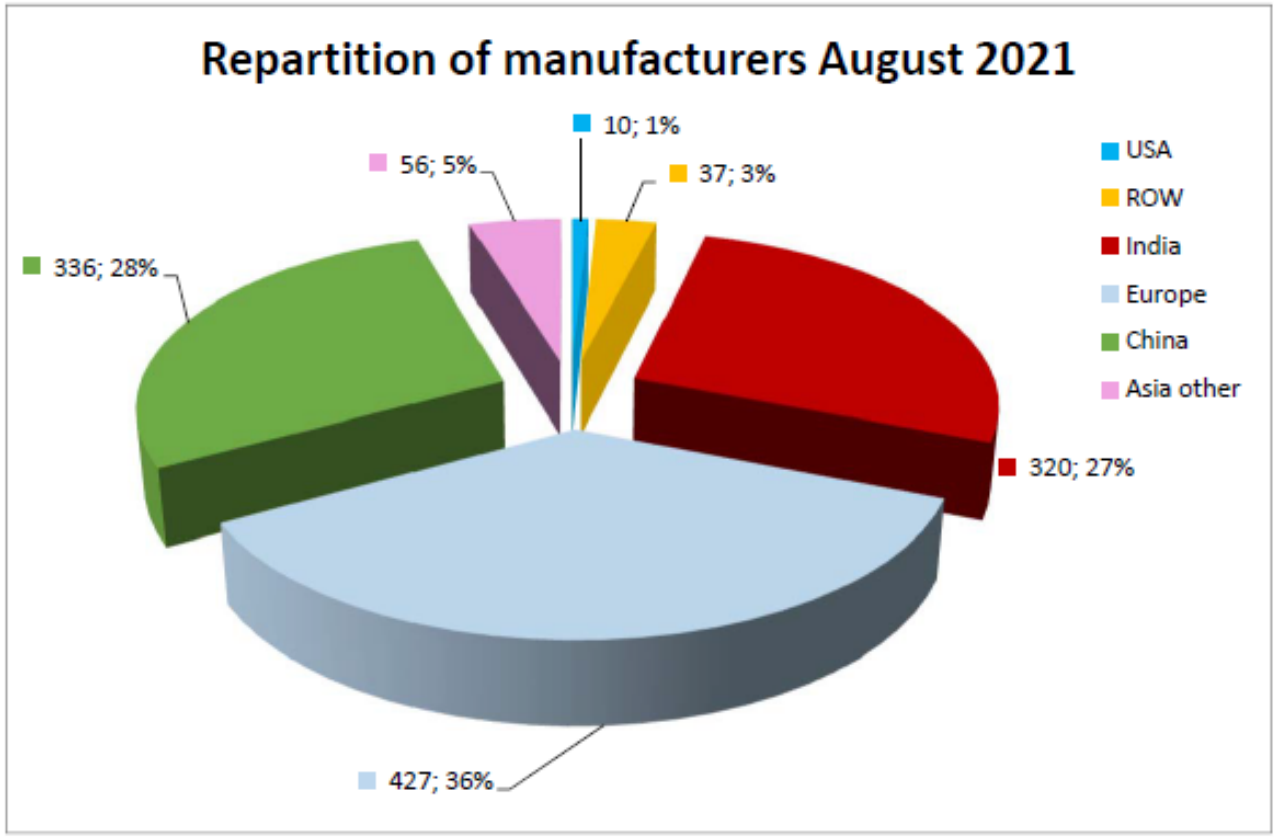


Fast track procedure

Harmonised assessments

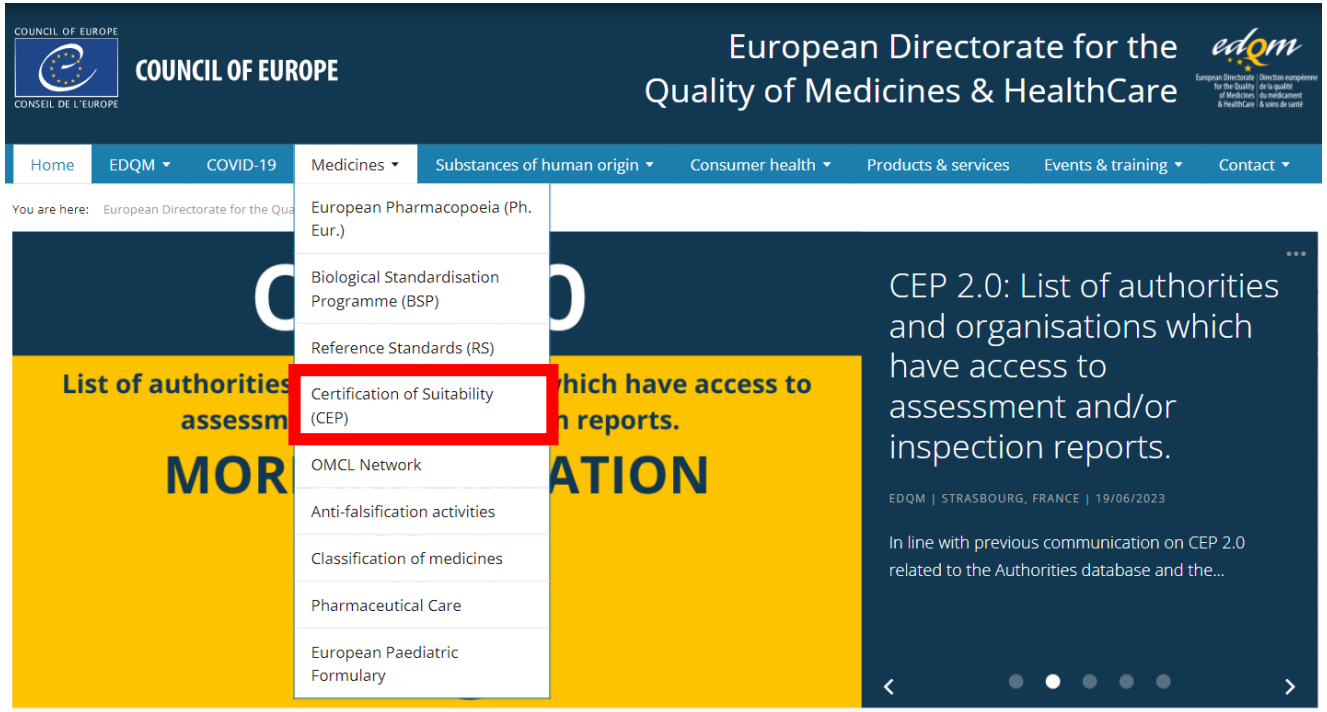
# Key figures

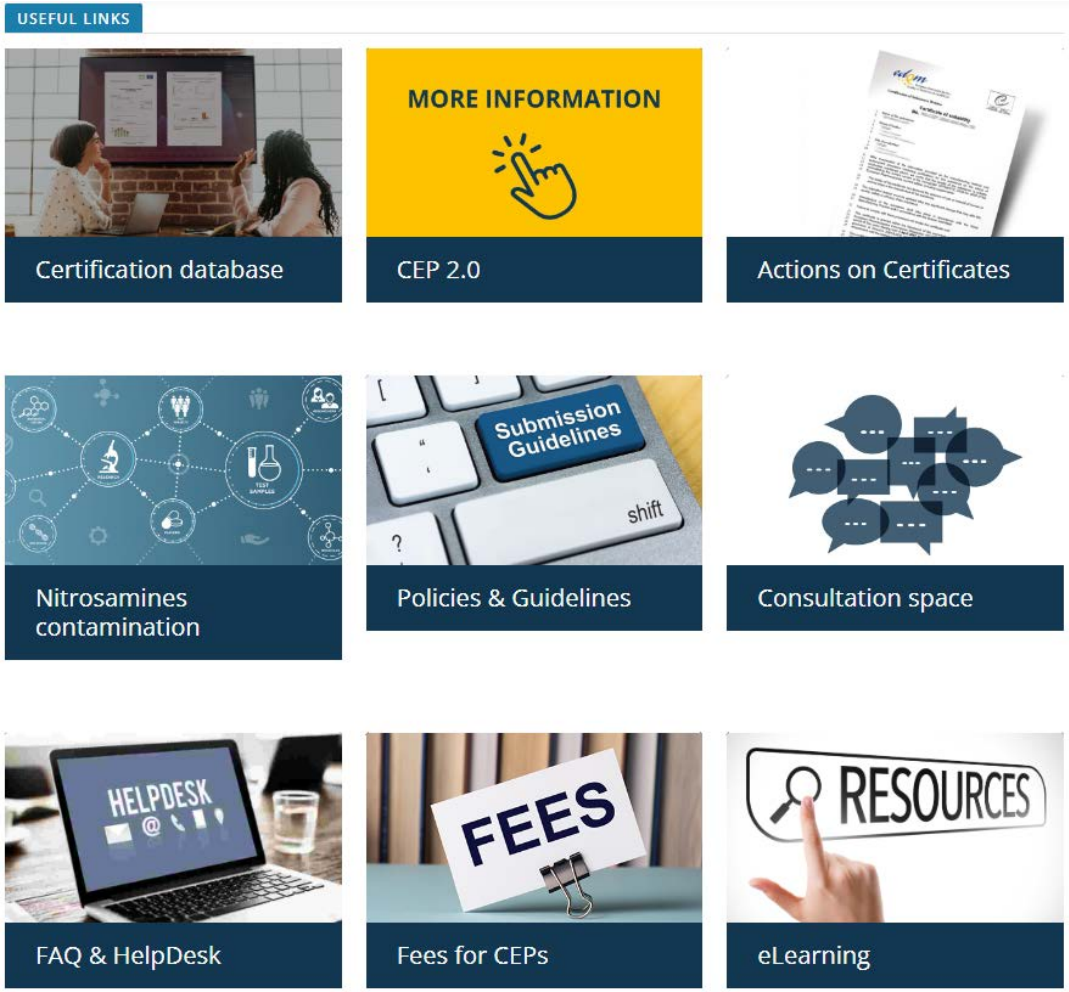
- Since 1994, close to 9000 CEP applications received for nearly 1500 different substances
- Currently more than 6000 valid chemical/double CEPs
- About 1470 manufacturers from >50 different countries (50% in India and China)



# Keep up-to-date with CEP activities

- EDQM Website (www.edqm.eu) > Medicines > Certification of Suitability



# Communication with EDQM

- General questions on CEPs: Look at the FAQs and if necessary use EDQM Helpdesk
- For queries specific to applications : via the email address included in EDQM communication
- Technical Advice: to meet the EDQM staff and get advice about applications (fee applicable)

# Thank you for your attention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