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

General overview of the CEP procedure

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Module 5: Fundamentals of the CEP Procedure (Live Webinar)
9th December 2024

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 and information available on EDQM website

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Certification – Background

- CEP = Certificate of Suitability to the monographs of the European Pharmacopoeia
- The procedure for the CEPs was established in 1994 and was initially only applicable to pharmaceutical substances
- In 1999, the procedure was extended to include products with a risk of transmissible spongiform encephalopathy (TSE)
- The procedure was further revised to allow for the control of herbal drugs and herbal drug preparations

EU legislation and Certificates of Suitability (CEP)

- EU Directive 2001/83/EC (human) and amendment 2003/63/EC state that active substances should comply with the Ph. Eur monograph if there is one

…"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…"

… "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."

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Governing document for the Certification procedure

- **Resolution AP-CSP(07) 1** on the "Certification of Suitability to the Monographs of the European Pharmacopoeia" and 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 procedure

- Substances described in monographs in the Ph. Eur. (active substances, excipients, herbal drugs)
  → "Chemical" or "Herbal" CEP

- Products with risk of TSE (SM, intermediates, reagents,..)
  → "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.

Scope of the procedure

- Substances described in monographs in the Ph. Eur. (active substances, excipients, herbal drugs)
  → "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

- CEPs are recognised by all member states of the Council of Europe and the European Union. They are also recognised by other countries such as Canada and Australia.

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

- A CEP is intended to demonstrate that the quality of a given substance can be suitably controlled by the relevant Ph. Eur. monograph(s), with additional tests if necessary

- 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!

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CEP and ASMF procedures

- Drug substance documentation is an integral part of a marketing authorisation application
- Based on **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 option selected

CEPs are not mandatory, but generally avoid any subsequent reassessment

Comparison between CEP & ASMF procedures

	CEP procedure	ASMF procedure
Purpose	➢ The CEP is independent from MAA ➢ It confirms that the active substance complies with European Pharmacopoeia requirements	The ASMF is submitted in the context of a specific MAA for medicinal products
Scope of material	Pharmacopoeial substances only ➢ Active substances or excipients ➢ Any substance for TSE CEP	Active substances only ➢ New chemical entities ➢ Existing substances
Dossier	➢ Content identical (CTD 3.2.S) ➢ Full dossier sent directly by the manufacturer to EDQM (will generally be the holder of the CEP)	➢ Content identical (CTD 3.2.S) ➢ AP sent to the marketing authorisation holder of medicinal product and the full dossier is submitted to the competent authorities (NCA / EMA)

Comparison between CEP & ASMF procedures

	CEP procedure	ASMF procedure
Evaluation	➢ **Single** evaluation centralised at EDQM ➢ Assessment is performed by assessors from Competent Authorities appointed by the Certification Steering Committee ➢ The pool of assessors is a mix of EDQM and assessors from NCA	➢ **Multiple** evaluations ➢ Assessment of ASMF by each competent authority in the context of assessing a specific marketing authorisation application or variation for medicinal products
Evaluation references and principles	Assessment against: ➢ ICH/EU guidelines for quality ➢ Ph. Eur monographs ➢ EDQM specific guidance	Assessment against: ➢ ICH/EU guidelines for quality ➢ Ph. Eur monographs (if applicable)

Comparison between CEP & ASMF procedures

	CEP procedure	ASMF procedure
Deliverable	➢ The Certificate is granted to the CEP holder (usually API manufacturer) ➢ CEP holder can provide a copy to their customers (users of the substance)	A Marketing Authorisation for the medicinal product using this particular API
Variations	➢ Changes to the CEP dossier centralised at EDQM ➢ 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 (including the UK) ➢ others (Australia, Canada, New Zealand, Tunisia, Morocco, Singapore, South Africa, Saudi Arabia, etc)	➢ EU/EEA member states ➢ UK ➢ Australia and Canada

Worksharing and cooperation accross Europe

- Holder's commitment / Annex 7 of the CEP application form foresees sharing EDQM assessment 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 (list on the EDQM website)

- ASMF reports may also be made available for EDQM (see NfG ASMF procedure CHMP/QWP/227/02 Rev 3 corr).

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How to apply for a (new) CEP

- Application form (for new applications) available on the EDQM website. It contains tables to be filled in, statements and declarations to be signed.
- Last version of this application form (June 2023) should be used.
- 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 €. ** In the case of TSE supported by a CEP the fees are only 8000 €.		

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

- Quality Overall Summary : new template available from January 2024

- Mandatory component of the CEP application
- Gives a concise overview of the technical dossier
- Highlights the control strategy applied

[Template for Quality Overall Summary to be submitted for Certification applications (PA/PH/CEP (15) 26 1R, January 2024)]

How to apply for a CEP

- Dossier in English (preferably) or French

- Content in compliance with:
  - EDQM guideline « 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"
  - NEW "Content of the dossier for sterile substances"

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

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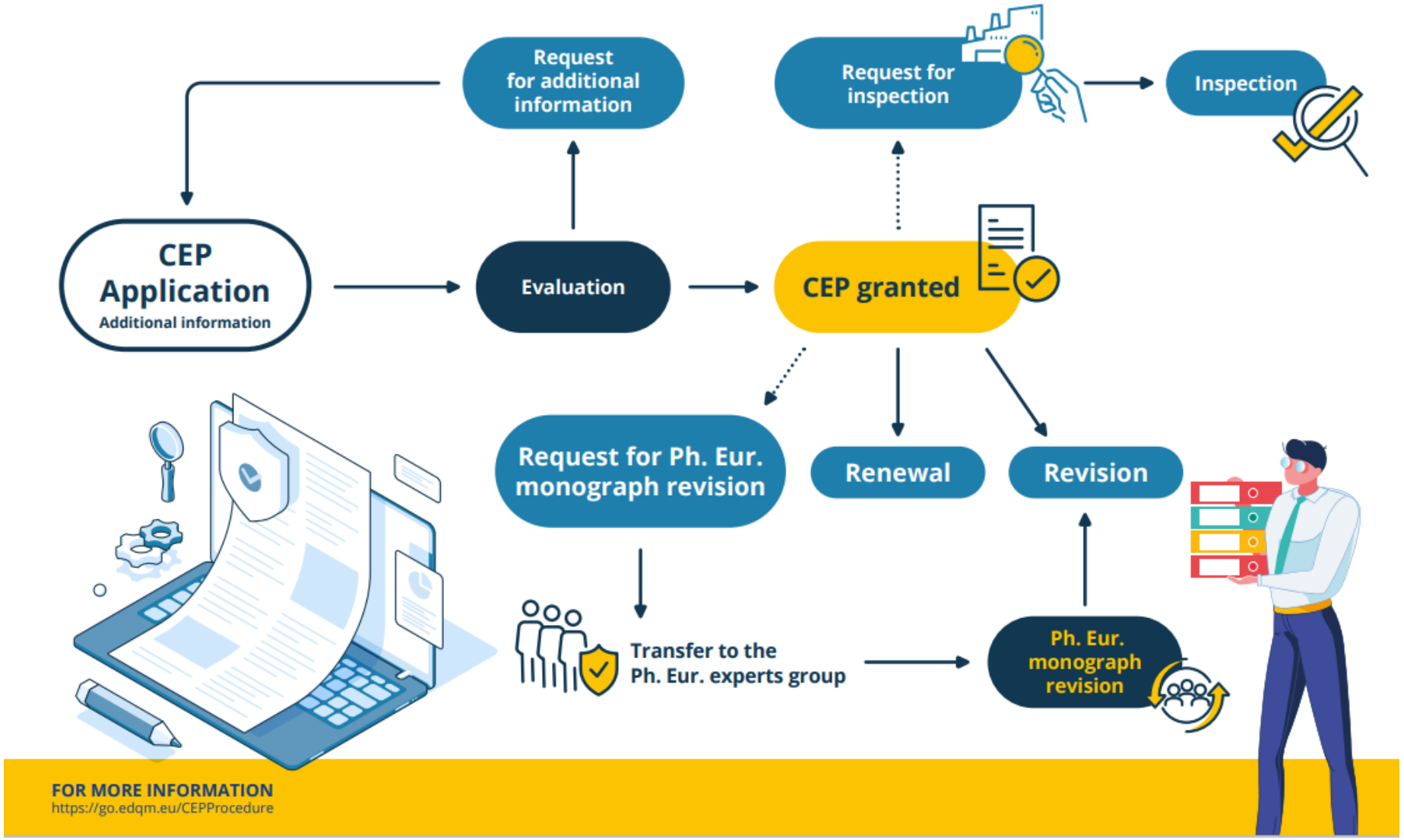
How it works



How it works

Submission of responses in additional rounds of assessment

After an assessment, the EDQM may send to a company a request for *additional information, for clarification or for dossier update.*

According to the EDQM policy document PA/PH/CEP (10) 85 "Changes to Submitted Documentation No Longer Accepted During the Assessment Phase" the company's response to such EDQM letters:

- should contain only information requested by EDQM
- should not contain any additional changes introduced within the responses not related to the questions asked by EDQM and omitted to be submitted in the initial round

Exceptions can be accepted only in cases of:

- administrative changes of company names/addresses
- dossier update after a revision of the monograph
- submission of stability data which would support longer re-test periods

How long it takes

For a new CEP application:

Type of application	EDQM Timelines for assessment of initial application	Applicant Timeline to reply to first request for additional information	EDQM Timelines for assessment of reply to request for information	Applicant Timeline to reply to second request for additional information	EDQM Timelines for assessment of reply to request for information	CEP revised if application accepted ?
New	115 WD °	180 CD*	92 WD*	90 CD *	92 WD *	New CEP issued
		30 CD #	23 WD #	30 CD #	23 WD #	

* if the request from EDQM relates to significant information required to address the issues identified

if the request from EDQM relates to clarification of minor issues or update of the dossier

° EDQM timelines are expressed in working days (WD): week-end, bank holidays and EDQM closures are not taken into account in the calculation

+ CD = Calendar days

Management of applications for new Certificates of Suitability, Requests for Revision or Renewal of Certificates of Suitability and applications using the 'sister files' procedure (PA/PH/CEP (13) 110, 3 R, November 2021)

We are still experiencing some delays

Who performs the evaluation?

- ✓ Assessors are proposed by National Competent Authorities and appointed by the CEP Steering Committee; EDQM assessors, also appointed by the Steering Committee
- ✓ New applications areassessed by 2 assessors: most commonly one from EDQM and one from NCA from Ph. Eur. member states and beyond
- ✓ About 100 assessors from authorities from 25 countries, including Canada
  - 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

- Documents available on the EDQM website :
  - ❖ Management of applications for new Certificates of Suitability, Requests for Revision or Renewal of Certificates of Suitability and applications using the 'sister files' procedure
  - ❖ Guidance on applications for «sister files»

Fast track procedure

Harmonised assessments

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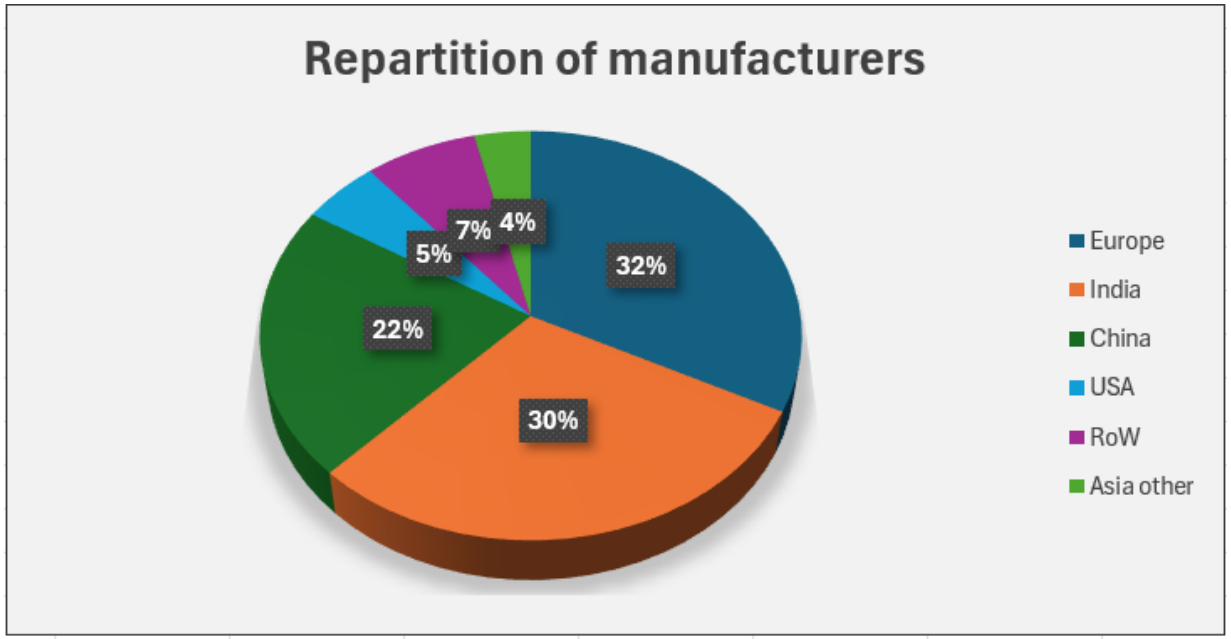
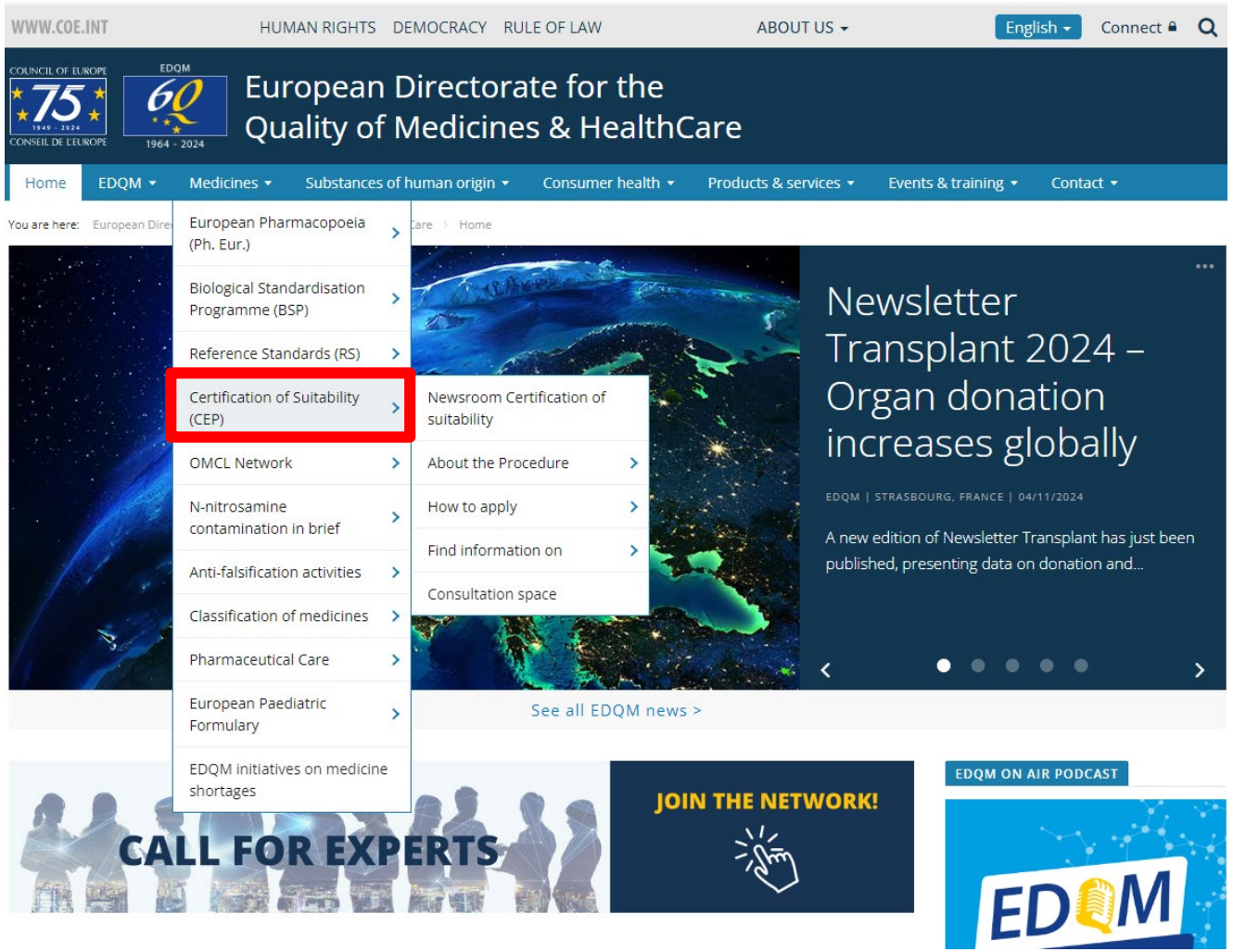
Key figures

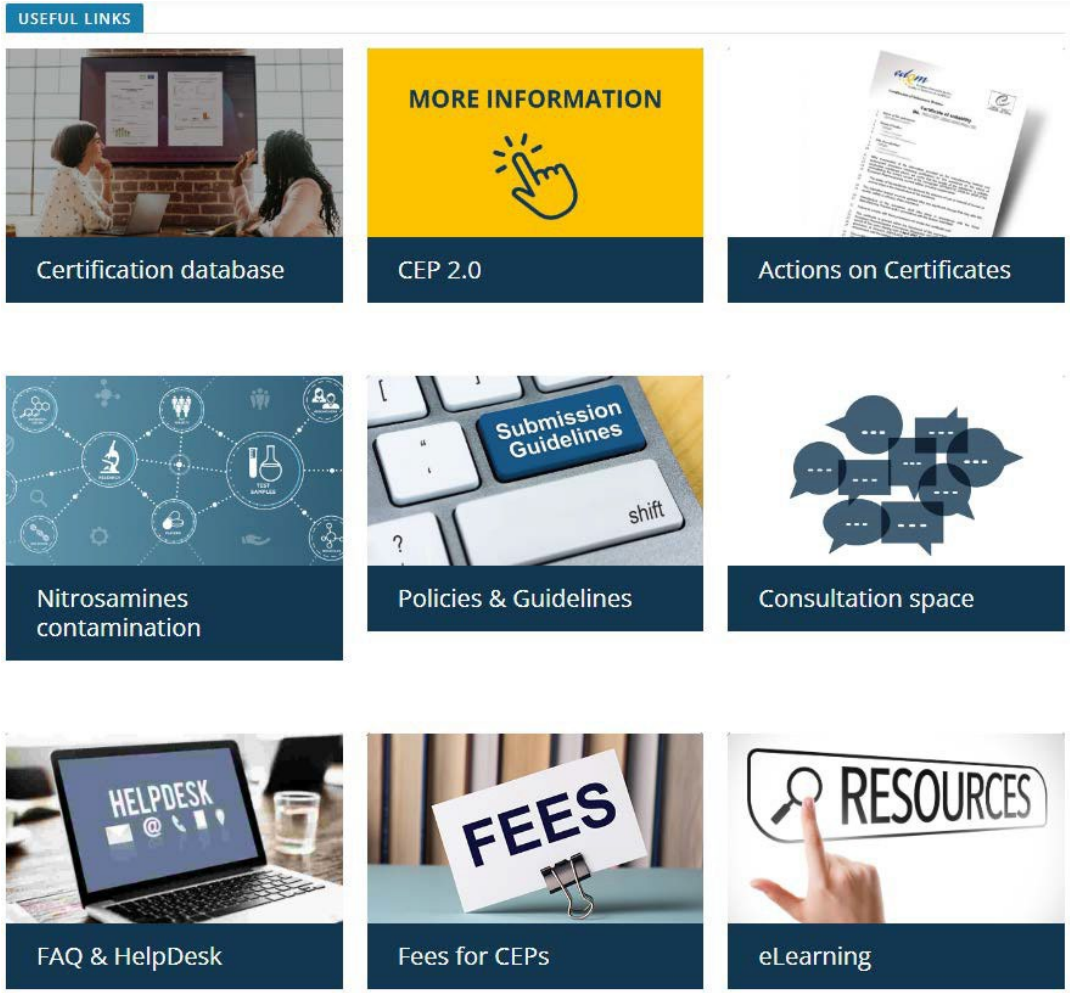
- Since 1994, close to 9000 CEP applications received for nearly 1500 different substances
- Currently more more than 6500 valid CEPs
- About 1500 manufacturers from >50 different countries (50% in India and China)



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

Stay connected with the EDQM

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X: **@edqm_news**
Facebook: **@EDQMCouncilofEurope**