General Presentation on the Role and Place of the Certification Procedure in the European Regulatory System

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Summary

- Regulatory background
- Comparison of CEP and ASMF
- The Certification procedure role
- The CEP
- Key figures
- How to communicate with EDQM

Regulatory background

How to deal with Active substances in marketing authorization applications?

Directives 2001/83/EC and 2001/82/EC as amended are the references.

They underline the fact that all monographs including general monographs and general chapters of the European Pharmacopoeia are applicable (legally binding)

Directive 2001/83/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
- The competent authorities shall inform the authorities responsible for the pharmacopoeia in question.

CEPs in the EU legislation

Directives state that where the active substance and/or excipient(s) are the subject of a monograph of the EP, 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…

NfG CHMP/QWP/297/97 rev. 1 corr « Summary of requirements for active substances in the quality part of the dossier »

Gives 3 basic choices for providing information regarding the active substance

2.1. Certificate of suitability

- requires Ph. Eur. Monograph (specific or TSE)
- used for "existing" substances

"where applicable, option 2.1 has the advantage of generally avoiding any subsequent reassessment"

The information required is the **same** regardless of the procedure selected.

NfG CHMP/QWP/297/97 rev. 1 corr. « Summary of requirements for active substances in the quality part of the dossier »

2.2 Active substance Master File (ASMF)
- Applicable to all active substances

2.3 Full details of manufacture in marketing authorisation application
- both procedures do not require Ph. Eur. Monograph
- can be used for “new” and “existing” substances

Differences between CEP & ASMF

Scope:

- CEP: pharmacopoeial substances only,
  -> active substances or excipients
  -> any substance for TSE CEP
- ASMF: active substances only,
  -> new or pharmacopoeial

Comparison between CEP & ASMF procedures

	CEP procedure	ASMF system
Dossier	Content identical (CTD 3.2.S) Full dossier sent directly by API manufacturer to EDQM (will be the holder of the CEP)	Content identical (CTD 3.2.S) Full dossier sent by API manufacturer to Competent Authorities 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: Assessment against ICH/EU guidelines for quality + Ph. Eur monograph + EDQM specific guidance	Principles identical: 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 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, Singapore, South Africa, 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, the EMA including all CHMP and CVMP Members and their experts.
- ASMF reports may also be made available for EDQM (see NfG ASMF procedure CHMP/QWP/227/02 Rev 3 corr).
- Goal: improved efficiency & harmonisation

The CEP procedure

- Official implementation in 1994
- An international platform for:
  - Assessment of the quality of substances for pharmaceutical use (APIs, excipients, herbals, TSE risk)
  - Coordination and conduct of GMP inspections of API manufacturers
- Keys for acceptance of CEPs:
  - Strong processes
  - Harmonisation of decisions
  - Transparency

The CEP Procedure role

- 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"

The CEP procedure

Provides:

- Centralised assessment - saves time and resources
- Information on the need to update Ph. Eur. monographs
- Facilitates management of MAAs and variations
- Application submitted directly to EDQM by the manufacturer of the pharmaceutical substance
- CEP accepted in all Ph. Eur. Convention member states (38) + other countries (e.g. Canada, Australia, Singapore, South Africa, WHO, etc.)

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 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 (PA/PH/CEP (09) 152 rev 01)
- Human tissues derivatives, blood derivatives, vaccines
- Finished products

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 using the template available on the EDQM website
- 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 €.

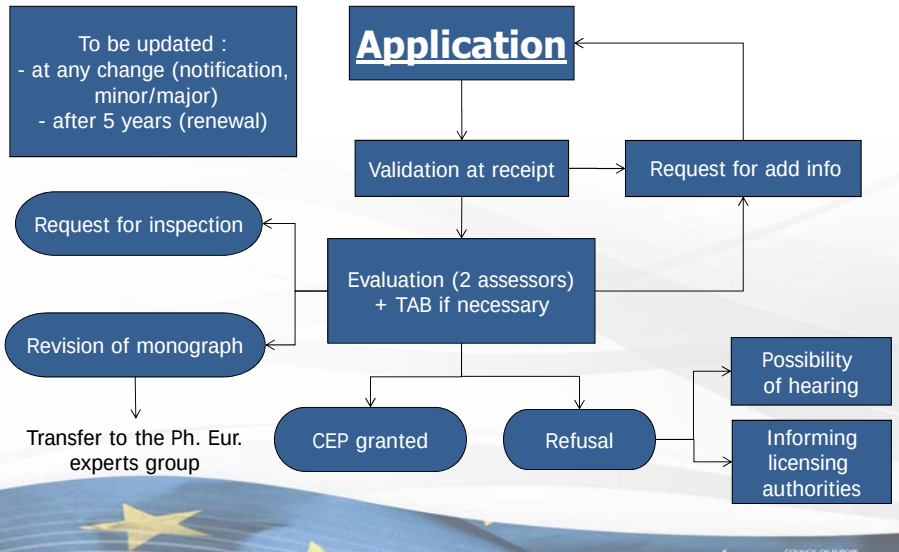
How to apply for a CEP

- 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
- All these documents are available on our website for free

Electronic submissions & CESP

- Electronic submissions of new applications in eCTD only from the 1st of January 2018
- To be submitted via CESP only
  - Users should register for a CESP account on the Heads of Medicines Agencies website

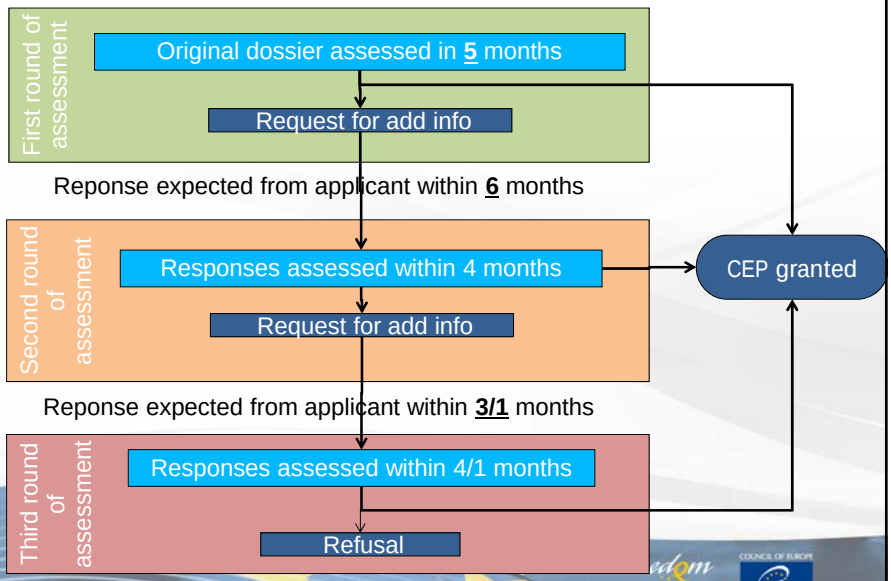
How it works



Who performs the evaluation?

- Assessors proposed by National competent Authorities and appointed by Steering Committee.
  - Skilled in the relevant domain (chemical evaluation, TSE risk, herbal products, toxicologists...)
  - Come regularly to EDQM premises for the evaluation of dossiers
- EDQM assessors also appointed by the Steering Committee.

How long does it take?

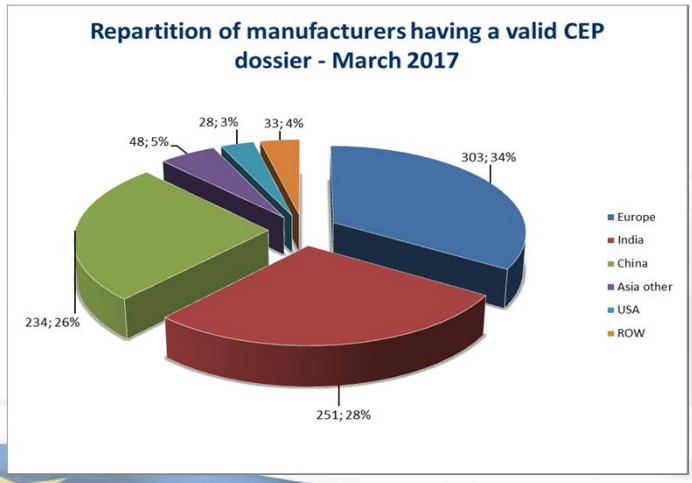


Key Figures and How to communicate with EDQM

Key figures

- Since 1994, # 7000 CEP applications received for >1000 different substances
- Currently about 4900 valid chemical/double CEPs
- 1200 manufacturers from 50 different countries
- These numbers change frequently as new applications are received and existing CEPs are revised daily.

Repartition of manufacturers



Keep yourself up-to-date with CEP news

Our performance figures are published in our monthly report on our website:

Certification Monthly Report of Activities: February 2018

CERTIFICATION OF SUITABILITY (CEP) PROCEDURE OF CERTIFICATION (GENERAL) | NEWS | 05 MARCH 2018 | STRASBOURG, FRANCE

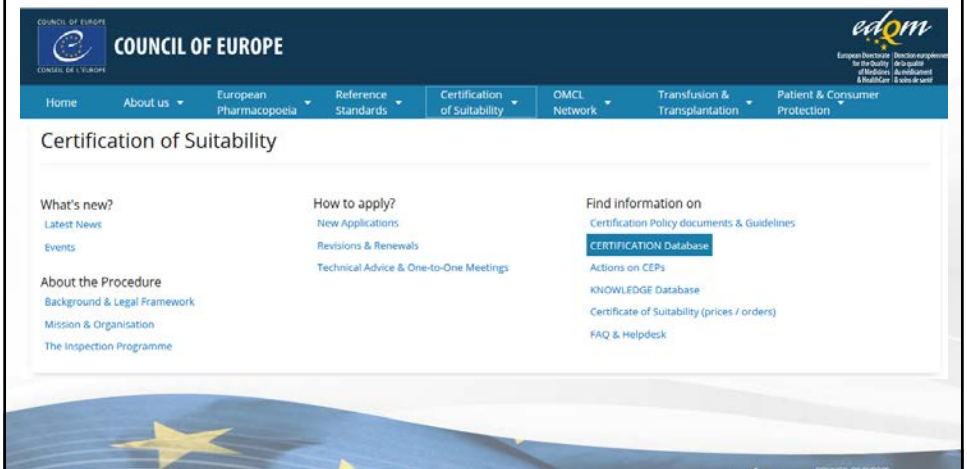
The latest monthly activity report for the Certification of Substances Department (DCEP) is now available.

February 2018 Certification Monthly Report.

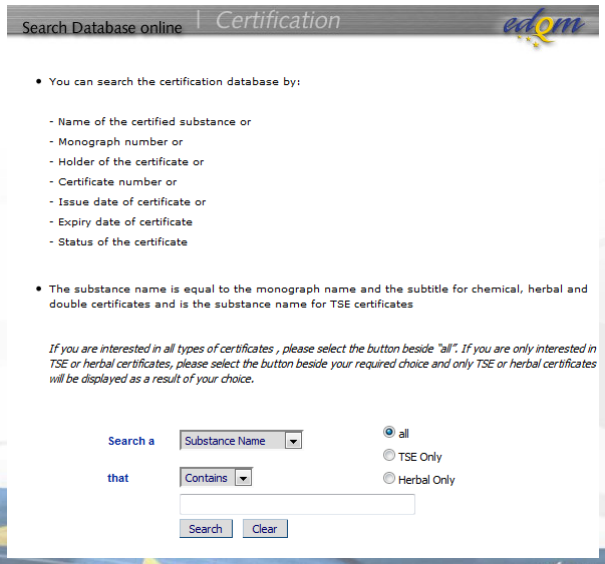
Includes also other news in the month (suspensions etc.)

Is a CEP valid ?

Check our database on www.edqm.eu



Is a CEP valid ?

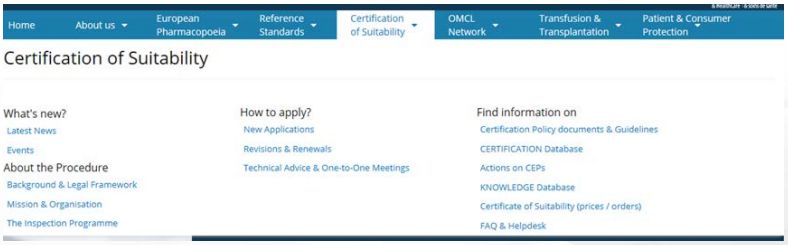


Is a CEP valid ?

Substance Number	Substance	Certificate Holder	Certificate Number	Issue Date	Status	End date	Type
721	Ibuprofen	Doctors Organic Chemicals Ltd IN 534 215 Tanuku (Po)	R0-CEP 2003-244-Rev 00	19/05/2005	EXPIRED	19/05/2010	Chemistry
721	Ibuprofen	PIRAMAL ENTERPRISES LIMITED IN 500 063 Hyderabad	R1-CEP 1998-012-Rev 08	24/05/2017	VALID		Chemistry
721	Ibuprofen	DR. REDDY'S LABORATORIES LIMITED IN 500 016 Hyderabad	R1-CEP 1997-082-Rev 01	17/07/2008	WITHDRAWN BY HOLDER	10/08/2011	Chemistry
721	Ibuprofen	SHANDONG XINHUA PHARMACEUTICAL CO., LTD. CN 255 086 Zibo	R1-CEP 2004-023-Rev 04	24/08/2015	VALID		Chemistry
721	Ibuprofen	IOL CHEMICALS AND PHARMACEUTICALS LTD IN 141 003 Ludhiana	R1-CEP 2008-316-Rev 00	01/10/2015	VALID		Chemistry
721	Ibuprofen	ARCH PHARMALABS LIMITED IN 400 072 Mumbai	R1-CEP 2000-114-Rev 03	15/04/2014	VALID		Chemistry
721	Ibuprofen	BASF Corporation US 78343 Bishop	R1-CEP 2000-087-Rev 02	04/08/2011	VALID		Chemistry
721	Ibuprofen	SI GROUP, INC. US 12301 Schenectady	R1-CEP 1996-058-Rev 05	02/10/2014	VALID		Chemistry
721	Ibuprofen "S250"; "S380"; "S500"; "SN"; "SHD"	STRIDES SHASUN LIMITED IN 600 032 Chennai	R1-CEP 1996-061-Rev 11	17/03/2016	VALID		Chemistry
721	Ibuprofen	HUBEI BIOCAUSE HEILEN PHARMACEUTICAL CO., LTD. CN 448 000 Jingmen City	R1-CEP 2002-099-Rev 03	01/12/2016	VALID		Chemistry

Communication with EDQM

EDQM Website – Certification of Suitability



- Procedure, guidelines, documents, news are available

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 our communication)
- Technical Advice: to meet the EDQM staff and get advice about applications (fee applicable)

Thank you for your attention!