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

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European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

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General presentation of the CEP procedure

its role and working procedures - comparison with the Active Substance Master File (ASMF) procedure in Europe

EUROPEAN PHARMACOPOEIA TRAINING WEBINARS

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Summary

- Regulatory background
- Comparison between CEP and ASMF procedures
- The CEP procedure
- 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

How to deal with Active substances in marketing authorisation 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 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
- The competent authorities shall inform the authorities responsible for the pharmacopoeia in question.

The CEP in the EU legislation

…"where the active substance or excipient 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.
  - Centralised assessment - saves time and resources
  - Facilitates management of MAAs and variations
  - Coordination and conduct of GMP inspections of API manufacturers
  - Source of information to update Ph. Eur. monographs

The CEP Procedure

- 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"

CEPs and ASMFs 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, -> active substances or excipients-> any substance for TSE CEP	active substances only, -> new or pharmacopoeial
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, Saudi Arabia, etc)	EU/EEA member states + Australia + Canada

How to apply for a CEP (2)

- 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

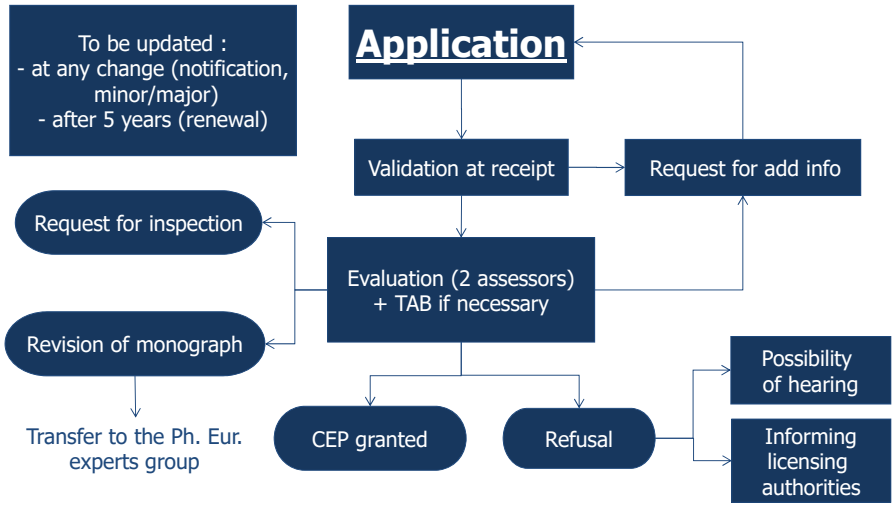
- Dossier in English (preferably) or French, content in compliance with:
  - Content of the Dossier for Chemical CEP: comparable to ASMF or 3.2.S of CTD
  - For TSE risk CEP: requirements from Ph. Eur. general text, 5.2.8 and Content of the dossier for TSE risk
  - Content of the dossier for herbal drugs/herbal 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 any applications (NDOS/Rev/Renewal) in eCTD only from the 1st of January 2020.
- To be submitted via CESP only
  - Users should register for a CESP account on the Heads of Medicines Agencies website

Evaluation of applications and granting of CEPs

How it works



Who is involved

- Steering Committee
  - 16 members, representing the main organisations & working groups in Europe and Ph. Eur member states
  - Takes decisions on scope, makes links with regulatory groups and adopts EDQM guidelines

Who is involved

Assessors approved by the Steering Committee :

- ➢ Experts proposed by National competent Authorities and approved 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
  - About 90 assessors from 25 countries, including Australia and Canada
- ➢ Work in binomes with EDQM assessors

Who is involved (2)

- Inspectors:

  # 30 inspectors from supervisory authorities from 16 EU/EEA countries + Switzerland

  - Perform inspections with EDQM
- EDQM Certification Department
  - All located in Strasbourg, France
  - 48 people: assessors, inspectors, scientific and administrative staff
  - Run the procedure, coordinate the activities and communication

A great and successful example of international cooperation!

How long does it take ?

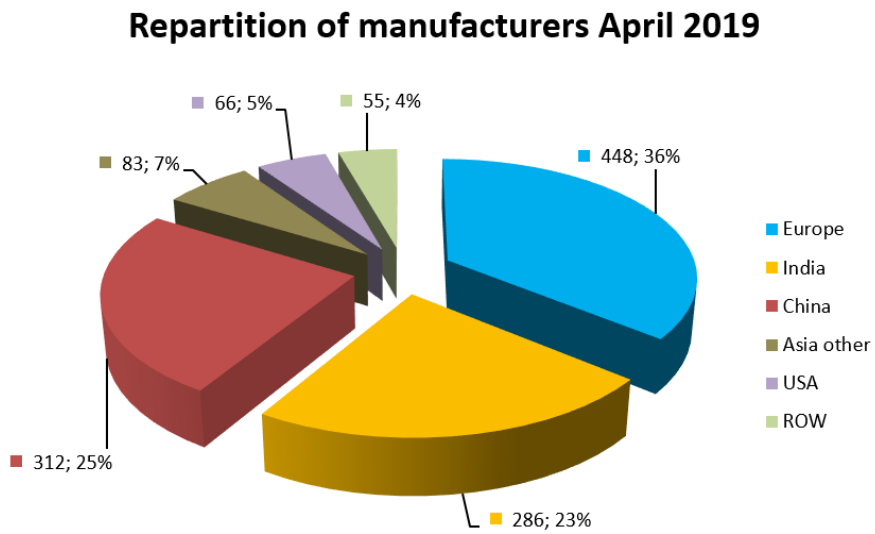
- "3-round policy":
  - Initial assessment
  - Letter of questions
  - Assessment of responses
  - 2nd request for information
  - Assessment of responses and decision to grant the CEP or to reject the application (or exceptionally a last request for information)
- Official deadlines for each milestone
- It takes between 5 months and up to 2 years to get a CEP

Key Figures and How to communicate with EDQM

Key figures

- Since 1994, close to 8000 CEP applications received for nearly 1500 different substances
- Currently more than 5300 valid CEPs
- 1250 manufacturers from >50 different countries (50% in India and China)

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: May 2020

CERTIFICATION OF SUITABILITY (CEP) PROCEDURE OF CERTIFICATION (GENERAL) | NEWS | 12 JUNE 2020 | STRASBOURG, FRANCE

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

- May 2020 Certification Monthly Report.

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

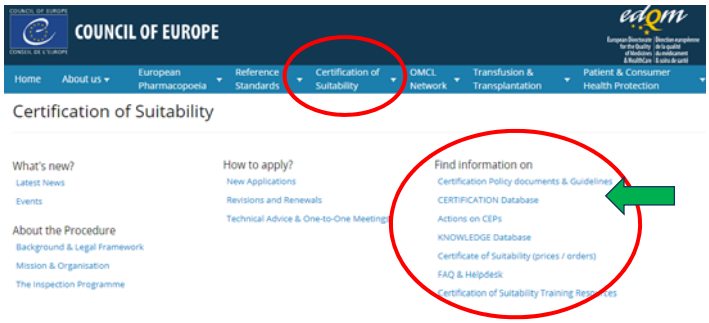
Actions on CEPs

Read the updates on the last six months:

- CEP suspensions
- CEP withdrawals
- CEP restoration

Keep up-to-date with CEP activities

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



- Several pages dealing with :
  - Procedure, news, etc
  - A page with the list of Certification Policy documents and Guidelines
  - A page with actions on CEPs

Is a CEP valid ?

Is a CEP valid ?

New Search

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 05	18/07/2019	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 SE DE 67056 Ludwigshafen	R1-CEP 2000-087-Rev 03	07/12/2018	VALID		Chemistry
721	Ibuprofen	IOL CHEMICALS AND PHARMACEUTICALS LTD IN 141 003 Ludhiana	R1-CEP 2008-316-Rev 03	12/09/2019	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"	SOLARA ACTIVE PHARMA SCIENCES LIMITED IN 600 032 Chennai	R1-CEP 1996-061-Rev 14	26/08/2019	VALID		Chemistry
721	Ibuprofen	HUBEI GRANULES-BIOCAUSE PHARMACEUTICAL CO., LTD. CN 448 000 Jingmen City	R1-CEP 2002-099-Rev 05	18/02/2019	VALID		Chemistry

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 (CEP@edqm.eu) included in our communication)
- Technical Advice: to meet the EDQM staff and get advice about applications (fee applicable)

Use of CEPs worldwide

- An increasing number of health authorities worldwide accept CEPs
  - e.g. Australia, Canada, Morocco, Saudi Arabia, Singapore, South Africa, TFDA, WHO, etc.
  - National requirements apply, a number of countries have published guidance on how to use CEPs
- Signature of confidentiality agreements/MOUs, to share confidential information, including assessment reports and inspection reports
  - Regular information on non-compliances with CEP procedure (GMP non-compliance, quality issues etc)
  - Sending assessment reports or inspection reports upon request
  - Sharing information in case of quality issues (eg. nitrosamines)

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

Conclusion

- The CEP procedure, as a platform for assessment and GMP inspections, is a powerful and helpful tool
- CEPs should be used in an informed way:
  - A chemical or a herbal CEP **certifies** that the quality of the substance is suitably controlled by the Ph. Eur. monograph with addition of tests if necessary (mentioned on the CEP)
  - A CEP **does not** replace testing and is not a certificate of analysis
  - A CEP **is not** a GMP certificate
- Communication between the CEP holder and the drug product manufacturer is key

Thank you for your attention

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