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

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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

Annick Dégardin

Certification Department,

European Directorate for the Quality of Medicines & HealthCare, Council of Europe

Summary

- Regulatory background
- 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

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 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 the 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

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

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

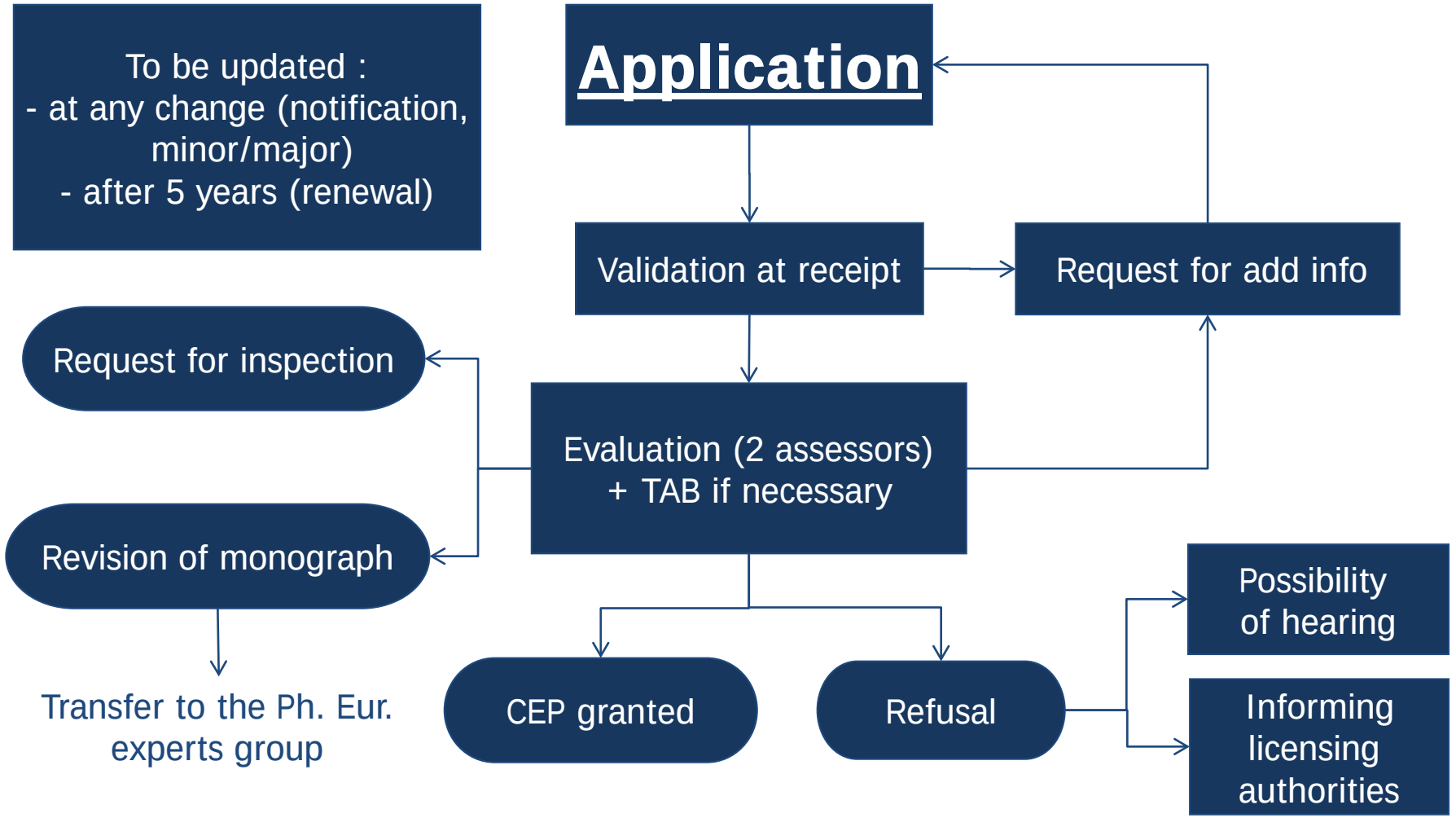
Electronic submissions & CESP

- Electronic submissions of any applications (NDOS/Rev/Renewal) in eCTD only

- 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 performs the evaluation

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 more than 20 countries, including Australia and Canada

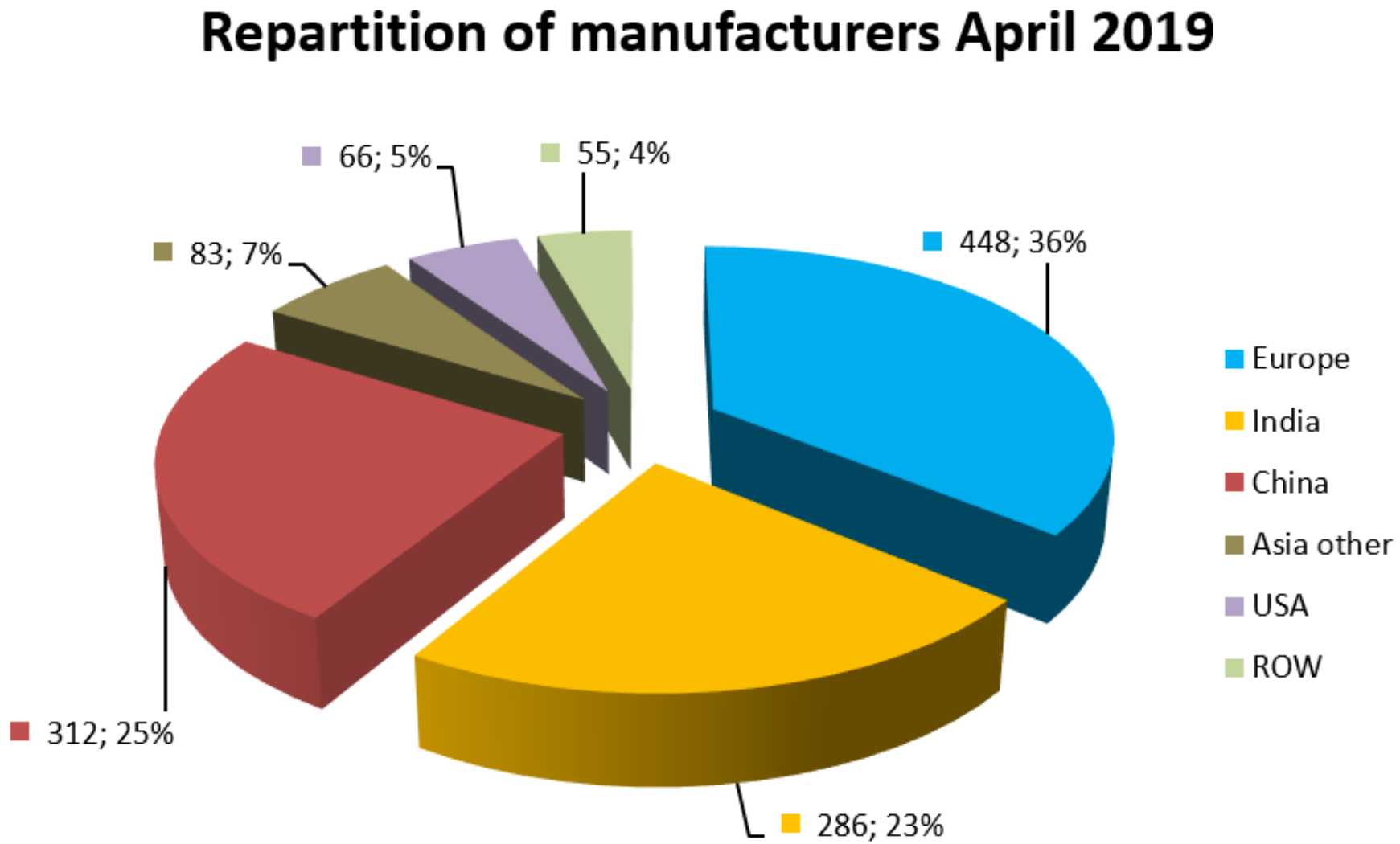
- Work with EDQM assessors

Key Figures and How to communicate with EDQM

Key figures

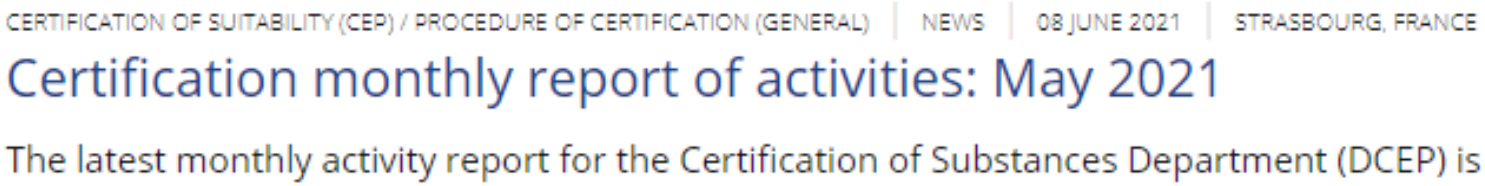
- Since 1994, close to 8500 CEP applications received for nearly 1500 different substances
- Currently more than 5500 valid chemical/double CEPs
- 1250 manufacturers from >50 different countries (50% in India and China)

Distribution of manufacturers



Keep yourself up-to-date with CEP news

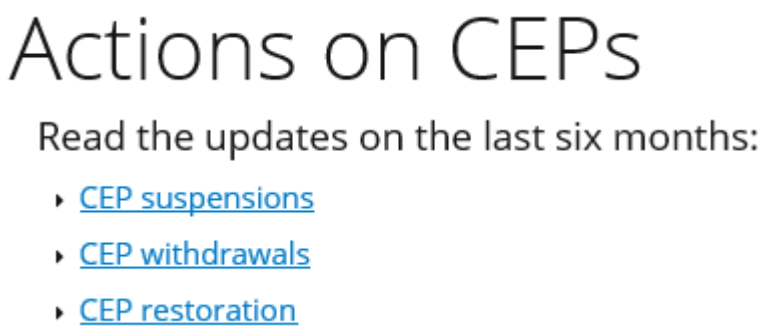
Our performance figures are published in our monthly report on our website:


CERTIFICATION OF SUITABILITY (CEP) / PROCEDURE OF CERTIFICATION (GENERAL) | NEWS | 08 JUNE 2021 | STRASBOURG, FRANCE

Certification monthly report of activities: May 2021

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

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

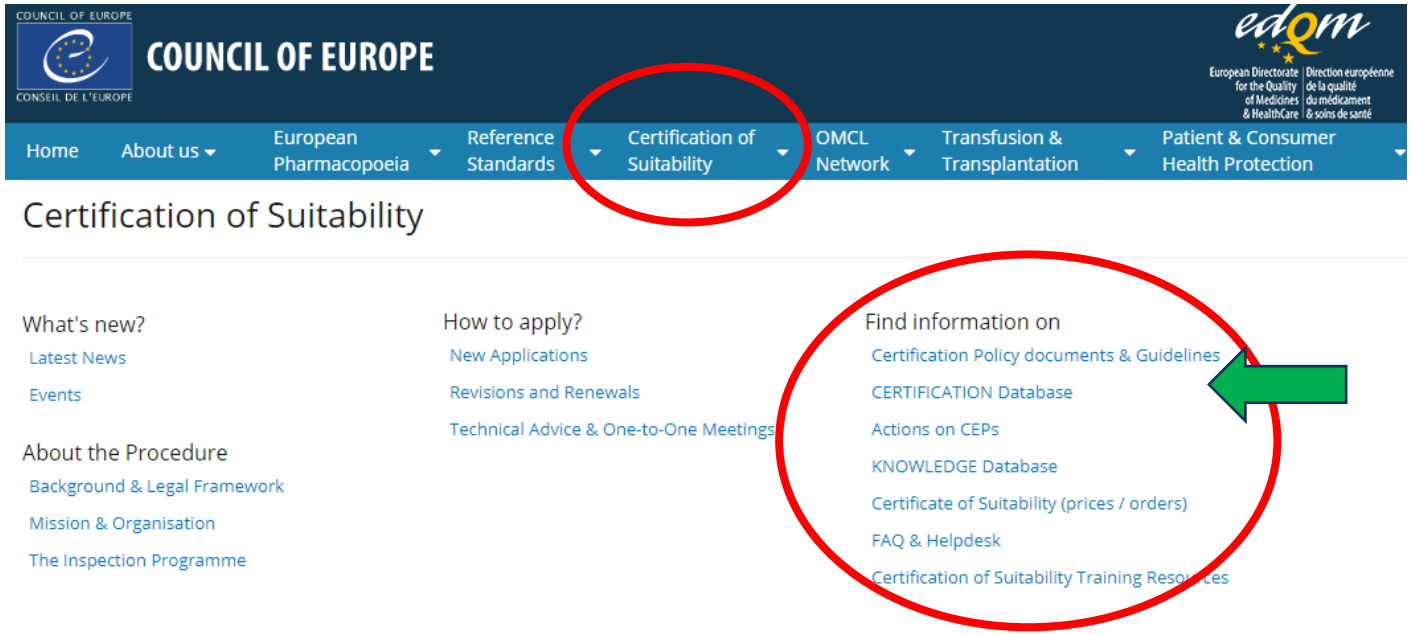

Actions on CEPs

Read the updates on the last six months:

- CEP suspensions
- CEP withdrawals
- CEP restoration

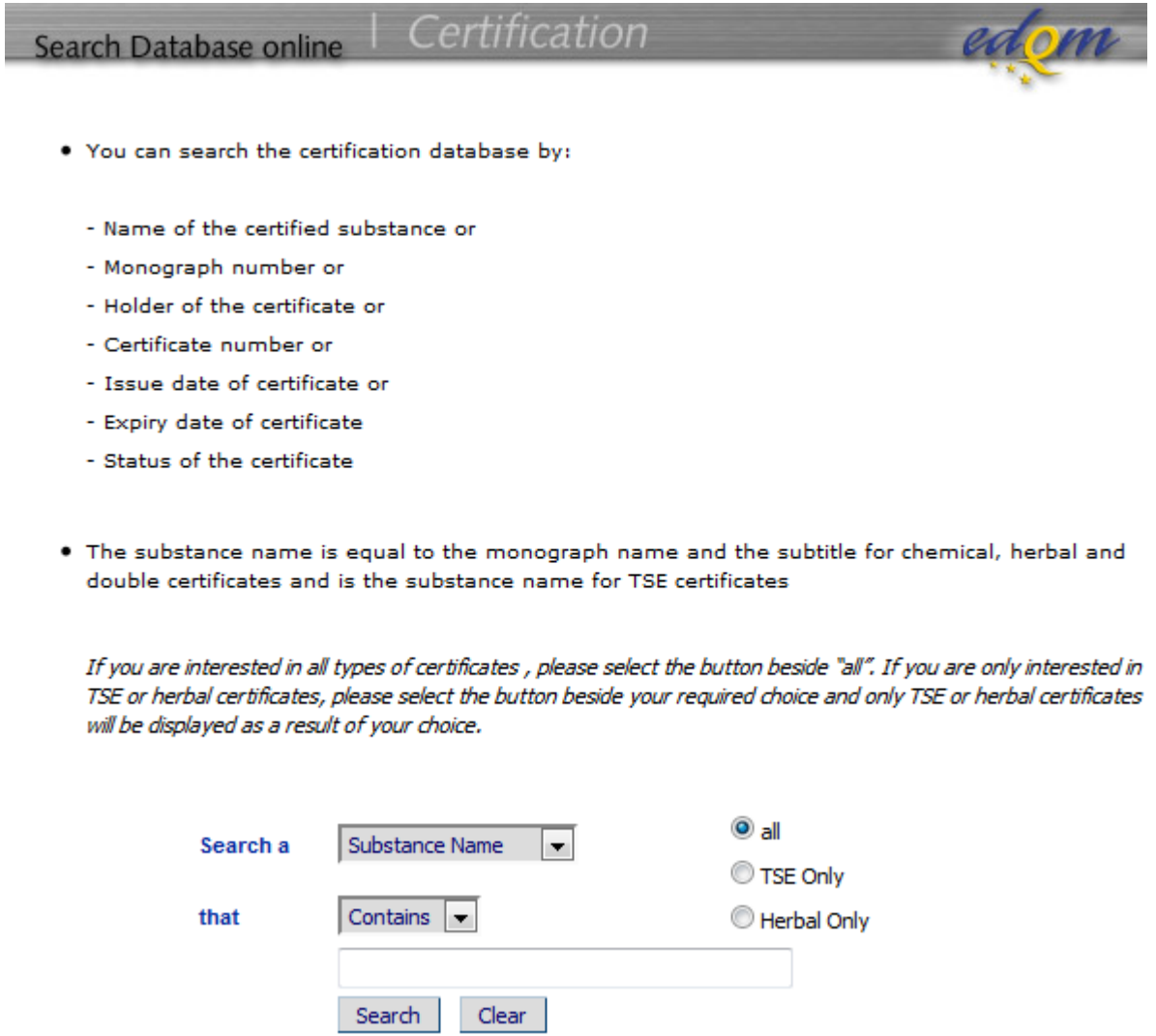
Keep up-to-date with CEP activities

- 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 ?

Substance Number	Substance	Certificate Holder	Certificate Number	Issue Date	Status	End date	Type
49	Paracetamol	Rhodia Organique SAS FR 69006 Lyon	R1-CEP 1996-004-Rev 02	14/02/2005	WITHDRAWN BY HOLDER	21/06/2006	Chemistry
49	Paracetamol	LIAOYUAN CITY BAIKANG PHARMACEUTICAL CO. LTD CN 136 200 Liaoyuan	R1-CEP 2007-054-Rev 03	06/11/2019	VALID		Chemistry
49	Paracetamol	Bristol Laboratories Ltd GB HA1 2EN Harrow	R0-CEP 2001-092-Rev 02	13/10/2004	WITHDRAWN BY HOLDER	25/10/2005	Chemistry
49	Paracetamol	FARMSON PHARMACEUTICAL GUJARAT PRIVATE LIMITED IN 391 340 Nandesari	R1-CEP 2002-020-Rev 08	15/10/2020	VALID		Chemistry
49	Paracetamol	SRI KRISHNA PHARMACEUTICALS LIMITED IN 500 039 Hyderabad	R1-CEP 2000-144-Rev 05	24/07/2018	VALID		Chemistry
49	Paracetamol	Weistar Industry Limited CN 313 000 Huzhou	R0-CEP 2006-156-Rev 00	17/04/2008	WITHDRAWN BY EDQM	16/04/2013	Chemistry
49	Paracetamol	ANHUI BBCA LIKANG PHARMACEUTICAL CO., LTD. CN 233 010 Bengbu	R0-CEP 2011-278-Rev 00	30/03/2012	EXPIRED	31/03/2017	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 and health organisations worldwide accept CEPs
  - e.g. Australia, Canada, Morocco, Saudi Arabia, TFDA Singapore, South Africa,, 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)

Thank you for your attention

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