THE EDQM CERTIFICATION PROCEDURE & INSPECTION PROGRAM FOR API MANUFACTURERS

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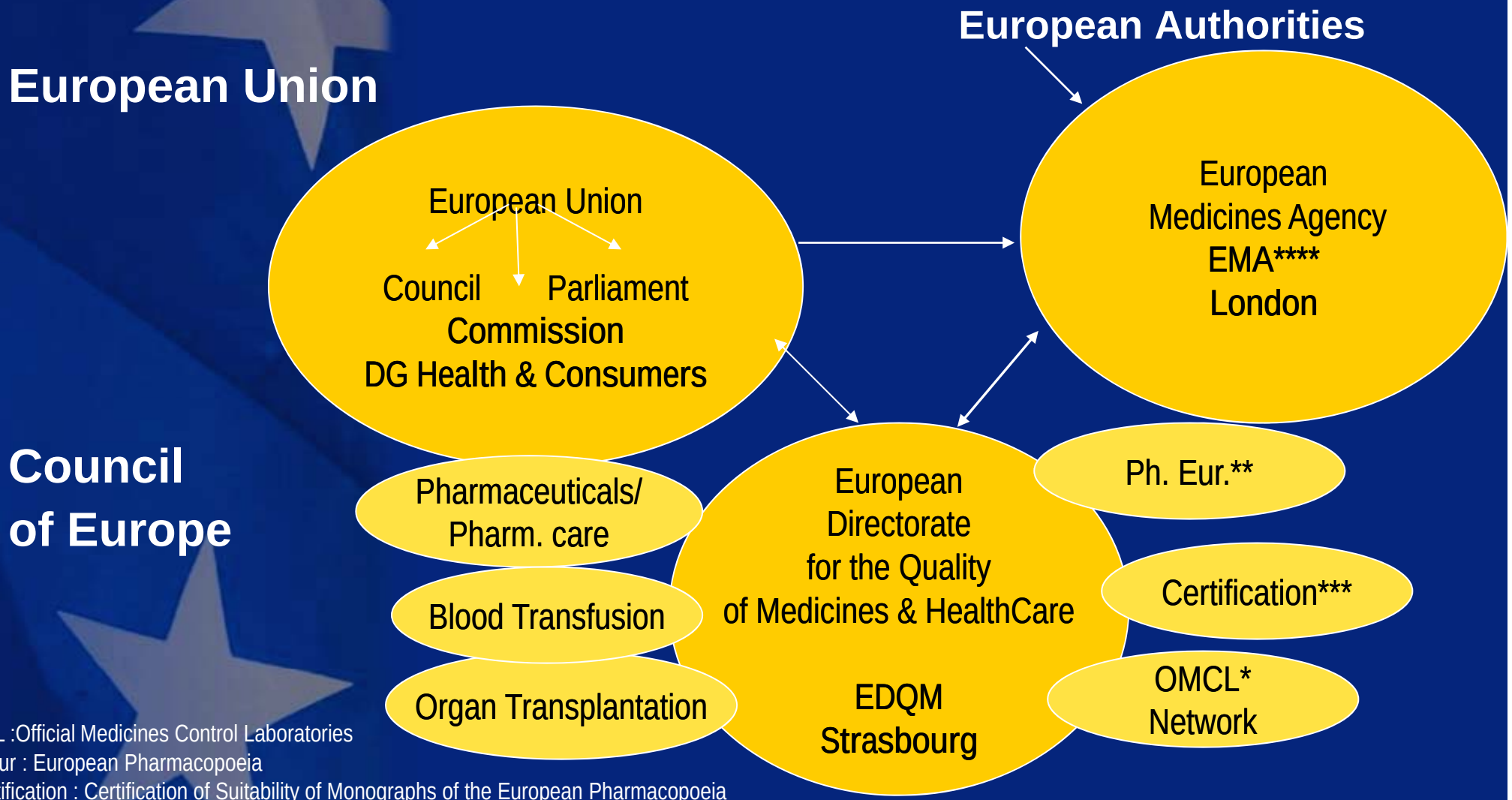
Overview

- The Certification Procedure
- Revisions/renewals of CEPs
- The EDQM inspection program
- Key figures

European Regulatory Network



*OMCL :Official Medicines Control Laboratories
**Ph.Eur : European Pharmacopoeia
***Certification : Certification of Suitability of Monographs of the European Pharmacopoeia
****EMA : European Medicines Agency

The Certification Procedure

Legal Background

For medicinal products in Europe:

- All monographs (incl. general monographs and general chapters) of the European Pharmacopoeia are legally binding
- In addition, there is a need to demonstrate the suitability of a monograph to control the quality of an API from a specific source

The Certification Procedure

- Official start in 1994, managed by EDQM
- Assessment of the quality of pharmaceutical substances with regards to the criteria of the Ph. Eur. monograph(s) (“quality” or “herbal” CEP)
  - Ensures that all possible impurities can be fully controlled by the monograph(s) and additional test(s) if necessary
- Demonstration of compliance with the general monograph on Products with TSE risk (“TSE” CEP)

The Certification procedure (2)

Benefits:

- Centralised assessment
- Easier management of marketing authorisation applications – CEP replaces main part of 3.2.S
- CEPs accepted in all Ph. Eur. countries (36) + others (eg. Canada, Australia, Singapore, etc.)

=> saving of time & money for applicants and National Authorities

- Contribution to revision of Ph. Eur monographs

Scope

- Substances described in monographs in the Ph. Eur.

  ➔Active substances, excipients, herbal drugs / herbal preparations
- Products with risk of TSE (APIs, raw materials, intermediates, reagents,..)

  Open to any manufacturer regardless of geographical origin

Outside the scope

For the quality evaluation:

- Substances not included in Ph. Eur*
- Human tissues derivatives, blood derivatives*, vaccines, biotech products
- Products extracted from animal tissues* (“biologicals”), since 2009

* Are within the scope for TSE evaluation

How does it work

- A manufacturer of a pharmaceutical substance submits a dossier to EDQM
  - Dossier describes manufacture & quality control of the substance + suitability of the Ph. Eur monograph
- Dossier evaluated by 2 assessors (from national authorities and EDQM)
- An official certificate (CEP) is granted

A CEP « quality »

- Certifies that the quality of a given substance can be suitably controlled by the Ph. Eur monograph - with additional tests if necessary (stated on the CEP)
- It DOES NOT replace a certificate of analysis
- It IS NOT a GMP certificate

A TSE CEP

- Certifies that the substance complies with the Ph. Eur general monograph on “Minimising the TSE risk”
- It DOES NOT certify that the quality of the substance can be controlled by the Ph. Eur monograph (if it exists)
- It IS NOT a certificate of analysis
- It IS NOT a GMP certificate

European Directorate for the Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

Certification of Substances Division

Certificate of suitability
No. R0-CEP 2007-001-Rev 00

Name of the substance:
ZINC UNDECYLENATE

Name of holder:
EDQM
7 allée Kastner
France-67081 Strasbourg

Site(s) of production:
EDQM
7 allée Kastner
France-67081 Strasbourg

After examination of the information provided on the manufacturing method and subsequent processes (including purification) for this substance on the site(s) of production mentioned above, we certify that the quality of the substance is suitably controlled by the current version of the monograph **ZINC UNDECYLENATE** no. 539 of the European Pharmacopoeia, current edition including supplements, only if it is supplemented by the test(s) mentioned below, based on the analytical procedure(s) given in annex.

- Test for residual solvents by gas chromatography (Annex 1)
  Ethanol not more than 5000 ppm

The holder of the certificate has declared the absence of use of material of human or animal origin in the manufacturing of the substance.

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance.

Manufacture of the substance shall take place in accordance with the Good Manufacturing Practice and in accordance with the dossier submitted.

Failure to comply with these provisions will render this certificate void.

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

This certificate is granted within the framework of the procedure established by the European Pharmacopoeia Commission [Resolution AP-CSP (93) 5 as amended] for a period of five years starting from **1 April 2007**. Moreover, it is granted according to the provisions of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

This certificate has one annex of 3 pages.
This certificate has:
lines.

On behalf of the
Director of EDQM & HealthCare

Strasbourg, 1 April 2007

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

EDQM, as holder of the certificate of suitability

R0-CEP 2007-001-Rev 00 for ZINC UNDECYLENATE

hereby authorises .....
(name of the pharmaceutical company)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): *(name of product(s) and marketing number(s), if known)*

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature *(of the CEP holder)*:

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

Revisions/renewals of CEPs

Basic principles

- Based on EU Regulation on Variations to Marketing Applications
- Specific guidelines for revisions of CEPs (available on EDQM website)
- Any change (administrative or technical) to be reported to EDQM, through an appropriate kind of revision
  - Notification
  - Minor revision
  - Major revision
- Revision of the Ph. Eur monograph triggers an update of the CEP dossier

Basic principles (2)

- Original CEP is valid 5 years - Need to apply for renewal in time
- After renewal, CEP valid for an unlimited period, provided the dossier is kept up-to-date
- Holder to inform customers and/or authorities when a change has been approved, and to provide revised CEP ➔Update of any relevant Marketing Applications

The EDQM Inspection Program

Legal Background: GMP for APIs

In Europe:

- Only APIs produced in compliance with EU GMP (Part II) can be used for the manufacture of medicinal products
- It is the responsibility of the Manufacturing Authorisation Holder to ensure GMP compliance of the API manufacturer
  - Declaration from the Qualified Person (QP) in the marketing application and any relevant variation application

Role of the Competent Authorities

- The Competent Authorities may carry out an inspection of an API manufacturer in order to ensure that a MA holder has fulfilled its obligations

- NB: in contrast to medicines, inspections are not carried out systematically

Role of the API manufacturer

- In the CEP procedure only, the manufacturer has to declare:
  - Compliance to GMP (EU Part II=ICH Q7)
  - Willingness to be inspected

EDQM Inspection Program

- Integral part of the Certification Procedure
- Based on mandate given by EU to establish an annual inspections program
- Companies holding or applying for a CEP
- Aim: to verify the compliance with the submitted dossier and GMP
- API manufacturers mainly outside Europe
- May be performed before or after the CEP is granted: risk-based decision whether to inspect

Selection of the sites

- Done in accordance with the EU guidance
  (Compilation of community procedures on inspections and exchange of information)
- Risk-based approach:
  - request from the assessors
  - sterile substances
  - regulatory environment of the manufacturing site
  - several triggers involved

Inspection progress

- The Team:
  - 1 EU/EEA inspector + 1 EDQM inspector
  - Local inspectors invited in non-Ph. Eur countries
- The Place:
  - >85% of EDQM inspections in Asia
- Compliance to the submitted dossier and to the EU GMP Part II is verified
- Inspection lasts about 3 days
- Oral observations at the closing meeting

Inspection outcomes

- Companies found compliant:
  - EDQM Attestation of Inspection sent to the company
  - Official GMP certificate granted by the EU/EEA inspector
  - Company may be re-inspected / re-evaluated within 2-5 years depending on the number and classification of deficiencies found
- Companies found “borderline”:
  - final decision taken after assessment of CAPA

Negative Outcome

- Decision-making process is aimed to ensure public health protection and equity
- Generally actions are taken immediately after inspection (=before report is issued)
- Policy document published on the EDQM website (“Suspension/cancellation”)

Suspension / cancellation of CEPs

- Actions taken if:
  - critical/major deficiencies found during an inspection
  - refusal to be inspected
  - temporary inability to produce the substance

➔Suspension of CEP, closure of application

➔Negative re-inspection after suspension leads to cancellation of CEP

➔Falsification of data leads to immediate cancellation of CEP

In case of suspension / cancellation of a CEP

- Suspension for 2 years, cancellation is definitive
- All relevant authorities informed (PhEur Member States, EMA, EU Commission, local Inspectorate)
- Public information: EDQM website (“News” for 6 months) + CEP on-line database
- Issue of non-compliance information by EU/EEA inspector
- Company must inform its customers

Suspension of the CEP

- CEPs are suspended for a period of 2 years
- Company is requested to apply within this timeframe for a re-inspection
- Lifting the suspension can only be done after an inspection with positive outcome
  - CEP revised, appears again as valid on the EDQM website
  - Relevant authorities informed (annual report)

International API Inspection Program

- Initiated by EMA in 2008
- Start with a pilot phase = 2 years (end 2010)
- Participants: EU inspectorates, EDQM, Australia, USA
- Inspections of API manufacturers outside the participating regions
- Sharing of inspections planning + reports, joint inspections

Results

- A total of 642 sites shared (“Master List”)
- # 100 inspection reports exchanged
- 9 joint inspections (Europe/TGA, FDA/TGA, Europe/FDA)
- Actions taken based on information received

Results (2)

- Confidence building, closer relationships
- No notable differences in preparation, conduct, conclusions of inspections between the regions
- Still some duplicate inspections, but efforts done to reduce them

- Report published in 07/2011 on TGA, USFDA, EMA, EDQM websites

Next steps

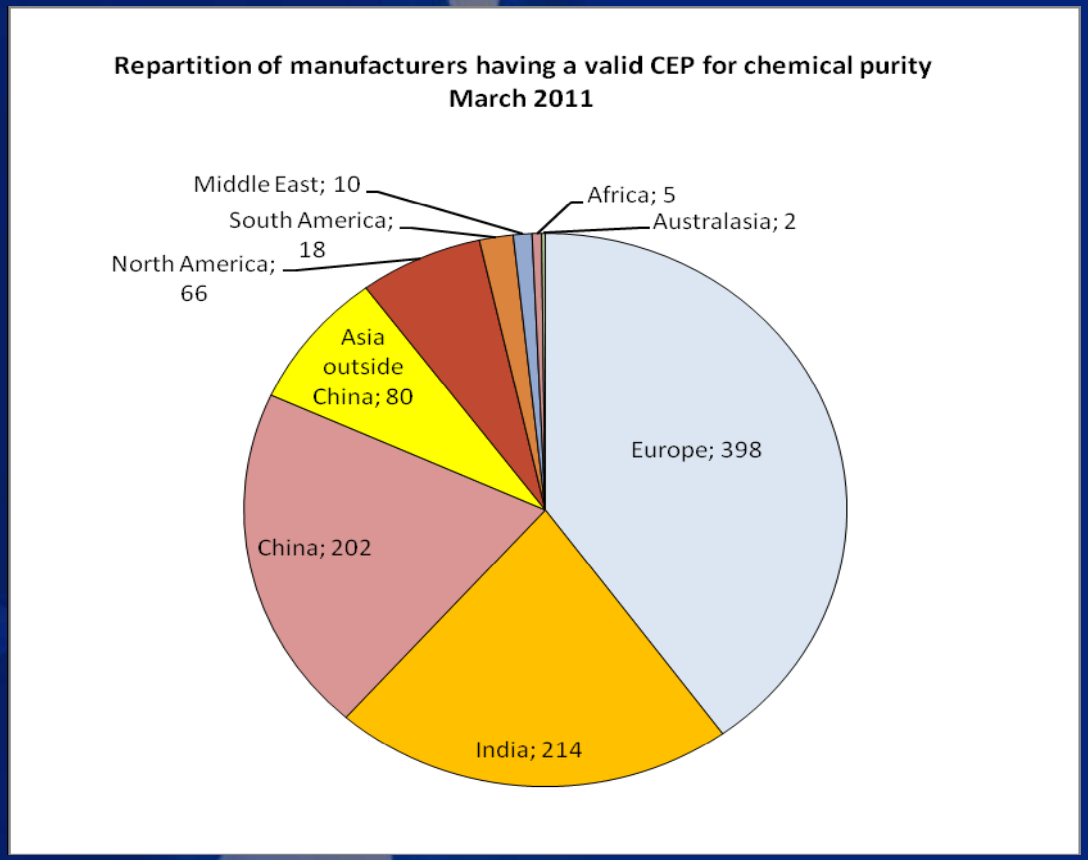
- To continue the program
- To improve process monitoring
- To enlarge the number of participating countries

Key figures

Key figures

- > 5000 CEP applications received (# 400 new/year, # 1000 revisions/year)
- > 2800 valid CEPs
- 960 manufacturing sites from 56 countries covered

Repartition of manufacturers (2011)



1. India 214 sites
2. China 206 sites
3. Italy 90 sites
4. USA 58 sites
5. Germany 57 sites

Inspections

- >250 inspections carried out, # 160 sites inspected
- in 26 countries
- A number of CEPs suspended/cancelled as result of inspection programme (32 in 2011)

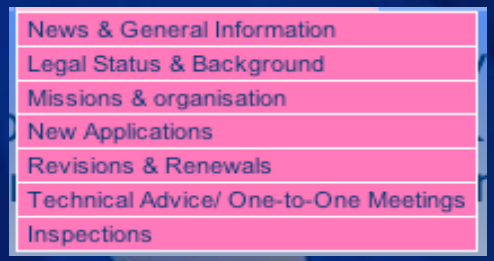
General Compliance Trends

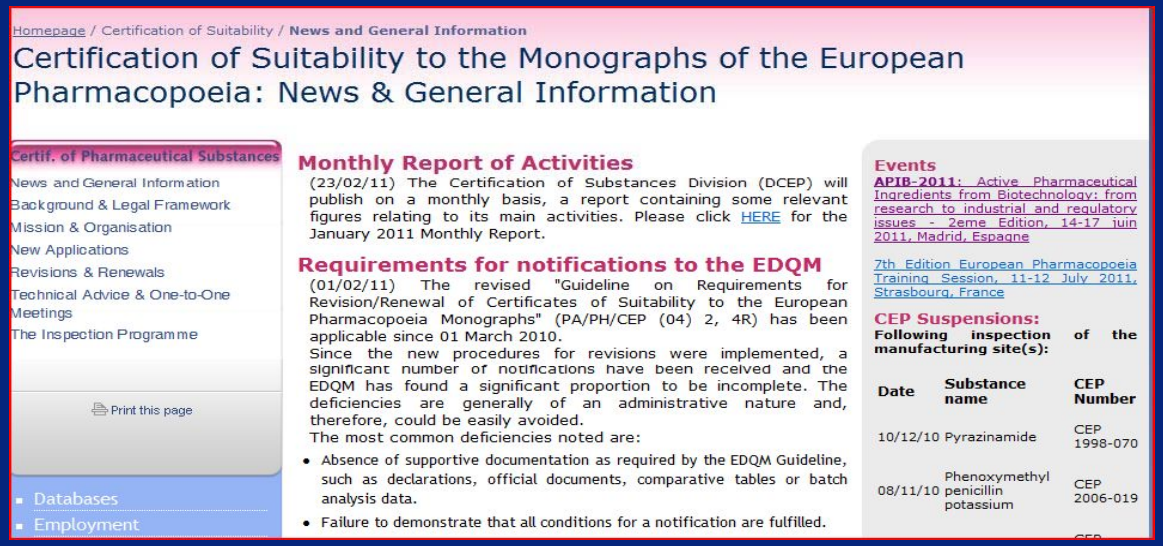
- Non compliant sites:
  - 2007: 18%
  - 2008: 21%
  - 2009: 34%
  - 2010: 18%

  This is seen as the result of the ability of EDQM to identify sites with higher risk of non-compliance and to focus on them

More information…

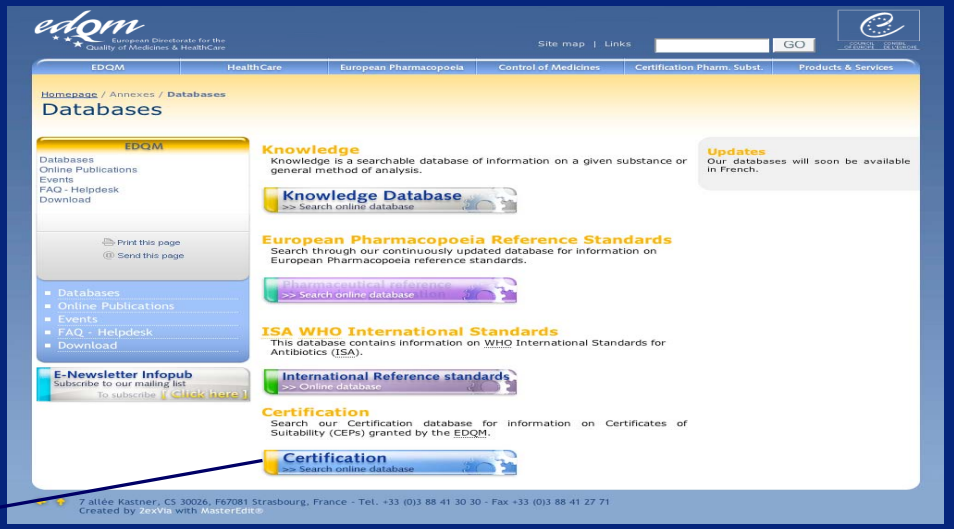
- EDQM Website-7 pages on Certification: procedure, guidelines, inspections, news, etc www.edqm.eu

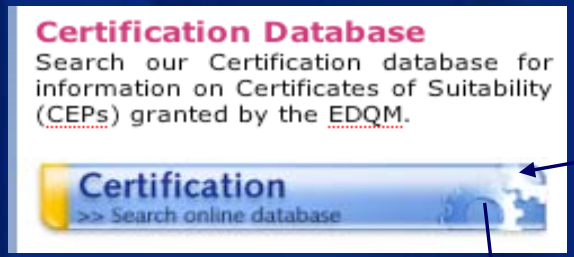


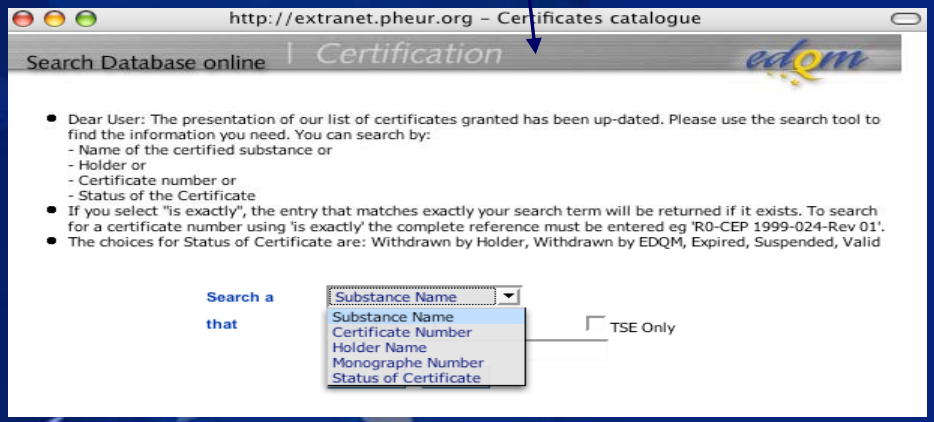


Is a CEP valid ?

- www.edqm.eu







Hints:
To see all certificates, search for all certificate numbers containing CEP.

In general you will get more hits with “contains” than “is exactly”.

Spelling is important

Is a CEP valid ?

New Search

Substance Number	Substance	Certificate Holder	Certificate Number	Issue Date	Status	Type
543	Carbamazepine	Bajaj Healthcare PVT Ltd IN 400 009 Mumbai	R0-CEP 2002-141-Rev 00	23/11/2004	SUSPENDED	Chemistry
543	Carbamazepine	PHARMACEUTICAL WORKS POLPHARMA S.A. PL 83-200 Starogard Gdanski	R0-CEP 2004-141-Rev 00	13/10/2006	VALID	Chemistry
543	Carbamazepine	Degussa AG DE 40474 Düsseldorf	R1-CEP 1996-001-Rev 01	13/10/2004	WITHDRAWN BY HOLDER	Chemistry
543	Carbamazepine product codes: S40029, S40126, S40020 and S50386	Taro Pharmaceutical Industries, Ltd. IL 60972 Yakum	R1-CEP 1998-087-Rev 04	08/11/2010	VALID	Chemistry
543	Carbamazepine	Farchemia S.r.l. IT 24047 Treviglio	R1-CEP 1997-119-Rev 02	22/02/2008	WITHDRAWN BY HOLDER	Chemistry
543	Carbamazepine Crystallization from Ethanol	Teva Pharmaceutical Industries Ltd. IL 49131 Petah Tiqva	R0-CEP 2005-008-Rev 01	28/07/2008	VALID	Chemistry

Holder name

Full CEP number

Issue date of the current CEP

Status

Thank you!