

The procedure of Certification of Suitability to the Monographs of the European Pharmacopoeia (CEP) and the EDQM Inspection Programme

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CEP

Certificate of suitability to the monographs of the
European
Pharmacopoeia

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Regulatory background



- In the EU, directives 2001/83/EC and 2001/82/EC as amended are the references
- The Marketing Authorisation applicant for a medicinal product is required to demonstrate that:
 - The active substance used is in compliance with the Ph. Eur. monograph(s)
 - The Ph. Eur. monograph is able to control the quality of this active substances (impurity profile)
- Active substances have to be manufactured under Good Manufacturing Practice (GMP)
 - Authorities inspect the sites that are identified « at risk »

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The Certification procedure role

- Centralised assessment of the quality of pharmaceutical substances with regards to the criteria of the Ph. Eur. monograph(s)
 - Ensures that all possible impurities of a source of substance can be suitably controlled (or not) by the monograph(s)
 - Demonstrates compliance of a source of a substance with European regulatory requirements
 - Demonstrates compliance with the general monograph on Products with TSE risk

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The CEP Procedure role (2)

- The procedure is optional, in EU there are 3 possibilities to submit the data:
 - CEP
 - Active Substance Master File (ASMF)
 - Full data in the Marketing Authorisation Application

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The CEP procedure provides

- Centralised assessment
- Facilitates management of MAAs and variations
 - CEPs are intended to be introduced in marketing applications and to replace the relevant data (Part 3.2.S of the CTD)
- ➔ saves time and resources for Authorities & Industry
- Information on the need to update Ph. Eur. monographs
- CEP accepted in Ph. Eur. Convention member states (37) + other countries (e.g. Canada, Australia, Singapore, South Africa, etc.)

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Scope

- Substances described in monographs in the Ph. Eur.
 - ➔ Active substances, excipients, herbal drugs / herbal preparations ("Chemical" or "Herbal" CEP)
- Products with risk of TSE (APIs, raw materials, intermediates, reagents,...regardless if there is a Ph. Eur monograph)) ("TSE" CEP)

Open to any manufacturer regardless of geographical origin



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Out of Scope of the CEP Procedure

- Substances not included in Ph. Eur.
- Biologicals according to EU legislation
- Human tissues derivatives, blood derivatives, vaccines



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How to obtain a CEP

- Intended holder to send an application to EDQM
 - Application form (available on the EDQM website)
 - Quality Overall Summary (Module 2 of CTD)
 - Technical documentation describing manufacture & quality control of the substance (Module 3 of CTD)
 - Fee (5000 Euros)

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Who performs the evaluation?

- Assessment takes place at EDQM
- Application assessed by 2 assessors (rapporteur and co-rapporteur), 1 from EDQM and 1 from a national authority from Ph. Eur member states, who both sign the report
 - A network of #100 national assessors from 24 countries, including from Canada, Australia
- Policies for assessment are based on ICH and EU requirements & quality guidelines for pharmaceutical substances
- Getting a CEP takes 12-18 months (including time for the applicant to respond to a letter of request for additional information)

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Validity of CEP



Once a CEP has been granted it must be maintained throughout its lifecycle

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Basic principles for maintaining a CEP

- Any change (administrative and technical) must be reported to EDQM → Revision process (notifications, minor, major revisions, renewals...
- Original CEP is valid 5 years
- Holder needs to apply for renewal
- After renewal, CEP valid for an unlimited period, provided the dossier is kept up-to-date
- Holder to inform their customers of any changes made
- Revised CEP to be sent to customers

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EDQM Inspection Programme



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EDQM Inspection programme

- Integral part of the Certification Procedure
- Inspections of sites holding or applying for CEP(s)
- Performed before or after the CEP is granted
- Mainly outside Europe (India and China)
- Aim: to verify the compliance with
 - submitted dossier
 - EU GMP Part II & Annexes (e.g. Annex 1 for sterile substances, Annex 7 for substances of herbal origin)
- Performed in accordance with the EU guidance
- According to a risk-based approach

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Risk-based selection of the sites

- Request from the assessors: inconsistencies in the data, suspicion of data manipulation
- Re-inspection: depending on the compliance level after initial inspection, or after CEP suspension when requested
- API related criteria: physico-chemical properties, therapeutic use, sterile etc.
- Company related criteria: information from other authorities (i.e. from inspection) or other suspicions
- Regulatory environment of the manufacturing site
- Several triggers involved

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How does the system work

- Inspection performed by team composed of an EDQM inspector and an inspector coming from an EU/EEA/MRA authority
- Normally 3 days
- An inspection report is issued within 6 weeks
- Immediate actions are taken in case of major/critical deficiencies (suspension / withdrawal of CEP)

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Positive Outcome

- In case of positive outcome, an inspection attestation is delivered by EDQM, stating compliance with the CEP dossier and with GMP
- A GMP Certificate should be issued by the EEA participating Inspectorate via the EUDRA GMDP database (public information)
- Companies found compliant may be re-inspected/ re-evaluated within 2-5 years depending on the numbers and classification of deficiencies found.

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Negative Outcome

- In case of critical/major GMP deficiencies or in case of major discrepancies compared to the dossier (failure in the declarations and commitments)
 - CEP(s) suspended or withdrawn
 - on-going CEP application(s) rejected
- Decision making process ("Suspension or Cancellation of a Certificate of Suitability" PA/PH/CEP (08) 17):
 - Actions recommended by the inspectors
 - discussed within the Certification Division
 - endorsed by an Ad Hoc Committee

Public (on EDQM website and authorities are informed).

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Key Figures



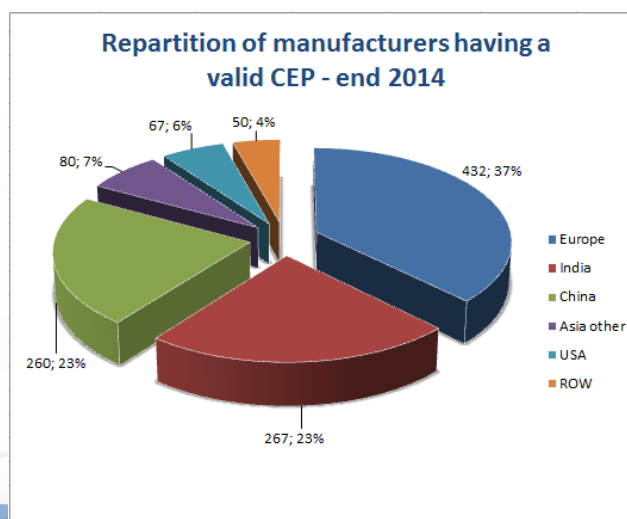
- > 6200 applications received
- More than 4200 valid certificates
- # 1100 manufacturers from 50 countries
- >350 sites inspected, in 26 countries

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Repartition of manufacturers (end of 2014)



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General Compliance Trends

➤ Inspected sites found non compliant:

- 2008: 21%
- 2009: 34%
- 2010: 18%
- 2011: 32%
- 2012: 40%
- 2013: 38%
- 2014: 12%
- 2015: 18%

The high proportion of non compliant sites is seen as a result of the ability of EDQM to identify sites with higher risk of non-compliance and to focus on them.

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Is a CEP valid ?



Certification of Suitability

What's new?

Latest News

Events

About the Procedure

Background & Legal Framework

Mission & Organisation

The Inspection Programme

How to apply?

New Applications

Revisions & Renewals

Technical Advice & One-to-One Meetings

Find information on

Certification Policy documents & Guidelines

CERTIFICATION Database

Actions on CEPs

KNOWLEDGE Database

Certificate of Suitability (prices & orders)

FAQ & Helpdesk

Check the database on www.edqm.eu

The image shows a search form for the EDQM Certification Database. It includes a search bar with a dropdown menu for 'Substance Name', a search button, and a 'Clear' button. There are also radio buttons for 'all', 'TSE Only', and 'Herbal Only'. A blue arrow points to the search bar. The form also includes a list of search criteria: Name of the certified substance or Monograph number or Holder of the certificate or Certificate number or Issue date of certificate or Expiry date of certificate or Status of the certificate. It also includes a note: 'The substance name is equal to the monograph name and the subtitle for chemical, herbal and double certificates and is the substance name for TSE certificates'. At the bottom, there is a note: 'If you are interested in all types of certificates, please select the button beside "all". If you are only interested in TSE or herbal certificates, please select the button beside your required choice and only TSE or herbal certificates will be displayed as a result of your choice.'

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Thank you for your attention!



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