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 »

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

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

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.)

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

Out of Scope of the CEP Procedure

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

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)

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)

Validity of CEP

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

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

EDQM Inspection Programme

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

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

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)

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.

Negative Outcome

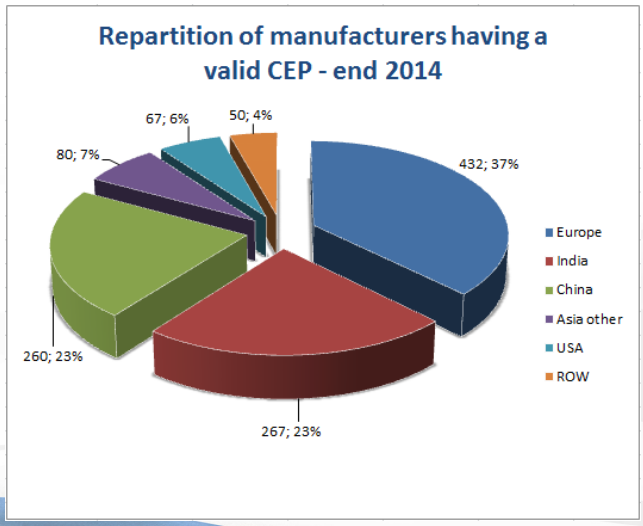
- In case of critical/major GMP deficiencies or in case of major discrepancies compared to the dossier (failure in the declarations and commitments)
  - CEP(s) suspended or withdrawn
  - on-going CEP application(s) rejected
- Decision making process ("Suspension or Cancellation of a Certificate of Suitability" 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).

Key Figures

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

Repartition of manufacturers (end of 2014)

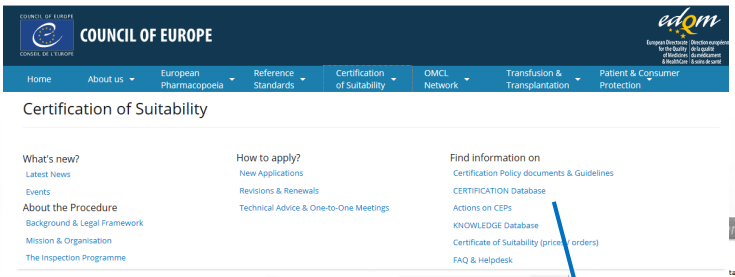


General Compliance Trends

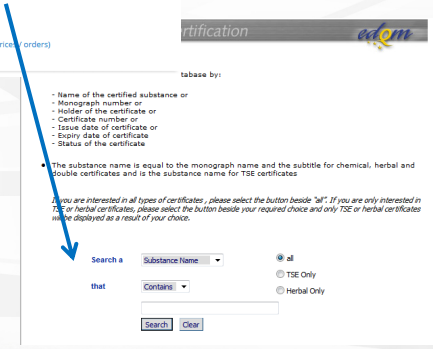
- Inspected sites found non compliant:
  - 2008: 21%
  - 2009: 34%
  - 2010: 18%
  - 2011: 32%
  - 2012: 40%
  - 2013: 38%
  - 2014: 12%
  - 2015: 18%

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.

Is a CEP valid ?



Check the database on www.edqm.eu



Thank you for your attention!