General Presentation on the Role and Place of the Certification Procedure in the European Regulatory System

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Summary

• Regulatory background
• Comparison of CEP and ASMF
• The Certification procedure role
• The CEP
• Key figures
• How to communicate with EDQM
Regulatory background

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

• In cases where a specification contained in a European Pharmacopoeia 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.
CEPs in the EU legislation

Directives state that where the active substance and/or excipient(s) are the subject of a monograph of the EP, 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...

NfG CHMP/QWP/297/97 rev. 1 corr « Summary of requirements for active substances in the quality part of the dossier »

Gives 3 basic choices for providing information regarding the active substance

2.1. Certificate of suitability

• requires Ph. Eur. Monograph (specific or TSE)
• used for “existing” substances

“where applicable, option 2.1 has the advantage of generally avoiding any subsequent reassessment”

The information required is the same regardless of the procedure selected.
NfG CHMP/QWP/297/97 rev. 1 corr. « Summary of requirements for active substances in the quality part of the dossier »

2.2 Active substance Master File (ASMF)
- Applicable to all active substances

2.3 Full details of manufacture in marketing authorisation application
- both procedures do not require Ph. Eur. Monograph
- can be used for “new” and “existing” substances

Differences between CEP & ASMF

Scope:
- CEP: pharmacopoeial substances only,
  -> active substances or excipients
  -> any substance for TSE CEP
- ASMF: active substances only,
  -> new or pharmacopoeial
**Comparison between CEP & ASMF procedures**

<table>
<thead>
<tr>
<th></th>
<th>CEP procedure</th>
<th>ASMF system</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dossier</strong></td>
<td>Content identical (CTD 3.2.S)</td>
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</tr>
<tr>
<td></td>
<td>Full dossier sent directly by API manufacturer to EDQM</td>
<td>Full dossier sent by API manufacturer to Competent Authorities</td>
</tr>
<tr>
<td></td>
<td>(will be the holder of the CEP)</td>
<td>AP sent by API manufacturer to marketing authorisation applicant or holder of medicinal product</td>
</tr>
<tr>
<td><strong>Additional data</strong></td>
<td>Holders commitments</td>
<td>Letter of access (to be sent by API manufacturer)</td>
</tr>
<tr>
<td><strong>Link with a medicinal product</strong></td>
<td>Independent from marketing authorisation applications</td>
<td>In the context of a specific marketing authorisation application or variation for medicinal products</td>
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**Evaluation**

<table>
<thead>
<tr>
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<th>CEP procedure</th>
<th>ASMF system</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Single evaluation centralised at EDQM by assessors nominated by Competent Authorities / Certification Steering Committee</td>
<td>Assessment of ASMF by each competent authority in the context of assessing a specific marketing authorisation application or variation for medicinal products</td>
</tr>
<tr>
<td></td>
<td>Principles identical: Assessment against ICH/EU guidelines for quality + Ph. Eur monograph + EDQM specific guidance</td>
<td>Principles identical: Assessment against ICH/EU guidelines for quality + Ph. Eur monograph if applicable</td>
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</table>
### Comparison between CEP & ASMF procedures

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<tr>
<td><strong>Deliverable</strong></td>
<td>A Marketing Authorisation for the medicinal product using this particular API</td>
</tr>
<tr>
<td>Certificate including annexes (additional tests to be performed) granted to manufacturer who supplies a copy to customers (users of the API)</td>
<td></td>
</tr>
<tr>
<td><strong>Variations</strong></td>
<td>Submission of changes to marketing authorisation applications, according to EU Variations regulation</td>
</tr>
<tr>
<td>Changes to the CEP dossier centralised at EDQM Submission of revised CEPs according to EU Variations regulation</td>
<td></td>
</tr>
<tr>
<td><strong>Use</strong></td>
<td>EU/EEA member states + Australia + Canada</td>
</tr>
<tr>
<td>Ph. Eur member states &amp; others (Australia, Canada, Singapore, South Africa, etc)</td>
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**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
The CEP procedure

• Official implementation in 1994
• An international platform for:
  ➢ Assessment of the quality of substances for pharmaceutical use (APIs, excipients, herbals, TSE risk)
  ➢ Coordination and conduct of GMP inspections of API manufacturers
• Keys for acceptance of CEPs:
  • Strong processes
  • Harmonisation of decisions
  • Transparency

The CEP Procedure role

• 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”
The CEP procedure

Provides:

• Centralised assessment - saves time and resources
• Information on the need to update Ph. Eur. monographs
• Facilitates management of MAAs and variations
• Application submitted directly to EDQM by the manufacturer of the pharmaceutical substance
• CEP accepted in all Ph. Eur. Convention member states (38) + other countries (e.g. Canada, Australia, Singapore, South Africa, WHO, etc.)

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 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 (PA/PH/CEP (09) 152 rev 01)

• Human tissues derivatives, blood derivatives, vaccines

• Finished products
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**:

<table>
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<tr>
<th><strong>NEW APPLICATIONS</strong></th>
<th><strong>Fees</strong></th>
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<tbody>
<tr>
<td>CEP 028 Simple chemical certificate</td>
<td>5000 €</td>
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<tr>
<td>CEP 027 Simple TSE or herbal certificate</td>
<td>3000 €</td>
</tr>
<tr>
<td>CEP 026 Double certificate (chemical + TSE)*</td>
<td>8000 €</td>
</tr>
<tr>
<td>CEP 025 Certificate for chemical purity and sterility</td>
<td>8000 €</td>
</tr>
<tr>
<td>CEP 024 Certificate for chemical purity and sterility + TSE**</td>
<td>9000 €</td>
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</tbody>
</table>

* 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 €.

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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 new applications in eCTD only from the 1st of January 2018
- To be submitted via CESP only
  - Users should register for a CESP account on the Heads of Medicines Agencies website

How it works

1. Application
   - Validation at receipt
   - Evaluation (2 assessors) + TAB if necessary
   - Request for add info

2. To be updated:
   - at any change (notification, minor/major)
   - after 5 years (renewal)

3. Request for inspection

4. Revision of monograph

5. Transfer to the Ph. Eur. experts group
   - CEP granted
   - Refusal

6. Possibility of hearing
   - Informing licensing authorities
Who performs the evaluation?

• Assessors proposed by National competent Authorities and appointed 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

• EDQM assessors also appointed by the Steering Committee.

How long does it take?

First round of assessment:
- Original dossier assessed in 5 months
- Response expected from applicant within 6 months
- Request for add info

Second round of assessment:
- Responses assessed within 4 months
- Request for add info
- Response expected from applicant within 3/1 months

Third round of assessment:
- Responses assessed within 4/1 months
- Refusal
- CEP granted
Key Figures and How to communicate with EDQM

Key figures

• Since 1994, # 7000 CEP applications received for >1000 different substances

• Currently about 4900 valid chemical/double CEPs

• 1200 manufacturers from 50 different countries

• These numbers change frequently as new applications are received and existing CEPs are revised daily.
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: February 2018

Includes also other news in the month (suspensions etc.)
Is a CEP valid?
Check our database on www.edqm.eu
Is a CEP valid?

Communication with EDQM

EDQM Website – Certification of Suitability

- Procedure, guidelines, documents, news are available
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 (included in our communication)
- Technical Advice: to meet the EDQM staff and get advice about applications (fee applicable)

Thank you for your attention!