Quality of Substances for Pharmaceutical Use: The EDQM Certification of Suitability to the European Pharmacopoeia Monographs (CEP)

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Summary

- Legal Background
- CEP versus ASMF
- How it works
- How to apply
- Certification Inspection Programme
- Exchanging information/advice, communication opportunities
Legal Background

Directive 2003/63/EC “Whereas”
(5) With respect to the quality part of the dossier, all monographs including general monographs and general chapters of the European Pharmacopoeia are applicable.
Directive 2003/63/EC

Chapter 3.2 Content: basic principles and requirements

(5) The monographs of the European Pharmacopoeia shall be applicable to all substances, preparations and pharmaceutical forms appearing in it. In respect of other substances, each Member State may require observance of its own national pharmacopoeia…
Directive 2003/63/EC

….However, where a material in the EP… has been prepared by a method liable to leave impurities not controlled in the pharmacopoeia monograph, these impurities and their maximum tolerance limits must be declared and a suitable test procedure must be described. In cases where a specification contained in a monograph of the EP… might be insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the marketing authorisation holder…
Directive 2003/63/EC

… The competent authorities shall inform the authorities responsible for the pharmacopoeia in question. The marketing authorisation holder shall provide the authorities of that pharmacopoeia with the details of the alleged insufficiency and the additional specifications applied.
Directive 2003/63/EC

(7) Where the active substance and/or raw and starting material 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 Module. Those certificates of suitability ... are deemed to replace the relevant data of the corresponding sections described in the Module...
Directive 2003/63/EC

… The manufacturer shall give the assurance in writing to the applicant that the manufacturing process has not been modified since the granting of the certificate of suitability by the European Directorate for the Quality of Medicines.
Options for Submitting API Information

- Certificate of suitability (CEP)
- Active Substance Master File (ASMF/EDMF)
- Substance Part of CTD
NfG CHMP/QWP/297/97 rev. 1 corr
“Summary of requirements for active substances in the quality part of the dossier”

2.1 Certificate of suitability
• requires Ph. Eur. Monograph (specific or TSE)
• used for “existing” substances
• guideline states: “where applicable, option 2.1 has the advantage of generally avoiding any subsequent reassessment”

2.2 Active substance Master File (ASMF)

2.3 Full details of manufacture in licence 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
Differences between CEP & ASMF

- **ASMF:**
  - Full dossier sent by manufacturer of API to national authorities
  - Applicants part sent by manufacturer of API to MA applicant or holder of medicinal product
  - Letter of access (to be sent by manufacturer of API)
  - Assessment of ASMF by each national authority in the context of assessing a specific marketing authorisation application or variation for medicinal products
Differences between CEP & ASMF

- Assessment of CEP applications:
  - Single centralised evaluation at EDQM
  - By assessors nominated by national authorities
  - Independent from marketing authorisation applications for medicinal products
  - Certificate including annexes (additional tests to be performed) granted to manufacturer of active substance who supplies it to users
Certificate of Suitability

Provides:

• Savings of time and resources
• Confidentiality of data (as ASMF):
  – Application submitted directly to EDQM by the applicant
• Facilitates management of marketing authorisation applications and variations
• CEP accepted in all Ph. Eur. convention member states (36) + other countries (eg. Canada (MoU 03/2007), Australia, Morocco, Tunisia, New Zealand etc.)
Regulatory Background

Directive 2003/63/EC and the various quality guidelines give options on how to fulfil the same basic requirements.

The information required is the SAME regardless of the route selected (CEP or ASMF or marketing autorisation application)
Scope of the Certification Procedure

- Substances described in monographs in the Ph. Eur. Active substances, excipients, herbal drugs / herbal preparations ➔ “Chemical” CEP
- Products with risk of TSE (SM, intermediates, reagents,..) ➔ “TSE “CEP
- Substances described in monographs in the Ph. Eur. and with risk of TSE ➔ “Double “CEP

Open to any manufacturer regardless of geographical origin
Out of Scope of the Certification procedure

- Substances not included in Ph. Eur.
- Biologicals
- Human tissues derivatives, blood derivatives, vaccines
- Finished products
Certification: Organisation

- Steering Committee
- Technical Advisory Boards (TAB)
  - Chemical
  - TSE
  - Herbals
- Assessors
- Certification Secretariat
Steering Committee

- Representatives of main regulatory bodies (14 members from EMA WP, EU Commission, Ph. Eur Commission, Non-EU licensing authorities, ...)
- Monitoring Certification procedure
- Appointment of assessors
- Appointment of Technical Advisory Boards (TABs) and their Chairperson
- Policy adoption
- Review and comment on issues raised by TABs
- Co-ordination of issues between the represented parties
Technical Advisory Boards (TABs)

- Consist of experienced assessors involved in the CEP procedure for a substantial time

Role

- To take decisions on technical matter
- To assist assessors in case of doubt or disagreement
- To prepare technical guidance
- To identify technical/scientific problems and seek advice of SC
Assessors and Certification Division

• Assessors appointed by agencies (about 80 from 16 countries)
  – Role: evaluation of dossiers

• Certification Division (EDQM scientific and administrative staff)
  – Role: execution of the procedure and coordination
New Application Requires:

1. Application form (for new application)
2. Signed Quality Overall Summary (+ e-version as Word file preferably)
   
   For templates of 1 & 2, visit:
   www.edqm.eu / Certification / New Applications

3. CV of expert who wrote QOS
New Application Requires:

4. Dossier:
   • 1 copy in English (preferably) or French
   • CTD format

Visit [www.edqm.eu / Certification / New Applications]:

- Content of the Dossier for Chemical CEP (PA/PH/CEP (04) 1, 4R) : comparable to ASMF or 3.2.S of CTD
New Application Requires:

4. Dossier (continued):
Visit www.edqm.eu / Certification / New Applications:

- Content of a dossier for a substance for TSE risk assessment (PA/PH/CEP (06) 2): requirements from Ph. Eur. general chapter 5.2.8 (= EU Note for Guidance)
- Content of a dossier for herbal drugs and herbal drug preparations - quality evaluation (PA/PH/CEP 026)
- Certificates of Suitability for sterile active substances (PA/PH/Exp. CEP/T (06) 13, 1R)
Confidentiality Aspects

- CEP dossiers submitted directly by applicant
  - No applicant (open) part (≠ ASMF)
- Independent from any marketing authorisation application
- Archived in a specific restricted area (EDQM)
- Assessment on the premises of EDQM by two assessors appointed by the steering committee
- Certificate granted independently of any product licence application.
- Certificate may be supplemented with appropriate specific data and is only supplied to applicant
How Long Does it Take?

• Timeframes:
  – Applicant notified by EDQM on the assessment conclusion within 5 months of receipt of new dossier
  – Responses from applicant expected within 6 months for initial application
  – Applicant notified by EDQM on the assessment conclusion within 4 months of receipt of any response containing additional information
  – ...

NB. Since 1/09/2008: strict procedure applied
  – only one request for additional information
Certificates of Suitability

- > 4000 applications since procedure launched
- ~ 2750 valid certificates
- > 760 substance monographs involved
- ...
Certificates of Suitability

... manufacturing sites from 47 countries
Certification: Benefits

- Single assessment
- Harmonised assessment
- Replaces Active Substance Master File
- Savings of time and resources
- Updating of monographs (impurities)
- Revision of monographs (new or replacement test methods)
The Certificate of Suitability:

- Certifies that the quality of a given substance can be suitably controlled by the PhEur monograph - with additional tests if necessary.
- It DOES NOT certify that a batch or batches of the substance complies with the Pharmacopoeia monograph.
- It IS NOT a GMP certificate
Is a CEP Valid?

- www.edqm.eu / Databases
## Is a CEP Valid? (2)

<table>
<thead>
<tr>
<th>Substance Number</th>
<th>Substance</th>
<th>Certificate Holder</th>
<th>Certificate Number</th>
<th>Issue Date</th>
<th>Status</th>
<th>Type</th>
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<tr>
<td>718</td>
<td>Glibendamide</td>
<td>Aurobindo Pharma Limited IN 500 038 Hyderabad</td>
<td>RO-CEP 2004-192-Rev 00</td>
<td>16/12/2005</td>
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<td>LUSOCHIMICA S.P.A IT 36122 Pisa</td>
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<td>Glibendamide micronised</td>
<td>Merck Santé S.A.S. FR 69008 Lyon</td>
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<td>RO-CEP 2001-361-Rev 02</td>
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<td>Sri Krishna Drugs Limited IN 500 039 Hyderabad</td>
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<td>Sanofi-Aventis Deutschland GmbH DE 65926 Frankfurt Am Main</td>
<td>RO-CEP 2003-223-Rev 01</td>
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</tr>
</tbody>
</table>
Certification Inspection programme
EU Pharmaceutical Legislation

Marketing autorisation holder (MAH) responsible for the quality of the medicinal product

Qualified Person of manufacturer(s) to certify GMP compliant manufacture of all API used in marketing autorisation application and/or relevant variations: MAH has to qualify/audit supplier(s)

Trigger based, but not routine GMP inspections by EU authorities!
Certification Inspections

In application of Directive 2001/83/EC as amended (Article 111) and Directive 2001/82/EC as amended (Article 80)

A mandate has been given to EDQM (by EC) to establish an annual programme for inspections

- Inspection inside and outside Europe
- Manufacturing sites and brokers/distributors holding CEPs
- Authorities to be notified of issues arising
Exchanging Information/Advice, Communication Opportunities
General Questions on CEP Procedure & its Requirements

TOPICS: 05- CERTIFICATES OF SUITABILITY

01- General information
02- Revisions/ Renewals
03- Inspections
Technical Advice Meeting

Possible i.e. when need to clarify requirements of CEP procedure / complex schemes / specific questions:

– prior to or during the submission of an application for a new CEP or for its subsequent revision or renewal
– To meet CEP Division representatives
– Need to apply in advance (at least 1 month)
– Procedure and application form on the web
– 1-2 sessions/month at EDQM premises (written response, or telephone conference may also be possible)
– Fee of 1000 euros / Meeting length ≈ 1 hour
One-to-One Meetings

- Same scope as technical advice meeting
- but organised during a conference or an exhibition
- Meeting length generally 15 to 30 minutes
- Registration at least 1 week before event
- Procedure and application form on the web - specific for each event
- Fee specific for each event
One-to-One Meetings

- Check “Events” pages of EDQM website
  www.edqm.eu

EDQM Events

The EDQM organises conferences and symposia on topics related to the quality control of medicines, and training sessions giving practical advice on how to use the European Pharmacopoeia. EDQM scientists play a key role in establishing the programmes and also speak and meet one-to-one with participants at these events. These events also give participants an opportunity to come together to learn and share their experiences, and engage in purposeful dialogues. The EDQM regularly participates in pharmaceutical fairs and exhibitions.

June 2008
EDQM-USE-NIBSC 2nd Workshop of the Characterisation of Hepatitis Products
19-20 June, Strasbourg, France

CPK China
24-26 June, Shanghai, China

July 2008
6th Edition European Pharmacopoeia Training Session
1-2 July, Strasbourg, France
Acknowledgements

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- And all the other 30 staff members of the CEP division

In case of questions: cep@edqm.eu
Thank you!