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EDQM
Beyond the European
Pharmacopoeia

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Is a Pharmacopoeia enough?

Chapter 1
The Certificate of suitability
to monographs of the European
Pharmacopoeia

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Legal basis

- **Directives 2001/83/EC and 2001/82/EC**
 - the monographs of the European Pharmacopoeia are mandatory
 - **BUT evidence is to be given that the quality of the material is suitably controlled by monograph**
 - **Otherwise any additional impurity to be limited**

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Why a certificate?

The situation in the late eighties

- **multiplication of various sources of supply**
- **a certain lack of transparency of Ph. Eur. monographs (impurity profile)**
 - applicants often asked to show that their product is suitably controlled by the monograph.

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How to solve the problem?

- **Improve up-date and transparency of monographs**
- **Procedure of centralised evaluation elaborated with**
 - the licensing authorities in Europe
 - recognition of its validity
 - Industry → assurance on the protection of the information provided

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The certificate of suitability:

- **Certifies that the quality of a given substance can be suitably controlled by the PhEur monograph.**
- **DOES NOT certify that a batch or batches of the substance complies with the Pharmacopoeia monograph.**

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TSE and certificates (CEP)

- **On request of EMEA, extension to the CEP procedure to TSE-risk products (revision of Resolution AP-CSP (99) 4)**
- **2 possibilities for submitting the info:**
 - in each MA dossiers or
 - via a CEP
- **EMEA recommends the use of CEP**

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Scope of the Procedure

- **Any substance described in the Ph. Eur.**
 - Active Substances
 - Excipients
 - Herbal drugs/preparations
- **TSE-risk products (incl. starting materials, reagents, intermediates,...)**
- **Excluded:**
 - Direct gene products (proteins)
 - Products derived from human tissues

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Who is involved?

- **Steering Committee** (11 members)
- **Independent Assessors** (80 from 16 countries)
 - nominated by CEP Steering Committee
 - impartiality guaranteed (status + signed declarations for each dossier)
- **2 Technical Advisory Boards** (Chemical ± TSE)
- **Certification Secretariat** (13 members)

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Confidentiality respected

- **CEP dossiers submitted directly by manufacturers**
 - No applicant part (≠ EDMF)
- **Independently of any marketing application**
- **archived in specific restricted area (EDQM)**
- **Assessment on the premises of EDQM by two assessors**

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How to apply?

- **Dossier in duplicate, in English (or French)**
- **Content of dossier described in annex of resolution AP-CSP(99)4**
 - Chemical evaluation: ± EDMF or Part IIC (3.2.S module 3 for CTD) of MA
 - TSE risk evaluation= Ph. Eur. general text, 5.2.8
- **Possibility of combined CEP** (eg for gelatin, tallow derivatives, aprotinin...)
- **Chemical CEP cannot be granted if TSE issue not solved**

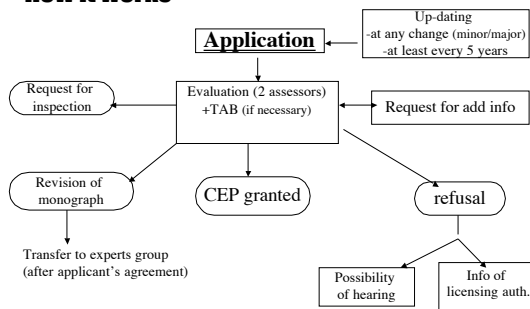
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Content of the dossier

- **Chemical evaluation**
 - General Information
 - Specifications and routine analysis
 - Manufacturing method
 - Impurities (incl. Solvents)
 - Other information
 - Expert report
- **TSE evaluation**
 - General Information
 - Origin of source material
 - Manufacturing method
 - QA system and Traceability
 - Expert report

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How it works



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A certificate specifies

- **Reference number**
(eg RO-CEP2000-001-Rev01)
- **Title: clear definition of the substance**
+ grade when necessary
- **Monograph(s) concerned**
- **Holder+manufacturing site(s)**
- **Quality assurance system applied**
- **Starting validity date**

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And for a “Chemical” CEP

As necessary

- **Additional impurities/ Solvents/Catalysts**
 - With limits and methods
- **Re-test period**
 - With storage conditions+container
- **Test for specific grade (eg sterility)**

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And for a TSE certificate

- **Country(ies) of origin of animals**
- **Animal and nature of tissue(s) used**
- **Manufacturing process applied**
(when relevant, eg gelatins)

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Certificate and follow-up

- **Validity= 5 years**
- **Any changes (minor/major) must be reported by the applicant to EDQM**
- **In case of revision of the monograph/general text/legislation**
→ **Revision of the CEP when necessary**

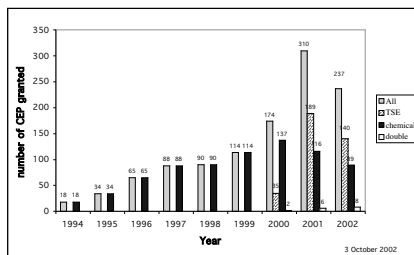
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Inspection of manufacturing sites

- Covered by a CEP
- with teams of 2 inspectors
- accompanied by a CEP unit representative
- focussing on compliance with dossiers
- GMP compliance for critical points

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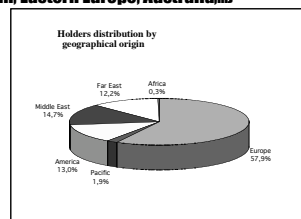
more than 1120 CEP granted so far (including about 360 for TSE)



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And also...

- Increasing number of revisions and renewals
- Geographical diversification of applicants (USA, India, China, Japan, Eastern Europe, Australia,...)



What is coming next?

- **Extension of the certification procedure to medicinal plants**
 - **Mainly extracts, tinctures and other preparations,**
 - **But also raw plant material**
 - **Good agricultural practices**
 - **Pesticides**
 - **Aflatoxins...**

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What is coming next ?

- **Viral safety**
 - **On the same model as TSE certificates**
 - **For vaccines and other biological products**

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Advantages of the CEP

- **Centralised evaluation :**
 - **Avoiding duplication of work**
 - **Preventing of divergences in evaluation**
- **Recognised by all member states of the Ph Eur Convention (31 incl. EU)**
- **In some cases outside Europe (Australia, NZ, Canada...)**
- **Independent from individual MA**
- **Respecting the confidentiality**
- **Updating of Ph. Eur. monographs**

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For Information/to contact us

- **EDQM internet site**
(CEP: procedure, lists of CEP and assessors, information)
<http://www.pheur.org>
- **Certification unit (for questions,...)**
certification@pheur.org



Reference Substances.

- **Over 1300 reference available**
 - **No declared content**
 - IR spectrophotometry
 - TLC
 - HPLC
 - ! **Physical tests : refractive index : Discontinued**
 - **Declared content**
 - **Mainly for assay : biologicals, antibiotics, hormones & vaccines**

Reference Substances

- **Some important principles**
 - **Guaranteed for use in relation with pharmacopoeia monographs only**
 - **No certificate of analysis**
 - **Safety datasheets available, downloadable for free on our web site**
 - **Potency expressed in I.U. According to WHO system**
 - **Unless specified, no pre-treatment necessary**

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Reference substances

- **Regularly monitored, therefore no expiry date is systematically given.**
 - **When a given batch is found to have decomposed, an expiry date is given in the catalogue and a new batch is established.**
 - **No expiry date can be given for an opened vial**
 - **The appearance of a new batch number, without an expiry date in the catalogue for the previous batch does not invalidate the previous batch.**

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Reference substances

- **Biological standards, a unique collection of more than 40 biological standards:**
 - **Vaccines: hepatitis A and B, Measles, Mumps, Rabies, ...**
 - **Sera and immunoglobulins: pertussis, tetanus, rabies...**
 - **Antisera: equine influenza...**
 - **Hormones: insulin, interferon alpha, gamma...**
 - **Blood products: factor VIII, heparins...**

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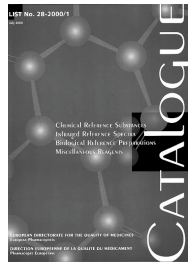
Reference substances

- **Most of the biological substances are established in close collaboration with other organisations such as:**
 - **Food and Drug Administration (USA),**
 - **World Health Organisation,**
 - **Office International des Epizooties (veterinary standards)**

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Sustancias de referencia de la Ph.Eur.

- Internet:
 - <http://crs.pheur.org>



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PDG and ICH

- **Early in the 1990s, the three Pharmacopoeias of Europe, Japan and the United States of America decided to harmonise a number of their monographs. An initial list of 15 excipients were identified as good candidates. This list was extended to more excipients (currently over 50) and to general methods of analysis.**

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Interchangeability

- **“Harmonised monographs” can still include *residual* differences in the three pharmacopoeias but the system is arranged such that compliance with the monograph of one pharmacopoeia ensures an easy compliance with the other two pharmacopoeias**

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Harmonisation work programme

- **See the web site of any of the three pharmacopoeias.**
- **Newly “signed-off”:**
 - **Lactose (anhydrous & monohydrate)**
 - **Amino-acids analysis**
 - **Capillary electrophoresis**
 - **Isoelectric focusing**
 - **Total proteins determination**
 - **Peptide mapping**

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Chapter 5

Can a Pharmacopoeia work in isolation?

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Conferences and Seminars

- **Quality Control of equine influenza vaccine**
 - 12 February, Budapest (Hungary)
- **Standardisation and Quality Control of Cell and Gene therapy products**
 - 24-25 February Strasbourg (France)
- **Foot-and-Mouth disease vaccines**
 - Planned in Spring 2003

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Training Sessions

- **How to use the European Pharmacopoeia, new approaches and media**
 - 12-13 December 2002
 - 6-7 March 2003
 - 26-27 June 2003
 - 4-5 December 2003

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Contacting us

- **General:** info@pheur.org
- **Publications:** publications@pheur.org
- **Reference standards:** crs@pheur.org
- **Certification:** certification@pheur.org
- **Monographs:** monographs@pheur.org
- **Web:** <http://www.pheur.org>
