QUALITY ON THE MOVE
DYNAMICS OF THE EUROPEAN PHARMACOPOEIA

Workshop Session
Certification

Moderators: D. Calam & C. Pouget

16:00-17:30

Review of the EDQM Programme for inspection of manufacturing sites

Corinne Pouget
Head of the Certification Unit
European Directorate for the Quality of Medicines (EDQM)

Programme for inspections of API sites holding CEPs

(certificate of suitability of PhEur monographs)

- Why and how it has been established
- How it works
- Review to date and perspectives

Why and how the CEP inspection programme has been established

Dossier = reality?

- Paper evaluation (as for EDMF or MA dossier)
- CEP dossier includes declaration on:
  - manufacture according to dossier and a suitable GMP/QA system
  - willingness to be inspected
  - Also applies when holder ≠ manufacturer

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CEP pilot phase for inspection

- Launched in 1999 in agreement with inspectorates and industry
- 5 manufacturing sites covered by a CEP
- voluntary basis of both inspectors and manufacturers
- focussed on compliance with dossiers
- GMP compliance for critical points

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Conclusions: inspectors/companies viewpoint

- Interesting and fruitful experience
- No major operating problem encountered
- Helpful if in complement to national inspections
- Endorsed by the CEP Steering Committee

- -> To be continued !!

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2nd phase of the programme

- voluntary prerequisite not necessary
- including other countries
  (incl. Eastern Europe, China, India,..)
- involving several national inspectors
- extending to various substances
  (excipients, TSE risk products, sterile APIs…)
- and to brokers (when are CEP holders)
- included in national programmes

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How the CEP inspection programme works

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Elaboration of the programme

- If requested during/after assessment
- To join a scheduled national inspection
- On companies request
- Use/interest of the products (eg some TSE-risk products, widely used substances)
- Geographical location of the sites
- Different sites producing the same substance

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The team

- Team of 2 inspectors
  - One from the country where the site is located
  - One from another PhEur member state
- Accompanied by a Certification unit representative
- Local inspector invited for non PhEur countries

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Inspection progress

- Lasts about 2-3 days
- Reference documentation:
  - Q7A and any other relevant GMP documents
  - Certification Dossier, CEP and assessment reports (product related inspection)
  - Questionnaire/site master file
- Visit of the manufacturing facilities (following the process flow)
- Study of production and QA management documents
- Conclusions orally presented to the company

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Follow-up of an inspection

- Report finalised and signed by both inspectors
  - sent to the inspected company + both inspectors
  - kept in confidential EDQM archives
- Company requested to answer remarks and deficiencies noticed
- When positive inspectors' opinion:
  - -> final summary report signed
  - -> EDQM Attestation of Inspection sent to the company

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Follow-up of an inspection (2)

- Any following action regarding the dossier/CEP
  - On EDQM's responsability
- Any following action regarding GMP issues
  - On national inspection's responsability

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Follow-up of an inspection (3)

in case of major/critical deficiency

- CEP may be suspended/withdrawn
  - information of all concerned authorities
    To take any necessary action
  - Information on EDQM website

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Review to date and perspectives

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To date

- 54 manufacturing sites inspected, incl.
  - 7 sterile/endotoxin-free APIs
  - 11 TSE-risk products (incl. 4 excipients, 3 APIs)
  - 6 distributors/brokers
- 20 countries involved
  (CH, F, S, SF, NL, B, UK, I, E, D, A, DK, P, H, SLO, Latvia, Slovak Rep., China, India, Mexico)

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To date

- No major operating problem encountered
- 5 cases where major/critical deficiencies noticed with inspected sites leading to suspension of CEPs (3 being held by European brokers)
  - 2 in China
  - 3 in India
- 1 where 'sterile ' grade was refused (India)

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Inspection findings

- Documentation and records (14%)
- Process equipment, Materiel management, Quality management (11-11.5%)
- Buildings & facilities, Lab controls (8-9%)
- Production and IPC, Validation (7%)
- Packaging & labellling, Personnel (3-4%)
- Rejection & re-use (2.5%)
- Others (< 2%)

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Inspection findings (2)

- For sterile substances (versus Annex 1)
  - 19% on general aspects (clean areas, classification, monitoring) and processing (reduction of contamination, bioburden monitoring..)
  - 12% on Personnel (training, clothing) and Premises (pipes, air-flow and pressure, warning syst)
  - 10% on Sterilisation (validation) and Filtration (integrity, re-use of filters)

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Inspection findings (3)

- Compliance with CEP dossier (5.2%)
  - Not up-dated (manufacturing process, control methods)
  - Manufacturing process not sufficiently detailled

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Follow-up/actions

- when critical problems encountered leading to the official suspension of the CEP
  - Information of all concerned authorities
    - To take any necessary action (regarding MAs, marketed substances,…)
  - Information of EMEA Working groups and EU Commission + EMEA
  - Information in the published CEP list
  - Re-inspection to be done
- ->to develop a system for harmonising the follow-up regarding sites/batches/MA concerned in collaboration with LA and Inspectors

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Some achievements

- Elaboration of documents
  - guideline for inspectors
  - report format
  - internal SOPs
- Active collaboration of inspectors
- Coordination of national/EDQM programmes
- Fruitful exchanges with TGA
- Good contacts with 'third parties' inspectorates (in particular in India)

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Perspectives for near future

- About 2 inspections per month
  - Priority to sterile drug substances and brokers, widely used/sold subst.
- Follow-up of defective inspections
- Enlarge experience
  - with other inspectorates, groups…
  - And other countries (Norway, Romania,…)

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Perspectives

- to promote inspections of drug substances and establish an adequate system
  - Collaboration/exchange with European/international inspection working groups
  - Renforce discussion/collaboration with EU/EMEA

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For Information/contacting us

- EDQM Internet site
  (CEP: procedure, lists of CEP and assessors, information)
  http://www.pheur.org
- Certification unit (for questions related to inspection,…)
  inspection@pheur.org

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Certificates of suitability of Ph. Eur. (CEP)

The main deficiencies found in the dossiers

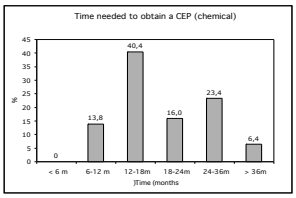
Hélène BRUGUERA
Scientific Officer
Certification Unit,EDQM

Main deficiencies found in the dossiers

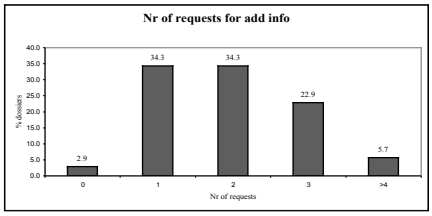
- Figures
- Top TEN of deficiencies
- The basic requirements of the procedure

CEP for chemical purity (2004):

Mean time to get a CEP: **20.5 months**
(min 6 months, max 4 years)

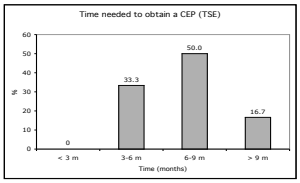


Nr of assessments for CEP for chemical purity

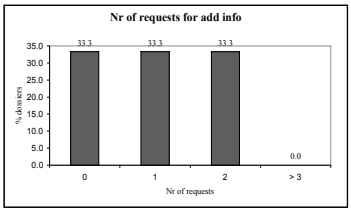


TSE CEP (2004):

Mean time to get a CEP: **6.5 months**
(min 3.5 months, max 10 months)



Nr of assessments for TSE CEP



Content of the dossier

- Resolution AP-CSP (99) 4:
  Content of dossier described in annex:
  - ⇨ Chemical purity (Revised document available soon)
  - ⇨ TSE risk application = Ph Eur general text 5.2.8
  - ⇨ Herbals: specific annex + requirements of NfG on *Specifications and Quality for Herbals*
- CTD format
- Application form (declarations)

Dossiers blocked at receipt

➢ **9%** of applications (chem. purity) received in 2004 (24% in 2002)

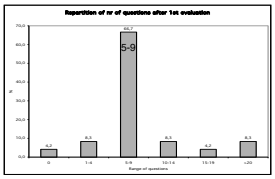
- Administrative reasons:
  - ⇨Missing application form/declarations/samples/ payment / QOS
- Technical reasons:
  - ⇨2 processes/incomplete documentation/ Class I solvents/Reference monograph ≠ current Ph. Eur monograph

Application form

- To be filled in carefully:
  - Details on holder, manuf. site: on the CEP
  - Details on contact person/company: for correspondence
  - History of the substance
  - Retest period: YES or NO
  - Declarations (templates)

Requests for add info after 1st assessment (chemical purity):

⇨**Average nr of questions: 9** (2002: 9)
(min 0, max 27)



TOP TEN of deficiencies

- Description of the route of synthesis of the declared starting material(s), description of impurity profile (related subst, reagents, solvents, catalysts), and carry-over of impurities to the final substance (58% of dossiers)
- Demonstration that all solvents used are removed or suitably limited (validated method) (42%)
- Proof of absence of particular reagents in the final substance (catalysts, alkylating agents) (42%)

TOP TEN of deficiencies (cont)

- Maximum/typical batch size (38%)
- Specification for all reagents, solvents. Include purity tests (38%)
- Limits for impurities should be in accordance with the specific monograph + general monograph 2034 (unspecified imp: 0.10%) (38%)
- Suitability of the Ph. Eur. method to control the impurity profile (29%)

TOP TEN of deficiencies (cont)

- History of the substance is not complete (29%)
- Specification of the starting materials should include suitable limits for impurities (29%)
- Suppliers of starting materials should be stated (or confirmation of in-house manufacture) (24%)
- Description and specification of packaging material (24%)

Basic Requirements

3.2.S.2.2 Manufacturing method

- Brief outline and flow chart
- Detailed description, including:
  - **typical/maximum batch size (Top 4)**
  - narrative description
  - all materials and reagents introduced and typical quantities, yields,..
  - operating conditions (ranges of T°, time, pH,..)
  - structure of isolated intermediates

- Semi-synthetic products:
  → Fermentation steps involved in synthesis of starting material
  – Characterisation of fermented starting material, incl. detailed impurity profile, compliance with the general monograph 1468
  – Carry-over of fermentation impurities
  – TSE risk substances !

- Sterile products:
  – Sterilisation method to be described: max bioburden prior to sterilisation, filter used, IPC,..
  – Sterilisation of primary packaging material
  – Validation of sterilisation process

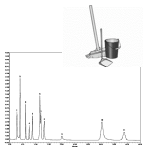
3.2.S.2.3 Quality control of Materials

- ! Definition of starting material(s) **(Top 1+9+10)**
  – manufactured in-house or purchased?
  – few steps synthesis: details of the synthesis of the starting materials (flow chart), detailed specification for impurities (organic impurities, solvents, catalysts)
  – fully characterised impurity profile
  – carry-over of impurities/by-products to the final substance

- **Suitable specification for all materials** used. Purity tests for solvents (benzene in toluene) - Quality of water. **(Top 5)**

3.2.S.3.2 Impurities

- Organic impurities
- Inorganic impurities
- Residual solvents



3.2.S.3.2 Impurities

- List of all potential impurities (incl. those from starting materials, by-products, isomers, degradation products, reagents)
  - Origin
  - Structural formulas
- Which impurities are actually present?
  - Theoretical / Actual impurities
  - Levels found in production batches
  - Typical chromatograms

Impurities (cont)

- **Suitability of the method(s) of the monograph must be demonstrated (Top 7)**
- Limits and their justification **(Top 6)**
  - Understand limits of the monograph
  - Individual limits for specified impurities
  - Individual limits for identified impurities
  - Limit for unspecified impurities

Qualification of “Additional” impurities

- Qualification by use
  - History of the product: Limits already approved (by licensing authorities)
  - Consistency with manufacturing capability (results from commercial batches)
  - Shown to be present in other products already approved
- Qualification by toxicological data
- Or limited to identification/qualification threshold (0.15%, 0.10% or 0.05%)

Particular impurities (Top 3)

- Inorganic impurities, residues of catalysts (Nickel, Boron)
- Toxic reagents: alkylating agents (alkyl halides, dimethylsulphate), nitroso compounds, ethylene oxide
- Mesilates formation

⇨ Appropriate limit to be set or absence to be demonstrated
⇨ CPMP draft guideline on catalysts (CPMP/SWP/4446/00; re-released for consultation)
⇨ CPMP draft guideline on genotoxic impurities (CPMP/SWP/5199/02; re-released for consultation)

Residual Solvents

⇨ ICH guideline Q3C
⇨ CPMP Concept paper (2003)

- **Data for all solvents used during synthesis (incl. 1st steps) (Top 2)**
  - Suitable methods + validation
- Batch results + typical chromatograms
- Solvents likely to be present/used in the last steps
  - justified limits (ICH or lower)
  - validated test methods
  - mentioned on CEP (+ method appended)

Residual Solvents (cont)

- class 1 solvents: to be avoided
  - Or use strongly justified
  - Decision by Technical Advisory Board
  - Appropriate limit (ICH) and validated method
  - Mentioned on CEP

➢ Use as starting material can be accepted:
  - Limited in an intermediate (suitable limit + method)
  - Shown absent in the intermediate or the final substance

3.2.S.4 Control of the Drug Substance

- Refer to the right monograph and its tests
- Include additional/alternative tests if necessary
- **Appropriate limits for impurities, solvents,…in accordance with the process and relevant guidelines - General monograph 2034 (Top 6)**
- Adequate methods description -> format to be appended to the CEP

3.2.S.4.3 Method validation

- All in-house methods should be validated (incl. non-routine methods)
  → ICH Q2B for methodology
  → Typical chromatograms
- Cross-validation against Ph. Eur methods:
  → comparative results obtained from the same samples

Other requirements

- 3.2.S.4.4 Batch data:
  – in line with specification
  – **Details on batches tested (batch nr, size, dates of manufacture, analysis)**
  – Numerical figures (“complies” not appropriate)
- Reference substances: use the Ph. Eur standards
- 3.2.S.6 Packaging material:

  Description + specification of materials

Stability

→ CPMP guideline "Stability testing of existing active substances"

- ICH conditions (long-term + accelerated) + Fit the monograph statements
- Study description - relevant parameters
- Detailed results (figures)
- Validation of in-house methods (stability indicating)

Stability (cont)

- Proposed retest period and storage conditions:
  - In accordance with stability results
  - Extrapolation possible but limited to 36 months

→CPMP guideline on "Declaration of storage conditions for medicinal products"

Conclusion

- Revised Annex I to Resolution "Content of the dossier" to be published
- Include the "TOP TEN" data in the application

Quality on the move:
Dynamics of the European Pharmacopoeia
Budapest 4-6 October 2004

Use of alternative analytical methods

Anne Ambrose, MHRA, UK

Use of alternative analytical methods

- Purpose of CEP assessment
- Additional vs Alternative methods
- Focus of CEP assessment
- Assessment outcomes
- Examples

CEP Assessment

- Purpose of Certification Assessment
  - To ensure that all possible impurities from the particular route of synthesis can be fully controlled by the tests of the Ph Eur monograph
- Or, if necessary
  - To fulfil this goal by using the Ph Eur tests in combination with additional, suitable test procedures provided by the manufacturer

Additional Methods vs Alternative Methods

- Additional Method
  - If method of monograph unsuitable to control all the impurities arising from the synthesis
    - » Additional method will need to be developed by CEP holder
- Alternative Method
  - CEP holder develops own in-house method
    - » Ph Eur methods suitable to control substance

ASSESSMENT

- Part B Report or "Request for revision of the monograph"
- Prepared for transmission to the relevant Group of Experts of the European Pharmacopoeia, when the rapporteurs consider that the monograph may need revision (e.g. updating of the transparency statement)

FOCUS OF ASSESSMENT Specifications and tests

- Applicant's specification is compared with the current monograph and any monograph revision that is in preparation.
- Any differences and additional / alternative tests and methods should be justified.
- Tighter limits than monograph will not be mentioned on the CEP.
- Alternative test methods must be cross validated with the official Ph Eur method.

ASSESSMENT
Focus on Impurities

- CEP dossier - details of potential impurities and indication of their origin (e.g. starting material, reagent, solvent, catalyst, intermediate, degradation product).
- Which of these impurities have you looked for, which method has been used to detect them, which ones were found and what were their typical levels
- Is an additional test and analytical method required?

Assessment
Focus on Impurities

- Guideline on Control of Impurities of Pharmacopoeial Substances (CPMP/QWP/1529/04)
- Consideration should be given to whether the method of the monograph is able to detect impurities at a level of 0.05%
- If not an additional or alternative method may be needed

CONCLUSIONS OF ASSESSMENT

Case 1

- The monograph can be used to control the quality of the substance manufactured by that particular route of synthesis
- The Certificate is granted
- Any alternative methods are not appended to the CEP

CONCLUSIONS OF ASSESSMENT

Case 2

- The monograph can be used to control the purity of the substance with additional tests and limits
  - The Certificate is granted with supplementary tests and limits
  - If appropriate a revision of the monograph is initiated

Supplementary Tests

- Residual solvents
- Residual catalysts
- Impurity not included in transparency statement

CEP Holder - Alternative Methods

- Use of alternative methods
  - monograph needs updating – in-house method superior / newer technology
  - economy – shorter run time of in-house method

Alternative Methods

- If the tests of the monograph are suitable to control the material:
  - Alternative method will not be stated on CEP
  - No recommendation to amend the Monograph
  - Details and validation of the alternative method should be submitted to Licensing Authorities
  - If manufacturer registered via Type IA#15 procedure it may be necessary to submit parallel # 13 to Licensing Authorities

Examples

- TLC of Ph Eur
- vs
- HPLC - In house

Example

- Consider if TLC method can detect all impurities to a level of 0.05%
- TLC method not suitable – but in-house HPLC can detect and control all impurities from this route
  - Additional HPLC method appended to CEP
- TLC method able to control impurities
  - Alternative HPLC method not appended to CEP

Example

- Use of NIR for identity testing
  - Non standard method
  - Ph Eur tests fully able to identify material
  - Method may not be evaluated during CEP assessment
  - Method will not be appended to CEP
  - Method plus validation will need to be submitted to National Authorities

Use of Alternative Methods

- Alternative methods may be used
- Important considerations:
  - Method validation
  - Method may not be stated on CEP
  - No recommendation will be made to update monograph
  - Additional information

Certificates of suitability of Ph. Eur. (CEP)

New procedures for revision/renewal of certificates

Hélène BRUGUERA
Scientific Officer
Certification Unit, EDQM

Background

- Appendix XI to Resolution AP-CSP (99) 4: revision of certificates
- Commission Regulation (EC) 1084/2003 and (EC) 1085/2003 on variations to MA

⇨ New policy for revision of CEPs:
  - *Guideline on requirements on revision/renewal of CEPs* (PA/PH/CEP (04) 2)
  - *New procedures for management of revision/renewal of CEPs* (PA/PH/Exp. CEP/T (04) 18)

What has changed:

- In line with EU regulation
- Big changes in procedures:
  - Classification of changes
  - Timetables
  - Limited nr of changes
  - Possibility of rejection of deficient requests

Implementation since September 2004

Unchanged:

- Any change (administrative or technical) to the content of the dossier should be reported to EDQM for approval
- The CEP is valid 5 years. Need to apply for renewal in time.

Guideline on Requirements

- Classification of changes
- Conditions
- Documentation

New classification of changes

- Notifications
- Minor changes
- Major changes

- Update of the dossier following monograph revision
- Quinquennial renewal

Documentation

- Application form (specific), with relevant annexes
- Described in the guideline:
  - Justification of change
  - Assurance that the conditions are fulfilled
  - Updated pages of the dossier
  - Specific supporting documents
- Batch data: size, date, site, full specification, quantitative results.

Procedures for revisions / renewals

- Timetables
- Administrative conditions
- Flows
- Fee

Procedure for Notifications

- Timetable 14 days
- Acknowledgement of valid notification sent <u>or</u>
- Rejection (need to reapply)

- Possibility to apply for ≤3 notifications at the same time (timetable 1 month, fee increased)

Notifications - examples

- Change in administrative references (holder, manuf. site, product code)
- Change in batch size (by ≤ x 10)
- Minor change to test procedures
- Tightening limits
- Post-stability commitment data
- Deletion of information from CEP (manuf. site, retest period, country of origin for TSE)

Procedure for minor changes

- Timetable: 1 month
- T0: AR within 5 days
- T30 days: approval or request for info
- Reply expected within 30 days
- New T30 days: Approval (revised CEP) or rejection (need to reapply)

- Multiple: ≤3 minor changes at the same time (timetable 2 months, fee increased)

Minor changes (chemical)

- Minor change in manufacture
- Upscaling (> x10)
- Change in specification (new or replaced test parameter)
- Change/Addition of manuf. site
- Change from a TSE risk to a non-TSE risk material
- Change/Addition of retest period

Minor changes (TSE)

- Change of manufacturing site (no process change)
- Minor change to process or specification of the final substance
- Change of quality system

Procedure for major changes

- Timetable: 3 months
- T0: AR within 5 days
- T90 days: approval or request for info
- Reply expected within 30 days
- New T30 days (90 days for TSE): Approval (revised CEP) or rejection (need to reapply)

- Multiple: $\leq$3 changes (incl. 1 major) at the same time, timetable and fee unchanged.

Major changes - examples

- Any changes not included in the guideline
- Examples (chemical):
  - Introduction of new manufacturing steps/new reagents, solvents
  - Alternative process (-> Spec of the final substance identical, otherwise new certificate)
  - Process replaced
- Examples (TSE):
  - Addition of new source countries or suppliers of materials

Monograph revision

- Revised monographs published 3 times a year
- EDQM gives instructions to the holders:
  - Compliance with the monograph
  - Suitability of the monograph
- Reply expected within 3 months
- No AR at receipt
- T120 days: acknowledgement of valid data or revised CEP or request for info

Monograph revision (cont)

- Reply expected within 30 days
- New T30 days: acknowledgement of valid data or revised CEP (or new request for info)
- ...

Quinquennial renewal

- Holder should apply about 6 months prior to expiry date
- Declaration that no change occurred <u>or</u>
- Updated dossier (CTD) with comprehensive list of changes
- Samples are required (except TSE)
- Possibility to introduce changes at that time

⇨ Not an administrative job!

Quinquennial renewal (cont)

- Timetable: 4 months
- T0: AR within 5 days
- T120 days: approval or request for info
- Reply expected within 30 days
- New T30 days (90 days for TSE): Approval (revised CEP) or new request for info

⇨ In the mean time: provisionally renewed CEP under conditions

Conclusion

- Recent implementation (09/2004)
- Changes in procedures
- Follow the guidelines/check conditions

- For more information:
  ceprevision@pheur.org