

The Certification of suitability to the European Pharmacopoeia monograph (CEP)

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CPhI Shanghai- June 2006

1

Summary:

- Figures
- Deficiencies at receipt & top ten deficiencies
- Other deficiencies (new development)
- Revisions & renewals
- Inspections
- Conclusions

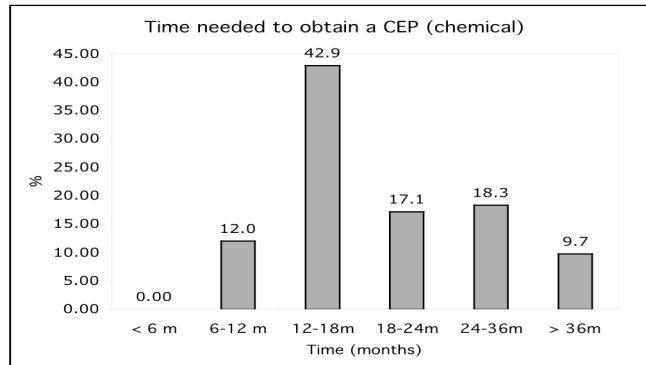
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2

Average time to get a CEP:

21 months (min 6 months, max 6 years)

With 2 or 3 request for additional info for the majority of the applications

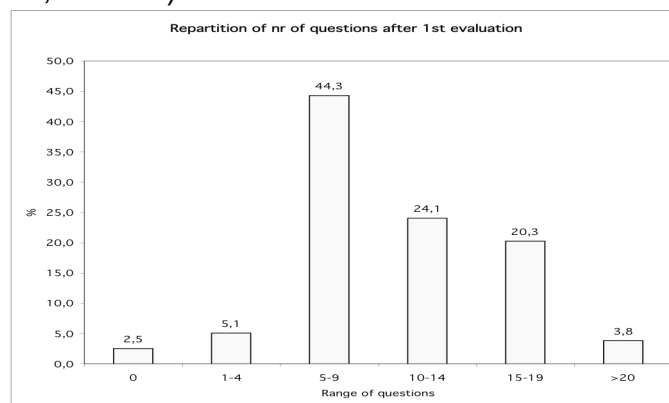


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3

Requests for add info after 1st assessment:

⇒ Average number of questions: 11 (9 in 2004)
(min 0, max 25)



4

Content of the dossier

- A complete dossier
 - Content of dossier for chemical purity (see document PA/PH/CEP (04) 1, 3R)
 - one copy (in English)
 - CTD format
- Application form (declarations)
- Fees (3000euros)
- Samples of commercial batches

Dossiers blocked at receipt

➤ **9%** of applications received in 2004 (24% in 2002)

- **ADMINISTRATIVE REASONS:**
Missing application form/declarations/samples/ QOS
- **TECHNICAL REASONS:**
2 processes / incomplete documentation / Class I solvents / Referred monograph ≠ current Ph. Eur monograph / related substances controlled by TLC

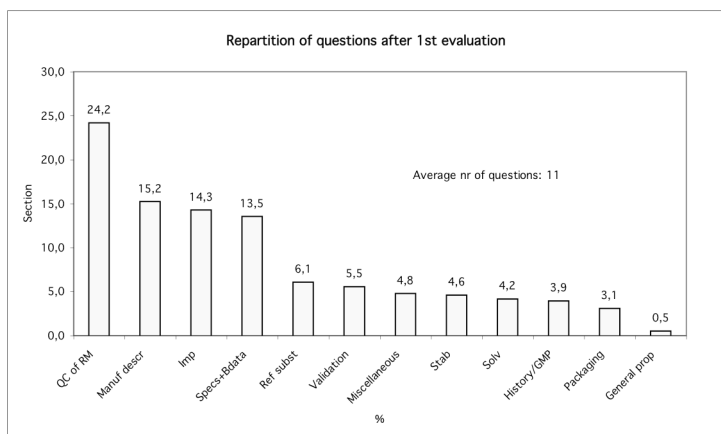
CTD format

- (3.2.S.1) General information
- (3.2.S.2.2) Manufacturing process
- (3.2.S.2.3) QC of Starting materials
- (3.2.S.3.2) Impurities / solvents / catalysts
- (3.2.S.4.1) Specifications and routine tests

CTD format (contd)

- (3.2.S.4.3) Analytical validation / suitability of the monograph
- (3.2.S.4.4) Batch results
- (3.2.S.5) Packaging material
- (3.2.S.7) Stability

Repartition of questions after the first evaluation



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9

TOP TEN of deficiencies

1. (3.2.S.2.3) 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 : 83.5% of dossiers (58% in 2004)
2. (3.2.S.2.3) Specification for all reagents, solvents and water. Include purity tests: 64.6% (38% in 2004)

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10

TOP TEN deficiencies (contd)

3. (3.2.S.2.3) Specification of the starting materials should include suitable limits for impurities and solvents: 48.1% (29% in 2004).
4. (3.2.S.2.2) Detailed description of each step of the manufacturing process: quantities of starting materials, reagents, solvents, ... operating conditions: 35.4%

TOP TEN deficiencies (contd)

4. Limits for impurities should be in accordance with the specific monograph + general monograph 2034 (unspecified imp: 0.10%): 35.4% (38% in 2004).
5. Demonstration that all solvents used are removed or suitably limited (validated method): 34.2% (42% in 2004)

TOP TEN deficiencies (contd)

6. (3.2.S.2.2) Maximum/typical batch size: 29.1%
(38% in 2004)
6. (3.2.S.5) Characterisation of reference standards: 29.1%
7. (3.2.S.2.3) Proof of absence of particular reagents in the final substance (catalysts, alkylating agents, ...): 27.8 % (42% in 2004)

TOP TEN deficiencies (contd)

8. (3.2.S.3.2) Illustration of the impurity profile based on typical chromatograms : 26.6%
- 9.(3.2.S.3.2) Detailed discussion on impurities:
 - origin, correspondence with transparency list : 22.8%
 - levels found, setting of limits: 22.8%

TOP TEN deficiencies (contd)

9. (3.2.S.4.4) Results on 3 batches (size + manufacturing date) : 22.8%

10.(3.2.S.1) History of the substance : 21.5% (29% in 2004)

Deficiencies linked to new developments of the procedure

- General monograph for substances for pharmaceutical use (2034)

=>Quantitative methods should be used for the control of related substances:

TLC IS NO LONGER ACCEPTABLE !!!

Deficiencies linked to new developments of the procedure (contd)

- Implementation PA/PH/CEP (04) 1, 3R:
Content of dossier for chemical purity:
Revision of annex 1 of the Resolution AP-CSP (99) 4:
 - CTD format
 - Declaration of the absence of any material of human / animal origin

Data presentation

- Data given in the dossier should be :
 - Clear
 - Concise
 - Readable
 - Obtained from recent analysis

Conclusions: how to avoid deficiencies ?

- Revised annex 1 to resolution « content of the dossier » (including CTD format)
- Top ten deficiencies
- Implementation of recent developments

Revisions/renewals of CEPs

- Change in the system implemented in 09/2004 and 01/2006
- Based on EU regulation on Variations to Marketing Applications 1084/2003 (EC) and 1085/2003 (EC) and new EU directives
- 2 documents available on EDQM website
 - “Guideline on requirements for revision/renewal of CEPs”
 - “New procedures for management of revisions/renewals of CEPs”

What has changed

- In line with EU regulation
- Classification of changes
 - Notifications
 - Minor changes
 - Major changes
 - Update following monograph revision
 - Renewal
- Timetables
- Limited nr of changes and possibility of rejection of deficient requests
- CEP renewed once after 5 years

Unchanged

- Any change (administrative or technical) to the content of the dossier should be reported to EDQM for approval
- The holder shall inform their customers and/or authorities with revised CEP
- The CEP is valid for a first period of 5 years. Need to apply for renewal in time

Documentation

- Application form (specific for revisions)
- 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 and renewals

- Timetables
 - Notifications 14 days
 - Minor revision 1 month
 - Major revision 3 months
 - RQ, monograph revision, consolidated revision 4 months
 - Deadlines for combined schemes

Procedures (contd)

- Workflows:
 - AR within 5 days
 - If request for info, deadline for manufacturer 1 month
 - Assessment of additional data 1 month (3 months for TSE)
 - CEP revised systematically except monograph revision and notifications (if content of CEP unchanged) ⇔ Request from Authorities

Continuation of the inspection programme

- Major for completing quality evaluation
- Mandate given by EU Commission in application of new EU Directives
- Programme approved by Certification Steering Committee
- In line with EMEA priorities

Inspection of manufacturing sites concerned by CEPs

- With national official inspectors
- In all Europe, Asia,...
- Local inspectors invited when site in non-Ph. Eur. member states
- Important collaboration also with Australian, Canadian authorities, WHO..
- Elaboration of documents in collaboration with participating inspectors

Follow-up of an inspection 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

For more information

- visit our stand 1G04
- The EDQM Internet site www.pheur.org
- And its helpdesk (FAQ+ possibility of sending questions)
- Request for technical advice
 - Meetings for technical/administrative issues
 - with EDQM representatives (at Strasbourg-France)
 - Procedure described on web page

THANK YOU