CEP submission: How to prepare a New Application?

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Summary

How to prepare a New Application?
– Requirements for a new CEP application
– Content of the dossier
– CEP process overview
– Validation at receipt
– Some figures

Deficiencies after evaluation

Recent changes
Perspectives
Conclusions
Requirements for a new CEP application

- Application form (specific to new application – see EDQM Website)
- Single copy of the dossier in CTD format in English preferably (or French)
  - Paper copy
  - Electronic submission recommended: NEES, eCTD, pdf (new instructions published on EDQM website)
- Quality Overall Summary: use the EDQM template
- Samples: commitment to provide samples upon request from EDQM (API and impurities if appropriate)
- Fee to be paid after receipt of application and invoicing
Content of the dossier

• CTD format
• See CEP policies on EDQM Website:
  – Resolution AP-CSP(07) 1 of the CoE: Describes the process for the Certification procedure
  – PA/PH/CEP (04) 1 4R « Content of the dossier for chemical purity and microbiological quality »
  – PA/PH/Exp CEP (06) 2 « Content of the dossier for a substance for TSE risk assessment »
  – PA/PH/Exp. CEP/T (06) 13 1R « Certificates of suitability for sterile active substances »
  – PA/PH/CEP 026 « Content of the dossier for herbal drugs and herbal drug preparation quality evaluation»
CEP Process Overview (1/2)

- Validation at receipt
- From September 2008, only 2 phases for evaluation:
  - 1 deficiency letter only
  - if responses unsuitable → dossier closed
- Changes when answering to deficiency letter no longer accepted
- Assessors to apply risk based evaluation
- Monitoring of deadlines for applicants
  - No « sleeping » applications
  - Possibility to ask for an extension (with justification)
  - Some applications closed
CEP Process Overview (2/2)

Validation at receipt

- Administrative
- Technical

Evaluation 1

- CEP granted or
- Additional information requested

Evaluation 2

- CEP granted or
- Application refused
Validation at receipt

If Administrative information incomplete and / or Technical information not sufficient:

→ Application blocked and additional data requested by letter

→ The clock does not start until suitable information is given and validation is complete

See PA/PH/Exp CEP/T (08) 37 Note for applicants: « Procedure for validation of new applications »
Administrative issues (1/3)

Dossier is blocked when:

- Dossier is not in CTD format
- QOS is missing
- Information on application form is missing:
  - Names and addresses of the parties involved
  - Agreement letters (Representative agent or when holder ≠ manufacturer)
  - Declarations
    - Manufacture according to the dossier and GMP (ICH Q7/EU GMP- Annex 1 if sterile)
    - Willingness to be inspected (Manufacturer and holder if different)
    - Use of animal (TSE risk or other origin) / human material
    - To provide samples upon request

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Administrative issues (2/3)

- Summarise the commercial history - make clear if, and in what product THIS source of API is on the EUROPEAN market (same site, process, specifications...).

- Provide information on ASMF submitted for the same substance.

- Give as much information as possible (companies, products names, countries, registration dates, marketing dates)

   ➔ Impact on qualification (limits) of impurities
Administrative issues (3/3)

• Retest period
  – Is an option, not mandatory
  – Specify the proposed retest period:
    • Justified by stability data
    • Studies performed according to ICH conditions
  – Recommended storage conditions
  – Specify the packaging material
    • Primary and secondary packaging will be mentioned on the CEP
    • Stability studies should have been performed on the declared packaging
Technical issues

Applications are blocked when:

- Reference is made to an old version of the Ph. Eur. monograph
- Description of route of synthesis and impurity profile of the starting material is missing
- Use of Class I solvents without justification and control
- Unsuitable information on impurities, solvents, catalysts …
- Absence of validation data for analytical methods
- Absence of a quantitative method to replace the non-specific TLC test in the monograph
- Sterile substances: absence of validation of the sterilisation
Some figures

Evolution of the percentage of files blocked at validation stage

- 2007: 38%
- 2008: 25%
- 2009: 22%

⇒ Only 3% of CEPs are granted after the first round of evaluation

⇒ Evaluation of additional information takes 4 months

⇒ An incomplete or deficient application delays the CEP!!!
CEP submission: Deficiencies after evaluation
Summary

• How to avoid them?
• Top 10 deficiencies
• Other deficiencies
How to avoid them?

- Keep in mind
  - The scheme is Certification of suitability to the monographs of the EUROPEAN Pharmacopoeia.
  - References, terminology, etc. should be to the Ph. Eur. or at least traceable to it.
  - Cross validation of in house method should be provided
  - There is a requirement to show that the monograph is suitable to control the actual quality of your substance.
Top 10 deficiencies (end 2008) (1/2)

1. Carry-over of impurities/solvents from the declared starting materials
2. Class 1 solvents as contaminants of other solvents
3. Genotoxic impurities
4. Container closure system
5. Specifications of the Starting Materials
Top 10 deficiencies (end 2008) (2/2)

6. Compliance with requirements of GM 2034

7. Purity test for solvents/reagents

7. Residual catalysts

8. Suitability of the monograph

10. Solvent recovery
1: Carry-over of impurities/solvents from the starting materials (1/2)

• Starting material specifications:
  – Assay (HPLC) NLT 97.0%, water content NMT 1.0%, impurity X NMT 0.5%, impurity Y NMT 0.8%, any other impurity 0.2%, total impurities NMT 2.5%

• Impurity X = impurity A of the monograph

• Methanol is used in the last step of the SM synthesis.

• API obtained from a 2-step synthesis
1: Carry-over of impurities/solvents from the starting materials (2/2)

Conclusion

- Starting material specifications should include suitable specifications for methanol and/or its carry-over in the API should be discussed.

- Impurity X (Ph. Eur. impurity A) should be found in the API ≤ limit of the monograph.

- Carry-over of Impurity Y in API should be discussed (justification of its absence/limit to be defined)
2: Class 1 solvents as other solvents contaminants (1/4)

The following solvents are known to be contaminated by Class 1 solvent (benzene):

- Acetone, Toluene, Ethanol, Methanol, Isopropanol, Xylene, Hexane, Petroleum ether

Refers to
- ICH guideline Q3C/EP General chapter 5.4
- Annexes to Specifications for Class 1 and Class 2 residual solvents in active substances (CPMP/QWP/450/03)
2: Class 1 solvents as contaminants of other solvents (2/4)

Where Class 1 solvent might be present in another solvent, a routine test for this solvent, on a suitable intermediate or on the final active substance, is not required when:

- Limit applied to parent solvent in the API is such that the Class 1 solvent will be present in the API at levels below the limits set out in the guideline, taking into account the maximum likely level of contamination of the Class 1 solvent.

Toluene is limited in API at NMT 200 ppm and Benzene is limited to 0.05% in toluene

=> Max level of benzene in the API : 0.1 ppm - Acceptable
2: Class 1 solvents as contaminants of other solvents (3/4)

Or

- Demonstration (validated method) that the Class 1 solvent is found below 30% of its ICH limit, in a suitable intermediate or the API. Supporting data on 6 consecutive pilot scale batches or 3 consecutive industrial scale batches should be presented.
  
  Benzene limited in suitable intermediate or API < 0.6 ppm

Or

- The specification for the originator solvent used includes a routinely performed test and limit for the Class 1 solvent.
  
  Benzene limited to 20 ppm in toluene and is tested routinely
Conclusion:

• If benzene level is 0.6 and 2 ppm in the final API
  ⇒ it will be mentioned on the CEP

• If benzene level is < 0.6 ppm,
  ⇒ Benzene will not be mentioned on the CEP
3: Genotoxic impurities (1/4)

Guideline on the Limits of Genotoxic Impurities (EMEA/CHMP/QWP/251344/2006), in force since 01/2007

- Compliance with the NfG to be demonstrated for substances not yet marketed in Europe, or for new routes of synthesis which may lead to a change in the impurity profile

- A specific discussion should be provided with regard to impurities with potential genotoxicity e.g. structural alerts

- The use of the substance may be taken into consideration
3: Genotoxic impurities (2/4)

If no structural alert:

- Provide a short illustrative discussion which includes reagents, solvents etc.
- Synthesis of starting materials should also be considered.

Examples of structural alerts:

N-hydroxyaryls, N-acetylated aminoaryls, aza-aryl N-oxides, alkylated aminoaryls, N Nitrosamines, nitrocompounds, epoxides, aziridines, hydrazines, alkyl esters of phosphonates, mesylates, primary halides …
3: Genotoxic impurities (3/4)

- **Carvedilol** (Treatment of hypertension)
  - Epoxy moiety is an alerting structure

- Maximum Daily Dose (MDD): 100 mg/day

- TTC (calculated based on the guideline): 15 ppm
3: Genotoxic impurities (4/4)

Conclusion

- TTC limit: $\text{TTC value} = \frac{1.5 \mu g}{0.1 \text{ g}} = \frac{15}{1} = 15 \text{ ppm}$

- If level > 15 ppm
  $\Rightarrow$ Toxicological study necessary

- If level is 4.5 ppm – 15 ppm (> 30% of TTC limit – TTC limit)
  $\Rightarrow$ Impurity is mentioned on the CEP

- If level < 4.5 ppm
  $\Rightarrow$ Impurity not mentioned on the CEP
4: Container closure system

- Provide a description of both primary and secondary packaging used (e.g. Double LDPE bags in a fiber drum)

- Provide specifications for the materials used (including appropriate identification test)

- Refer to compliance with appropriate guidelines (i.e. EMEA CHMP Plastic Primary Packaging Materials (CPMP/QWP/4359/03))
5: Specification of the starting materials (1/3)

• The approved starting material is the starting point for GMP and must be representative of the overall synthetic process and not just a late intermediate resulting in a shortened synthesis.

• Applicant must justify the proposed starting material which may or may not be accepted by the assessor and could lead to a redefinition of the starting material (refer to CPMP/QWP/130/96 Rev 1).

• External suppliers may thus become suppliers of intermediates and consequently corresponding GMP declarations would be necessary.
5: Specification of the Starting Materials (2/3)

- Suitable specifications for assay and purity with consideration for mass balance. Limits for impurities should be justified by batch data and should include a limit for unspecified impurities.

<table>
<thead>
<tr>
<th>Specification</th>
<th>Batch data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay</td>
<td>Assay</td>
</tr>
<tr>
<td>NLT 90%</td>
<td>&gt;98%</td>
</tr>
<tr>
<td>Impurity X</td>
<td>Impurity X</td>
</tr>
<tr>
<td>nmt 3%</td>
<td>&lt; 0.5%</td>
</tr>
<tr>
<td>Total impurities</td>
<td>Unspecifieds</td>
</tr>
<tr>
<td>nmt 5%</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

Conclusion:
Specifications not sufficiently detailed and not justified based on batch data. Mass balance only 95%! ⇒ to be tightened.
5: Specification of the Starting Materials (3/3)

- Specification for SM (e.g. p-aminophenol) should include limits for critical compounds used in its synthesis e.g. p-nitrophenol and also likely impurities e.g. ortho isomer.

![Chemical reaction diagram]

$p$-nitrophenol $\rightarrow$ $p$-aminophenol $\rightarrow$ paracetamol
6: Compliance with requirements of GM 2034 (1/2)

- In addition to the requirements of the individual monograph, the requirements of the General Monograph 2034 ‘Substances for Pharmaceutical Use’ must be met for limits.

If the individual monograph is not in compliance with GM 2034, the applicant should include an appropriate test and limits (i.e., supplement the monograph).

<table>
<thead>
<tr>
<th></th>
<th>Daily dose</th>
<th>Reporting threshold</th>
<th>Identification threshold</th>
<th>Qualification threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;2g</td>
<td>0.05%</td>
<td>0.10%</td>
<td>0.15%</td>
</tr>
<tr>
<td></td>
<td>&gt;2g</td>
<td>0.03%</td>
<td>0.05%</td>
<td>0.05%</td>
</tr>
</tbody>
</table>
6: Compliance with requirements of GM 2034 (2/2)

Metronidazole benzoate monograph states:

- Impurities A, B & C NMT 0.1%
- Any other impurity NMT 0.1%
- Total: NMT 0.2%
- Specified impurities: A, B & C

Conclusion:

⇒ The above specifications must be completed by a limit for any unspecified impurity set at NMT 0.10%.
⇒ This additional limit will be mentioned on the CEP.
7: Purity test for solvents/reagents

- Acetone: water NMT 0.6%, residue on evaporation NMT 0.001%.
- Dimethylbutyryl chloride (used as reagent in the last step): assay NLT 98.0%.

Conclusion:
⇒ Purity should be defined.
⇒ Suitable mass balance should be observed between purity and related substances limits.
8: Catalysts (1/2)

• CHMP guideline on the specification limits for residues of metal catalysts or metal reagents (CPMP/SWP/4446/00; effective from 1st September 2008) should be used.

• Pd/C is used in the 2nd step (out of 3) in the manufacture of substance Z.

• The substance complies with the heavy metal test

• Pd tested on 5 batches by AAS : results up to 4 ppm

• Substance Z is for oral use only
Conclusion:

- Test for heavy metals is not suitable to control palladium.
- Results from AAS need to be taken into account.
- CPMP/SWP/4446/00: limit for Pd is 10 ppm (oral use).

⇒ Pd found at significant level (> 30% of 10 ppm) will be limited on the CEP.
9: Suitability of the monograph (1/2)

- Acitretin monograph:
  - Impurities A & B are specified (each NMT 0.3%)
  - Total impurities NMT 1.0%

- Applicant has developed an in-house method which allows the control of Ph. Eur. impurities A & B and impurity X which is limited to 0.15%. Total impurities are limited to NMT 1.0%

- It should be demonstrated whether the Ph. Eur. method(s) is(are) able to detect all impurities present in the substance
9: Suitability of the monograph (2/2)

• If the method of the monograph is not suitable, the additional (validated!) method will supplement it. The use of an in-house method for Ph. Eur. and in house impurities should be supported by cross-validation data.

Conclusion:

– If methods are equivalent:
  → impurity X is limited on the CEP by the Ph. Eur. method

– If the Ph. Eur. method cannot control impurity X:
  → impurity X is limited on the CEP by the in-house method (appended to the CEP)

• Appropriate limits to be proposed for impurity X
10: Solvent recovery

- If recovered solvents are used:
  - Specifications of recovered solvents should be given and compared to those of pure solvents
  - Steps where recovered solvents are used should be highlighted
  - Any potential impact on the impurity profile should be considered
Other deficiencies

• Impurities
• Manufacturing Process
• Control of Materials
• Control of Critical steps and Intermediates
• Stability
Impurities (3.2.S.3.2)

- In addition to the requirements of the individual monograph, the requirements of the General Monograph 2034, Substances for Pharmaceutical Use, must be met for control method.

- This particularly applies for monographs not yet revised which still include a non-specific & non-quantitative TLC method:

  Suitably validated QUANTITATIVE test method for related substances & suitable limits for these impurities must be proposed.
Limits for impurities

• Impurities of the monograph: apply the limits of the monograph

• Additional impurities:
  – Propose individual limits for specified impurities
  – Propose individual limits for identified non-qualified impurities
  – Propose limit for unspecified impurities
  – Include limit for total related substances
How to qualify impurities?

• Qualification by use
  – History of the product
  – Consistency with manufacturing capability
  – Shown to be present in other products already approved

• Qualification by toxicological data

• Impurities limited to qualification/identification threshold
Impurities: special cases

• For products out of the scope of the general monograph 2034 (e.g. antibiotics):
  – Characterise the impurity profile
  – Apply the principles of the general monograph (set limits for specified, unspecified, total impurities)
  – Justified limits (not necessarily ICH Q3A) → will be mentioned on the CEP

• For peptides, revised general monograph 2034:
  – Identification threshold: 0.5%
  – Qualification threshold: 1.0%

• Policy applied for new applications and renewals
You should provide:

- Brief outline and flow chart for your process
- Detailed process description:
  - typical/maximum batch size (in line with provided CoAs)
  - narrative description of the synthesis (temperatures, quantities, times etc.)
  - structure of isolated intermediates
3.2.S.2.2 Manufacturing Process and Process Controls (2/3)

• Different sites, different manufacturing methods (including alternatives) and reprocessing can be included in one dossier if the impurity profile of final substance is the SAME, i.e. solvents, impurities, reagents etc

• Re-working is not allowed as typically implies the use of alternate reagents and/or solvents and consequently leads to a different impurity profile
3.2.S.2.2 Manufacturing Process and Process Controls (3/3)

For semi-synthetic products:

→ Fermentation steps involved in synthesis of starting material, must address:

• Characterisation of fermented starting material, incl. detailed impurity profile, compliance with the General Monograph 1468 ‘Products of Fermentation’

• Carry-over of fermentation impurities, proteins, DNA,…

• Use of TSE risk substances in manufacture?
3.2.S.2.3 Control of Materials

If material of animal origin is used:

- If a TSE risk substance is involved: a chemical CEP will not be granted until the TSE risk has been assessed → “Double” CEP (chemical and TSE)

- The use of animal or human origin material will be mentioned on the CEP and the viral safety risk has to be assessed for the relevant marketing application.
3.2.S.2.4 Control of Critical steps and Intermediates

Provide sufficient information on the intermediate control and the in-process controls.

*Especially important if you use this control to avoid a control later in the process!!*
3.2.S.7 Stability

- CPMP guideline “Stability testing of existing active substances” (CPMP/QWP/122/02 Rev. 1)
- Retest period is optional, it does not block the granting of the CEP
- ICH conditions, incl. accelerated studies
- Study description - relevant parameters
- Detailed results
- Validation of in-house methods (stability indicating) + cross validation with Ph. Eur. method
- Majority of monograph methods are stability indicating but some older methods may need to be supplemented by (validated!) in-house methods
Recent changes
« Sister Files » procedure

- See the procedure PA/PH/CEP (09) 141 dated October 2009
- To facilitate treatment of similar dossiers:
  - A CEP already granted for a substance
  - A new application for the same substance, same manufacturer (holder) with some changes which justify a new application (eg. Different purification steps, new site)
  - Treated by a fast track procedure (3 months)
Quality of water – transparency of CEPs

- EMEA guideline on Water for pharmaceutical use is the basis
- By default: Potable water is used
- Specific quality required only if particular use for the API (eg. Sterile)
- Quality of water to be addressed in Marketing Autorisation Application if needed
- Transparency of CEPs: water mentioned on the CEP each time when used in the final steps (change of policy)
E-submissions

• Encouraged!
• New procedures since 09/2009, no duplication of supports (will be revised soon)
• Choose either paper or electronic submissions on the application form (updated accordingly).
• e-CTDs, NEES, pdf welcome
• Routine communication sent by e-mail only
Perspectives

• Efficient treatment of new applications:
  – Reinforce risk management in assessments
  – Reduce delays
  – Continue with centralisation / harmonisation of APIs policies

• EU regulation on Variations ➔ Changes to revisions of CEPs:
  – Classification of changes revised accordingly
  – Introduction of ‘Do and Tell’ process
  – Harmonisation of processes and timelines
  – EDQM Guidelines will be published soon
Conclusions

• The CTD format should be used, with recent batch data
• Complete administrative information should be provided
• Data provided should be clear, concise and readable
• The common deficiencies should be kept in mind in order to provide a file in line with the current EDQM policies
• E-submission is encouraged
• Technical advice meetings for one to one discussions with Certification assessors
THANK YOU!

PRACTICE MAKES PERFECT ......
QUESTIONS?