API assessment: Critical issues

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API quality information in a dossier

**API information from the API manufacturer:**

How the API is prepared and controlled by the API manufacturer.

**API information from the FPP manufacturer:**

How the API is controlled (retested) by the FPP manufacturer, including parameters that influence the FPP performance.
There are different options that can be used by applicants to submit API information in a dossier to PQ.

- Use of a prequalified API (Certificate of PQ API= CPQ)
- Use of a European Certificate of Suitability (CEP)
- Use of a DMF/APIMF (open and restricted parts)
- Provision of full API information in the product dossier.

The use of these 4 options is described in our Quality Generic Guideline (http://apps.who.int/prequal/info_general/documents/TRS970/TRS_970-Annex4.pdf)
Regardless of the option chosen the same quality standard is required for the API.

This is also regardless of whether the API is pharmacopoeial or not.

The only difference is that for CEPs, the majority of the assessment is done by EDQM.

The API information assessed within PQ is compiled in the Common Technical Document format (CTD)
3.2.S.1. General information
3.2.S.1.1. Nomenclature
3.2.S.1.2. Chemical structure
3.2.S.1.3. General properties
3.2.S.2. Manufacture
3.2.S.2.1. Manufacturer(s)
3.2.S.2.2. Description of Manufacturing Process and Process Controls
3.2.S.2.3. Control of Materials
3.2.S.2.4. Controls of Critical Steps and Intermediates
3.2.S.2.5. Process Validation and/or Evaluation
3.2.S.2.6. Manufacturing Process Development
3.2.S.3. Characterization
3.2.S.3.1. Elucidation of Structure and other Characteristics
3.2.S.3.2. Impurities
3.2.S.4. Control of the API
3.2.S.4.1. Specification
3.2.S.4.2. Analytical Procedures
3.2.S.4.3. Validation of Analytical Procedures
3.2.S.4.4. Batch Analyses
3.2.S.4.5. Justification of Specification
3.2.S.5. Reference standards or Materials
3.2.S.6. Container closure system
3.2.S.7. Stability testing
3.2.S.7.1. Stability Summary and Conclusions
3.2.S.7.2. Post-approval Stability Protocol and Stability Commitment
3.2.S.7.3. Stability Data
What API information do you get?

- A CEP
- A CPQ
- A complete DMF (open + restricted parts)
- Full API dossier
- The complete open part of the DMF
- Other…

What do these mean?

What are the critical aspects?

Can the API be fully assessed?
In this presentation

1) API critical issues: what is important for APIs?

2) Procedures to submit API information in the dossier (CEP, CPQ, DMF)
What is important for APIs?

1. What is the API?
2. Who makes the API?
3. How is the API prepared?
4. How is the API controlled?
5. Can a retest period and recommended storage conditions be established for the API?
What is important for APIs?

1. What is the API?
2. Who makes the API?
3. How is the API prepared?
4. How is the API controlled?
5. Can a retest period and recommended storage conditions be established for the API?
What is the API?

- Chemical form – simple, complex?
- Origin- synthetic, semi-synthetic, fermentation, herbal origin
- Chirality - one or more chiral centres?
- Acid, base, salt, hydration state
- Crystalline or amorphous form
- Physicochemical properties – polymorphism, particle size, solubility
- Sterile
What is important for APIs?

1. What is the API?
2. Who makes the API?
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5. Can a retest period and recommended storage conditions be established for the API?
Who makes it?

There are two aspects to this question:

- What is/are the API manufacturing site(s)?

Traceability of manufacturing chain/ changes in manufacturers (if changes tracked).

- GMP compliance status of the API manufacturer

The guarantee of quality API is the result of good manufacture and control throughout all the steps (GMP). Comprehensive testing of the final API does not replace this.

What is the evidence – From who? For what? Issued when?
Who makes it?

Sites of manufacture (incl. manufacturing, packaging, labelling, testing and storage of the API):

- What's the address?

- PQ requests that the applicant declares the API manufacturing blocks involved, since different blocks at the same site can have varying GMP compliance.

- Are there external suppliers for intermediates? The manufacturers of intermediates should also work under GMP.
Who makes it?

How far back in the manufacturing chain to go?

- If you do not have access to a DMF/full dossier then you will probably be limited to the API site.

- With a DMF/full dossier you can determine:
  - If they are undertaking all the steps themselves, or if they are buying in intermediates.
  - Who are the suppliers of the starting materials.
What is important for APIs?

1. What is the API?
2. Who makes the API?
3. How is the API prepared?
4. How is the API controlled?
5. Can a retest period and recommended storage conditions be established for the API?
How is the API prepared?

To assess how the API manufacturer is making the API you are going to need access to the DMF (full DMF including restricted part) or to full API details in the dossier.
How is the API prepared?

The assessment of the API preparation will allow you to conclude on:

- The potential impurities that may need to be controlled in the specifications.

- How the API is being controlled throughout the process (in-process controls, critical steps, control of intermediates...).

- The quality of the materials used in its production (starting materials, reagents, solvents, catalysts), since these can have an impact on the API impurity profile.

- How well and consistently the API is being manufactured.
How is the API prepared?

Is the starting point of the manufacturing process acceptable?

API starting material(s) (SM)

API intermediate(s)

Final API intermediate

Crude API

Final API

X + Y

Z

Not under GMP + brief information

Under GMP + detailed information
Traditionally, the API manufacturer produced the API from simple raw materials at their own facility.
Now it is very common that intermediates late in the synthesis are being purchased externally by the API manufacturer.
API Starting material

Choice of API-SM

Simpler molecules → ASSESSORS → INDUSTRY → Final API
API Starting material

API manufacturers prefer to have the starting material defined as late in the synthesis as possible because:

- The API-SM introduction is the point at which GMP applies to manufacture.

- This can be financially advantageous when API manufacturers buy reaction intermediates from secondary manufacturers that do not operate under GMP.
API Starting material

The problem for assessors is:

- There is a concern that critical steps are not carried out under GMP.

- Information on the preparation of a complex API from only one or two steps makes determination of impurities in the API very difficult.

- If the API-SM is complex it is hard to judge the acceptability of the API-SM specifications.

- There is a concern that impurities from the API-SM may be carried over with the API.
Potential impurities

- API SM impurities
- Reaction by-products
- Degradation products

API starting material

- Reagents
- Solvents
- Catalysts

API intermediate

- Reagents
- Solvents
- Catalysts

Crude API

- Crystallisation solvent

Final API
Potential impurities

- Impurities in the API-SM
- Residue of the API-SM
- Residue of the intermediate
- Reagents
- Solvents
- Catalysts
- Reaction by-products
- Degradation products
How is the API prepared?

- What are the potential impurities?
- Can the potential impurities be carried over into the final API?
- If so, are the potential impurities detectable by the analytical procedure?

If the absence of certain impurity in the final API cannot be demonstrated, a test and limit needs to be included in the API specification or in raw material or intermediate.
What is important for APIs?

1. What is the API?
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4. How is the API controlled?
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How is the API controlled?

- Even without access to a DMF you can at least ensure the presence of certain tests.

- Unfortunately, if you do not know the preparation of the API (DMF or full dossier), you cannot be certain on the potential impurities and their control (i.e. toxic metals, genotoxins...).
How is the API controlled?

There may be tests for:

- Identification. Chiral API? – test for optical rotation
- Assay
- Impurities – Organic, inorganic, solvents, residue on ignition/sulphated ash, heavy metals, chiral impurities
- Water
- Physical properties – Polymorphism; Particle size
- Microbial quality for sterile APIs
What if a monograph is available?

- Monographs are developed based upon how the API was prepared historically. A particular manufacturer's method of preparation may lead to unexpected impurities, due to a different route of synthesis, different reagents, etc.

- Regardless of whether a pharmacopoeial standard is claimed, a discussion should be provided of the potential and actual impurities arising from the synthesis, manufacture or degradation of the API.

- The discussion should not be limited to the impurities specified in the API monograph
What if a monograph is available?

- It is important that when you read an API monograph you also consider the general monographs that are also applicable to the API. These also form part of the monograph and are not optional or nice to know.

- For example any API monograph in the European Pharmacopoeia needs to be read in conjunction with the general monographs:
  - Substances for Pharmaceutical Use (2034) and
  - Control of Impurities In Substances For Pharmaceutical Use (5.10)
What if a monograph is available?

**EP 2034 and 5.10 General Monographs:**

- The limits for impurities of the monograph only apply to the specific impurities listed in the monograph.
- If the API monograph does not provide suitable control for a new impurity, a suitable test for control must be developed and included in the API specification.
- Residual solvents and impurities (except the ones limited in the monograph) are limited according to the ICH principles (see ICHQ3C and ICHQ3A).
How is the API controlled?

Do not forget the test method. The limits are important but having a validated test method is a prerequisite underlying everything.

- The API methods should be able to separate/detect the potential impurities/solvents of the manufacturing process.

- All non-pharmacopoeial methods must be fully validated, particularly assay, related substances and residual solvents methods, as outlined in ICHQ2.

- The pharmacopoeial methods should also be shown suitable for determination of impurities related to the manufacturer's specific route of synthesis and not covered by the monograph.
What is important for APIs?

1. What is the API?
2. Who makes the API?
3. How is the API prepared?
4. How is the API controlled?
5. Can a retest period and recommended storage conditions be established for the API?
What API information do you get?

A CEP

A CPQ

A complete DMF (open + restricted parts)

Full API dossier

The complete open part of the DMF

Other…

What do these mean?

What are the critical aspects?

Can the API be fully assessed?
European Certificate of Suitability (CEP)

The DMF has already been assessed by EDQM
European Certificate of Suitability (CEP)

- This means the EDQM has already assessed the applicant’s DMF (method of preparation etc…) to determine if the API quality is adequate and if the API can be fully controlled by the Ph.Eur. monograph.

- There will be two possible conclusions in the CEP:
  
a) The API can be fully controlled by the monograph.

b) The API can be fully controlled by the monograph only if additional tests and limits are applied.

See www.edqm.eu
The API quality is adequate and the monograph (limits and test methods) is able to control the quality of the API.
CEP WHERE ALL IMPURITIES ARE CONTROLLED BY THE MONOGRAPH

Certificate of suitability
No. RX-CEP-Year-XXX-Rev XX

Name of the substance: XXX
Name of holder: XXX
Site of production: XXX

<p>| | |</p>
<table>
<thead>
<tr>
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<tr>
<td>we certify that the quality of the substance is suitably controlled by monograph XXX</td>
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The following impurities are also detected and their limits are set at:

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Manufacture of the substance shall take place in accordance with Good Manufacturing Practice and in accordance with the dossier submitted. Failure to comply with these provisions will render this certificate void. This certificate is granted within the framework of the procedure established by the European Pharmacopoeia Commission [Resolution AP-CSP (99) 4] for a period of five years starting from XXX. Moreover, it is granted according to the provisions of Directive 75/318/EEC amended and Directive 81/852/EEC amended, and the related guidelines. This certificate does not replace a batch analysis certificate.

(…)


3.2.S.1. General information
3.2.S.1.1. Nomenclature
3.2.S.1.2. Chemical structure
3.2.S.1.3. General properties
3.2.S.2. Manufacture
3.2.S.2.1. Manufacturer(s)
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3.2.S.4.5. Justification of Specification
3.2.S.5. Reference standards or Materials
3.2.S.6. Container closure system
3.2.S.7. Stability testing
3.2.S.7.1. Stability Summary and Conclusions
3.2.S.7.2. Post-approval Stability Protocol and Stability Commitment
3.2.S.7.3. Stability Data

The API quality is adequate and the monograph is able to control the quality of the API only if it is supplemented by the limit and test(s) given in the CEP annex.

Additional tests (e.g. impurities, solvents, catalysts...not detected by the methods of the monograph)
Name of the substance: XXX
Name of holder: XXX
Site of production: XXX

After examination of the information provided on the manufacturing method and subsequent processes (including purification) for this substance on the site of production mentioned above, XXX, we certify that the quality of substance is suitably controlled by the monograph X (...) only if it is supplemented by the following test(s), based on the analytical procedure(s) given in annex.

- Test for impurities/related substances/residual solvents by (...) chromatography (annex X)
  XXXX not more than XXX

Failure to comply with these provisions will render this certificate void.

This certificate is granted within the framework of the procedure established by the European Pharmacopoeia Commission [Resolution AP-CSP (99) 4] for a period of five years starting from XXX. Moreover, it is granted according to the provisions of Directive 75/318/EEC amended and Directive 81/852/EEC amended, and the related guidelines.

(...)
European Certificate of Suitability (CEP)

- Check that the CEP is valid ([www.edqm.eu](http://www.edqm.eu), databases, certification database).

- RX-CEP-Year-Number-Rev XX:
  - R=renewal (R0= first CEP; R1= renewal once after the first 5 years, then unlimited validity)
  - Rev= revisions (i.e. Rev 00, Rev 01, Rev 02, etc), after:
    - Changes
    - Revisions of the monographs (the manufacturer has to show compliance with the new requirements)

- Check that declaration of access has been filled in for the Marketing Authorisation Applicant and that it comes with all annexes (if any).
Certificate of suitability
No. RX-CEP-Year-Number-Rev XX

Name of the substance:
XXX

Name of holder:
XXX

Site of production:
XXX

After examination of the information provided on the manufacturing method and subsequent processes (including purification) for this substance on the site of production mentioned above, XXX, we certify that the quality of the substance is suitably controlled by monograph XXX (…).
The following impurities are also detected and their limits are set at:
—
—
The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance.

Manufacture of the substance shall take place in accordance with Good Manufacturing Practice and in accordance with the dossier submitted.

This certificate is granted within the framework of the procedure established by the European Pharmacopoeia Commission […] for a period of five years starting from XXX. Moreover, it is granted according to the provisions of Directive (…) and the related guidelines.
This certificate has XX lines only.

Signature

Strasbourg, XXX

A CEP does not indicate GMP compliance, it is not a GMP certificate.
European Certificate of Suitability (CEP)

Please also note that:

- Compliance with the specifications can only be shown by certificates of analysis from the API manufacturer (the CEP does not replace a CoA).

- Applicants for a CEP can decide whether a retest period is mentioned in the CEP or not.

- If a retest period is not mentioned, stability data need to be provided and assessed (not assessed by EDQM!) in order to establish a retest period and storage conditions.
CEP and retest period

- If a retest period is mentioned, the storage conditions applied are those of the EU guideline CPMP/QWP/609/96/Rev 2 (i.e. those for climatic zone I/II, the relevant zone for the EU).

- Therefore if you see a CEP with a retest period but no storage statement mentioned, it should be assumed that the temperature statement for the API is at least "store below 25°C".
Prequalified APIs (CPQ)

The DMF has already been assessed by WHO PQ
Prequalified APIs (CPQ)

The API quality is adequate AND the API manufacturing site has been verified GMP compliant.
Prequalified APIs (CPQ)

List of PQ APIs Website (Public) + WHO inspection report Website (Public)

Confirmation Document (CPQ)
Prequalified APIs (CPQ)

- The CPQ provides an assurance that the supplied API is of good quality (assessment + GMP).

- The API specifications, assay test method and related substances test method accepted for the API are appended to the CPQ.

- The approved details can be verified in the list of PQ APIs (http://www.who.int/prequal/info_applicants/API_PQ-List.htm).

- Also, the DMF assessment report is potentially available for National Medicine Regulatory Authorities.
Drug Master File (APIMF/ASMF)

DMF assessment is conducted in conjunction with an FPP application.
DMFs protect the confidentiality of the API manufacturer information and are divided in two parts:

- The Applicant's part (AP) or open part contains the information that the DMF holder regards as non-confidential to the FPP applicant. It should contain sufficient information to enable the FPP applicant to take full responsibility of the API.

- The Restricted part (RP) or closed part contains the information that the DMF holder regards as confidential.
Drug Master File (APIMF/ASMF)

3.2.S.1. General information
  3.2.S.1.1. Nomenclature
  3.2.S.1.2. Chemical structure
  3.2.S.1.3. General properties
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How is the API prepared?

The assessment of the API preparation will allow you to conclude on:

- The potential impurities that may need to be controlled in the specifications.
- How the API is being controlled throughout the process (in-process controls, critical steps, control of intermediates...).
- The quality of the materials used in its production (starting materials, reagents, solvents, catalysts), since these can have an impact on the API impurity profile.
- How well and consistently the API is being manufactured.
Drug Master File (APIMF/ASMF)

- Our APIMF procedure is described in [http://apps.who.int/medicinedocs/documents/s19971en/s19971en.pdf](http://apps.who.int/medicinedocs/documents/s19971en/s19971en.pdf)

- A DMF procedure serves to bring the API manufacturer under closer regulatory examination. It creates a direct link between the regulator and the API manufacturer.

- It is of little use if there is no communication between the FPP manufacturer and the API manufacturer, especially if changes to the DMF are not communicated to the FPP manufacturer.
What API information do you get?

<table>
<thead>
<tr>
<th>Information</th>
<th>Full API assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A CEP</td>
<td>has been already done</td>
</tr>
<tr>
<td>A CPQ</td>
<td></td>
</tr>
<tr>
<td>A complete DMF (open + restricted parts)</td>
<td>can be done</td>
</tr>
<tr>
<td>Full API dossier</td>
<td></td>
</tr>
<tr>
<td>The complete open part of the DMF</td>
<td>cannot be done</td>
</tr>
<tr>
<td>Other…</td>
<td></td>
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</table>
Conclusion

- There are critical issues to be assessed in the API information provided by the API manufacturer.

- These critical issues can only be assessed if full information on the API is provided.

- The assessment work does not need to repeated in the case of CEPs and WHO Prequalified APIs.
Thank you

Please feel free to email me at: ortegai@who.int

Thank you to Dr Fake (API focal point) for his slides. Feel also free to contact him at fakea@who.int
Questions?
Abbreviations

AP: Applicant's part of a DMF (or Open part)
API: Active Pharmaceutical Ingredient
CEP: Certificate of suitability to the monographs of the European Pharmacopoeia
CoA: Certificate of Analysis
CPQ: Confirmation of API Prequalification document
CTD: Common Technical Document
DMF: Drug Master File (in PQ APIMFs= API Master Files, in the EU ASMFs=Active Substance Master Files)
EDQM: European Directorate for the Quality of Medicines & Healthcare
EU: European Union
FPP: Finished Pharmaceutical Product
GMP: Good Manufacturing Practice
Ph. Eur.: European Pharmacopoeia
RP: Restricted part of a DMF or closed part
SM: API Starting Material
WHOPIR: WHO Public Inspection Report