Specific monographs: Finished products

2019 Training Session
“The European Pharmacopoeia”

10 – 11 September 2019, Iselin, New Jersey, USA
Monographs on „finished products“
- development for chemically defined active principles

2012: Ph. Eur. Commission reconsidered its strategy
    pilot phase initiated with examples of single-source and multi-source products

2014: strategy decided to widen the scope of Ph. Eur.
    start with focus on single-source products
    first monograph published in Pharmeuropa

2015: adopted and published in Ph. Eur. 8.7

2016: first monograph has come into force on April, 1st:
    Sitagliptin tablets

Content of FP monograph

<table>
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<tr>
<td></td>
<td>Tests <strong>mandatory</strong> unless otherwise specified</td>
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**Current focus**

Follows critical assessment and discussions:

Takes into account the impact on registered products

- **Single-source monographs** on products that are potential future generics (Procedure 4)
- **Multi-source monographs** also possible: new expert group as from November 2019 (group 17, Procedure 1)
- **Immediate release** dosage forms
- **solid and liquid** formulations
- Will be expanded subsequently

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**Work program**

**Adopted monographs**

<table>
<thead>
<tr>
<th>Product</th>
<th>Monograph number</th>
<th>Ph. Eur. supplement</th>
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<tr>
<td>Sitagliptin tablets</td>
<td>2927</td>
<td>8.7</td>
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<td>Raltegravir tablets</td>
<td>2938</td>
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<td>Lacosamide oral solution</td>
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<td>Lacosamide infusion</td>
<td>2991</td>
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<tr>
<td>Deferiprone tablets</td>
<td>2986</td>
<td>9.8</td>
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<tr>
<td>Deferiprone oral solution</td>
<td>2990</td>
<td>9.7</td>
</tr>
<tr>
<td>Rosuvastatin tablets</td>
<td>3008</td>
<td>10.1</td>
</tr>
</tbody>
</table>
**Work program**

- In total **27** further monographs are on the work program
- Single source and multi-source monographs
- First multi-source monograph adopted at the 163rd session of the Commission in March 2019: Rosuvastatin tablets

**General documents**

➢ General policy described in:
   « General principles for Monographs on Finished Products (FPs) containing chemically defined active substances »

➢ From this guide is derived the:
   Draft « Technical Guide for the elaboration of Monographs on Finished Products containing chemically defined active substances » (still under discussion, not yet approved)
“Since the choice of analytical procedures may be affected by the formulation and/or the manufacturing process, it must be demonstrated that the testing procedures described in an FP monograph are suitable for the specific FP. This demonstration has to be documented in the marketing authorisation application. The assessment of these data shall be part of the marketing authorisation procedure.”

Principles and challenges of monograph elaboration

- Title and Definition
- Identification tests
- Impurity policy
- Assay
- Dissolution tests
- Harmonisation
Title and Definition

**Title:** active moiety name
- INNs used
- Degree of hydration and salt are omitted

- **Definition:** includes statement on the scope:
  - The exact pharmaceutical form
  - The API covered: specific salt and/or hydrate

- If appropriate states that the preparation is sterile
- Cross-reference to dosage form monograph
- **Content** as percentage of active moiety declared on the label (e.g. 95.0% - 105.0%)

Identification tests (1)

*Draft technical guide for finished products*

Examples for possible identification tests:

- Spectrophotometric analysis, such as recording of infrared spectra (IR)
- Chromatographic examination by means of liquid chromatography (LC)
- Ultraviolet and visible absorption spectrophotometry (UV-Vis)

Typically a combination of UV and LC (size and retention time of principal peak, compared to CRS) is used, but

- IR direct (Sitagliptin tablets) or after extraction is also possible:

  C. Infrared absorption spectrophotometry (2.2.24)
  Preparation: crude is mixed with powdered and homogenised.
  Comparison: 300 PH.3 solution monohydrate CRS
  
  Prepare the spectrum obtained shows absorption maxima at about 1660 cm⁻¹, 1512 cm⁻¹, 1429 cm⁻¹, 1297 cm⁻¹, 880 cm⁻¹ and 644 cm⁻¹, similar to the spectrum obtained with 300 PH.3 solution monohydrate CRS. Other absorption maxima may be present in the spectra.
Identification tests (2)

Rosuvastatin tablets

IDENTIFICATION
A. Record the UV spectrum of the principal peak in the chromatograms obtained with the solutions used in the assay, with a diode array detector in the range 210-400 nm.

Results: the UV spectrum of the principal peak in the chromatogram obtained with the test solution is similar to the UV spectrum of the principal peak in the chromatogram obtained with reference solution (a).

B. Examine the chromatograms obtained in the assay.

Results: the principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

Ideally each Lab should define acceptance criteria

Impurity Policy

In accordance with ICH guidelines:

➢ « Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical Substances », ICH Q6A
➢ « Impurities in new drug products », ICH Q3B R2

The monograph limits degradation products arising during manufacture and shelf-life of the finished product, including those impurities of synthesis that are also degradation products.

Synthetic impurities not taken into account -> they are identified using a CRS and then excluded
Synthetic impurities are controlled in the relevant API monograph
How impurities are identified and limited:

*Reference solution (b).* Dissolve 7mg of *rosuvastatin for system suitability CRS* (containing impurities A, B and C) in 2.5 mL of acetonitrile R and dilute to 10 mL with water R.

*Reference solution (c).* Dissolve the contents of a vial of *rosuvastatin impurity mixture CRS* (containing impurity D) in 1 mL of the solvent mixture.

*Reference solution (d).* Dissolve 2mg of *rosuvastatin ethyl ester R* (impurity FP-A) in 20 mL of solvent mixture. Dilute 1 mL of this solution to 100 mL with the solvent mixture.

**Identification of impurities:** use the chromatogram supplied with *rosuvastatin for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and C; use the chromatogram supplied with *rosuvastatin impurity mixture CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity D; use the chromatogram obtained with reference solution (d) to identify impurity FP-A.

**Relative retention** with reference to rosuvastatin (retention time = about 11 min):

- impurity A = about 0.9;
- impurity B = about 1.1;
- impurity C = about 1.7;
- impurity D = about 2.2;
- impurity FP-A = about 3.1.

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**System suitability:** reference solution (b):

- peak-to-valley ratio: minimum 2.0, where $H_B$ = height above the baseline of the peak due to impurity B and $H_V$ = height above the baseline of the lowest point of the curve separating this peak from the peak due to rosuvastatin.

**Calculation of percentage contents:**

- correction factor: multiply the peak area of impurity C by 1.4;
- for each impurity, use the concentration of rosuvastatin calcium in reference solution (a).

**Limits:**

- impurity C: maximum 1.5 per cent;
- impurity D: maximum 1.5 per cent;
- impurity FP-A: maximum 0.5 per cent;
- unspecified impurities: for each impurity, maximum 0.2 per cent;
- total: maximum 2.5 per cent;
- reporting threshold: 0.1 per cent; disregard the peaks due to impurities A and B.

*Synthetic impurities A and B not taken into account*
**Assay**

- Specific, stability indicating assay for content (usually HPLC)
- Standard specification: 95.0 to 105.0 % of the content stated on the label
- At least 5 tablets used to prepare the test solution
- Repeatability requirements of chapter 2.2.46 (chromatographic separation techniques) only valid for APIs. Standard rsd is still under discussion, currently case-by-case decision.
- When the CRS of the API monograph is used, a conversion factor may be required
  
  e. g. Rosuvastatin calcium CRS used for determination of rosvastatin in rosuvastatin tablets -> conversion factor 0.96

**Dissolution test-Disintegration test**

- **Current policy**: testing procedures (test conditions, limits and acceptance criteria), if specified in the monograph, are mandatory
  
  - Flexibility: The tablets comply with the method and acceptance criterion as described below, unless otherwise justified and authorised

  Under discussion

- Dissolution tests and limits should be sufficiently discriminatory to assure batch-to-batch consistency (purpose is not to demonstrate bioequivalence)
- Provided for quality control only

- According to ICH Q6A: For solid oral drug products for immediate release containing highly soluble APIs, disintegration may be used instead of dissolution (Sitagliptin tablets, monograph 2927) => in line with General Principles

- Quantification: by LC or UV-Vis using either a CRS with assigned content (rosuvastatin tablets) or validated value for specific absorbance (dronedarone tablets, not yet adopted)
Dissolution test-ongoing discussions

Discussion on dissolution tests is still ongoing

EDQM launched a survey to get the opinion of all possible stakeholders

Two options proposed:

1. Monograph text: “The tablets/capsules comply with the following dissolution test (method and acceptance criterion). If, for a given medicinal product, this method and the acceptance criterion prove not to be sufficiently discriminatory to assure batch-to-batch consistency, a different method and/or acceptance criterion must be provided in the marketing authorisation application and is subject to approval by the competent authority.”

2. No dissolution test would be provided in individual FPMs; nonetheless, the performance of dissolution testing would remain mandatory through the requirements of the dosage form monograph (e.g. Tablets (0478), Capsules (0016), etc.). A dissolution test (method and acceptance criterion) would need to be developed by each marketing authorisation applicant and submitted in the marketing authorisation application for assessment and approval by the competent authority.
Harmonisation

Informal prospective harmonisation (Ph. Eur. and USP)
- In total 19 monographs harmonised
- 13 API monographs and 6 finished product monographs

- Further 15 monographs on the work program

Outcome of 10th edition conference

- FPMs = important tool to standardise and harmonise the quality of medicines
- Innovators and generic manufacturers as well as OMCLs confirmed usefulness of FPMs
- P4 procedure (single-source products) best option for innovators to have a monograph before the end of the patent exclusivity
- Facilitate Market Surveillance Studies performed by OMCLs

- Important to note: Demonstration of the suitability of the methods and limits included in a monograph for a specific FP needs to be submitted in the marketing authorisation application (not simply « Complies with Ph. Eur. »)

- It is important that manufacturers and assessors provide input, at the latest during Pharmeuropa stage
Conclusion

- A number of FP monographs has been elaborated under the P4 procedure (single source products)
- Several monographs are under elaboration under the P1 procedure (multi-source products)
- A first monograph under P1 has been adopted: Rosuvastatin tablets
- Policies for identification, impurities, assay are clear and agreed
- Revision of the current policy of dissolution tests still under discussion

Call for candidate FP monographs (± API)

epd@edqm.eu

Chemically defined active substances
Single-source products
Elaboration of new FP monographs
Multisource products
Immediate release tablets & capsules
Oral solution
Solution for injection & infusion
Powder for injection & infusion
Thank you for your attention

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