THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

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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

- TITLE
- DEFINITION
- IDENTIFICATION
- TESTS
- RELATED SUBSTANCES
- DISSOLUTION
- ASSAY
- IMPURITIES

Tests mandatory unless otherwise specified

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

Work program

Adopted monographs

Product	Monograph number	Ph. Eur. supplement
Sitagliptin tablets	2927	8.7
Raltegravir tablets	2938	9.5
Raltegravir chewable tablets	2939	9.5
Lacosamide tablets	2989	9.8
Lacosamide oral solution	2990	9.7
Lacosamide infusion	2991	9.7
Deferiprone tablets	2986	9.8
Deferiprone oral solution	2990	9.7
Rosuvastatin tablets	3008	10.1

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 »

(https://www.edqm.eu/en/technical-guides)

➢ 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)

General principles document

"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%)

LACOSAMIDE INFUSION

Lacosamidi praeparatio ad infusionem

DEFINITION

Sterile solution for infusion of *Lacosamide (2992)*.

It complies with the monograph Parenteral preparations (0520) and the following additional requirements.

Content: 95.0 per cent to 105.0 per cent of the content of lacosamide ($C_{13}H_{18}N_2O_3$) stated on the label.

ROSUVASTATIN TABLETS

Rosuvastatini compressi

DEFINITION

Tablets containing *Rosuvastatin calcium (2631)*.

They comply with the monograph Tablets (0478) and the following additional requirements.

Content: 93.0 per cent to 105.0 per cent of the content of rosuvastatin ($C_{22}H_{28}FN_3O_6S$) stated on the label.

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: crush a tablet to a powder and homogenise.

Comparison: sitagliptin phosphate monohydrate CRS.

Results: the spectrum obtained shows absorption maxima at about 1669 cm^{-1}, 1513 cm^{-1}, 1425 cm^{-1}, 1207 cm^{-1}, 880 cm^{-1} and 844 cm^{-1}, similar to the spectrum obtained with sitagliptin phosphate 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 wi
the solutions used in the assay, with a diode array detector in the range 210-400 n

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

Impurity Policy: Rosuvastatin tablets (1)

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.

Impurity Policy: Rosuvastatin tablets (2)

System suitability: reference solution (b):

– *peak-to-valley ratio*: minimum 2.0, where H_p = 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*: maximum1.5 per cent;

– *impurity D*: maximum1.5 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 rosuvastatin 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

Mandatory

Non mandatory

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

Dissolution test-ongoing discussions

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

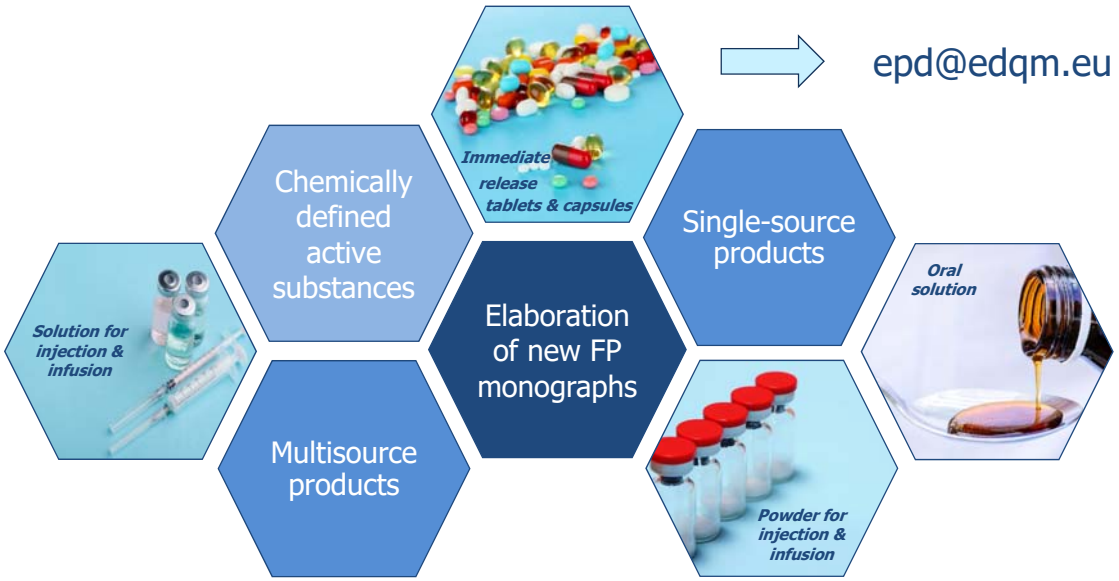
- FPMs = important tool to standardise and harmonise the quality of medicines
- Innovators and generic manufacturers as well as OMCLs confirmed usefulness of FPMs
- P4 procedure (single-source products) best option for innovators to have a monograph before the end of the patent exclusivity
- Facilitate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



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