Finished product monographs containing chemically defined active substances

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Topics covered by the talk

• Brief introduction to the Ph. Eur.
• General principles for finished product monographs with chemically defined active substances
• Content of such monographs
• Example of Sitagliptin tablets (2927)
• Current focus and work programme
• How to participate in the work
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**Place of the Ph. Eur. within EU regulatory network**

- Lays down common, compulsory quality standards for all medicinal products in Europe.
- **Mandatory** on the same date in 37 states (CoE) and the EU (European Union Directives **2001/82/EC** and **2001/83/EC**, as amended, on medicines for human and veterinary use).
- The Ph. Eur. is legally binding. The legislation also includes a mechanism to provide the pharmacopoeia authority with information on the quality of products on the market;
- The European Pharmacopoeia needs to keep pace
  - with the regulatory needs of licensing, control and inspection authorities in the public health area,
  - with technological and scientific advances, and with industrial constraints.
1. General Notices

Ph. Eur. texts

- Apply to all monographs and other texts of the Ph. Eur.
- Essential reading before starting to use general chapters and monographs

Validation

Reduction of animal testing (3Rs)

Alternative methods

PAT / RTRT
Ph. Eur. texts

**General chapters**

- Dissolution test for solid dosage forms (2.9.3)
- Liquid chromatography (2.2.29)
- Potentiometric determination of pH (2.2.3)
- Disintegration of tablets and capsules (2.9.1)
- Uniformity of content of single-dose preparations (2.9.6)

**Individual monographs**

- General monographs
- Reference standards

**Individual monographs**

- General monographs
- Reference standards

**General chapters**

- Quality aspects that cannot be dealt with in each individual monograph
- Quality aspects that are common to a class of products
- General monographs apply to all substances and preparations within the scope of the **Definition section of the general monograph**, except where a preamble limits its application
**Ph. Eur. reference standards**

- Established specifically for intended use in monographs or general chapters of the Ph. Eur., as prescribed in the methods given
- Chemical Reference Standards (CRSs) and Biological Reference Preparations (BRPs)
- Secondary standards within each laboratory possible

**Ph. Eur. texts**

**Product specific**

- Active substances:
  - Paracetamol (0049)
  - Rosuvastatin calcium (2631)
  - Sitagliptin phosphate monohydrate (2778)

- Finished products:
  - Sitagliptin tablets (2927)
  - Cyanocobalamine (57Co) capsules (0710)

- Specifications for individual product
- Based on approved specifications backed up by batch data
- analytical procedures and acceptance criteria to demonstrate that the substance or product meets required quality standards
“Finished product” monographs – something new?

- Radiopharmaceutical preparations
- Insulins
- Coagulation factor solutions
- Vaccines
- Other biologicals

Monographs on „finished products“ - development for chemically defined actives

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 will come into force on April, 1st
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A revolution?

- Provide public standard to harmonise specifications throughout Europe
- **Following existing rules** for elaboration and revision
- Public consultation in Pharmeuropa online
- Based on approved specifications in Europe
- Backed up by batch data
- **Active substance monograph** exists or is elaborated in parallel
An evolution

- Basis for independent judgement on quality of the medicine
- Cover different formulations and strengths
- Full flexibility in framework offered by Ph. Eur.
- Provide shelf-life specifications
- Demonstration of suitability of monograph needed

Demonstration of suitability

Monograph tests mandatory unless otherwise justified and authorised

Each MAA still to provide to the competent authority

- A complete dossier including P2 pharmaceutical development
- Demonstrate that tests in the monograph are appropriate for the quality control of their product (e.g. dissolution, related substances)
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Content

Tests **mandatory** unless otherwise specified

Labelling is subject to supranational and national regulation and to international agreements: no intention to add additional requirements
**Content - Title**

Usually consists of:
- Active moiety
- Dosage form

**Content - Definition**

- Specific salt or hydrate covered
- Cross-reference to dosage form monograph
- Content in percentage of active moiety
### Content - Identification

<table>
<thead>
<tr>
<th>Title</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDENTIFICATION</td>
<td>Provide confirmation of the identity of the product</td>
</tr>
<tr>
<td>TESTS</td>
<td>e.g. combination of 2 chromatographic procedures to ease work of the analyst</td>
</tr>
</tbody>
</table>

### Content - Tests

<table>
<thead>
<tr>
<th>Title</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>TESTS</td>
<td>All mentioned tests are mandatory</td>
</tr>
<tr>
<td>RELATED SUBSTANCES</td>
<td>Additional ones may be necessary to control specific quality parameter of individual products, e.g. water</td>
</tr>
</tbody>
</table>
Content – Related Substances

- Limit the impurities within the finished product
  - Includes degradation products throughout shelf-life
  - Includes impurities of synthesis at levels greater than the limit for unspecified ones
- Additional controls may be necessary for impurities not controlled by the Ph. Eur. method.

Content - Dissolution

- Provided for quality control only
- Should be sufficiently discriminatory to assure batch to batch consistency of specific product
- Not intended to demonstrate bioequivalence
- Not intended to compare profiles in the case of a bio-waiver
- Does not replace requirements in a marketing authorisation application
- Might be substituted by disintegration, if correlation is demonstrated (cf. ICH Q6A)
Content - Assay

Method to quantify content

Content - Impurities

- Impurity section contains transparency list as for APIs
- Impurities also relevant to the API keep their designation
- Impurities specific to the finished product are designated by “FP-” followed by a letter (e.g. FP-A)
Flexibility in the Ph. Eur. – Alternative methods

- **Ph. Eur. tests** are *reference methods*, essential in cases of dispute.
- Compliance is required, but **alternative methods** may be used as long as they lead to the *same pass/fail result*.
- It is the responsibility of the user to demonstrate their suitability. **Approval of the competent authority** is necessary in many cases.

Acceptance criteria/specifications in Ph. Eur. in view of RTRT

- **Conventional specifications** are needed!
- Correlation to be made between the prediction (RTRT) and the conventional specifications
- Conventional expression of specifications will always be needed for:
  - Product development
  - Independent controls (*e.g.* Official Medicines Control Laboratories)
  - Stability studies
  - Applicants that decide to apply the "conventional approach"
- **Need for a tiered system**, providing "conventional" specifications, but enabling the implementation of new approaches, *e.g.* PAT
- **PAT and public standards are compatible** with each other
Flexibility in the Ph. Eur. – Waiving of tests

“Demonstration of compliance with the Pharmacopoeia (1) An article is not of Pharmacopoeia quality unless it complies with all the requirements stated in the monograph. This does not imply that performance of all the tests in a monograph is necessarily a prerequisite for a manufacturer in assessing compliance with the Pharmacopoeia before release of a product. The manufacturer may obtain assurance that a product is of Pharmacopoeia quality on the basis of its design, together with its control strategy and data derived, for example, from validation studies of the manufacturing process.”

General Notices – Supplement 8.2.

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Sitagliptin tablets - Definition

Title
No chemical structure, already in active substance monograph

Relevant active substances, only applicable if monograph exists

Reference to dosage form monograph as information for user

Content of active moiety

Sitagliptin tablets - Identification

2 alternative subsets with 2 tests each

- UV spectra of principle peak of LC assay testing (DAD necessary)

- Retention time and size of principle peak of LC assay testing, always prescribed

- Direct IR measurement of powdered tablet – check for absorption maxima

First subset allows to use data acquired from assay
Sitagliptin tablet: Related Substances

Isocratic LC test:
- sample preparation by dissolving whole tablets
- in-situ degradation for system suitability test

UV detection
- System suitability test with in-situ prepared impurity
- following ICH Q3B/Q6A principles
**Sitagliptin tablets – limits of impurities**

**Tablets:**
- Limit for total of impurities not contradictory
- Special case, different thresholds needs to be taken into account:
  - All synthetic impurities are disregarded for this special case

**Active substance:**
- Limit for total of impurities not contradictory

Special case, different thresholds needs to be taken into account:
- All synthetic impurities are disregarded for this special case

**Sitagliptin tablets – disintegration**

**Disintegration (2.9.1).** The tablets comply with the test.

**Medium:** water R.

**Time:** 5 min.

Intended for quality control only, substitutes dissolution

- Follows ICH Q6A principles
- Highly soluble active substance, rapidly dissolving product
- More discriminatory than dissolution test
- Strict limit to ensure accurate release

**Does not demonstrate** bioequivalence or replace comparison in case of bio-waiver
Sitagliptin tablets – assay

**Assay**
Lipid chromatography (2.2.29) as described in the test for related substances with the following modifications:
Injection: test solution and reference solution (a).
Run time: twice the retention time of sitagliptin.
Calculations: reference solution (a):
- Repeatability: minimum relative standard deviation of 1.5 per cent determined on 6 injections.
- Calculate the percentage content of sitagliptin \( \left( C_{26} H_{35} F_5 NO_4 \right) \) taking into account the assigned content of sitagliptin phosphate monohydrate CRS.

**Repeatability:** individual criterion, drug products not covered by 2.2.46

**Calculation of content of active moiety**
Do not forget to convert assigned content of CRS for salt to active moiety.

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Sitagliptin tablets – impurities

**Impurities**
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph). They are limited by the general acceptance criterion for other unspecified impurities. It is therefore not necessary to identify these impurities for demonstration of compliance: FP-I, FP-II, FP-C, FP-III, FP-E.

- **FP-A**: 2-[[2R]-4-oxo-4-[3-(trifluoromethyl)5,6-dihydro-1,2,4-triazolo[4,3-a]pyrazin-7(8H)-yl]-1-cyclopentyl]-1-(trifluoromethyl)butan-2-y]ammonium trifluoroacetate.

**Transparency list given**
Designation starts with FP - all specific for FP (“FP-A” to “FP-C”)
Designation of impurity kept, if mentioned in API monograph.
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Current focus

Follows critical assessment and discussions:
Takes into account usefulness of Ph. Eur. monograph and impact on registered products

- Single-source monographs on products that are potential future generics (Procedure 4)
- Immediate release dosage forms
- Solid and liquid formulations
- Will be expanded subsequently
**P4 Procedure: focus for FPs**

**Procedure 1**

- A
- B
- C
- D

**Procedure 4**

- A

**MONOGRAPH**

Valid for A, B, C & D, E

Revision

**Work programme: 13 finished products**

- Raltegravir tablets
- Raltegravir chewable tablets
- Deferasirox dispersible tablets
- Deferiprone tablets
- Deferiprone oral solution
- Lacosamide tablets
- Lacosamide oral solution

- Lacosamide solution for infusion
- Fosaprepitant powder for solution for infusion
- Sorafenib tablets
- Rivaroxaban tablets
- Regorafenib tablets
- Rosuvastatin tablets (P1)
Work programme: 13 finished products

For details see Knowledge Database

Gives information on status of work and more details
After publication examples of chromatograms, trade names of columns used, history, etc.

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Procedure 4 (P4)

- One single interested party
- Usually substance still under patent protection in Europe
- Aim to publish 2 years before patent expiry at the latest
- Roughly 3 years from first contact till publication
- Manufacturers may send proposals to NPAs or if from outside Europe to the EDQM

Participate in the public consultation

Send comments within deadline to

- National Pharmacopoeial Authority for manufacturers within Ph. Eur. convention
- EDQM helpdesk for manufacturers outside the Ph. Eur. convention

http://pharmeuropa.edqm.eu
Call for candidates 2016

- The Ph. Eur. Commission has opened up the nomination process of experts to non Ph. Eur. members.
- **Expert nominations:** experts from non Ph. Eur. member states will be able to participate to Ph. Eur. activities upon appointment by Ph. Eur. Commission
- P4 is limited to experts from national authorities in Europe

Acknowledgements

**All the experts and specialists of the European Pharmacopoeia!**
Additional information

www.edqm.eu

- General principles
- Procedure 4 Elaboration of a monograph
- Guide for the work of the European Pharmacopoeia (revised January 2016)
- Principles in Technical Guide for the elaboration of monographs

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