Keynote Speaker

Functionality-related Characteristics of Excipients in the European Pharmacopoeia

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Functionality-related Characteristics of Excipients in the European Pharmacopoeia

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European Pharmacopoeia, EDQM
Outline

1. The European Pharmacopoeia (Ph.Eur.)
2. The importance of excipients
3. Functionality-related Characteristics (FRCs)
4. FRCs in the Ph.Eur. and beyond
1. The European Pharmacopoeia
The Council of Europe is the continent’s leading human rights organisation

- Founded in 1949
- 47 member countries
- Development of European common and democratic principles
- Headquartered in Strasbourg
- Core values:
  - protection of human rights
  - pluralist democracy & the rule of law
- NOT the European Union
EDQM’s mission is to contribute to access to good quality medicines

- **EDQM**: The European Directorate for the Quality of Medicines & HealthCare
- **A Council of Europe Directorate**, based on the *Convention on the Elaboration of a European Pharmacopoeia* (PA, 1964)
- **Amongst other activities**, responsible for the European Pharmacopoeia (Ph.Eur.)
- **Access to good quality medicines and healthcare** is a **basic human right**
Global impact of the European Pharmacopoeia

- Founded 1964
- 37 member states + the European Union
- 27 observers
  - 8 European countries
  - 17 non-European countries
  - World Health Organization (WHO)
  - the Taiwan Food and Drug Administration (TFDA) of the Ministry of Health and Welfare

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The mission of the European Pharmacopoeia is to

- promote public health by the provision of **recognised common standards** for the quality of medicines and their components,
- facilitate the **free movement** of medicinal products in Europe,
- design **European Pharmacopoeia monographs and other texts** to be appropriate to the needs of:
  - regulatory authorities,
  - manufacture and **quality control** of medicinal products and their components
The Ph.Eur.: one common standard to protect public health

Legal impact

• The Ph. Eur. is the official pharmacopoeia in Europe – can be complemented by national pharmacopoeias for texts of interest to only one Member State.

• Mandatory at the same date in 37 Member States (Ph.Eur. Convention) and the EU

• Legally binding quality standards for ALL medicinal products in its member states, i.e. raw material, preparations, dosage forms, containers must comply with the Ph. Eur. requirements when they exist.
The Ph.Eur. contains more than 2200 monographs and 340 general methods to date.

Ph. Eur. Monographs per topic
- 2014-

- Chemicals: 56.5%
- Biologicals: 3.3%
- Herbs: 11.8%
- Fats: 6.3%
- Radiopharm.: 3.1%
- Human Vaccines: 3.9%
- Antibiotics: 6.7%
- Blood deriv.: 1.4%
- Dosage forms: 1.3%
- Med. Devices: 0.6%
- Gases: 0.6%
- Homoeopathy: 1.1%
- Plastics: 0.2%
- Vet. Vaccines: 3.4%
- Antibiotics: 6.7%

65 FRC sections
The 8th Edition of the Ph.Eur. has been implemented in Jan. 2014


Calendar of the Editions of the Ph.Eur.

<table>
<thead>
<tr>
<th>Commission session</th>
<th>Edition Supplement</th>
<th>Implementation Date</th>
</tr>
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<tbody>
<tr>
<td>November 2012</td>
<td>8.0</td>
<td>1 January 2014</td>
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<td>March 2013</td>
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<td>1 July 2015</td>
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</tr>
<tr>
<td>November 2015</td>
<td>8.8</td>
<td>1 January 2017</td>
</tr>
</tbody>
</table>

www.edqm.eu
2. The importance of excipients
Excipients are not APIs…

Definition of excipients in Ph.Eur. General notices

Excipient (auxiliary substance). Any constituent of a medicinal product that is not an active substance. Adjuvants, stabilisers, antimicrobial preservatives, diluents, antioxidants, for example, are excipients.

Image Source: www.forum.co.uk
...but they are important

- used in pharmaceutical formulation/ medicinal product due to their functionality
- can constitute a large part of the formulation
- Impact the manufacture and quality of the finished products

AND

- Must comply with quality standards, e.g. Ph.Eur. Monographs, when they exist
Excipients come from various sources & different chemical classes

**Most used excipients in US-manufactured drug products**

<table>
<thead>
<tr>
<th>Magnesium Stearate</th>
<th>Sodium Starch Glycolate</th>
<th>Croscarmellose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>Gelatin</td>
<td>Hydroxy Propyl Cellulose</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>Talc</td>
<td>Ethylcellulose</td>
</tr>
<tr>
<td>Starch (corn)</td>
<td>Succrose</td>
<td>Calcium Phosphate (dibasic)</td>
</tr>
<tr>
<td>Silicon Dioxide</td>
<td>Calcium Stearate</td>
<td>Crospovidone</td>
</tr>
<tr>
<td>Titanium Dioxide</td>
<td>Povidone</td>
<td>Shellac</td>
</tr>
<tr>
<td>Stearic Acid</td>
<td>Pregelatinized Starch</td>
<td>Bold: FRC section</td>
</tr>
<tr>
<td></td>
<td>Hydroxy Propyl Methylcellulose</td>
<td></td>
</tr>
</tbody>
</table>

*source: IPEC AMERICAS, amended*
One excipient can have different functionalities.

**Functional categories of excipients**

- e.g. lubricant, binder, filler, disintegrant, colouring agent, controlling release: coating, matrix former, … in solid dosage forms

- e.g. viscosity increasing agent, gel former, emulsifier, antimicrobial preservative … in semi-solid dosage forms

- e.g. surfactant, co-surfactant, solubiliser, emulsifier, dispersing agent, taste masking agent … in liquid dosage forms.

**Identity and purity testing not sufficient to ensure product performance**
3. Functionality-related Characteristics (FRCs)
What are FRCs?

**Functionality-related characteristics of excipients:**

controllable physical or chemical characteristics of an excipient that **impact on its functionality**
Functionality depends on the excipient material properties

- **Physical properties:**
  - e.g. particle morphology, particle size distribution, specific surface area, bulk density, flowability, water sorption, polymorphism, crystallinity, density.

- **Chemical properties:**
  - e.g. (polymeric) composition, degree of substitution, chemical incompatibilities.

**Additionally: by-products or additives can impact**

- e.g. co-surfactants
FRCs are needed because excipient functionality may be sensitive to variations...

...and may have an impact on product performance!

- Different excipient grades available
- Batch-to-batch variability
- Manufacturer-to-manufacturer variability
Profound knowledge of excipients functionalities is part of a sound development strategy

How to develop and manufacture a robust medicinal product?

1. A successful strategy for pharmaceutical development has always been based on a sound scientific approach.

→ profound knowledge of excipients functionalities is needed!

→ FRCs

2. This has been taken up in “ICH Q8 Pharmaceutical development” and the “Quality by Design” paradigm

• Critical Quality Attributes (CQAs) → FRCs can be described as CQAs

A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. (ICH Q8 (R2) - Glossary)
Functionality-related characteristics started at the Ph.Eur. in 1995

Development of FRCs in the Ph. Eur.

Ph.Eur. Commission: decision to include functionality-related tests in the Ph.Eur.

Dedicated FRC Working Party established

General chapter 5.15 on FRCs adopted

First FRC section introduced: Lactose anhydrous

Approval of ICH Q8 Pharmaceutical Development

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General Chapter 5.15 explains FRC section in excipient monographs

- Information and Guidance: How to use the FRC section
- Excipients, Excipient monographs, FRCs
- Physical and chemical characteristics of excipients
- Pharmacopoeial Harmonisation
1. Ph.Eur excipient monograph: assures Identity and Purity

DEFINITION
PRODUCTION
POTENTIAL ADULTERATION
CHARACTERS
IDENTIFICATION
TESTS
ASSAY
STORAGE, LABELLING

mandatory part
Quality standard assuring Identity and Purity
2. Ph.Eur excipient monograph: provides information on FRCs

DEFINITION
PRODUCTION
POTENTIAL ADULTERATION
CHARACTERS
IDENTIFICATION
TESTS
ASSAY
STORAGE, LABELLING

FRC →

mandatory part:
Quality standard assuring
Identity and Purity

informative part:
Control parameters for
specific excipient use
The FRC section of an excipient monograph is informative

- **Additional, non-mandatory part of a Ph.Eur. excipient monograph:**

Main use of the excipient

+ FRC
+ FRC and example method
+ FRC, example method and typical values

**Example:** FRCs for *Lactose monohydrate* used as filler/diluent in *solid dosage forms*:

- Particle size distribution (2.9.31 or 2.9.38)
- Bulk and tapped density (2.9.34)
Example FRCs Hypermellose (HPMC) (1)

The following characteristics may be relevant for hypromellose used as binder, viscosity-increasing agent or film former.

- **Viscosity**: see Tests.
- **Degree of substitution**: see Assay.
Example FRCs Hypromellose (HPMC) (2)

The following characteristics may be relevant for hypromellose used as matrix former in prolonged-release tablets.

- **Viscosity**: see Tests.
- **Degree of substitution**: see Assay.
- **Molecular mass distribution** (2.2.30).
- **Particle-size distribution** (2.9.31 or 2.9.38).
- **Powder flow** (2.9.36).
The following characteristics may be relevant for povidone used as solubiliser and stabiliser in liquid dosage forms.

- **Viscosity (2.2.9).** Determine the dynamic viscosity using a capillary viscometer on a 10 per cent solution (dried substance) at 25 °C. Typical values are shown in Table 0685.-1.

- **Molecular mass** (see Viscosity, expressed as K-value) Typical values are shown in Table 0685.-1.

Table 0685.-1. – *Typical viscosity ranges and ranges for viscosity, expressed as K-value*

<table>
<thead>
<tr>
<th></th>
<th>Viscosity range (mPa·s)</th>
<th>Molecular mass: viscosity, expressed as K-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Povidone K 12</td>
<td>1.3-2.3</td>
<td>11-14</td>
</tr>
<tr>
<td>Povidone K 17</td>
<td>1.5-3.5</td>
<td>16-18</td>
</tr>
<tr>
<td>Povidone K 25</td>
<td>3.5-5.5</td>
<td>24-27</td>
</tr>
<tr>
<td>Povidone K 30</td>
<td>5.5-8.5</td>
<td>28-32</td>
</tr>
<tr>
<td>Povidone K 90</td>
<td>300-700</td>
<td>85-95</td>
</tr>
</tbody>
</table>
Example FRCs Povidone (2)

The following characteristic may be relevant for povidone used as binder in tablets and granules.

- **Molecular mass** (see Viscosity, expressed as K-value). Typical values are shown in Table 0685.-1.

Table 0685.-1. – *Typical viscosity ranges and ranges for viscosity, expressed as K-value*

<table>
<thead>
<tr>
<th>Povidone K 12</th>
<th>Viscosity range (mPa·s)</th>
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<td>85-95</td>
</tr>
</tbody>
</table>
Example FRCs Magnesium stearate

The following characteristics may be relevant for magnesium stearate used as a lubricant in tablets and capsules.

- **Particle-size distribution** (2.9.31).
- **Specific surface area** (2.9.26, Method I). Determine the specific surface area in the $P/P_o$ range of 0.05 to 0.15.
  
  *Sample outgassing:* 2 h at 40 °C.
  
- **Water content and polymorphic form** (Thermogravimetry (2.2.34))
3 . FRCs in the Ph.Eur. and beyond
Almost 20 years experience with FRCs in the Ph.Eur.

- *User needed training to fully appreciate the informative character of the FRC section*

- FRCs help to **identify the right excipient quality/grade** for a specific purpose

- FRCs **support the QbD approach**

- FRCs are a helpful tool for a **successful pharmaceutical development strategy**

→ Control of FRCs helps to assure **consistent quality and performance of formulations and drug products**
FRCs’ concept has been included in other compendia

**USP:**
chapter on Excipient performance

**Chinese Pharmacopoeia:**
Guidance to research on functionality-related characteristics of pharmaceutical auxiliary materials
FRC is part of IPEC Europe’s QbD Checklist for Excipient Manufacturers/Suppliers

2. Development of the Dosage Form

2.1 Is it understood what the customer application is for the excipient and have they selected the most appropriate material or grade?
2.2 Can any of the variables be categorised as not being Critical Quality Attributes in the customer’s specific application and have the relevant Functionality related Characteristics been identified?
2.3 Is the customer using the selected excipient at the correct level in the formulation to optimise robustness?
Manufacturers are welcome to contribute to FRCs

New FRCs or potential optimisation of existing ones

- Proposals via:
  - Europe: National pharmacopoeia authority (NPA)
  - Outside Europe: EDQM helpdesk
  - IPEC Europe, or other industry associations

Pharmeuropa, public enquiry

- Free access at http://pharmeuropa.edqm.eu
- Comments via:
  - Europe: National pharmacopoeia authority (NPA)
  - Outside Europe: EDQM helpdesk
  - IPEC Europe or other industry association

Get actively involved – join a Ph.Eur. Working Party

- Contact the Ph.Eur. Secretariat via the helpdesk: www.edqm.eu/hd
- Contact your NPA
Next Steps

- Continue to draft new and update FRC sections
  - E.g. Poly (vinyl alcohol) (1961), Poloxamers (1464), Sorbitan stearate (1043), Polyoxypropylene stearyl ether (2602), Carmellose Sodium (0472), ...

- Revise general chapter « 5.15 Functionality-related characteristics of excipients » to further clarify how FRCs help the users in the context of QbD
Thank you for your attention

website: www.edqm.eu