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

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# The European Pharmacopoeia enabling QbD and Continuous Manufacturing

**2019 Training Session**
**"The European Pharmacopoeia"**
**Mrs Cathie Vielle**
**EDQM Head of European Pharmacopoeia Department**

**10 – 11 September 2019, Iselin, New Jersey, USA**

## Principles of Quality by Design

**QbD:**

Product quality achieved and demonstrated through **process control and knowledge** instead of **end product testing**

**Ph. Eur.:**

- Mandatory **quality standards** for drug substances, excipients and drug products defined by **end product testing**
- **general chapters** and **methods**

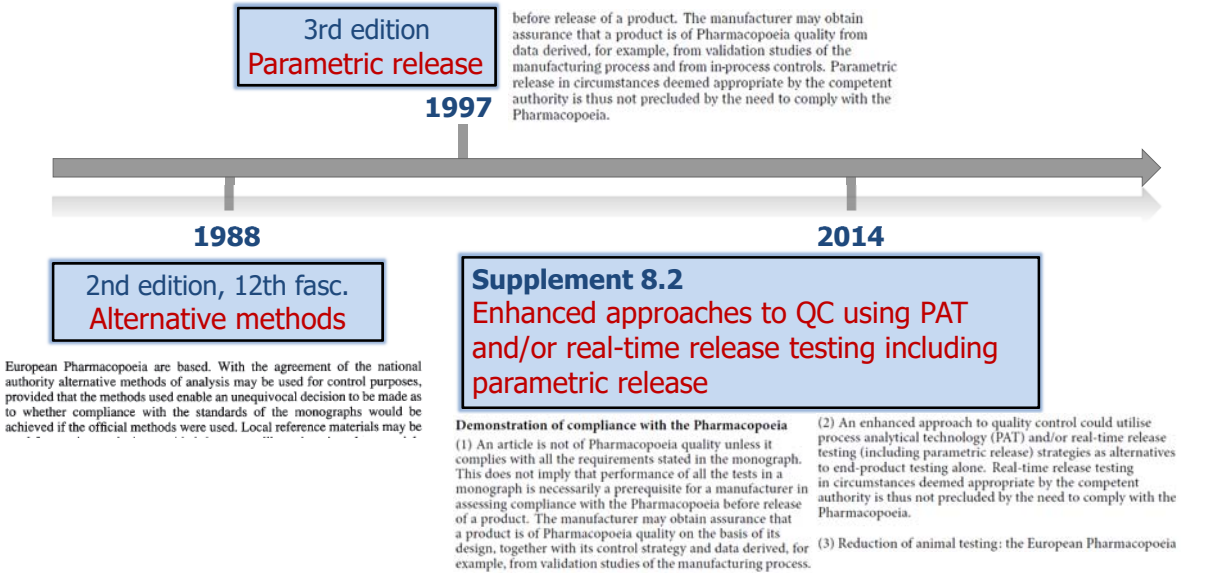
**COMPATIBLE?**




## QbD concept already integrated in the Ph. Eur.

- QbD and Ph. Eur. are both about ensuring quality
- Ph. Eur. enables and supports QbD with PAT applications through **flexibility**:
  - ✓ Alternative methods and enhanced approaches to quality control in **General Notices**
  - ✓ **Revision** of analytical **methods**
  - ✓ Elaboration of **supportive texts**
  - ✓ Non-mandatory **Functionality-Related Characteristics**

# History General Notices (1.)




before release of a product. The manufacturer may obtain assurance that a product is of Pharmacopoeia quality from data derived, for example, from validation studies of the manufacturing process and from in-process controls. Parametric release in circumstances deemed appropriate by the competent authority is thus not precluded by the need to comply with the Pharmacopoeia.

European Pharmacopoeia are based. With the agreement of the national authority alternative methods of analysis may be used for control purposes, provided that the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used. Local reference materials may be

**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.

(2) An enhanced approach to quality control could utilise process analytical technology (PAT) and/or real-time release testing (including parametric release) strategies as alternatives to end-product testing alone. Real-time release testing in circumstances deemed appropriate by the competent authority is thus not precluded by the need to comply with the Pharmacopoeia.

(3) Reduction of animal testing: the European Pharmacopoeia




# General Notices: Alternative methods

- Ph. Eur. tests = reference methods, alone authoritative in cases of doubt or dispute.
- Compliance required, but alternative methods may be used: same pass/fail decision
- Users' responsibility to demonstrate their suitability. Approval of *competent authority* needed in any case

The EDQM does not decide if acceptable or not!

# Flexibility in the Ph. Eur. : Waiving of tests

**Compliance ≠ Performance**

↓ prerequisite

↓ no prerequisite

- In some cases, some **tests may be omitted** based on validation data or other suitable justification
- Tests for process-specific impurities may be omitted if it is demonstrated that they will not occur with the particular process used




# Flexibility in the Ph. Eur. : PAT

"(2) *An enhanced approach to quality control could utilise process analytical technology (PAT) and/or real-time release testing (including parametric release) strategies as alternatives to end-product testing alone. Real-time release testing in circumstances deemed appropriate by the competent authority is thus not precluded by the need to comply with the Pharmacopoeia."*

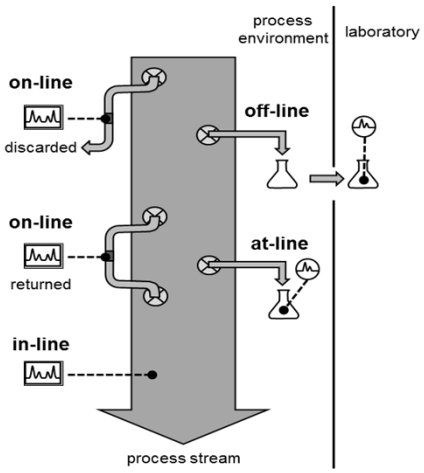
# 5.25 Process Analytical Technology

- Included in 10th edition (published July 2019)
- Non-mandatory, informative chapter
- Gives clear definitions
- Introduces process interfacing
- Summarises implementation of PAT in the Ph. Eur. (work ongoing already for a long time)
- Reference to specific chapters




# Interfacing Process and Analytics

- Central to PAT
- In-line and on-line support rapid and automated adjustments
- **In-line**: directly in process stream
- **On-line**: automated diversion of portion, returned or not depending on detrimental nature
- **At-line**: within the production environment
- **Off-line**: at distance from process environment and delayed analysis.

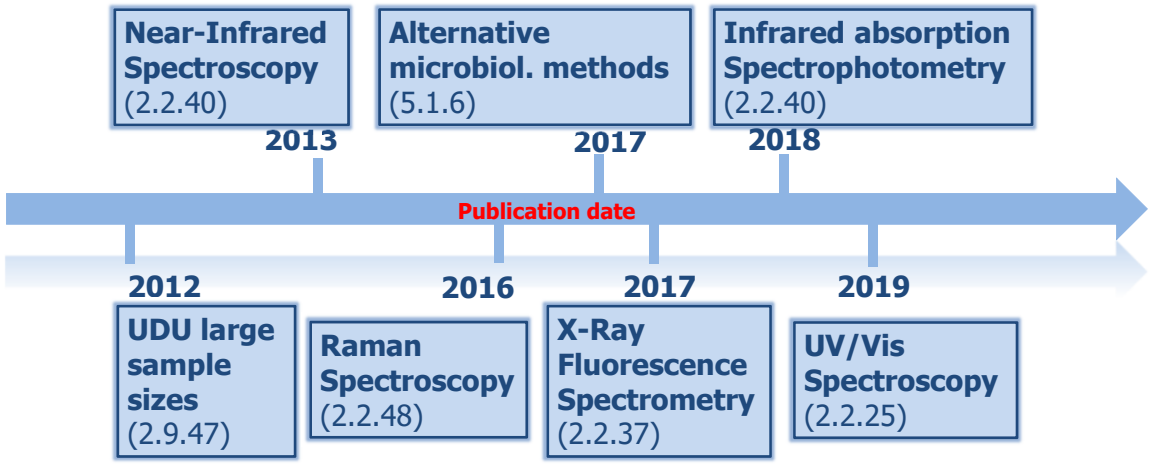


# Comparing conventional testing and PAT

- **No conventional sampling** with in-line and on-line interfacing - **smaller portions** analysed:
  - need to consider **scale of scrutiny**
  - **physical attributes** such as particle size, surface roughness **may interfere**
- Rapid continuous monitoring allows process control
- Possibly different criteria for **validation and control of instrument performance**, but **same principles apply**

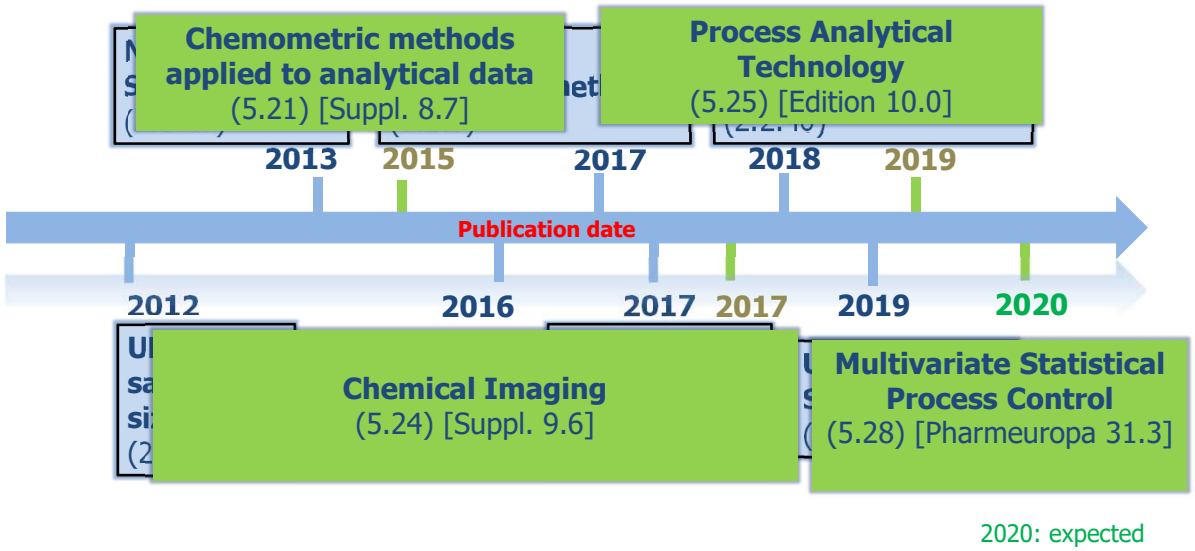
 

# General Methods - Revisions for PAT



# General texts

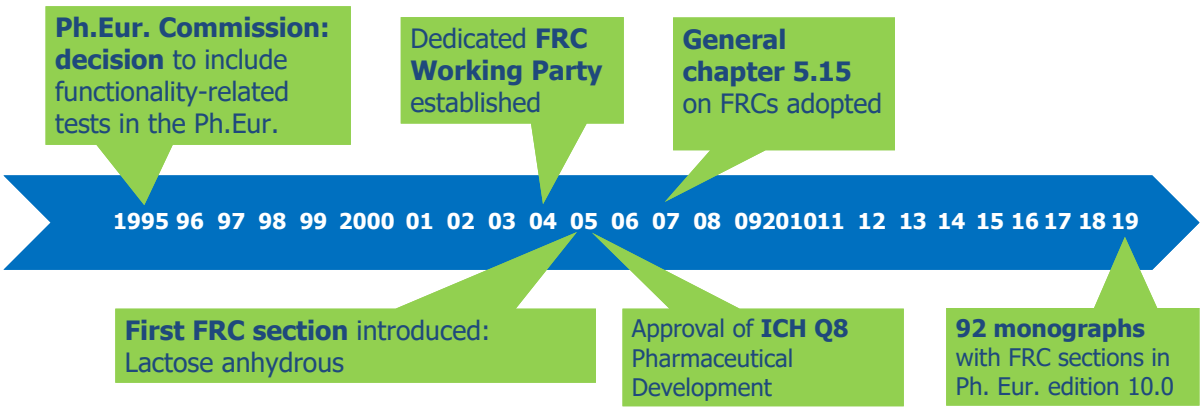



2020: expected




# Functionality-related characteristics started in 1995

## Development of FRCs in the Ph. Eur.



## Chapter 5.15 Functionality-related characteristics

- FRC sections are non-mandatory
- FRCs are not exhaustive, but they are typical for the excipient:
  - Particle size distribution
  - Powder flow
  - Bulk and tapped density
  - Viscosity
  - Melting point
- Knowledge of FRCs may facilitate the application of process analytical technology (PAT)

## FRC & ICH Q8

- FRC concept in line with "quality by design" cf. ICH Q8
- Critical material attributes to be identified during development work
- Depending on the application, an FRC may or may not be relevant, thus …
- FRC section contributes to desired **regulatory flexibility**
- FRCs **can be essential critical characteristics** for Continuous Manufacturing

# Conclusion: Ph. Eur. provides framework

**FLEXIBILITY**
**General Notices**

**MODERN GENERAL METHODS**


**SUPPORTIVE GENERAL TEXTS**

**FUNCTIONALTY-RELATED CHARACTERISTICS**

➔ Ph. Eur. quality standards and requirements **apply regardless of control strategy**

➔ Ph. Eur. **allows and supports Continuous Manufacturing** via QbD and PAT included as one way of demonstrating quality




# Thank you for your attention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