The European Pharmacopoeia – Facilitating Continuous Manufacturing

D. Leutner *
European Directorate for the Quality of Medicines & HealthCare (EDQM), Council of Europe
7, allée Kastner, Cs 30026, F-67081 Strasbourg (FRANCE)

INTRODUCTION

Process Analytical Technology (PAT) applications are essential to enable Quality by Design (QbD) and Continuous Manufacturing (CM).
The European Pharmacopoeia (Ph. Eur.) Commission and its working parties have made great efforts to facilitate the implementation of PAT applications in quality control.
The General Notices, General Methods and General Chapters of the Ph. Eur., which provide legally binding quality standards in 38 European countries, have been revised or elaborated to provide state-of-the-art methods and to support PAT applications.

FLEXIBILITY (GENERAL NOTICES)

Flexibility is provided by the General Notices, which apply to all texts of the Ph. Eur.

- **Alternative methods (first introduced in 1988)**

Compliance with Ph. Eur. reference methods is required, but alternative methods may be used, if the same pass/fail result is achieved. Approval from the competent authority is needed in any case.

- **Waiving of tests**

Tests may be omitted based on validation data or other suitable justification.

- **Parametric release (1997), Enhanced approaches (2014)**

The General Notices allow an enhanced approach to quality control using PAT and/or real-time release testing strategies as an alternative to end-product testing.

MODERN METHODS

- **Uniformity for large sample sizes (2012)**

Chapter 2.9.47 allows sample sizes that are markedly larger than 30 units to be tested for Uniformity of Dosage Units (UDU). It is considered that compliance with this chapter demonstrates compliance with 2.9.40, the UDU test that uses small sample sizes.

- **Near-Infrared Spectroscopy (2013)**

Chapter 2.2.40 introduces PAT concepts and is complemented by the relevant EMA guideline.

- **Raman Spectroscopy (2016)**

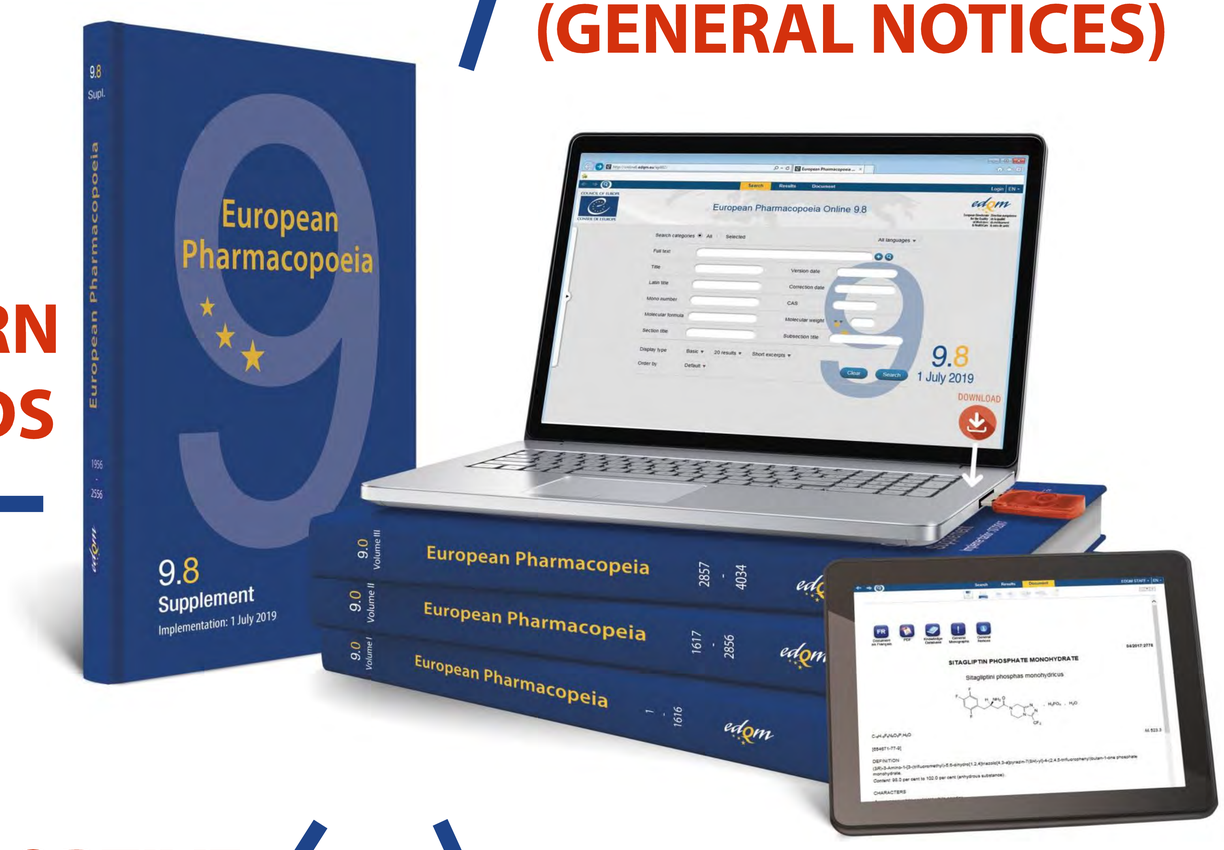
Chapter 2.2.48 covers the potential use of this technique within a PAT environment, including hand-held instruments. It further describes updated requirements adapted to different instrument types.

- **Alternative microbiological methods (2017)**

Chapter 5.1.6 takes account of technological developments and provides information on the use of PAT.

- **X-Ray Fluorescence Spectrometry (2017)**
- **IR Absorption Spectrophotometry (2018)**
- **UV/Vis Spectrophotometry (2019)**

These chapters (2.2.37, 2.2.24 and 2.2.25) have been updated to take account of PAT applications and to introduce recent instrument usages. For example IR spectroscopy focusses on ATR and Fourier-transform transmission instruments.



SUPPORTIVE GENERAL TEXTS

- **5.21 Chemometric Methods Applied to Analytical Data (2015)**

Chemometrics has proven to be well suited for PAT and CM. The investigation of large data sets and processing of intricate signals requires alternative analytical tools to those used in a one-variable-at-a-time approach.

- **5.24 Chemical Imaging, CI (2017)**

CI can be used in process development, improvement or understanding as well as root cause analysis.

- **5.25 Process-Analytical Technology (2019)**

A dedicated chapter on PAT will be published in 2019. It introduces into the Ph. Eur. the concept of interfacing analytical techniques with a manufacturing process. This chapter defines the different interfacing modes and compares conventional testing with PAT. It also refers to the other Ph. Eur. texts that support PAT applications.

FUNCTIONALITY-RELATED CHARACTERISTICS

Functionality-related characteristics (FRCs) have regularly been included in non-mandatory sections of excipient monographs since 2005.
These sections highlight characteristics that may be critical material attributes for specific manufacturing processes like CM. Whether they are critical or not needs to be identified during development.
The introduction of FRCs contributes to the desired regulatory flexibility.

CONCLUSION

Ph. Eur. quality standards and requirements apply regardless of the control strategy. They not only ensure quality by end-product testing, but also allow and support QbD/PAT applications – essential for Continuous Manufacturing (CM) – to foster innovative approaches in the development and production of medicinal products and their ingredients. The upcoming general chapter 5.25 summarises the implementation of PAT in the Ph. Eur.

* Corresponding author email: dirk.leutner@edqm.eu

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