Reference: PA/PH/Exp. PAT/T (17) 2 ANP

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5.25. PROCESS ANALYTICAL TECHNOLOGY

1. INTRODUCTION

Process analytical technology (PAT) can be defined as a system for designing, analysing and controlling manufacturing processes through timely measurements (i.e. during processing) of critical quality attributes (CQA), and critical performance characteristics of raw materials, in-process materials and processes, in order to ensure the quality of the final product. It is important to note that the term 'analytical' in PAT is used in a broad sense to include chemical, physical and microbiological measurements conducted in an integrated manner and combined with data analysis. The goal of PAT is control of the manufacturing process and enhanced process understanding, guided by risk management. Interfacing manufacturing processes with analytical techniques is therefore essential in PAT, as it facilitates process development in accordance with quality by design (QbD) principles, enables real-time release testing (RTRT) and supports continuous manufacturing processes.

Time delays between obtaining a sample for testing, analysis of that sample and any consequent outcomes must be taken into consideration when applying PAT. When the analytical results are used on a continuous basis to monitor and control a process, it is important to minimise such delays. This can be achieved most effectively with sensor-based continuous measurement systems directly interfacing with the process stream during a specific unit operation. The sensors continuously measure the process conditions and material characteristics within the process environment (*in situ*) and send the measured data (e.g. a spectrum) to an operating system where it is recorded and analysed, and where any necessary adjustments to processing conditions can be determined on a continuous basis. These *in situ* measurements can generate very large volumes of data representative of the process.

2. PROCESS ANALYTICAL INTERFACING MODES

The interfacing of analytical techniques with the manufacturing process is central to the application of PAT.

The terms 'off-line', 'at-line', 'on-line' and 'in-line' describe interfacing modes (see Figure 5.25.-1), and examples of their uses are given in Table 5.25.-1. Measurements using on-line and in-line systems generally support rapid and automated process adjustments. Results generated by analytical equiment interfaced with a process can be used for automated feedback or feedforward loops ensuring that the process is kept under control.

Off-line measurements

These correspond to conventional analytical testing in which the sample is removed from the manufacturing process environment and tested in a laboratory, typically located away from the production environment. This transfer of samples away from the process stream can result in a significant time lag and does not permit immediate process adjustments.

At-line measurements

With at-line measurements, the sample is also removed from the process stream for testing, but the testing equipment is usually located within the production environment, i.e. in close physical proximity to the process stream, and testing can therefore take place without delay. This results in a shorter time frame for obtaining information, thereby distinguishing at-line measurements from off-line measurements. It is therefore possible to make process adjustments based on the results of at-line measurements.

On-line measurements

On-line measurements typically involve sensor-based measurements made under real-time conditions by diverting a portion of the process stream into a measuring device.

Depending on the nature of the test, e.g. whether or not it is detrimental to the product, the diverted portion may be returned to the process stream or may be discarded after testing.

In-line measurements

In-line measurements are taken by placing measuring devices, typically sensors, directly into the process stream, meaning no portions of the stream are removed.

In-line measurements must also be non-detrimental to the product.

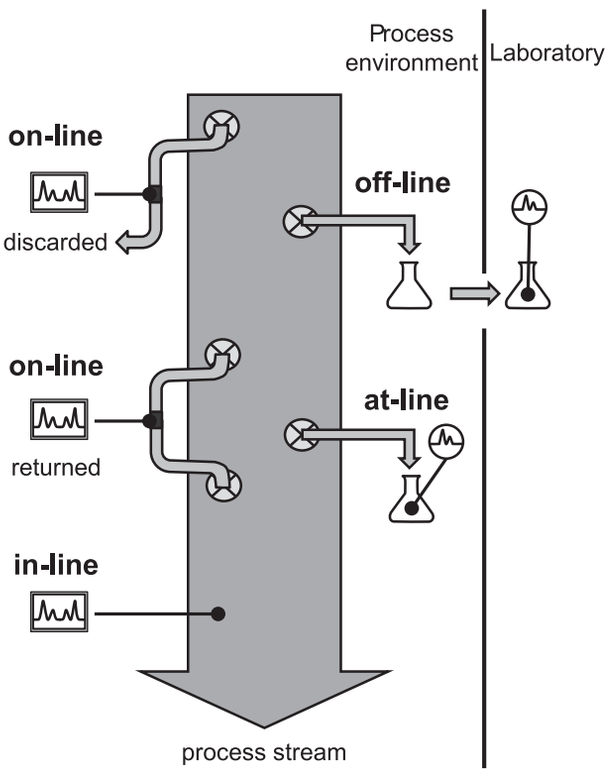

Figure 5.25.-1. – *Process analytical interfacing modes*

Table 5.25.-1. – *Examples of interfacing options*

Process interface	Unit operation and purpose	Measuring system	Typical result turnaround time
off-line	Reaction end-point detection for a chemical synthesis	HPLC/GC	hours to days
	Blend uniformity by thief sampling	HPLC	
at-line	Testing weight and content during tablet compression	Gravimetry and transmission NIR spectroscopy	minutes to hours
on-line	Reaction monitoring	Transmission probe installed in a bypass coupled to a suitable spectroscopic system	seconds to minutes
	Cleaning verification	UV-Vis spectroscopy	
in-line	Drying process or blend uniformity	NIR spectroscopy	milliseconds to seconds
	Monitoring of a fermentation process (drug substance or metabolites)	Raman spectroscopy	

3. COMPARISON OF PROCESS ANALYTICAL INTERFACING MODES

Both off-line and at-line measurements are based on analysis of discrete samples removed from a process stream or bulk material. These samples are considered representative of the batch at the time they are removed. Frequent at-line measurements also provide data supporting the application of PAT, as they are carried out within a short time frame and in the immediate vicinity of the process stream.

Neither in-line nor on-line measurements involve sampling in the conventional sense. The tested portion might not be separated from the process stream, and is usually smaller than a conventional sample.

Scale of scrutiny must be considered and will determine the frequency and duration of each measurement. Furthermore, measurements can be influenced by physical attributes interfering with the acquisition properties of the measuring system. When measuring solids or suspensions, for example using spectroscopic methods, consideration must be given to the surface and bulk scattering properties of samples, and movement of the material. Influencing factors such as particle size, surface roughness and solid density can cause significant spectral differences, which must be taken into account when a method is designed and used in order to ensure that the process and material are described adequately.

One advantage of in-line and on-line modes is the fast acquisition of data, which allows a high frequency of measurements, thus enabling rapid continuous monitoring as well as immediate action and control of the process.

In some cases there is no direct correlation between sample properties measured by some PAT tools and the CQAs. The measurements may, however, serve to develop process trajectories which can be used to characterise the process and identify unusual behaviour. If the trajectories are used for the purpose of process control, the causal relationship with CQAs must be demonstrated, as measurments obtained using systems designed for this purpose are considered to be of higher impact.

While validation criteria for in-line or on-line measurements may be different from those of conventional quality control methods, the same validation principles apply. For example, the process and equipment design may restrict the conditions under which analytical validation can be performed.

4. STATISTICAL PROCESS CONTROL

Statistical process control (SPC) comprises a set of data analysis methods applied in order to monitor and control a process based on analysis of process variability (e.g. of CQAs). For PAT purposes, SPC can be used for real-time measurements, i.e. analysing process variability within a single batch, and can therefore be applied in order to take full advantage of the benefits of PAT.

SPC can be used, for example, to analyse the process and incorporate corrective actions (that ensure the process remains under control), to maintain optimal and stable process conditions, and to perform overall trend analysis of quality characteristics or process variables during either batch processes or, more particularly, continuous processes.

SPC outcomes can be used to measure process capability (i.e. the ability of a process to produce a product that complies with requirements) and process variability, with a view to reducing it through enhanced process understanding, thereby improving lifecycle management.

If only 1 CQA is of interest, univariate SPC methods are applied, whereas if several attributes are analysed together, multivariate statistical process control (MSPC) methods are used.

5. PH. EUR. TEXTS SUPPORTING THE APPLICATION OF PAT

Typically, the analytical techniques described in the Ph. Eur. include qualification criteria designed for off-line analytical systems. These criteria are not always relevant and practical in a PAT setting. However, certain general methods and general chapters (including *2.2.40. Near-infrared spectroscopy*, *2.2.48. Raman spectroscopy* and *2.9.47. Demonstration of uniformity of dosage units using large sample sizes*) support and promote the use of the techniques described in conjunction with PAT.

The following table is shown for information but will not be published in the European Pharmacopoeia.

Chapters revised or elaborated to support the application of PAT.

General chapter	Title	Publication
1.	General Notices	Ph. Eur. 8.2
2.2.25	Absorption spectrophotometry, ultraviolet and visible	Pharmeuropa 29.4
2.2.37	X-Ray fluorescence spectrometry	Ph. Eur. 9.3
2.2.40	Near-infrared spectroscopy	Ph. Eur. 8.0
2.2.48	Raman spectroscopy	Ph. Eur. 8.7
2.9.47	Demonstration of uniformity of dosage units using large sample sizes	Ph. Eur. 7.7
5.1.6	Alternative methods for control of microbiological quality	Ph. Eur. 9.2
5.21	Chemometric methods applied to analytical data	Ph. Eur. 8.7
5.24	Chemical imaging	Ph. Eur. 9.3

General Notices

In section 1.1 under Demonstration of compliance with the pharmacopoeia, it is stated that a substance can be demonstrated to be of pharmacopoeial quality on the basis of product design, together with its control strategy and data derived, for example, from validation studies of the manufacturing process.

Furthermore, it is also stated that an enhanced approach to quality control could utilise PAT and/or real-time release testing strategies (including parametric release) as alternatives to end-product testing alone.

Absorption spectrophotometry, ultraviolet and visible

General chapter *2.2.25* covers the use of PAT in the UV-Vis range using modern detectors such as photodiode arrays (PDA) or charge-coupled devices (CCD). Both transmission and diffuse reflection measurement modes are possible with off-line, at-line, on-line and in-line measurements. The table with reference wavelengths for the control of wavelength accuracy includes wavelengths in the UV range down to 180 nm.

X-ray fluorescence spectrophotometry

General chapter *2.2.37* includes references to modern equipment and the current applications of the XRF technique.

Substantial advances in miniaturisation and automation have led to the development of hand-held energy dispersive XRF (ED-XRF) spectrometers for rapid field measurements. In addition, as XRF is potentially non-destructive, it lends itself to in-process testing and in particular, applications of PAT such as the analysis of unwanted trace catalysts in active pharmaceutical ingredients (API).

Near-infrared spectroscopy

General chapter *2.2.40* takes into account the increasing use of NIR spectroscopy for process monitoring and control, and the development of modern NIR spectrometers. NIR measurements can be performed off-line, but the technique also lends itself to at-line, on-line and in-line testing.

The ‘Sample preparation/presentation’ section includes moving materials or samples, and the use of fibre-optic probe systems in different measuring modes (i.e. transmission, diffuse reflection and transflection). The use of internal referencing for process analysis purposes is permitted when it is impossible to remove a probe for reference background data collection. A detailed table for the control of instrument performance depending on measuring mode and instrument used (benchtop, mobile or process instrument) is also provided. The chapter includes a section on qualitative analysis for identification and characterisation of a substance in addition to sections on limit analysis (e.g. for dryer end-point control) and trend analysis (for monitoring blend uniformity).

Raman spectroscopy

General chapter *2.2.48* includes the many recently developed Raman technologies that have potential uses for the application of PAT, including hand-held instruments.

Wavenumber shifts and acceptable tolerances for the reference materials cyclohexane, paracetamol and polystyrene (values derived from an inter-laboratory study) are described for both bench-top and hand-held Raman systems.

Demonstration of uniformity of dosage units using large sample sizes

General chapter *2.9.47* allows the determination of dosage unit uniformity in a PAT environment where the sample size is markedly greater than 30 units.

Compliance with the acceptance criteria of general chapter *2.9.47* is considered as evidence that the batch would also comply with general chapter *2.9.40. Uniformity of dosage units* if tested using a small sample size (e.g. 30-unit). Therefore, general chapter *2.9.47* does not constitute stand-alone acceptance criteria.

Alternative methods for control of microbiological quality

General chapter *5.1.6* describes alternative methods that might be used for the application of PAT in order to contribute to real-time or near-real-time microbiological quality control (e.g. test for microbiological examination of non-sterile products or for sterility based on laser-induced fluorescence) of in-process samples, active substances, medicinal products or excipients (particularly water). The chapter also provides guidance on how to validate these alternative methods.

Chemometric methods applied to analytical data

Chemometrics (*5.21*) has proven to be well suited for PAT. The investigation of large data tables and treatment of intricate signals, i.e. data collections with a hidden structure, of the type accumulated during measurements in PAT setups, requires alternative analytical tools to those used in a one-variable-at-a-time approach.

Chemical imaging

Chemical imaging (CI) (*5.24*) can be used to support PAT applications. CI measures spatial distribution and contributes to the understanding of the properties of materials such as finished products, pharmaceutical intermediates, excipients, APIs and starting materials.

The uses of CI include, for example, detection of defects such as cracks in tablet coatings and identification of foreign particles. It is a versatile tool used in process development and improvement, root cause analysis (e.g. for out of specification results), and may also be used to enhance process understanding.