Techno Pharm
Fokus: Messen/Steuern/Regeln

A Case Study to Introduce Process Analytical Technologies in Pharmaceutical Manufacturing

Dr. Hubertus Rehbaum • Dr. Rehbaum Technology Consulting, Berlin

Correspondence: Dr. Hubertus Rehbaum, Dr. Rehbaum Technology Consulting, Friedrichstr. 68, D-10117 Berlin;
e-mail: h.rehbaum@rehbaum.info

Abstract

Today, Process Analytical Technologies (PAT) are well recognized as a set of tools within the pharmaceutical industry. However, the application for in-line or on-line measurements did not find the same response throughout the industry. Instead, the level of implementation ranges from a few pharmaceutical manufacturers using PAT as a key tool in the quality control process to many companies not yet engaging in the use of PAT at all. This article provides an overview on PAT, followed by an analysis for the use case of upgrading a container blending process with PAT. As such it is meant to be a guideline for management, technical operation and quality assurance in the understanding and decision towards the introduction of PAT.

Key Words

- OSD Secondary Manufacturing
- PAT
- Quality by Design
- Spectroscopy
- Data Processing
- MVA

Introduction

The concept of the Process Analytical Technologies (PAT) for the pharmaceutical industry started more than 15 years ago, although the technologies such as Near-InfraRed (NIR) spectroscopy have been used for much longer. One of the key drivers was the U.S. Food and Drug Administration (FDA), which in 2004 released a 'Guidance for Industry' [1] as part of their PAT initiative. It is important to emphasize that PAT cannot be reduced to the use of analytical instruments such as NIR spectroscopy in a laboratory environment. Instead, PAT must be understood as a holistic approach to design, analyze and improve the production processes by monitoring Critical Process Parameters (CPPs) and Critical Quality Attributes (CQAs), to use the information gained in controlling the processes. The PAT-based process control targets improved drug quality and increased efficiency of the manufacturing process while minimizing product loss. Obviously, PAT and Quality by Design (QbD) complement each other [1].

To exploit the full potential of a holistic PAT approach especially for commercial manufacturing, the complexity increases significantly. That is, the analyzer equipment, the process machine with integrated recipe management and control system, as well as the pharmaceutical product itself must be considered together to design a new, PAT-enabled process.

The technical component further needs to be augmented by knowledge and experience on the use of equipment, data processing and interpretation. Only then, the benefits of PAT and the return on investment can be achieved.

This obviously applies both for primary and secondary manufacturing. For simplicity, this article will focus on batch-oriented secondary manufacturing of oral solid dosage forms and use blending as an exemplary unit operation to be equipped with PAT.

Autor

Dr. Hubertus Rehbaum

Dr. Hubertus Rehbaum studierte Elektro- und Informationstechnik (Dipl.-Ing.) sowie Betriebswirtschaftslehre (Dipl.-Wirt.Ing.) an der RWTH Aachen. Während seiner Promotion in Angewandter Informatik an der Georg-August-Universität Göttingen entwickelte er Algorithmen für die Analyse von Biosignalen zur Steuerung von Handprothesen. Mit der Stelle als Manager Scientific Operations bei L.B. Bohle wechselte er anschließend in die Pharmaindustrie, um dort den Fokus auf Softwaresysteme, Automatisierung und PAT zu legen. Seit 2016 arbeitet er als freiberuflicher Technologieberater für die Pharmaindustrie.

TechnoPharm 7, Nr. 3, 138–143 (2017)

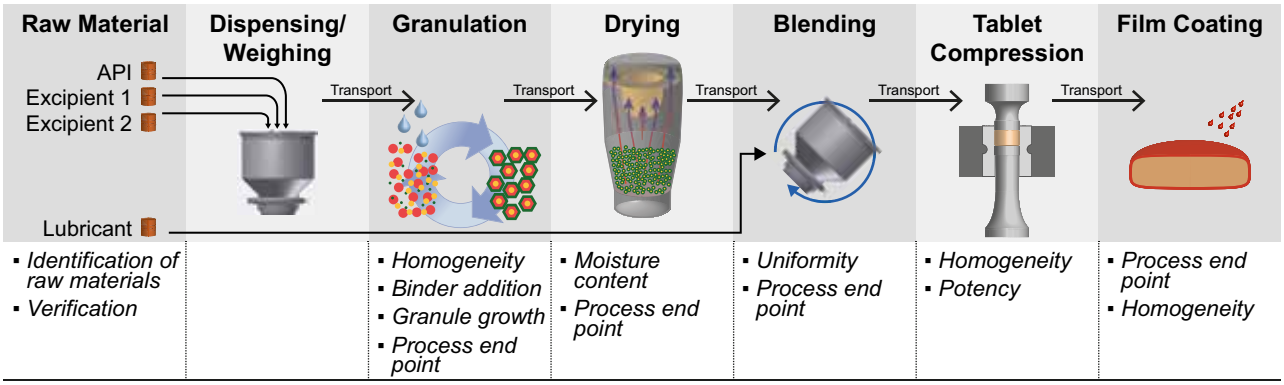

Figure 1: Overview of PAT applications established in the pharmaceutical industry (source: Dr. Rehbaum Technology Consulting).

PAT Applications in the Pharmaceutical Industry

With the use of different analytical technologies (such as NIR or Raman spectroscopy) successful applications have been implemented in secondary manufacturing for all unit operations. A non-exhaustive overview is provided in Fig. 1. Widely spread PAT applications are in batch process equipment for blending and fluid bed processing, especially using NIR for process end point detection.

After all, for all given applications the potential is to improve the manufacturing process towards increased product quality and reduced costs along the entire processing chain.

But, PAT by itself is a multidisciplinary topic, requiring knowledge and experience in the following areas:

- Process equipment and production processes
- Analyzer equipment (e.g. NIR, Raman spectroscopy or special image processing)
- Data processing, Multivariate Data Analysis (MVA) and quality data management in regulated environments
- Process control design, software interfaces and system integration

While selected vendors for processing equipment offer PAT-enabled systems, these off-the-shelf solutions will only in few cases meet the actual requirements of the pharmaceutical manufacturer. In the end, PAT should also be able to be installed as an upgrade on existing process equipment. Consequently, in most cases the system owner will have to invest own knowledge and resources to successfully introduce PAT.

For this reason, the questions and challenges resulting from an upgrade scenario for batch blending are outlined in the following, but they also apply to any other unit operation.

PAT for Batch Blending

This example covers the case of an existing or newly purchased container blender for a drug product, to be equipped with NIR for in-process monitoring. The pharmaceutical manufacturer (further referred to as client) aims at stopping the blending process based on CQAs acquired.

Current Blending Process

Until now, all blending processes at the client are performed using container blenders, like the equipment shown in Fig. 2. The production recipes are characterized by the given rotational speed as well as the process time. At the end of the process, samples [2] are taken to be analyzed in the laboratory, e.g. using high-performance liquid chromatography (HPLC), and used to approve the intermediate product.

The CQAs determined in the laboratory are the Active Pharmaceutical Ingredient (API) content (%) in all samples taken and thereby homogeneity. As such, the client uses state of the art methods for pharmaceutical production.

Motivation for PAT

Expectations towards a PAT-enabled blending process originate both from a quality and cost perspective. Considering the quality, the sampling from the container has an inherent risk for uncertainties. Moreover, manual processing and analysis in the laboratory imply a risk for human errors.

Furthermore, laboratory work can require hours or even days, thus increasing the lead time significantly. If

Figure 2: Exemplary container blender (source: L.B. Bohle).

the laboratory results reveal insufficient quality attributes, either the blending process must be repeated or the product is discarded. In any case, this causes increased costs and additional delays for manufacturing.

Using PAT based on NIR spectroscopy, an in-process assessment of the CQAs (API content or blend homogeneity) replaces the manual sampling and laboratory analysis. Thus, not only the human error factor is removed, but also the CQAs are acquired instantaneously during the manufacturing process.

But for successful implementation, technical challenges need to be resolved. Furthermore, process-specific knowledge and chemometric modeling have to be established. Finally, also the PAT approach requires a validated process, as does the existing approach.

Mechanical Integration of NIR

NIR spectroscopy equipment can be purchased off the shelf from various vendors (e.g. Bruker, Brimrose, Sentronic, Viavi), featuring angle sensors, in-built PCs with battery and wireless connectivity. Ideally, no product contact is required, reducing also the requirements for the NIR equipment. Instead, the mechanical port to connect the probe to the blending container, ensuring a consistent and representative sample presentation, should be resolved with the supplier of the container. Typically, a modified container lid with a sapphire window and port (e.g. tri-clamp) to receive the NIR probe head will be supplied by the equipment vendor. Therefore, whenever the container is upside down, the window is covered by product, which is why a sample is taken automatically by the spectrometer and made available for processing and analysis.

With the mechanical connection established, the NIR spectral data can be acquired from the process.

Software Integration and Data Processing

In contrast to the selection of the analyzer hardware and mechanical integration, the data processing and software integration implies a much higher customization and depends on expectations and knowledge level of the client. But the raw data processing and MVA to extract the CQAs can be separated from the technical software integration.

Data Analysis and CQA Extraction

The multivariate NIR spectrum acquired by the analyzer does not provide direct insight on the actual process or CQAs. Instead, the spectral data needs to be processed and interpreted using multivariate data analysis based on chemometric modeling including data pre-processing. This is illustrated in Fig. 3 for the assessment of blend uniformity.

Thus, the client has to decide on the MVA software product and develop the chemometric model. Still, chemometric model building requires training and sufficient experience of the chemical properties to be analyzed. If the necessary knowledge is not available among staff, it must either be acquired or external service providers can be used for model building. It is important to stress that very often the chemometric model is process-specific. A change of the product or even the raw material supplier for an existing product typically requires the chemometric model and parameters to be adjusted. Furthermore, acquisition of reference data for model building should be planned and carried out based on the targeted CQAs and expected information content.

PAT Architecture

With the analyzer equipment in place and the chemometric model developed, still the gap between the acquired CQA and the control system of the process unit remains. Therefore, the second and often most complex task is the design of the allover data infrastructure and modification of the machine's automation system. Three different scenarios can be considered:

- The simplest option is to not have any integration between PAT data acquisition with MVA and the process machine. That is, PAT data acquisition and processing is operated as a standalone system, displaying the CQA on a computer screen. If the CQA is used to terminate the process, it is within responsibility of a human operator to transfer the result to the control system of the process machine. This is illustrated in Fig. 4. Obvi-

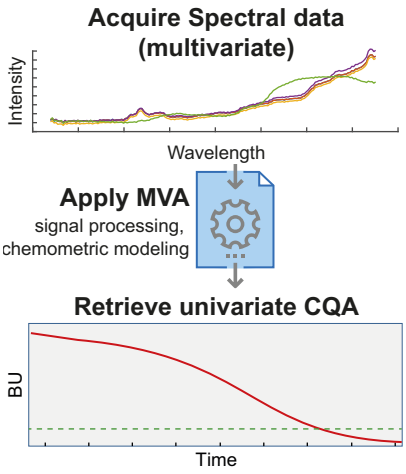

Figure 3: Extracting blend uniformity (BU) as CQA from multivariate spectral data (source: Dr. Rehbaum Technology Consulting).

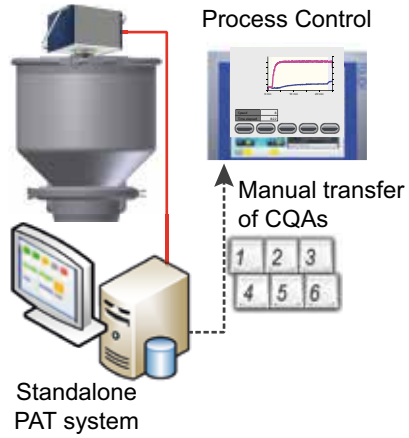

Figure 4: Basic PAT setup without any integration (source: Dr. Rehbaum Technology Consulting).

ously, this solution bears the same risks for human errors as the state of the art model. It should only be considered during an evaluation phase or during process development.

- A more advanced solution is to establish a data connection between the standalone PAT setup and the process control system as shown in Fig. 5. For this approach, often the proprietary software of the analyzer vendor can be used, implying a vendor-specific solution. In this scenario, the CQA is provided digitally to the control system and used to end the process automatically. Drawbacks of this solution are dependency on the software of the analyzer vendor and, in case of expanding PAT usage, multiple isolated systems to be maintained.

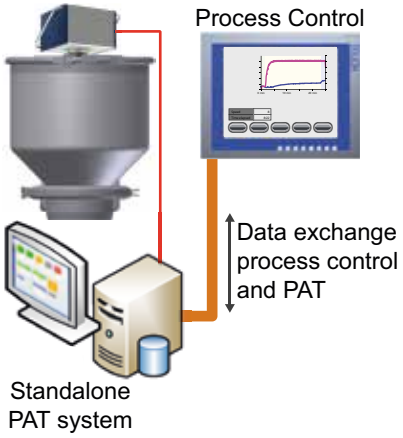

Figure 5: Standalone PAT system with vendor specific data integration (source: Dr. Rehbaum Technology Consulting).

- Finally, a complete PAT data management infrastructure can be established, serving multiple process machines and analyzers (Fig. 6).

This implies using a third-party solution such as Optimal synTQ or Siemens SIMATIC SIPAT, providing vendor-independent PAT data acquisition, processing and storage.

Data acquisition is not limited to the CQAs by the analyzer, but bi-directional connections with the control system of the unit operations can be used to augment quality data by process information.

Especially for companies considering using PAT in several unit operations, this approach allows for centralized management of data, processing and knowledge. The centralized PAT data management can be used to generate comprehensive reports, track CQAs and CPPs along the processing chain and harmonize the technologies.

Obviously, the decision on the PAT data architecture depends on the current and future strategy of each client.

Connectivity to Process Control System

For both the vendor specific standalone integration and the centralized PAT data architecture, a data connection must be established to the control system of the unit operation. This includes the Programmable Logic Controller (PLC) and/or Human Machine Interface (HMI), therefore affecting also validation of the equipment. In most cases, control loops are added on unit operation level to receive and process the quality information at hand, for instance to compare them to threshold or target values in the recipe. Consequently, this step implies to modify the existing PLC code, HMI design and recipe management. Such software modification requires the original source code or support of the system manufacturer to be available. Obviously, modifications must also be specified, aligned with requirements of the PAT analyzer equipment and communicated to the implementing entity.

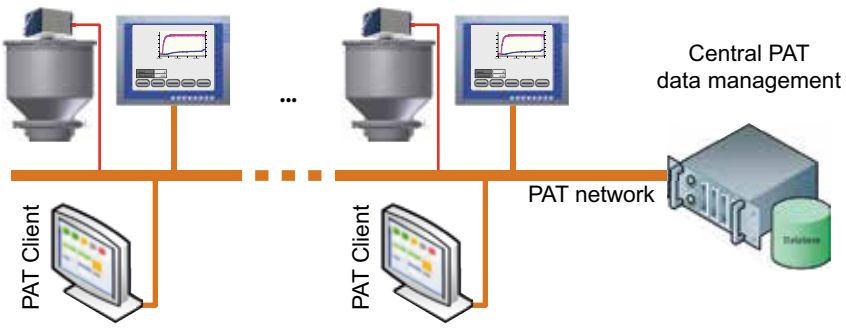

Figure 6: Centralized PAT data architecture with full integration into process control (source: Dr. Rehbaum Technology Consulting).

Conclusion

As shown in this article, introduction of PAT requires a multidisciplinary toolset, with thorough understanding of the topics process analyzers/spectroscopy, data management, process equipment and control systems. Targeting a seamless integration between PAT systems and the control systems of various unit operations, software modifications and defining the interfaces become increasingly critical.

Although the example shown above considers a very applied approach, introduction of PAT should be advanced strategically. That is, a long-term PAT strategy including a roadmap has to be developed for the client. This strategy has to consider factors such as existing knowledge, product portfolio, product innovation and company size. Only then, a lasting PAT roadmap can be derived, avoiding disappointment and overspending.

Critical decisions to be made in this PAT strategy are:

- Unit operations and viable product for implementation roadmap
- Integration level for process control
- PAT data architecture
- Chemometric modeling (make-or-buy decisions)
- Maintenance of PAT models

- Reporting of CQAs and CPPs (centralized vs. local)
- Regulatory considerations and current Good Manufacturing Practice (cGMP) or Good Automated Manufacturing Practice (GAMP)
- Validation

In conclusion, pharmaceutical companies are suggested to seek professional advice on technologies and requirements allowing them to successfully introduce PAT and eventually build up internal working groups which suit their business cases and capabilities best.

References

[1] U.S. Department of Health and Human Services, FDA: Guidance for Industry; PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance, *https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070305.pdf* (last access: 20/04/2017).

[2] Muzzio et al, Sampling and characterization of pharmaceutical powders and granular blends, Int. Journal of Pharmaceutics 2003, *http://doi.org/10.1016/S0378-5173(02)00481-7* (last access: 20/04/2017).

Redaktion: Chefredakteur: Claudius Arndt, Redakteur: Jens Renke. Verlag: ECV · Editio Cantor Verlag für Medizin und Naturwissenschaften GmbH, Baendelstockweg 20, 88326 Aulendorf (Germany). Tel.: +49(0)81 91-9 85 78 12, Fax: +49(0)81 91-9 85 78 19. e-mail: redaktion-tp@ecv.de. http://www.ecv.de.
Herstellung: Reemers Publishing Services GmbH / Holzmann Druck GmbH & Co. KG.