

Successful Introduction of PAT Requires a Strategy

By Dr. Hubertus Rehbaum, Pharma/Life Sciences Consultant



Dr. Hubertus Rehbaum

For the past years, Process Analytical Technology (PAT) has been a hot topic in pharmaceutical production, both considering product development and commercial manufacturing. PAT summarizes the concept and technologies to design, analyze, and control the production processes by monitoring process parameters and Critical Quality Attributes (CQAs) of the product. One of the key drivers for PAT in the USA was and still is the PAT initiative by FDA¹, targeting to improve drug quality and efficiency of manufacturing processes, while minimizing the loss of product during production. This is achieved by an in-depth process understanding to identify and control critical manufacturing steps, based on quality information extracted using PAT. Consequently, PAT and Quality by Design (QbD) complement each other. As result of the initiative, the regulatory framework for PAT was summarized in the corresponding guidance for industry², published in 2004.

Frequently, PAT is reduced to the use of measurement systems such as Near-infrared (NIR) spectroscopy as a common sensor, e.g. for monitoring or verification in a laboratory environment. As such, PAT is simplified to the level of using a thermometer to check the water tem-

perature. In reality however, to exploit the full potential of a holistic PAT approach especially for commercial manufacturing, the complexity increases significantly. That is, the analyzer equipment, 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. Only then, the benefits of PAT and the return on investment can be achieved.

After all the efforts are worth it, as the potential to improve the manufacturing processes towards increased product quality and reduced production costs is along the entire production chain. In **Figure 1**, a non-exhaustive overview of established PAT applications in secondary manufacturing of OSD is provided for convenience.

As indicated before, PAT is a multidisciplinary technology built on the following technologies:

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

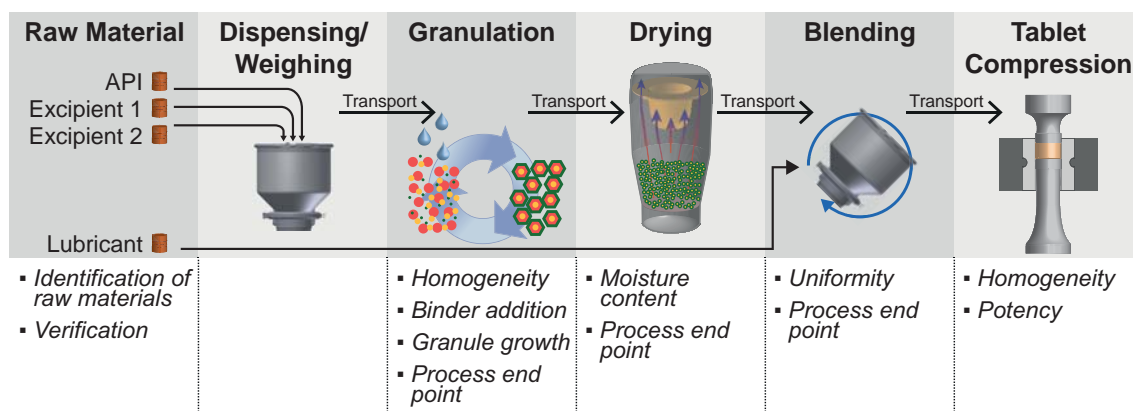


Figure 1: Overview of established PAT applications in the pharmaceutical production environment under GMP conditions.

Nowadays, a few selected equipment suppliers offer processing equipment either prepared or even equipped for PAT integration as an option. But in most cases, the system owner is left to source and integrate the technologies themselves, especially if existing equipment is retrofitted. From an economic perspective, the upgrade of existing, proven unit operations is more likely than the purchase of a new unit operation. For this reason, such an upgrade scenario is considered and discussed in the following:

STATE OF THE ART

The example considered is a pharmaceutical company (further referred to as customer), intending to upgrade an existing fluid bed dryer with NIR. The current production processes include a sampling step, where product retrieved from the process is analyzed for product moisture as Critical Quality Attribute (CQA), using Loss on Drying (LoD)³. In this case, the operator(s) must perform both sampling and analysis. Based on the assessed product moisture content, the drying process is stopped using the machine's user interface. Of course, the sampling and manual analysis implies a risk for human errors. Similarly, the analysis with LoD is time-consuming (up to a few minutes). Still, this scenario represents the state of the art found in pharmaceutical production.

TRANSITION TO A PAT-ENABLED PROCESS

Using PAT based on NIR spectroscopy, an in-process measurement of the CQA (product moisture) will replace the manual sampling and analysis. The output is, therefore, an equivalent value to the LoD measurement but has several advantages. For instance, multiple measurements can be performed per minute and the CQAs are available instantaneously. Similarly, as the measurements are performed non-destructively in the process, no product is lost as in the case of manual sampling. If it comes to the NIR spectroscopy equipment, this can be purchased off the shelf from various vendors (e.g. Sentronic or Bruker). But the actual implementation requires to consider various perspectives:

Firstly, the technical clarification of the probe integration must be performed, i.e., a mechanical port to mount the probe and ensure a consistent and representative probe presentation. Ideally, an existing port can be used, avoiding the need for mechanical modifications to the process machine. The successful mechanical integration provides the basis to acquire NIR spectra from the process.

But the multivariate NIR spectral data does not deliver direct insight on the process or CQAs. Instead, acquired spectral data needs to be interpreted using MVA/chemometric modeling, to extract the qualitative or quantitative, univariate information such as the product moisture content. This is illustrated in **Figure 2**. For this purpose, the customer must decide on the MVA software and

development of the chemometric model. Furthermore, the chemometric model building requires training and sufficient experience, but it can alternatively be purchased as an external service. It is important to underline that each model is process specific. A change of the product and even raw materials often implies the chemometric model to be updated.

With the analyzer equipment in place and the chemometric model developed, still, the gap between the acquired CQA and the automation system of the process machine 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. Roughly three different scenarios can be considered:

1. The most basic option is to not have any integration between PAT data acquisition with MVA and the process machine. That is, the 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 the responsibility of a human operator to transfer the result to the control system of the process machine. This is illustrated in **Figure 3**. Obviously, this solution bears the same risks for human errors as the state of the art.

2. A more advanced solution is to establish a data connection between the standalone PAT setup and the process control system as shown in **Figure 4**. In this scenario, the CQA is provided digitally to the control system and used to terminate the process. Typically, this also includes merging audit trail and reporting.

3. Finally, an entire PAT data management infrastructure can be established, serving multiple process machines and analyzers, see **Figure 5**. Especially for companies intending to PAT-enable various process machines and allow for a centralized management, this option is highly recommended. The centralized PAT data management can be used to generate extensive reports, track CQAs along the processing chain and harmonize the technologies.

While the decision on the PAT data infrastructure is a strategic question, the last two scenarios typically require a modification of the process control system. This

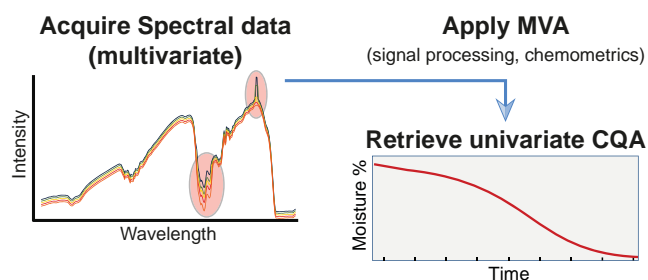


Figure 2: Multivariate data needs to be processed, to extract qualitative or quantitative, univariate CQAs.

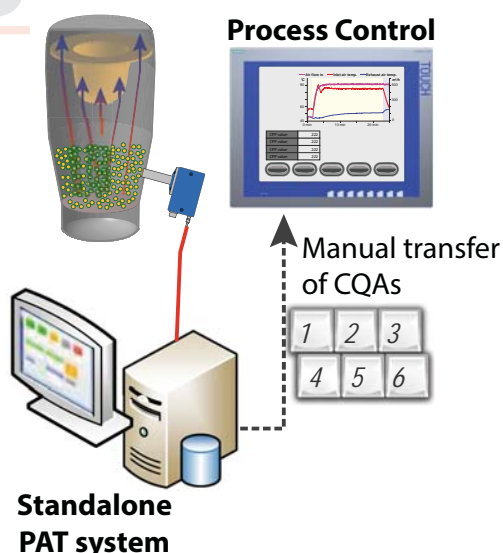


Figure 3: Basic PAT setup without any integration

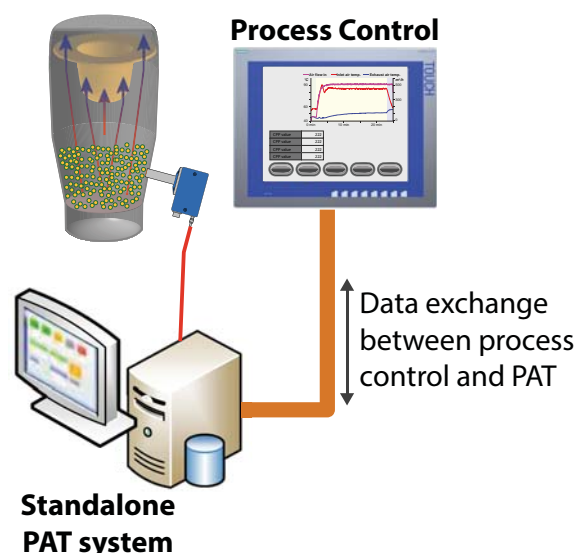


Figure 4: Standalone PAT system with data integration

includes the Programmable Logic Controller (PLC) and Human Machine Interface (HMI), affecting therefore also the validation of the equipment. Control loops must be added to accept and process the CQAs, for instance, compare them to target values in the recipe. Consequently, this step implies to modify the existing Programmable Logic Controller (PLC) code. This software modification typically requires the original source code to be available or support of the original supplier. Obviously, the modifications must also be specified clearly and aligned with requirements of the PAT analyzer equipment.

An overview of a PAT data infrastructure with integration to the control logic is **Figure 6**.

From the process as well as PAT instrumentation, data is acquired and provided to the MVA for interpretation. In case of the fluid bed drying process, this will extract the product moisture content as CQA. This quality information is finally fed back to the automation system, to be used in the phase control to terminate the process once the target moisture level is reached. The PAT data structure must, of course, comply with industry standard, including audit trail, data storage, and user policies.

PAT STRATEGY AS A STARTING POINT

Obviously, to run such a project successfully in-house, the team must have a thorough

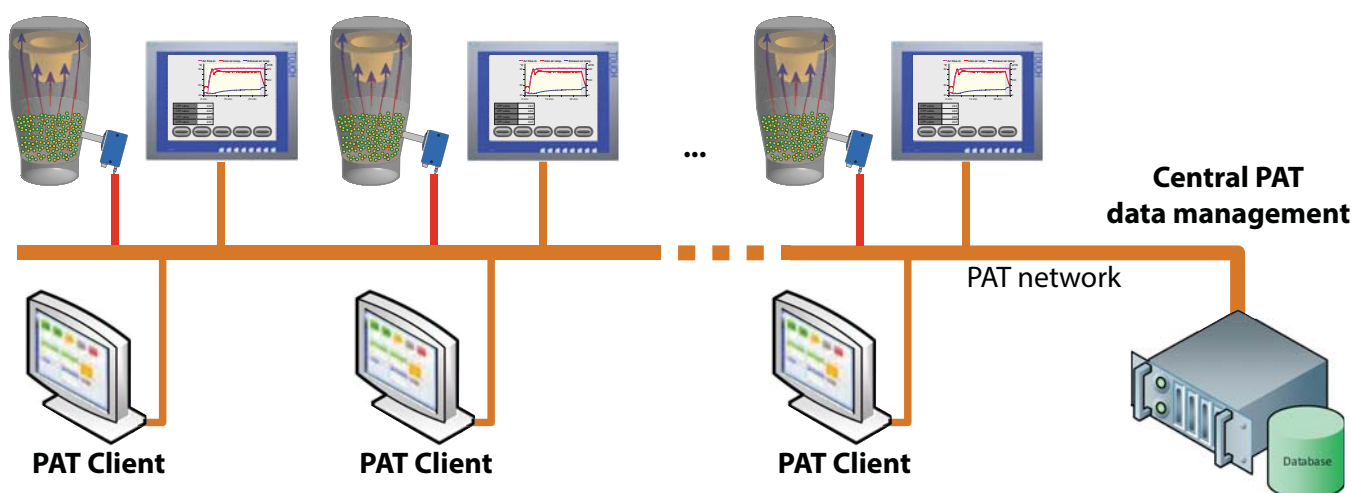


Figure 5: Centralized PAT data management

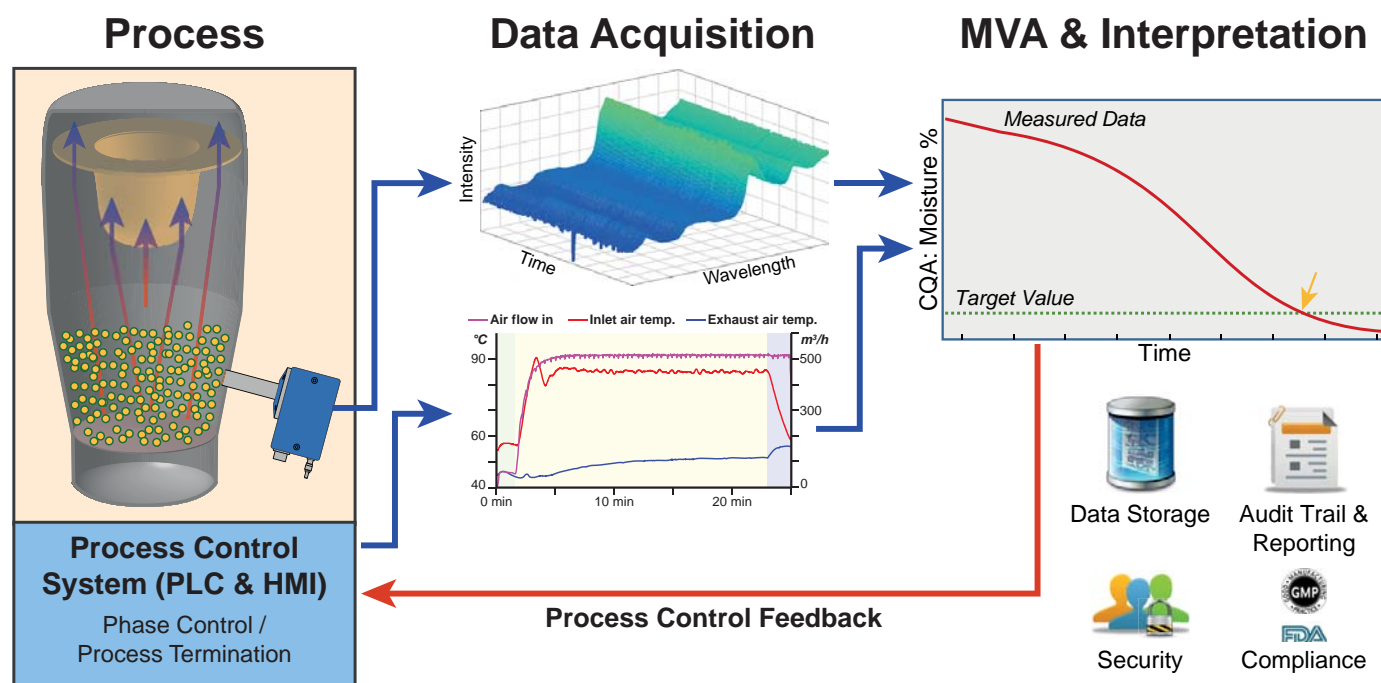


Figure 6: PAT data infrastructure with integration into process control logic

understanding of the topics process analyzers/spectroscopy, data management, process equipment, and control systems. Especially the software interfaces between PAT and PLC of the unit operation must be specified, based on thorough understanding of both software environments. The customer must be aware of this and be sure to understand the different requirements, to then coordinate between the vendors to ensure data exchange between NIR system, model engine and unit operation.

Although the previous example considers a gradual implementation, the correct approach towards PAT should be much more strategic. That is, a long-term PAT strategy including roadmap must be developed for the company. This strategy must 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 in this PAT strategy are:

- Unit operations and product candidates for implementation roadmap
- Integration level for process control
- PAT data infrastructure (standalone vs. centralized)
- Chemometric modeling (make or buy)
- Maintenance of PAT models
- Reporting of CQAs and CPPs (centralized vs. local)
- Regulatory considerations and cGMP/GAMP

CONCLUSION

Introducing PAT as an integrated approach towards improved quality and process control is a complex and difficult project. While the analyzer equipment is proven and available on the market, the chemometric modeling and software integration within a regulated manufacturing environment represents the major challenge. Furthermore, the establishment of necessary resources, knowledge, and qualification must be accounted for.

The implementation of a PAT strategy and roadmap ensures that the project execution does not surprise the team and stakeholders. And with a dedicated strategy the PAT architecture is prepared from the beginning to fit the future needs and plans for the company. Most importantly, the implementation team will be sure to have the necessary skill sets to tackle the actual introduction.

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

REFERENCES

- ¹ <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm088828.htm>
- ² <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070305.pdf>
- ³ <https://hmc.usp.org/sites/default/files/documents/HMC/GCs-Pdfs/c731.pdf>

2017 OSD CONTINUOUS MANUFACTURING TECHNOLOGIES TOUR

Participating Companies and Contacts



Driam USA, Inc.

181 Access Road
Spartanburg, SC 29303
864-579-7850
www.driamusa.com
Adam Stearns
info@driamusa.com

INTERPHEX Booth No. 2771



GEA North America

9165 Rumsey Road
Columbia, MD, 21045
844-432-2329
www.gea.com
Tim Hoover
Tim.Hoover@gea.com

INTERPHEX Booth No. 2421



Gebrüder Lödige Maschinenbau, GmbH

Elsener Strasse 7-9
DE-33102, Paderborn, Germany
310-918-6772
www.loedige.de
www.modwave.com
Par Alnhem
par.almhem@modwave.com

INTERPHEX Booth No. 3063



Glatt Air Techniques, Inc.

20 Spear Road
Ramsey, NJ 07446
201-825-8700
www.glatt.com
Mark Garber
Mark.Garber@glatt.com

INTERPHEX Booth No. 2505A



LB Bohle LLC

700 Veterans Circle, Suite 100
Warminster, PA 18974
215-957-1240
www.lbbohle.com
Martin Hack
m.hack@lbbohle.com

INTERPHEX Booth No. 3345