PAT leads the way in the adoption of continuous manufacturing processes

The use of data to gain actionable insight into manufacturing and processing activities, to optimise them and attain continuous flows, is at the heart of the fourth industrial revolution. In the chemical and biotechnology sectors, where complex chemical reactions and bio processes may be required to deliver key products, it is essential to have an in-depth, data-driven understanding of how critical process parameters (CPPs) influence a product's critical quality attributes (CQAs). To achieve this, businesses should implement Process Analytical Technology (PAT) strategies. In this way, they can manage the complexity of, and effectively control, their processes. This article describes the benefits of this approach and what should be considered when deploying PAT for continuous processing and manufacturing.

Martin Gadsby, CEO & Director at Optimal Industrial Technologies, and Flavio Belvedere, 2Co-Founder of ABCS Srl, looks at what the benefits of PAT are and the aspects to consider when deploying it.

The fourth industrial revolution, or Industry 4.0, is driving the digital transformation of business. For example, the latest advances in artificial intelligence (AI) and machine learning are supporting drug discovery and clinical trial evaluation by utilising their powerful data mining capabilities.[1] On the factory floor, manufacturers are seeing the benefits of connected machines, processes and systems as well as the power of Big Data. There is the potential to create intelligent networks along the value chain that can control each other and optimise production.

As a result, businesses can benefit from efficient, highly productive, self-automated manufacturing processes that are self-monitoring, able to both flag up and address anomalies in quality in real time. The outcome is a plant that operates at optimal conditions, maintains peak performance and produces high-quality product automatically.

In addition to improving existing production lines, the adoption of Industry 4.0 strategies allows businesses to make significant advances in their manufacturing, as they are given a unique platform to shift from batch to continuous processing. This involves integrating all process stages, without any interruption and minimal intervention from one step to another.

[1] Fleming, N. How artificial intelligence is changing drug discovery. Nature, 557(7707), S55–S57 (2018).

This approach heavily reduces downtime, in particular the time required for off-line quality control at the end of each manufacturing stage, which is replaced by continuous process verification and quality assurance. As a result, cycle times are shortened and higher volumes of end products can be delivered. Consequently, moving away from batch manufacturing can further optimise operations by reducing production times and manufacturing costs while increasing throughput.

For example, one study found that a plant producing active pharmaceutical ingredients (APIs) and formulating them into tablets, with a production scale of 2,000 tonnes per year, could reduce its capital expenditures (CAPEX) by up to 76% by moving from batch to continuous manufacturing.[2] Similarly, another study investigating the production of two APIs, ibuprofen and artemisinin, estimated operating expenses (OPEX) savings of up to 51.6% and 29.3% for continuous operations.[3]

Continuous processes operate in a quasi-steady state, where the stages are not independent and fixed, but rather dynamic and interconnected. Therefore, continuous manufacturing requires control systems that are able to constantly monitor product quality to ensure that a suitable output is fed to the following stage, from the characterisation of raw material being fed to the manufacturing line until the product is finished.

Industry 4.0 technologies that are necessary for continuous flow include real-time in-line and on-line analytics, Big Data semantics, factory and process automation as well as digital twins (or cyber-physical systems). The first two are necessary to obtain actionable insight and predictions about processes and operations. The acquired knowledge is then used by digital twins and automation equipment. While cyber-physical systems support the evaluation of various continuous production scenarios, the selection of the most suitable automated process control is also key to promptly adjusting processes to maintain optimal operating conditions.

The combination of these Industry 4.0 solutions for process improvement and intensification have something else in common. They all fall under the framework of PAT.

The importance of PAT

PAT is a Quality by Design (QbD)-driven approach that aims to deliver products of consistent and high quality by designing, analysing, and controlling manufacturing through timely measurements of the CQAs of raw and in-process materials as well as

[2] Schaber, S. D., Gerogiorgis, D. I., et al. Economic Analysis of Integrated Continuous and Batch Pharmaceutical Manufacturing: A Case Study. Industrial & Engineering Chemistry Research, 50(17), 10083–10092 (2011).
[3] Jolliffe, H. G. and Gerogiorgis, D. I. Plantwide design and economic evaluation of two Continuous Pharmaceutical Manufacturing (CPM) cases: Ibuprofen and artemisinin. Computers & Chemical Engineering, 91, 269–288 (2016).

CPPs. These not only act as quality assurance, but also lay the foundations for process understanding and continuous process verification.

In effect, the large volume of end-to-end material and process data regularly collected on the production line allows businesses to continuously assess and validate this information against regulatory guidelines. In this way, they can verify that their processes are always in their validated state to ensure regulatory compliance.

Even more, by correlating CPPs and CQAs, it is possible to determine how one influences the other as well as their impact on the output of each stage and, ultimately, on end product quality. As a result, process understanding can unlock statistical process control and quality prediction for manufacturers. More precisely, manufacturers can predict differences in product quality from variations in process conditions and ingredient properties. This ability, in turn, makes it possible to reduce product variability by maintaining target values within specific ranges.

Complexity as a resource

The correlation between CQAs and CPPs is complex, and it is only possible to describe it by using multi-factorial relationships. It is necessary to apply chemometrics, i.e. mathematical and empirical statistical methods, to physicochemical data. Therefore, businesses interested in adopting PAT need to use two main strategies to deal with the great complexity that may be found in some processes. These are Design of Experiments (DoE) and multivariate analysis (MVA).

The first tool, DoE, allows manufacturers embarking on a PAT implementation journey to design an experimental plan with the objective of collecting the data and samples necessary to build multivariate calibration models. In practice, this strategy helps define the most effective way to collect key data – gathering the maximum amount of information while using the minimum amount of time and resources.

When preparing to design and execute a DoE, it is crucial to clearly define a suitable analytical target profile (ATP). This identifies what should be measured and why, in addition to when and how the measurements should take place. By having a clear answer to these points, it is possible to select the most effective analytical instruments, sensors and analysers.

Once relevant, high-quality measurement data are collected, as defined by the DoE set up, a knowledge management software can ease the building of data sets and analytical results. These can then be exported to the selected MVA package, in order to build the instrument calibration models. It is important to note that MVA is data-driven, i.e. it does not rely on a priori system knowledge, therefore it generates information even in the absence of an existing fundamental or mechanistic understanding of the process. Even more, it minimises biases from operators and chemometricians.

To create a suitable MVA and predictive model, it is possible to use different methods, such as principal component analysis (PCA), partial least squares (PLS), discriminant analysis (DA), factor analysis (FA), multivariate curve resolution (MCR), maximum autocorrelation factors (MAF) or a combination of them. Each of these alternatives can provide a different insight into the relations between the data collected and CQAs. For example, PCA provides a linear combination of variables, while FA offers a measurement model of a latent variable. Therefore, it is crucial to select a suitable MVA method that can provide the most relevant insight into a specific process.

Once a suitable MVA model has been finalised and validated, it can be used as a component of a digital twin of the physical process. Provided with suitable data sets, this allows manufacturers to avoid running real experiments to test and refine PAT methods without the need to run a physical process and incur raw material usage and staffing costs. In effect, businesses can use the digital twin to simulate the process itself and vary its CPPs without using any physical resources. Furthermore, as more operational data are collected, the MVA and digital twin can be improved, delivering ever more accurate actionable insight and supporting continuous improvement.

Knowledge management to address the challenges of continuous processing

The MVA and digital twin are also form key components to embark on the journey to establishing a multivariate statistical process control (MSPC) based, closed-loop, quality-centric control system within a PAT knowledge manager, such as Optimal's synTQ. The PAT knowledge manager needs to connect to physical systems such as instruments and unit operations, interface to 3rd party control and software systems, run complex PAT methods (orchestrations), and interface with all users, in order to make this quality-driven control approach a reality. In this way, it is possible to collect measurements and make quality predictions in real time, while the manufacturing process is taking place, and check if the data are within specified parameters to deliver high-quality results. If they are not, then it is possible to manually, if preferred, or automatically adjust CPPs to maintain optimal conditions and obtain products of consistent, high quality.

Setting up a control system for continuous processing is more complex than for batch processing. In a batch process, it is possible to break down the control functions into different, independent and confined unit operations. The control system for continuous processes, however, needs to make the various stages work together simultaneously and seamlessly. If something is not in sync, it can affect the entire manufacturing line.

Therefore, similarly to batch processes, it is important to make sure that the operator interface can provide a comprehensive view of the process, from incoming raw materials to end products, in order to easily detect any unwanted deviation – and provide information on the reason for the deviation. This platform, also known as a PAT knowledge manager, is connected to all different elements of a PAT system and

should offer an easy to use dashboard, where all users, from operators to management, have an overview of CPPs, CQAs and real-time reporting of the manufacturing process. In addition, it should clearly flag anomalies and parameters that require attention, so that any issue can be dealt with before it irremediably affects end-product quality.

By combining all the different elements of PAT together, PAT knowledge management solutions can support complex PAT methods (orchestrations), making the different stages work in complete synchronisation. As a result, manufacturers can ensure that they have a holistic monitoring and control system for their continuous processes.

Finally, an effective PAT knowledge manager is necessary to reap the benefits of PAT and provide the necessary regulatory compliance and data integrity. By storing all the data collected on the manufacturing line, it can generate regular reports, including documents to ensure regulatory compliance. Therefore, it supports continuous process verification strategies and real-time release testing (RTRT).

Conclusions

Continuous processing offers extensive benefits to manufacturers that can substantially optimise their operations, reducing CAPEX and OPEX while increasing profitability. Businesses interested in moving from batch to continuous operations require suitable Industry 4.0 technologies to create highly effective PAT systems for real-time process control and monitoring. The result is an interconnected, smart manufacturing line that maintains optimal process conditions to deliver high-quality, regulatory-compliant products.

When implementing PAT, manufacturers should plan carefully and select the most suitable analytical tools to model and control their processes. In addition, they need to develop the MVA method(s) to calibrate the analytical instruments and enable the development of a scientific approach to manufacturing as well as, in turn, establish the relationships between CQAs and CPPs. Finally, it is essential to set up a PAT knowledge management system that supports process visibility, simple orchestration development and verification.

To address these challenges, businesses should engage with a vendor that will provide the necessary supporting services in a constructive and helpful way. For example, they can rely on specialists, such as Optimal and ABCS, who can assist with all stages of PAT implementation and can provide all the necessary tools, including synTQ, which is currently used by over half of the top ten global pharma manufacturing

companies.[4] By choosing skilled partners, companies can succeed in the creation of highly effective PAT systems that can optimise their production.

Image Captions:

Image 1: PAT helps manufacturers leverage the power of data to gain actionable insight into manufacturing and processing activities, to optimise them and attain continuous flows.

[4] DMA Europa. Pharma manufacturing's production revolution continues to gather pace. http://www.dmaeuropa.com/Clients/Optimal/News/tabid/2991/itemid/4261/Default.aspx (last checked on May 21st 2020)

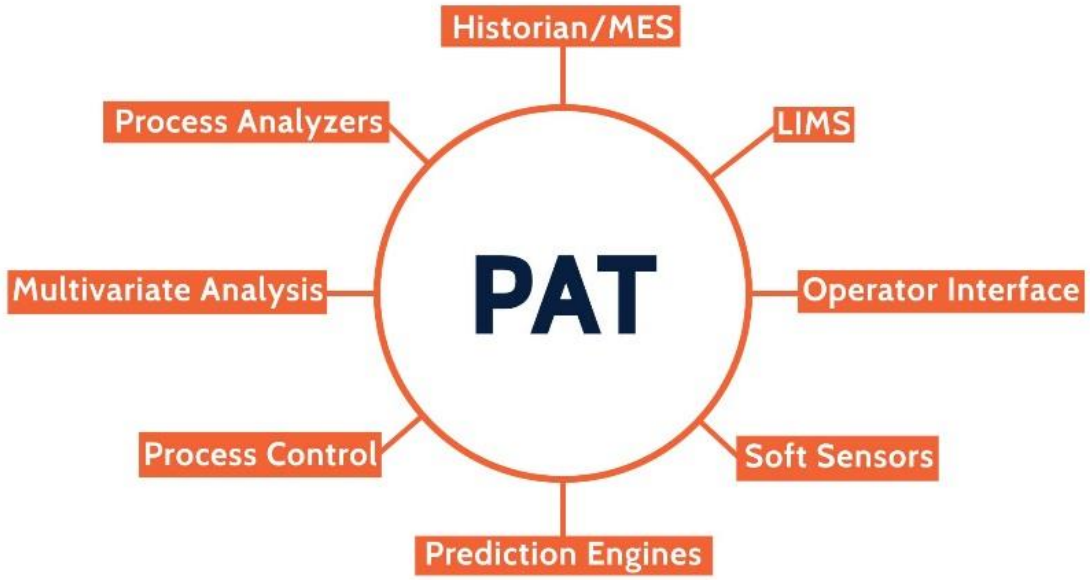

Image 2: The PAT knowledge manager is connected to all different elements of a PAT system.

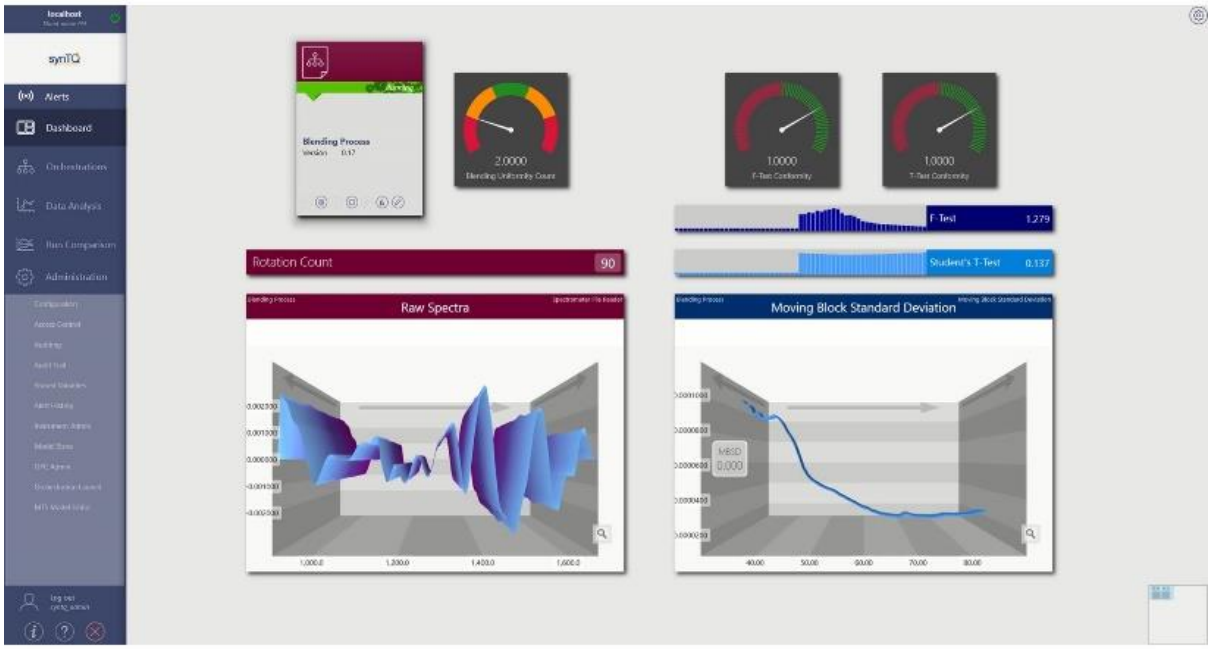

Image 3: The PAT knowledge manager should offer an easy to use dashboard, where operators can have an overview of CPPs, CQAs and real-time reporting of the manufacturing process.

About Optimal Industrial Technologies

Within the Optimal group, we have more than 30 years' experience in the automation and optimisation of control and data management systems for the food, chemical, pharmaceutical, biotech, life science and other process industries.

The demands being placed on manufacturers in relation to getting products to market sooner, minimising development and production costs together with increasing product quality and business sustainability are ever increasing. Our primary aim is to deliver measurable improvements in all these target areas.

In addition to practical automation and system integration expertise, Optimal Industrial Technologies has also developed the world-leading PAT Knowledge Management software platform – synTQ® – which is used by over 60% of the world's leading pharmaceutical and biotech companies, and is now being adopted by other process industries. synTQ has been a proven enabler of QbD via PAT by significantly increasing productivity and quality, while reducing waste, time to manufacture and time to market for batch and continuous processes.

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