synTQ Supports Future-Oriented Decentralised Drug Manufacturing

Innovative mobile and compact continuous manufacturing systems are reshaping the pharmaceutical sector, offering a unique solution to enhance patient access to medicaments. The use of Process Analytical Technology (PAT) is fundamental to maximising the benefits of these Pharmacy on Demand (PoD) setups, which hold the key to the fast, highly responsive production of critical drugs. Teams from Virginia Commonwealth University (VCU) in Richmond, VA, U.S., in collaboration with On Demand Pharmaceuticals, Rockville, MD, leveraged Optimal Industrial Technologies' PAT knowledge management platform, synTQ, to create an agile and efficient PoD system.

Martin Gadsby
Owner
Optimal Industrial Automation Ltd

Martin graduated from the University of Bath in the late 1970's, and after working through a few positions in industry, he became the new European R&D Process and Process Automation Group Leader for Kraft Foods. After a few years at Kraft, Martin decided to set up a process automation business with a colleague, Dave Richards, and Optimal was born.

Optimal Industrial Automation was formed over 33 years ago, with Martin now being the main owner and CEO. Optimal Industrial Technologies was formed more recently as the products division and is the market leader in the field of Process Analytical Technology (PAT) with its PAT Knowledge Management product – synTQ. Martin is intimately involved with progressing the evolution of synTQ and advising the Optimal development team on what he believes to be the optimum development direction. Over the last few years, he has taken on the overall responsibility not only for the company, but also for the sales and marketing of synTQ whilst remaining very active in ensuring that the development of synTQ continues unabated. On the personal front, Martin is a bit of a 'petrol head' and enjoys flying aerobatics and racing cars.

The pharmaceutical sector is continuously seeking ways to improve universal access to medicaments. This commitment is fundamental to enhancing the support available to patient communities living in remote areas and regions affected by catastrophes, where adequate supply is needed to ensure good healthcare access. In addition, innovative practices, such as personalised medicine, also require fresh perspectives on pharmaceutical manufacturing.

As medicinal products are often challenging to store and transport, serving patients globally in a timely and cost-effective way can be difficult. For example, keeping medicines at their ideal temperature at all times is perhaps the most challenging issue. In addition, short shelf lives, coupled with highly centralised manufacturing facilities and limited freight capacities, can exacerbate supply chain challenges.

On-demand pharmaceutical manufacturing close to the point of care, also known as PoD, offers a sustainable solution to improve the availability of key treatments. By making the decentralised production of drugs financially feasible, even for small batches, it is possible to increase the agility and capabilities of the sector as a whole, benefitting patients worldwide.

Reshaping pharmaceutical manufacturing and quality testing

In order for PoD to consistently deliver high-quality medicinal products that are on spec and ensure regulatory compliance, robust quality control strategies need to be in place. These should deliver the levels of safety equivalent to current products while avoiding the creation of new, unnecessary barriers that can reduce the effectiveness of PoD setups.

This means favouring real-time quality assurance systems in place of conventional, off-line quality testing. The sampling of end products can be particularly time consuming, as this requires extended downtime to bring the materials to analytical laboratories, conduct the necessary investigations and process the results.

Conversely, real-time process control and quality assurance, supported by PAT, can form the backbone of highly efficient PoD solutions. Moreover, a data-driven quality-centric approach can support continuous processing, enhancing the benefits offered by decentralised, compact and mobile on-demand manufacturing systems.

An innovative PoD setup for ciprofloxacin

Based on these principles, a research group from VCU led by Thomas Roper, PhD, decided to implement PAT on an innovative PoD system for the production of ciprofloxacin. This is a broad-spectrum antibiotic used to treat a wide range of bacterial infections that also induces growth inhibition and apoptosis in various cancer cell lines.

The resulting PAT-driven manufacturing setup would offer a reconfigurable, mobile continuous processing solution for the synthesis of the active pharmaceutical ingredient (API). This could then support a wider system that also includes the purification of the drug molecule and formulation of 1,000 quality-compliant ciprofloxacin tablets per day.

The real-time control offered by PAT can greatly improve the synthesis of the pharmaceutical considered. Yuma Miyai, Graduate Research Assistant at Virginia Commonwealth University - College of Engineering, explains: "The formation of ciprofloxacin in continuous flow is a particularly challenging 5-step process. Some of the stages are characterised by very fast reactions, which require approximately 30 minutes, and it can often lead to solid precipitation, affecting product quality and the system itself, as it can cause clogging.

"Therefore, to progress our existing PoD setup, having a deep understanding of the process and how to optimise the parameters of reaction intermediates to ensure end product quality was a must. This was only achievable with PAT, as it helps us monitor the process conditions on-the-fly to deliver on-spec APIs."

Addressing the needs of compact flow-chemistry systems

The main challenge to overcome in this project was the creation of a suitable control system that would support real-time data sharing and analytics while fitting in the existing unit. More precisely, in addition to selecting relevant analysers that would offer a suitable characterisation through the different reaction steps, the research team needed to address matrix limitations as well as space constraints. Moreover, it was essential for the instruments to communicate with predictive models for product quality purposes, a PAT data collection and management platform as well as pumps, reactor heaters and balances within the PoD.

Optimal's synTQ, a vendor-neutral software, was instrumental in addressing these challenges. Paul Gillham, Innovations Team Director at Optimal, comments: "The synTQ PAT knowledge management platform collects, processes, stores and visualises process data to provide unique actionable insights. As the main hub for PAT-driven manufacturing, it is designed to support the integration of a broad range of PAT sensors, chemometric models, optimisation and process control algorithms as well as control hardware."

Thanks to the level of interoperability and flexibility offered by synTQ, the researchers at VCU could freely select the instruments that would best meet their demanding matrix and system requirements. Specifically, in-line Fourier-transformed infrared (FT-IR) and Raman spectroscopy were identified to support the second and fifth part of the 5-step synthesis, respectively.

By leveraging synTQ, scientists were in a position to quickly advance the continuous on-demand manufacturing of ciprofloxacin. In fact, they were able to complete the 5-step reaction in a record time of 16 hours, with no interruptions required to perform off-line quality checks. Yuma Miyai adds: "The PAT knowledge management system featured a number of tools that helped us in the realisation of a highly effective PoD setup. The graphical interface is intuitive, easy to use and supports the visualisation and inspection of spectra and the manufacturing process itself, for example, via the Dashboard. In addition, key functions such as the Orchestration tool played a key role in the rapid design of custom PAT environments – and when our team needed additional support, Optimal's specialists offered their help and quickly resolved our questions and requests."

Paul Gillham concludes: "We are extremely pleased to see synTQ being used to create such an innovative pharmaceutical manufacturing system and look forward to supporting the VCU team in the future. The PAT-driven PoD unit represents a key milestone in improving access to medicaments. We are thankful for the positive feedback received – it attests to our commitment to advancing the pharmaceutical manufacturing sector with cutting-edge solutions."

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