Injecting Innovation into the Vaccine Market

How to Speed up Vaccine Development and Manufacturing Output with 'Live' Process Management Solutions

The market demand for innovative solutions to develop and manufacture vaccines has recently skyrocketed. Thanks to new advances in automated process control, it is now possible to shorten development times and up-scale plant productivity using the same equipment footprint. Process Analytical Technology (PAT) 'live' continuous process management software can simultaneously guarantee product quality and consistency, supporting Real-Time Release Testing (RTRT).

Martin Gadsby, Director at Optimal Industrial Technologies, looks at how PAT can enable vaccine developers and manufacturers to boost their capabilities, without increasing the footprint of their existing production sites.

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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 market for vaccines has grown substantially, with the sector estimated to have reached USD 41.7 billion in 2019[1]. However, the complexity of such treatments means that there are still some key challenges for developers and manufacturers. Namely, establishing methods of production that consistently deliver high-quality biopharmaceuticals, yet are economical, efficient and – more importantly – fast.

Traditional pharmaceuticals are created through purely chemical synthesis, and their molecular structure is relatively compact. For example, two of the most prescribed generic drugs in the UK, atorvastatin calcium and simvastatin, have molecular weights of 1153.3 g/mol and 418.566 g/mol respectively. Conversely, vaccines and other biopharmaceuticals originate from living organisms, thus their molecules can be over 100 times larger than conventional pharmaceuticals, weighing as much as 150,000 g/mol.

The upstream operations in vaccine manufacturing rely on cultured cells or other living organisms. These are extremely sensitive to surrounding environmental conditions, such as temperature, nutrient feed and media composition. Therefore, maintaining cell or microbiological cultures in a suitable incubation system is crucial and adds complexity to the manufacturing process. When handling microorganisms, vaccine developers and manufacturers also need to demonstrate evidence of microbial safety in order to comply with quality standards. This means that the conditions for proliferation of pathogens or contamination should be minimised and controlled carefully to enable early detection.

Figure 1: PAT can enable vaccine developers and manufacturers to boost their capabilities, without increasing the footprint of their existing production sites.

Managing Complexity in Biopharmaceutical Manufacturing

A convenient way for vaccine developers and producers to address the multiple challenges and, consequently, quickly increase their production scale is to implement advanced control strategies on their factory floor. For instance, PAT is now being used by many leading manufacturers as a method for measuring and controlling the variables that can affect production.

PAT is a system aimed at delivering process understanding, analysis and control in order to ensure product quality and regulatory compliance. More precisely, it allows scientists to fully understand key biological mechanisms and thus control production to maximise vaccine effectiveness. Also, it enables researchers and manufacturers to conduct real-time, on-line or in-line measurements of critical quality attributes (CQAs) on raw and in-process materials. This data can provide a unique insight into the multivariate influences that the critical process parameters (CPPs) have on the end product quality, such as how process temperature, pH and nutrient feeding can affect cell proliferation in upstream vaccine manufacturing processes.

Having defined meaningful correlations between CQAs and CPPs via multivariate analysis (MVA), manufacturers can adjust their production processes on-the-fly, in accordance with the results obtained from timely physicochemical analyses. For example, operators and automation systems in biopharmaceutical plants can dose glucose in real time to maintain its level within the most favourable range for organism growth, hence maximising product's health. Such precise insight and control mean developers and manufacturers can maximise the quality and consistency of their end products. In addition, they can minimize waste associated with off-spec materials, substantially improving cost-, energy-, and resource-efficiency.

Further, unlike univariate or bivariate regressions, MVA can process the multidimensional and multicollinear data that represents biological systems in upstream processes as well as CPPs in downstream operations.

This comprehensive analysis can handle variability and deviations within data, which can often occur in living samples.

An aspect of particular importance to vaccine developers and manufacturers is that by allowing manufacturers to evaluate and ensure the quality of in-process and final product based on process data, PAT supports RTRT and can dramatically shorten development and manufacturing times. Therefore, it is possible to bring new products to market sooner.

The PAT framework therefore has the ability to help enhance processes throughout vaccine development and manufacturing. In particular, it's the scope to conduct MVA within the PAT framework that could prove crucial in supporting the sector's continued growth.

The Right PAT Framework for Bioprocessing

Not all PAT setups are equally suitable for bioprocessing. Due to the particular nature of vaccines and their production processes, it is important for businesses to consider some key aspects when implementing such methodology.

Firstly, as biological systems are highly complex, the PAT system needs to monitor many CQAs and control multiple CPPs. Therefore, the chosen PAT system must be able to handle extremely large volumes of data generated during upstream and downstream processes. This data processing capability becomes even more crucial as Industry 4.0 and Smart Manufacturing push for data-driven operations. Within the vaccine sector, this means choosing a robust data processing system that can support both high-throughput sample screening and high-resolution CQA analytics.

Furthermore, the structure of vaccine and other biopharmaceutical manufacturing facilities is known as 'the bioprocess train', as it consists of several sequential process unit operations; each of which has a specific contribution in defining end-product quality. The interactions between different consecutive process unit operations, which can be defined as 'inter-CPPs', can have as much impact as the conventional 'infra-CPPs' of the unit operations themselves. To address

Figure 2: Tackling the unique challenges of vaccines calls for an advanced PAT knowledge management platform, such as Optimal's synTQ, as a central hub. This collects and stores all sensor data, converts it into live actionable insight and presents it via easily readable data visualisations and graphic representations for effective process control.

this issue, it is important to use the data on the vaccine's CQAs measurements at the end of one stage as the foundation for the next consecutive stage. This calls for a holistic approach to data mining. Only in this way is it possible to properly assess these 'inter-CPP' relationships.

Finally, the elevated costs associated with bioprocess development and vaccine manufacturing do not normally allow businesses to run large-scale tests to generate the necessary process relationships between CQAs and CCPs. The results obtained by small-scale operations in a conventional setting may not scale to allow direct knowledge transfer to larger-scale industrial scenarios. Therefore, it is important to set up data processing tools that can take these aspects into account to help maximise the insight offered by small-scale PAT methods (or orchestrations) and minimise the scale-up process and effort.

A Holistic and Responsive Data Processing Tool

Tackling the unique challenges of vaccines calls for advanced PAT knowledge management platforms. A knowledge management platform acts as a central hub that collects and stores all sensor data, converts it into live actionable insight using MVA models, and presents it to automation systems and plant operators for effective process control via easily readable data visualisations and graphic representations. An example of state-of-the-art PAT knowledge management is Optimal's synTQ software. This is a regulatory-compliant tool that is currently being used by over half of the top ten global pharmaceutical manufacturing companies, as well as leading biotech and biopharmaceutical producers, some of which have reported the tripling of productivity.

synTQ supports Industry 4.0 at its core, as the key aspects of Industry 4.0 are pillars within the application. Its automated functionalities, such as data integrity, provide a critical additional reason to use the software. In addition, the platform is highly automated, offering self-regulating closed-loop feedback control to promptly adjust both inter- and infra- CPPs.

In order to optimise PAT orchestrations, developers and manufacturers can benefit from the latest 'digital twin' function within Optimal's PAT knowledge manager. This tool allows plant operators to create and test process data flows virtually, without the need to start a real test process on the manufacturing line, reducing resource use and waste generation. The functionality can then be used to optimise the process as more operational data and knowledge is generated and the MVA models are refined.

By choosing an industry-leading PAT knowledge management solution, such as synTQ, vaccine developers and manufacturers can thrive in an increasingly demanding and competitive sector, delivering high-quality products in higher volumes, using production facilities as efficiently and cost-effectively as currently possible.

References

1. *https://www.marketsandmarkets.com/PressReleases/vaccine-technologies.asp*