Getting ready for the future of pharmaceutical manufacturing

Industry 4.0 applications can help businesses boost their manufacturing processes, making them faster, more responsive, integrated and productive. Despite these key advantages, adopting new Industry 4.0, or Pharma 4.0, solutions within (bio)pharmaceutical manufacturing lines can be particularly challenging. However, the implementation of the right advanced digital technologies can overcome these issues and deliver substantial, value adding benefits to businesses in the pharmaceutical sector.

Martin Gadsby, Chairman at Optimal Industrial Technologies, looks at the most significant opportunities for PAT in the digital era and how to implement them.

The future of manufacturing is digital, and several industries have already taken large strides in their digital transformation journeys. Whilst processing industries and pharmaceutical manufacturing are not at the forefront of these trends, digital technologies that support Pharma 4.0 applications can drive considerable improvements. They promote innovation that can increase the productivity and efficiency of key operations whilst futureproofing them. The broad range of automated solutions available can be used in a variety of settings to achieve different goals. This means that pharmaceutical companies can confidently embark on digital transformation journeys that address their most pressing requirements or applications that are most in need of upgrades.

Although there is a multitude of technologies available, most of them share the need for an advanced, quality-compliant Process Analytical Technology (PAT) framework where they can be implemented. Embracing PAT is a Quality by Design (QbD)-driven approach that aims to deliver products of consistent and high quality by leveraging the power of data.

More precisely, this smart manufacturing strategy relies on the timely characterisation and analysis of raw and in-process materials achieved by measuring their critical quality attributes (CQAs). These are then controlled with critical process parameters (CPPs) to define the optimum operating conditions and adjust them in real-time. Therefore, PAT supports in-depth process understanding and data-driven control whilst also laying the foundation for quality assurance, continuous process verification as well as material tracking and tracing.

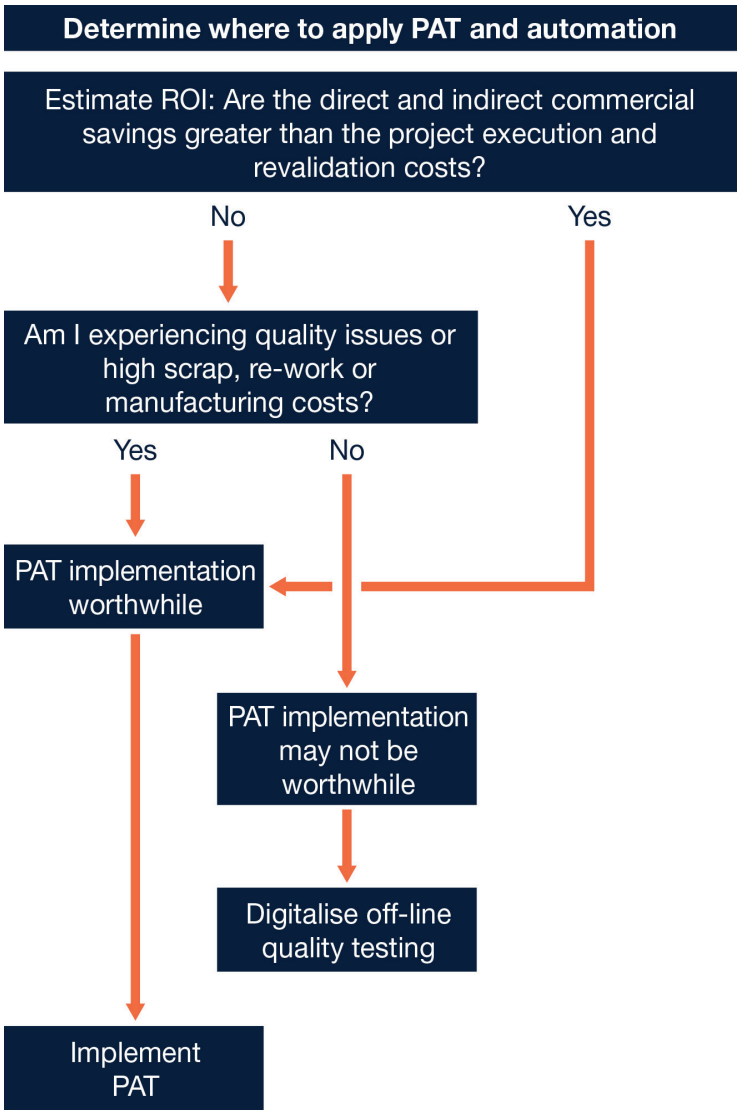
To revalidate or not to revalidate?

Early on in the evaluation of a suitable automation project, businesses should consider whether the process will require revalidation. If so, they should determine to what extent and if the return on investment (ROI) of the total project, including any revalidation costs, meets corporate objectives.

Even in cases where revalidation is not an option or the ROI is not attractive enough, pharmaceutical companies can still leverage digital technologies and PAT-like environments to improve quality control activities in off-line analytical laboratories. These tasks generally take considerable portions of manufacturing cycle times and an increasing amount of manpower. Conventional mid-sized companies producing a variety of small-market OSD forms are estimated to spend approximately half of their cycle times on necessary quality controls.[1]

Key automated technologies can cut the downtime associated with these quality control

activities and, in turn, optimise the speed and productivity of the entire production process. For example, robots can speed up testing by performing repetitive tasks, such as liquid or solid sample collection and delivery to off-line testing facilities. There, samples can be automatically prepared and analysed. Additionally, businesses can implement serialisation and data management systems to create state-of-the-art data repositories that enhance data integrity for material tracking and tracing.



Flowchart assessing the benefits of PAT and digital technologies as well as the impact of manufacturing process revalidation within pharmaceutical companies.

Selecting your first digital transformation project

Once the environment in which digital technologies are to be implemented has been selected – namely, R&D, manufacturing or testing facilities – pharmaceutical companies should define what their goals are. This, in turn, helps to select the solutions that are most suited to addressing these ambitions.

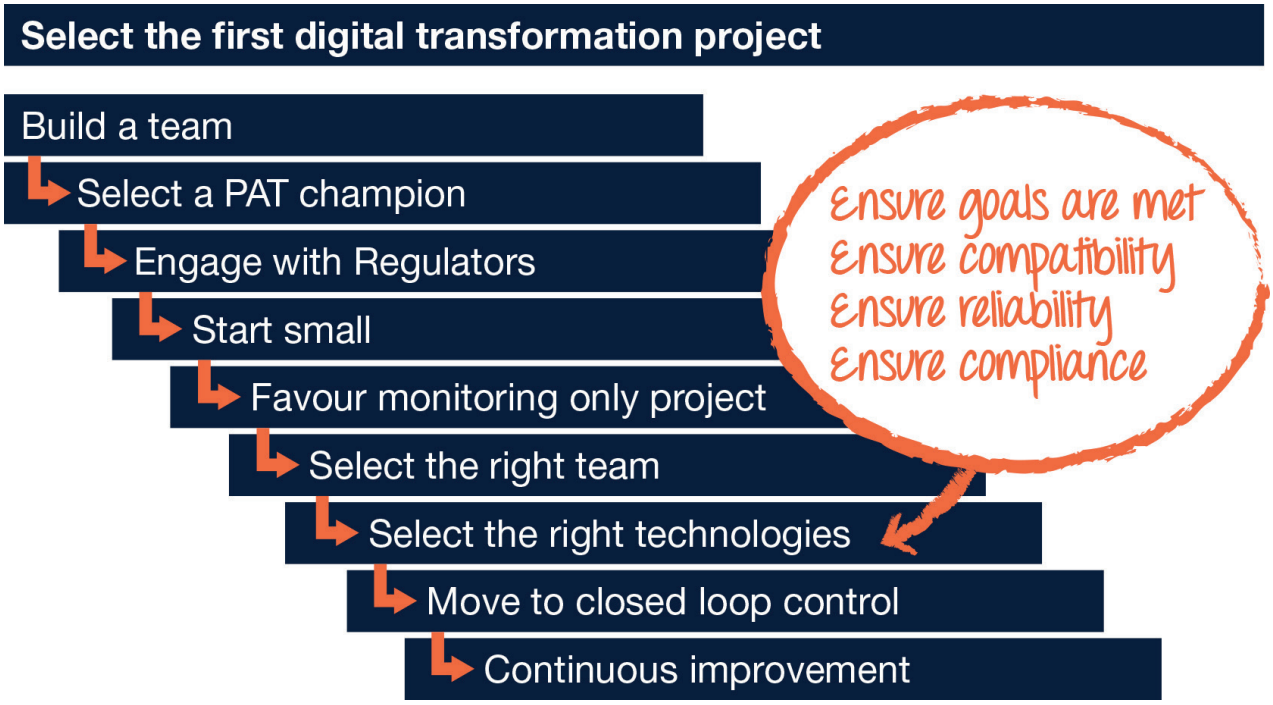
To succeed in the implementation of PAT and digital technologies, sustainability is key. This means that companies should start with small projects, ideally where there is already a level of process understanding available and it is clear to see how this can be optimised. In addition, it is generally recommended to initially use PAT and data-driven solutions to solely monitor processes, without including control activities. This helps to simplify the requirements of the project and streamline implementation while gathering more knowledge on CQAs, CPPs and the entire production process.

After supervision activities have been improved, pharmaceutical companies can determine whether automated, quality-centric control strategies could further enhance production activities. If automated control model building is used, then generally these are highly cost effective, but they may generate less process knowledge.

Identifying and implementing complementary technologies

Once this groundwork has been completed, companies should define the technologies that can complement PAT in their applications. For example, when looking at enhancing manufacturing processes, businesses may be interested in improving sterile manufacturing. This can be addressed by setting up robots that rely on automated closed-loop feedback control.

Similarly, continuous processing applications can greatly benefit from effective and accurate dynamic flow modelling for material tracking and tracing. This helps businesses monitor the product movement throughout continuous



Key elements to put in place to set the foundations for a successful data-driven application based on PAT.

processes, coordinate sampling and rejection systems, and identify raw materials in the final products. As a result, dynamic flow modelling supports closed-loop feedback process control at the core of good manufacturing practices (GMP), quality assurance and regulatory compliance strategies. As continuous processing and flow chemistry applications become increasingly popular, a PAT knowledge management platform needs to feature advanced mathematical predictive models, combined with extensive empirical data, to accurately forecast product and material movement.

When handling complex processes, advanced data processing strategies can provide a solid foundation for effective control. In particular, multivariate control – the ability to direct the control of more than one CPP in concert with others in order to control the desired CQA value – is highly valuable. It is possible to model such functionality with automated intelligent control (AIC), where the control algorithm is automatically derived, indicating the optimum CQA values that should be delivered. By adopting this type of multivariate control, it is possible to do more than simply keep CPPs as close as possible to their set-points, as it can drive a CQA value from its current state to the desired state. Ultimately, this can help (bio)pharmaceutical producers to make their processes more flexible and adaptable while enhancing end product quality and process efficiency.

Finally, if businesses want to ensure consistency across different plants or R&D laboratories, a common platform used by each plant together with a secure Cloud-based environment is ideal. This approach also supports advanced Big Data analytics and mining for next-level PAT applications. In effect, Cloud computing facilitates interconnectivity and offers near unlimited space for storage and data processing power on demand. The common platform allows knowledge, orchestrations, models and IP developed in one location to be shared in a traceable and GMP-compliant way with another.

A digital transformation that is sustainable for your business

Based on these requirements, it is crucial for (bio)pharmaceutical manufacturers to select a PAT framework that can support the necessary digital technologies. In addition, it is important to consider analytical instruments and sampling solutions. In particular, it is fundamental to check the ability of these technologies to converge to a central PAT knowledge management platform, where all data and the insights they produce are revealed, stored, visualised and processed. Businesses should not be limited by vendor-specific components when building effective Pharma 4.0 applications. Therefore, selecting a multi-vendor, multi-instrument PAT knowledge management platform is highly beneficial.

Compatibility should also be evaluated across the entire network infrastructure, particularly when enterprise-wide digital technologies are applied. When setting up IIoT applications that merge the operational technology (OT) domain, typical of the shop floor, with information technology (IT) of higher-level systems, the PAT platform should be able to link both worlds. In practice, this means that the software should be able to seamlessly interconnect with Edge devices and other key nodes, such as virtual machines.

If businesses want to utilise Cloud computing, it is also essential that their chosen PAT knowledge management system can support data transfer to, or run within, these environments. Additionally, pharmaceutical manufacturers should ensure that information is transmitted in accordance with existing regulations. This means that the ideal solution must meet regulations on electronic signatures and records (ERES), such as the European Union's GMP Annex 11 and/or the U.S. Food and Drug Administration's (FDA) 21 CFR part 11. In particular, if advanced cyber security is a top priority, a data pump system that transfers information from a PAT platform to the Cloud should be based on 'push' methods, as they support controlled access. These operate by periodically sending data from each monitored system to a central, Cloud-based data lake. More precisely, push architectures prevent a network from opening to areas that should be restricted.

Independent of the network components utilised, it is crucial to evaluate latency and reliability. As PAT-driven Pharma 4.0 applications rely on real-time communications with machines and instruments on the factory floor to adjust their operations on the fly, time-critical data should be transmitted in a timely manner. Otherwise, these could compromise productivity and end product quality, ultimately reducing the benefits of digital strategies.

This may be particularly challenging as larger volumes of data are produced, and advanced analytical and predictive models become more powerful. Thanks to key technologies, such as Cloud computing, these solutions are becoming increasingly accurate and widespread. In effect, the Cloud offers near-unlimited space to process and store large volumes of data. Nonetheless, speed should remain the top priority in order to effectively control operations. The creation of highly effective networks that rely on advanced communications technologies is key to overcoming these challenges and setting up successful IIoT environments for pharmaceutical operations.

Finally, businesses interested in the digitalisation of their manufacturing lines using PAT should look for a solution that can create Digital Twins, to simulate process orchestrations in a virtual environment. In this way, it is possible to test if the selected conditions and operating parameters are effective or need to be refined without running physical processes, which are resource, cost and time consuming. This functionality can be extremely helpful during commissioning, particularly for complex manufacturing and quality prediction functions – for example, predictive dissolution.

Beyond the implementation

The future of pharmaceutical manufacturing lies in digital technologies. Players in the sector should therefore begin to embrace them to maintain a competitive edge. To succeed in this, it is crucial that companies select the most suitable solution, such as the PAT knowledge management platform, synTQ, and implement it correctly. By following the recommendations provided and by partnering with a leading specialist, such as Optimal, (bio)pharmaceutical companies can truly succeed in their digital transformation and maximise the end benefits.

References

[1] Cogdill, R.P., Knight, T.P., Anderson, C.A. et al. The Financial Returns on Investments in Process Analytical Technology and Lean Manufacturing: Benchmarks and Case Study. *Journal of Pharmaceutical Innovation* 2, 38–50 (2007)

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.a

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.

Contact

Optimal Industrial Technologies Limited
5 Monarch Court,
Emersons Green,
Bristol
BS16 7FH
UK

Call +44 (0) 1173 742 222

Email PAT@optimal-tech.co.uk

Visit www.optimal-tech.co.uk