

# PAT has worked its way down the production line



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**Dave Drew,**  
*Pharmaceutical Director of Matcon*

Process Analytical Technology (PAT) was an initiative supported and driven by the FDA after “pressure was applied by the multi-national pharmaceutical manufacturing industry to reduce the need for expensive testing and inspection at every point of production,” explains Dave Drew, Pharmaceutical Director of Matcon. In accordance with the FDA definition, PAT is a system for designing, analysing, and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.

So what does this mean for OEMs and why should they be involved in the development of PAT? Steve Foster, ex Senior Engineer involved with the implementation of PAT in Operations at AstraZeneca and now an independent PAT implementation specialist and Director of Casburt TMS Ltd, provides an insight into how manufacturers are implementing PAT: “Current approaches to the design, manufacture and quality assurance of pharmaceuticals are untenable and in many respects lag behind other industries. The industry has thrived for many years and practices have remained largely unchanged. However, there is an increasing number of drivers for change including:-

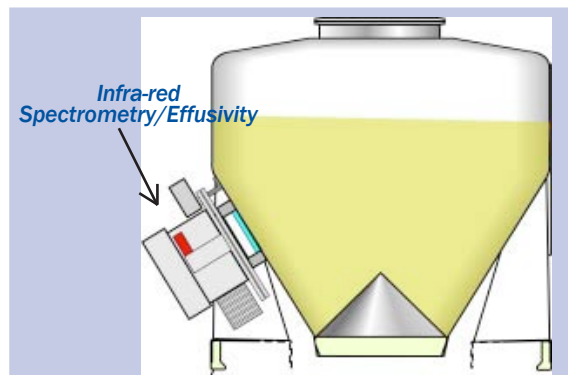
- **Downward pressure on profit margins** which is being driven from a) Government health spending budgets, b) increasing competition from leaner organisations within the market
- **New product types** with lower production volumes
- **Complex drug delivery systems**
- The need to **facilitate innovation**, and **continuous improvement**”

Dave agrees: “The multi-national pharmaceutical manufacturers (Pfizer, GSK, Novartis etc) are now under extreme business pressure to reduce costs and become more efficient. The purpose of PAT is to allow them to compete with manufacturers of generic drugs

who are more efficient yet still compliant with cGMP production rules on quality. Why PAT should be introduced is interesting:-

- It should be introduced if it makes the process more efficient and reduces down time (‘sweat the asset’)
- It should be introduced if it increases quality and reduces process risk
- Because it applies to both batch and continuous manufacturing

Matcon’s adoption of PAT through the use of infra-red spectrometry on some of our pharmaceutical powder blending applications, means that continuous automatic monitoring of a process can be carried out and avoids intrusive and time consuming samples being taken to prove the blend is correct. Equipment working more efficiently to produce higher quality products is what pharmaceutical manufacturers want.”



*Even though infra-red spectrometry/effusivity is used to ‘prove’ the blend in the IBC is perfect, the blend can still segregate back into its individual constituents if the powder flow design to the next process (e.g. a tablet press or a packaging machine) is poorly designed.*

*Dave Drew, Pharmaceutical Director, Matcon*

There is no doubt that PAT will enable manufacturers to become more efficient. Steve explains: “PAT clearly has the potential to be a key enabler facilitating an integrated product development and quality systems approach that supports reliable and efficient production of drug substances and medicinal products, delivering continuous improvements without extensive regulatory oversight. As such, all major functions in the industry will be affected. At the operational level, a notable percentage of the industry is currently developing and evaluating PAT tools. Current focus is on New Product Introductions (NPIs) which is understandable considering the enormous advantages that could be leveraged from process knowledge and mapping throughout the complete development and scale-up phases.

The launch of a new medicinal product spans several years, so manufacturers need to start considering, in a

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timely way, how they will successfully accommodate the new PAT technology. How, for example do they learn about the interfacing techniques, what works and what does not?

Active support and sponsorship of PAT initiatives is required from senior operations management in order to balance short-term production needs, and often longer term continuous improvement. Whilst potentially of more limited value, it is my opinion that a great deal can be gained from applying PAT selectively to medical products currently in manufacture. At a minimum this enables the process to be visualised and potentially helps identify the limits of process variation. However, organisations will have different strategies, some will want to evaluate the new technology for suitability in particular plant areas/ conditions in a full scale manufacturing environment and feed the results back to development. Others will implement the technology unilaterally within production.

Implementing the new technology in existing plants with existing processes will facilitate the learning necessary to develop: successful instrument interfaces, compliant data handling and storage systems, development of multivariate data models, batch reports and SPC charts, technical and operator



**"A significant change in paradigms will be required to move from the current 'testing to document quality', to one of 'built-in' or 'by-design' quality."**

*Steve Foster, PAT Implementation Consultant*

training requirements. These are just a few of the things that need to be addressed in the building of a robust infrastructure to accept the technology - the learning curve is significant."

Although PAT has been a working initiative for 5 years, it is probably no surprise that OEMs are just starting to get involved. Steve comments: "Many OEMs have been hesitant to introduce innovative new systems for a number of reasons. One reason often cited is the perception that the regulatory system is rigid and unfavourable to the introduction of innovative systems, for example, many process changes having to be managed through regulatory submissions. Other

scientific and technical issues have also been quoted as reasons for this hesitancy. However, OEMs are increasingly recognising the potential benefits of PAT to enhance the understanding and control of manufacture through timely measurement with the goal of ensuring final product quality."

This is true of **Oystar Manesty** which has been working on PAT projects as explained by Head of Process and Validation, Dipankar Dey: "PAT is essential to the production of safe and effective medicines, and as such is central to the Manesty product development strategy. It helps us produce equipment which monitors and controls product quality, and systems which should ensure no wastage occurs during tablet manufacture. We are currently working on a project with TeraView Ltd and the Universities of Cambridge and Liverpool which looks at on-line monitoring and the control of tablet compression and coating. The aim of the project is to determine how terahertz technology can

be used to provide real time information of tablet quality during manufacturing and how it can be used to ensure product quality. This is a 2 year Technology Strategy Board programme part funded by the UK government.

The underlying benefit is that PAT technology challenges us to keep innovating to provide better equipment and it has led us to invest more in our R&D programmes."

Interestingly, PAT is not just affecting process OEMs. Packaging companies are realising the bigger picture too says **Carsten Peters, PAT specialist of Schubert**: "Since PAT was introduced by the FDA 5 years ago, we can see that our business is becoming more of an engineering company rather than a machine manufacturer. This change means that we needed a different category of employees with a certain level of skills in order to handle these systems and implement the systems into production lines. Our expansion in PAT has also meant that we are able to stay ahead of China and other countries trying to enter the pharma market. Due to their early stage in the development lifecycle, these overseas competitors have not yet started to develop or integrate PAT technology - but no doubt they soon will. It is because of these developing countries that European machine manufacturers are being driven into high-end technology in order to differentiate themselves and stay one step ahead."



*PAT imager from TeraView*



*Carsten Peters, PAT Specialist, Schubert*

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