Process Analytical Technology: The Route to Process Understanding and Control

Measuring, understanding and ultimately controlling manufacturing processes offers pharmaceutical companies a route to greatly enhance the business effectiveness of both their product development process and facilities. PAT creates technological, business process and regulatory frameworks to enable this. This paper looks at a PAT overview within the context of developing and manufacturing a tablet product, highlighting the potential of FT-NIR spectroscopy.

Today's pharmaceutical company is driven by the need to create and execute effective and efficient processes if its business model of exploiting the revenue generation of the new product pipeline is to be realized. The challenges within drug discovery are to discover new entities, screen them for safety and efficacy, and then pass them swiftly into the product development process.

In product development the challenge is to handle the product pipeline effectively. Early culling of entity and product failures is important if the focus is to be on recognizing new products with high success potential and driving them through the product pipeline, ultimately leading to routine manufacture and sale.

Technological and scientific innovation has been very high in the discovery phase of the process, but, until recently, not followed through to the same extent into the later stages of product development and the routine manufacturing parts of the pharmaceutical product life cycle.

The pharmaceutical industry has been performing process analytics in one form or another for well over 20 years, but had stated that innovation is not encouraged, enabled or supported by the traditional good manufacturing practice (GMP) used in

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pharmaceutical manufacturing. Likewise, the industry regulators (e.g., FDA) had been similarly frustrated by a lack of scientific basis for product development, the utilization of innovative manufacturing practises and the reliance of the industry on traditional quality assurance/quality control (QA/QC) strategies.

Things have changed. Coming out of this dual frustration is the process analytical technology (PAT) initiative, which is driven by both the regulators and the industry. PAT is a framework for innovative pharmaceutical development, manufacturing and QA, and promises to revolutionize the way the industry operates its product development, manufacturing and quality systems.

Consistent Product Quality

Ultimately, PAT is about ensuring consistent product quality, from which springs manufacturing business benefits. Creating consistent product quality means designing in quality at the earliest part of the product and process development phases of a new product. Design for manufacturing, a well-established concept in most manufacturing industries, is now brought into the pharmaceutical manufacturing context via PAT. The key steps in this process are summarized and illustrated in Figure 1.

Process understanding. Gaining a deep and fundamental understanding of the manufacturing process is at the heart of PAT. This is about truly understanding how processes create products from input materials and what influences the unit operations have over critical product quality attributes. Measuring and understanding sources of variability through the process are often the first steps in this.

Getting to this understanding is facilitated by the use of PAT principles, tools and techniques, and usually starts with looking at the raw materials used in the formulation and then working through each unit operation before finishing with the final product.

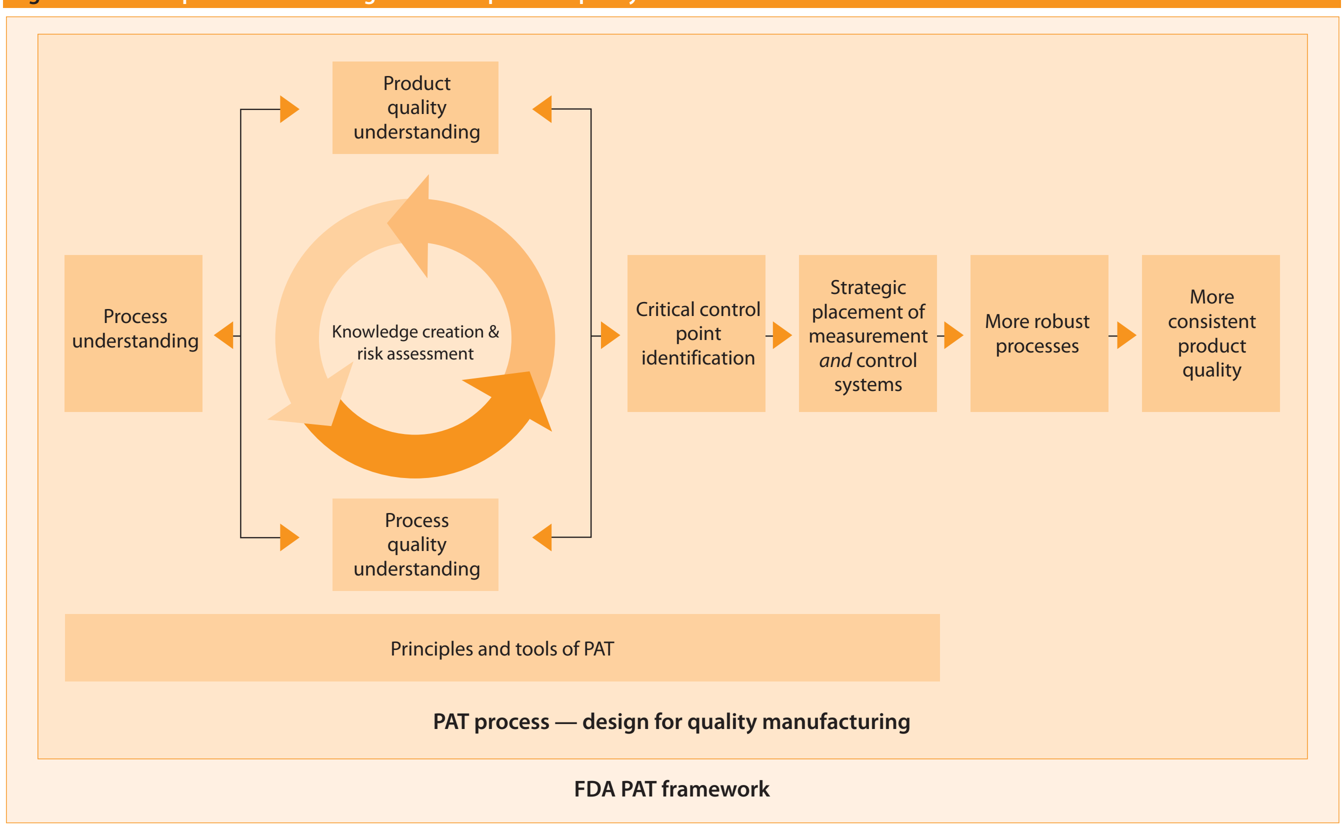
Once the process is understood from a scientific and engineering context, then the risks to product quality can be identified, quantified and rated. Links between product quality and process quality are established, and the iterative process of steadily gaining more and more knowledge as the new product formulation and manufacturing process are developed is started. Process understanding allows the high-risk process steps to be identified, leading to the identification of critical control points.

Process Understanding Example

A simple starting point in gaining process understanding is to start at the beginning of any process — knowing and understanding the quality impact of the sources of variation in the raw materials.

Traditional approaches to measuring the quality of raw materials are based around identity, chemical purity and pharmacopoeial methodologies. Clearly, using the correct material and it being of a

Figure 1 The PAT process for creating consistent product quality.



suitable chemical quality is fundamental to creating a superior product, but in the tablet manufacturing process steps (which are essentially based around the handling, mixing, modifying and compression of powdered materials) it will be the physical attributes of raw materials that have substantial process impact.

It is not unknown for the cause of a failed tablet batch to be traced back to a raw material ingredient physical property issue; the raw material having passed all the current traditional incoming materials inspection process!

A basic tool that can be used to help process understanding within PAT is FT-near infrared (FT-NIR) spectroscopy.

Well established as an analytical tool in pharmaceutical testing, FT-NIR has the ability to provide information on both chemical quality attributes and physical properties quickly, easily and without destroying the critical information. Its speed of deployment and operation makes it a fast way of creating a database of raw material information that contains valuable chemical, physical and batch-to-batch variance information, and one that can give rapid paybacks to an organization.

Figure 2 shows the FT-NIR spectra for a series of lactose raw materials of different grades. Both chemical information, from the absorption peak positions and shapes, and basic particle size information, from the broad baseline and relative offsets of the spectra, are obtained from a single, simple measurement.

Once a raw material database is established, then links between quality performance later in the process and ingredient FT-NIR spectra can often be established. From this, causal relationships can be explored and investigated, or the FT-NIR system can be deployed with the ability to 'screen' incoming raw materials for suitability in the process. Raw material qualification by FT-NIR is often the first process critical control point.

Critical Control Points

From process understanding comes the ability to identify the critical control points (CCPs) — the risk to product quality at those points and the appropriate limits that the process must be within at these points. CCPs in a process are where product quality attributes are created and product quality may be at its highest risk.

The points offer a position in the process where appropriate monitoring and active feedback or feed forward control interventions can be deployed to ensure consistent quality.

Strategic placement of measurement and control systems. Once CCPs are identified, then appropriate monitoring and control strategies and techniques can be deployed. The placement of these depends on the type of product being manufactured, the degree of process knowledge in place at that time and the quality risk profile of the process.

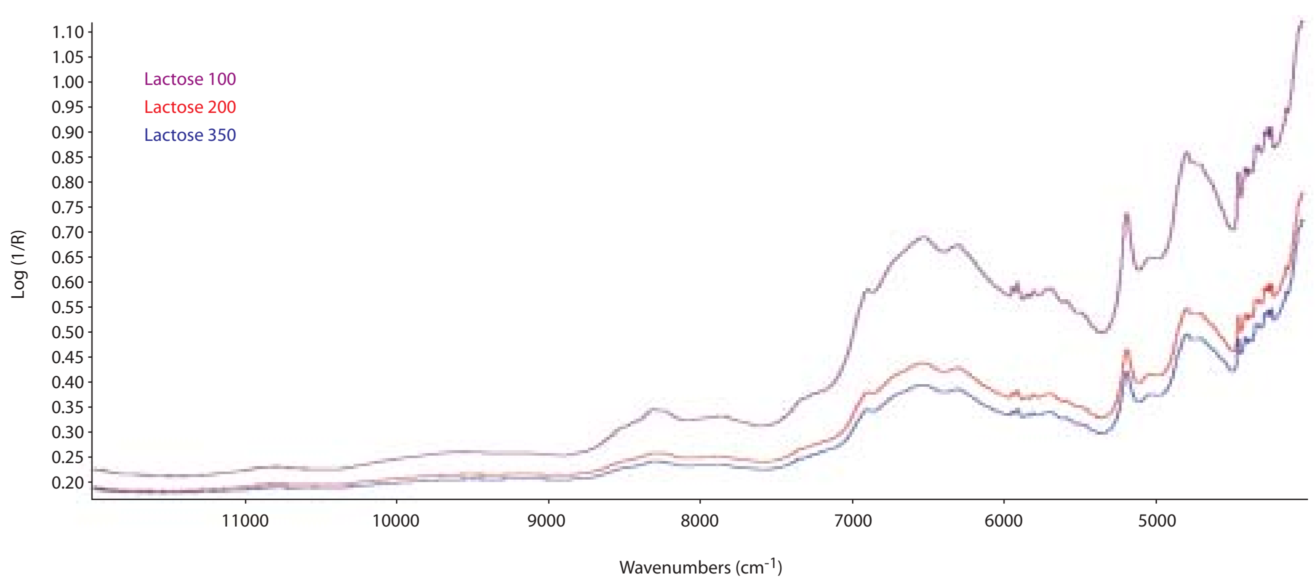
Measurement and control systems can range from simple monitoring of raw material process feedstock (the example used in this article) through to integrated monitoring and active feed forward or feedback process control loops implemented within the manufacturing stages.

Monitoring systems can be in-line, on-line or at-line depending on the required speed of decision making necessary to intervene effectively in the process. The process knowledge and risk assessments performed earlier in the deployment process will guide decision making here.

The Benefits of PAT

The scientific, technical and business benefits of PAT are manifold, and can be realized throughout the product development and manufacturing value chains. Tablet manufacturing is a challenging process with process steps that have high product risk associated with them (used here as an example process).

Figure 2 Process understanding — raw material chemical and physical information from FT-NIR.



This example is based around the use of FT-NIR as the principal monitoring and control tool for a tabletting process (Figure 3). The business benefits of this example are summarized in Figure 4.

R&D Benefits

A robust manufacturing process that leads to a consistently high quality product is a major business goal for pharmaceutical R&D. Another major objective is meeting the time-to-market challenges of ensuring that the product licence is created and approved as fast as possible, to exploit the revenue generation period given by the patent process.

PAT, used correctly, can not only lead to a better manufacturing process, but also speed up the R&D process itself, especially formulation development, scale up, clinical trial manufacture and the technology transfer into the manufacturing part of the business.

As PAT tools are used in R&D to gain process and product knowledge, the same tools can speed up the development process. Using the FT-NIR deployment example, raw material knowledge can be created rapidly, blenders can be monitored and tablets analysed swiftly — allowing formulation development experiments to be performed faster compared with using traditional laboratory support techniques to analyse blends or finished tablets. Imaging techniques can be used on powder blends or finished tablets to identify causes of failure during formulation development and speed up remediation or optimization.

PAT also allows R&D teams to gain sufficient knowledge to challenge the current approaches to specification setting. This could have a significant positive impact in defining raw material specifications in terms that represent not only chemical quality, but also attributes that guarantee successful processability and in-process specifications that ensure onward process success.

As product and process knowledge is gained, and as PAT tools are introduced into product licence applications and rolled out into manufacturing technology, transfer times and costs should reduce. The process is likely to be better understood and more robust than previous generations — and offer less regulatory risk.

Manufacturing Benefits

Once implemented in manufacturing facilities, PAT-enabled processes should produce significant business benefits, typical of those seen in other industries adopting widespread monitoring and control, and leveraging it to adopt lean manufacturing approaches.

Looking at the tablet manufacturing process example again these would include:

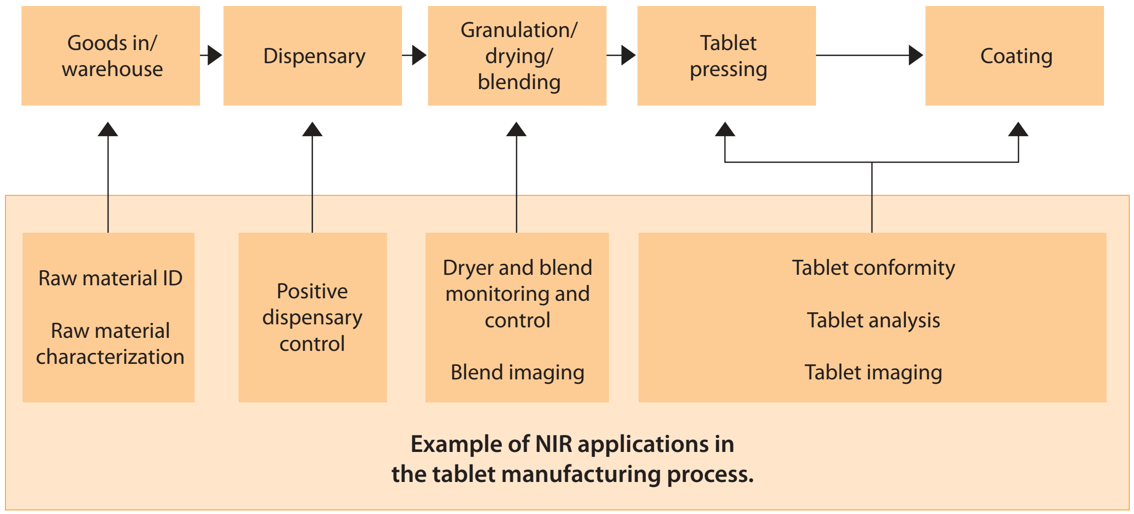
Raw materials monitoring. Faster testing of incoming raw materials, judged against both material identity and processability criteria. This leads to a faster disposition of the material and release for manufacturing. Exploited effectively this can be part of a just-in-time manufacturing regime and lead to:

- Lower inventory levels — quarantine stock and manufacturing available stock.
- Higher velocity of raw materials into the process.
- More stock turns.
- Lower poor quality and QA testing costs.
- Smaller storage buildings needed and/or reduced expansion of current facilities.
- Increased consistency in finished product quality.

Dryer and blender monitoring and control. Monitoring the blender and dyer allows the process steps to be terminated at the optimum product dryness or blend homogeneity for further processing. These are both high-risk processes and process failure here often results in quality failures in the finished product. As well as leading to a more consistent product quality, the batch is released faster and passed on to the next process step quicker. Other benefits can be:

- Higher asset utilization rate.
- Higher process step velocity/faster stock turns.
- Lower work-in-progress inventories.
- Faster cycle time.

Figure 3 Example of NIR applications in the tablet manufacturing process.



Tablet analysis. At-line or in-line tablet analysis to ensure compliance with product conformity specifications offers a near real-time confirmation of a successful blend compression and early warning of problems.

Used in conjunction with other at-line or in-line physical measurement techniques, most of the critical quality attributes of the finished tablet can be measured in the manufacturing area. Batches can be forwarded to the packing stage faster with higher confidence that any subsequent QA release testing will be within specification, allowing the product to be released to the market.

Regulatory Benefits

A manufacturing process created by an R&D organization that understands its product and processes; knows the relative risks associated with each process step; and has risk-mitigated the process with careful placement of monitoring and control systems, will produce products of highly consistent quality. It will be robust enough, through the use of positive controls, to absorb reasonable, and known, amounts of raw material variances and produce quality output batch after batch.

This next generation of controlled and monitored processes should give regulators more confidence in manufacturers' products and allow them to focus their activities elsewhere. A reduced regulatory burden is often quoted as one of the benefits to implementing this approach.

Future Benefits?

While the current emphasis on PAT is getting it up and running in R&D, into product licences and deployed in routine manufacturing, the future benefits of being able to gain high levels of product knowledge, and monitor and control processes are largely untapped.

From PAT tools will stem the ability to recognize a finished product by the chemical or physical 'fingerprint' that a process has to put on it, perhaps leading to tools and techniques that better identify counterfeit products. Each process may put a unique fingerprint or signature of itself onto the product. This could be an artifact of the input materials, physical processing or the tablet press itself. This 'fingerprint' could be used to identify counterfeit from real materials.

Figure 4 The benefits of PAT in the product development and manufacturing of tablets.

	Raw material ID Raw material characterization	→ Dryer and blend Monitoring and control Blend imaging	→ Tablet conformity Tablet analysis Tablet imaging
R&D PAT	Ingredient characterization Specification setting — new definitions Baseline PAT knowledge Supplier qualification Library building early in new product development	Rapid measurement of drying profile — endpoint establishment Rapid measurement of blending profile — endpoint establishment Establish critical control point Limits for a new process Imaging — check ingredient distribution in blend	Rapid at-line or on-line tablet conformation testing Imaging — check ingredient distribution in table Faster formulation development
Manufacturing PAT	Rapid material identification Material qualification — fit for manufacturing Lower material inventory Smaller stores infrastructure Higher stock turns	Monitor and control dryer — optimum cut-off Monitor and control blender — optimum blend cut-off Optimum quality WIP Higher asset utilization Faster cycle time Imaging — advance warning of failed or non-optimum blend	At-line or on-line tablet analysis
Business benefits	Regulatory: earlier licence approval less regulatory scrutiny Quality: more robust process, more consistent product quality Inventory: reduced goods-in inventory, reduced WIP inventory, reduced finished goods inventory, higher stock turns Assets: higher process velocity, higher asset utilization Cost: less scrap, lower cost of poor quality, lower inventory costs		

New ways to define input and work-in-progress specifications, as well as producing multivariate process 'maps' through which actively controlled processes will 'navigate' with appropriate measurement and control technologies, may lead research-based pharmaceutical companies towards strategies for the protection of product revenues after the patent expiry.

Summary

The tools to obtain a deep scientific and engineering understanding of its products and processes are now available to the pharmaceutical industry. This paper has illustrated how just a single analytical technique, FT-NIR, can be used to gain product and process insights and control over quality-critical parts of tablet processes without great investment or infrastructure. Many other tools and techniques are available to scientists and engineers for use in other product processes and to obtain different types of information.

The vision and will to deploy the tools to revolutionize product development and manufacturing, returning high value business benefits, is well established and accelerating within the industry. Regulatory support and facilitation for this is in place through FDA's PAT framework. Increasingly, other regulators throughout the world are also looking to see how they can contribute and harmonize.

PAT will bring substantial technological, quality and business benefits to the pharmaceutical industry — and ultimately to its customers.

What will be interesting to see is the uptake of PAT and the rate at which these benefits will be realized and exploited, and by which parts of the pharmaceutical industry.

The PAT train has left the station, how many passengers it has and how many will join at later stops is a question often asked — not only by the industry itself and its regulators, but by those creating the PAT goods and services vital to ensuring success.

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