Spectroscopy in industry might be primarily a science-based endeavor but ultimately it is about adding commercial value to an organization. Industrial spectroscopists need to become as expert in understanding and delivering business value as they are in the technology and applications.

The pharmaceutical industry is in a unique position at the beginning of the 21st century. It is under unprecedented commercial and societal pressures to deliver value to all its stakeholders, and has been offered one route to achieving this from its principal regulating body, the US Food and Drug Administration (FDA) Process Analytical Technology (PAT) initiative. The method by which pharmaceutical firms can revolutionize the way they bring quality products to market and commercial gains to their shareholders.

Well documented elsewhere, the PAT initiative is about gaining a fundamental understanding of the science and engineering that underpins the manufacturing of a pharmaceutical product, then applying that understanding to intervene and control the manufacturing process, positively influencing the quality of the product.

The breadth of the impact of PAT in pharmaceutical R&D and manufacturing potentially is enormous. This article focuses on only a small part — that of employing spectroscopic tools to investigate, understand, and control the manufacturing process, positively influencing the quality of the product.

A simple starting point in gaining process understanding is at the beginning of any process — knowing and understanding the impact of the sources of variation in the raw materials on the quality of the finished product and any intermediate states. Traditional approaches to measuring the quality of raw materials are based upon identity, chemical purity, and pharmacopeial methodologies. Clearly, using the correct material of suitable chemical quality is fundamental to creating a quality product; but in many pharmaceutical processes, such as tablet manufacturing, it is the physical properties of the materials that have the greatest impact upon product quality. These processes essentially are based upon the handling, mixing, modifying, and compression of powdered materials.

Fourier-transform near-infrared spectroscopy (FT-NIR) is a basic tool used in the process understanding part of PAT. Well established as an analytical tool in pharmaceutical testing, FT-NIR has the ability to give information on both chemical quality attributes and physical properties quickly and easily when coupled with a diffuse reflectance sampling technique. Figure 1 illustrates the optical layout of a typical diffuse reflectance sampling system. The data obtained from the reflection of the sample carries both chemical and physical information. Its speed of deployment and operation also make it a rapid way of creating a database of raw material information that contains valuable chemical, physical, and batch-to-batch variance. Used as part of a PAT implementation, the technique can give rapid paybacks to an organization when integrated into a control strategy.

Figure 2 shows the FT-NIR spectra of a typical raw material library. All are quite different chemically; their FT-NIR spectra are unique, and therefore distinguished easily by eye and by the use of automated identification software. This is one of the main deployment roles for FT-NIR in a pharmaceutical firm but the technique can go well beyond this application; the FT-NIR spectrum can contain information on the physical properties of the material being investigated.

Figure 3 shows the FT-NIR spectra of three microcrystalline cellulose of differing particle size grades. The diffuse reflectance sampling technique used to collect the spectra reveals the particle size difference information. In this example, chemical information from the absorption peak positions, shapes, and basic particle size information, to the broad baseline and relative offsets of the spectra, is obtained from a single simple measurement.

With its abilities to measure both chemical and physical properties of powdered materials, FT-NIR is a primary investigative and control PAT tool. For deployment in GMP areas, the technique also benefits from well-established standardization, qualification, and validation practices readily accepted by regulators and software that can automate the PAT workflow.

**Spectroscopy, Raw Materials, and Process Analytical Technology**

This article explains how Fourier-transform near-infrared spectroscopy (FT-NIR) can be used to gain product and process insights and gain a degree of control over a process by enabling raw material measurement and informed decision-making.

Brian Davies and Scot Ellis

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**Spectroscopy** Solutions for Materials Analysis

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Brian Davies and Scot Ellis
Applying Spectroscopy to Material Characterization PAT

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 often are the first steps in this. The process usually starts with looking at the raw materials used in the formulation, then working through each unit operation leading to the finished product.

At this knowledge-gaining step of the PAT process, the process is investigated from a scientific and engineering context and, importantly, the risks to product quality are 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 processes are developed is started.

Process understanding allows the high-risk process steps to be identified and from that base, it leads to the identification of critical control points. This approach can be achieved as part of a product improvement activity for an existing market authorization or as part of the product and process development stage for a new product. Increasing the body of knowledge in a product and process goes on throughout the whole lifecycle of the product, continuing throughout the manufacturing phase.

Figure 4 shows a basic PAT process flow for a new product. For this article, the focus on FT-NIR for control through knowledge of raw materials is added but a similar scheme can be applied generically. The typical flow is:

- Gain process and product understanding through applying a variety of PAT tools (for example, FT-NIR) in the product development and process development phases of R&D.
- Use a risk-based assessment of the process to identify critical control points.
- Create and deploy a quality control strategy for the process and product based upon PAT principles.

Figure 4 also shows the FT-NIR raw materials characterization part of the control strategy. As the strategy is implemented, the data and process knowledge created by it are fed back into the body of process understanding as part of its refinement loop.

FT-NIR and Raw Material Characterization

Raw material characterization allows a number of control strategies to be deployed. This article illustrates how a pharmaceutical manufacturer can exploit a series of progressive control measures utilizing the information-rich FT-NIR spectrum of a raw material.

How and when each strategy is deployed will depend upon the product, the robustness of the manufacturing process, and risk profile determined in the knowledge-gathering phase of the PAT project. The three levels of control described here are triaging raw materials effectively at the early stage of manufacturing before value is added through processing. At this point, a control intervention is relatively easy and low cost to implement.

0th order control: Passive Control. At this basic level of control, a raw material arriving at a manufacturing plant is tested by an FT-NIR system situated in the goods-in or receiving facility. The spectrum of the material is checked against a raw material identification library to confirm its identity. The same spectrum also is tested against a
FT-NIR enabled control of process through raw material knowledge management.

If the material fails to belong to either category, it is rejected as a batch suitable for manufacturing. Often, raw materials are inexpensive and, depending upon how the supplier relationship is set up and/or the type of material, the batch could be returned to the supplier for remediation or simply scrapped. At this point, even the scrapping of a material batch is better than moving it into the process, wasting manufacturing assets, tying up QA/QC people in CAPA investigations, and contributing to the cost of poor quality budget of the organization.

One other strategy is to outsource this part of the PAT control strategy to the raw material supplier. In essence, the supplier carries out this step as their final product QA and does not ship materials that are unfit for purpose. Accepting the material then becomes simply a confirmation of identity in case of a transit or labeling failure.

1st order control: Simple Active Control. This more advanced control strategy uses process knowledge to direct a batch of raw material to a specific product or process that will result in an optimum product quality. During the process knowledge generation phase, it is determined that some batches of a material with a certain FT-NIR spectrum go on to process well for a given product. Other batches of the same material process well for another product. Typically, this will be for an excipient and the spectral characteristic will be some expression of physical form such as particle size or particle size distribution. This is a type of supervised discriminant analysis, and many spectral matching and discriminant algorithms exist for distinguishing between materials. The approach is shown diagrammatically in Figure 5. A matching metric is used to discriminate between the FT-NIR spectra of different batches of a raw material that perform well in Product A and Product B. Defining which batches belong to which group is part of the training of the system, and the product knowledge comes from the process understanding phase of the PAT project.

The test sample batch is evaluated against both groups and is found to lie within the boundary of Group B. That batch of material then is used in Product B in preference to Product A. The assumption is that whatever characteristic in the material that allows it to perform well in the process is expressed in the FT-NIR spectrum.

2nd order control: Complex Active Control. The next level of control relies upon establishing a more complex link between the FT-NIR spectrum and the process step. It assumes that during the process knowledge generation phase, it is determined that a relationship exists between the FT-NIR spectrum of a raw material and a specific process setting, say mixing time, drying time, or tablet compression pressure, that leads to an optimal process step outcome.

This complex relationship then is used to feed forward into the process settings from an evaluation of the FT-NIR spectrum. The three levels of control described here, and their application within a raw material characterization regime, are shown schematically in Figure 6.

The degree to which these levels of control are implemented and executed will depend upon the process, raw materials, and the causal links established at the process knowledge generation phase of the project. This will be linked closely to the risk mitigation strategy decided for the overall manufacturing process.

It is likely that an organization will start off with the Passive Control model at first and progress through Simple Active Control as more process knowledge is revealed. Progression to the Complex Active Control will only happen if and when a direct process control relationship is discovered, explored, and validated.

Automated Deployment of an FT-NIR PAT System
To be effective, the FT-NIR system must be deployed in a GMP controlled environment and ideally should be automated and integrated into the manufacturing quality and process control infrastructure. Figure 7 shows a typical PAT workflow that can be run automatically by an FT-NIR system. Samples are analyzed and results generated automatically. The data and derived identity, chemical, and physical information then are stored in a database for adding to the PAT body of knowledge for the product and an OPC connection made to facilitate control.

The principal benefit of implementing PAT control through knowledge of raw materials and FT-NIR will be more reliable product quality. Clearly, more reliable, predictable product quality has benefits for the patient in ensuring a secure supply of effective medicines, a main driver for both the pharmaceutical manufacturer and their regulating bodies. However, many other benefits to the pharmaceutical manufacturer can be realized from using FT-NIR to gain an understanding of the impact of raw materials on the process and

Figure 6. FT-NIR enabled control of process through raw material knowledge management.
The time-to-market challenges of ensuring the product license is created and approved as fast as possible to exploit the revenue-generation period given by the patent process. PAT, correctly used, can not only lead to a better manufacturing process but also can 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.

PAT also allows R&D to gain knowledge to challenge the current approaches to specification setting, especially using the FT-NIR spectrum of a material as part of its specification. This could have 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 license 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 in manufacturing plants, 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. This includes faster testing of incoming raw materials, judged against both material identity and processability criteria, leading 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 cost of poor quality costs and QA testing costs
- Reduced warehouse requirements or expansion of current facilities cut back
- More consistent finished product quality

These are summarized in Figure 8.

**Summary**

The tools used to obtain a deep scientific and engineering understanding of its products and processes are now available to the pharmaceutical industry and encouraged through the PAT initiative. This article has illustrated how a single analytical technique, FT-NIR, can be used to gain product and process insights and gain a degree of control over a process from simply measuring raw materials and making a set of process decisions. Many other spectroscopic tools and techniques, such as Raman and hyperspectral imaging, also 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 spectroscopic tools like FT-NIR to create scientific and engineering knowledge is well established and accelerating within the pharmaceutical industry. Raw material characterization is the first step in the use of NIR spectroscopy; blender control, dryer control, and tablet analysis come next.

**R&D Benefits**

A robust manufacturing process that leads to a consistently high-quality product is a major business goal for pharmaceutical R&D, as is meeting product, and then apply this understanding to control.

**Figure 7.** PAT workflow for characterizing raw materials and feeding information into process control infrastructure.

**Figure 8.** Summary of business benefits from characterizing process raw materials.

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