

JOINT PHARMACEUTICAL ANALYSIS GROUP

# Process analytical technology: the challenge for analytical science

*The science base underpinning pharmaceutical development and manufacture has failed to keep pace with available technology. The drivers, means and benefits of adopting a process analytical technology strategy, its facilitation in the regulatory environment and its impact on analytical science and the analyst were reviewed in a workshop held by the Joint Pharmaceutical Analysis Group at the Royal Pharmaceutical Society's London headquarters on 4 December. Dr Joseph Chamberlain reports*

**K**en Leiper, of Benson Associates, reviewed the present situation and the drivers for the development of process analytical technology (PAT). The largest cost to pharmaceutical companies was in manufacture so that even a 1 per cent improvement in this area would mean a saving of hundreds of millions of dollars. Yet, the pharmaceutical industry compares unfavourably with other major industries (food, automobiles) in its efficient use of resources, characterised by large, inefficient batch equipment, low product yields, long lead-times due to stage and final product testing, high operating costs, high inventories and excessive warehouse space. It is capital and labour intensive, and improvement is invariably limited by regulatory constraints.

In the analytical area, too much emphasis is placed on aspects of the analysis that are least critical, and a typical analytical procedure involves consecutive, time-consuming steps. The analytical emphasis needs to be on timely provision of information that contributes to final quality. Although the current approach is probably delivering as much as is reasonably possible in respect of safety and efficacy, this is at the cost of a significant impact on regulation and manufacture.

Process analytical technology is not new: there has been industry interest for at least 35 years as a problem-solving tool but there has been little or no industry pressure to bring it into the mainstream regulatory environment. The United States Food and Drug Administration is now preparing to discuss mechanisms to redress this situation. The aim now is to institute systems for analysis and control of manufacturing processes based on timely measurements, during processing, of critical quality parameters and performance attributes of raw and in-process materials and processes to assure acceptable end product quality at the completion of the process. The FDA will encourage companies to move away from current univariate prescriptive testing to multivariate process-focused measurements.

These initiatives provide a dynamic regulatory framework that will address the causes of poor performance rather than the symptoms, drive the introduction of innovative manufacturing measurement and control technologies, and allow quality and performance to be designed into manufacturing scale processes.

We must understand all our processes, said Mr Leiper, and promote a regulatory

and industry environment where relevant science is used to drive quality by design in development and manufacture.

## THE CURRENT TOOLBOX

Because of the demands of a wide range of potential applications encompassing chemical, physical and spatial characterisation, PAT requires a toolbox of suitable techniques, said Don Clark, of Pfizer R&D, Sandwich, Kent. Such a toolbox contains the full range of spectroscopic techniques from X-rays to radio waves. Near infrared (NIR) spectroscopy is a well-established technique for on- and off-line applications for both the solution and solid state; it is non-invasive, non-destructive, and no sample preparation is needed. NIR can be used for real-time process monitoring (qualitative and quantitative analysis of excipients and active ingredients, blending end-point determination, determination of polymorphism) and is easy to use with simple, low-cost equipment. However, NIR data interpretation is not intuitive or chemist-friendly and substantial data manipulation is often needed to extract useful quantitative information. NIR cannot always link results to simple properties of the system and is essentially a black box approach.

Fourier transform infrared spectroscopy (FT-IR) is another well-established technique for on- and off-line use for solution and solid-state material; it gives direct information on molecular vibrations and is relatively amenable to direct interpretation. FT-IR is not so useful for polymorphism (compared with other spectroscopic techniques) but it is readily available at low to medium cost.

Raman spectroscopy is a powerful technique, becoming much more widely used and provides chemical and physical information. On-line systems are commercially available at reasonable cost. It is a particularly powerful technique for polymorph identification.

Although ultraviolet spectroscopy is a central technique in analytical chemistry (for example, as a high performance liquid chromatography detector), it is of limited use in process monitoring; analytes must have a chromophore, they must be in solution, and chemical discrimination is poor.

*Dr Chamberlain is a former editor of the Journal of Pharmacy and Pharmacology*

Acoustic emission spectroscopy is an emerging technique as described elsewhere in this report.

Chemical imaging combines microscopy with spectroscopic information to give spatial characterisation of solid samples. A particularly impressive example was the demonstration of the distribution of individual particles of active drug material in a tablet using X-ray microtomography. Imaging technology is evolving rapidly, the first imaging system being demonstrated in 1998. However, at the moment, it is still an expensive, low-throughput technique.

Additions to the toolbox are likely to include nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry. Although NMR is a solution-based technique, it provides much structural information and newer technologies may make it viable for on-line use in manufacturing areas. Mass spectrometry is sensitive and can track single components in a mixture using molecular weights.

## FORMULATION AND PROCESS DESIGN

Robust formulation and process design starts in R&D, said Dr James Krausnoe, AstraZeneca, Charnwood, Leicestershire. The impact of process analytical technology is to emphasise that R&D must employ a holistic approach and understand the nature of all parts of the manufacturing process; in practice this will mean carrying out a thorough review of raw material and the viability of intermediary processes. Available information must be maximised to build process understanding.

NIR may be used both for screening of raw materials and for characterisation of the final product (hardness, content uniformity of tablets). Its importance in improving the manufacturing process can be illustrated by considering the effect of including NIR early in the analysis cycle, providing prediction of final properties to correlate with measured properties at a later stage. This continual evaluation of the manufacturing process provides information on such parameters as dry mixing, granulation, drying, milling, compression and subsequent formulation of a control strategy.

The full implementation of PAT will involve the integration of analysts, formulators, process engineers, and support functions including quality assurance, engineering and regulatory affairs, requiring management commitment across the

whole of R&D. Any new product introduction will require a strategy that includes PAT technology. R&D should ensure the analytical function stays off the critical path of the manufacturing process, Dr Krausnoe said.

#### VARIABILITY IN MANUFACTURE

Martin Warman, of Pfizer Global Manufacturing, Sandwich, Kent, said that the role of PAT was to provide process knowledge during, rather than at the end, of the process. This would be achieved by monitoring multiple parameters to enhance process knowledge. Attributes of critical process parameters need to be established and used for direct feedback control to reduce variability where possible and ultimately put an end to the monitoring of non-critical parameters. For example, NIR data were used to monitor a reaction to ensure completion, but more importantly confirmed the reproducibility of the time course of the reaction. In another example, crystal size was monitored during a crystallisation step to allow the control of fines or agglomerates as well as control of particle size and the elimination of the need for milling. NIR was used to monitor blending, with subsequent benefits for safety (no operator contact), reduction in sampling errors, real-time information, multi-ingredient uniformity, process understanding, and reduced cycle times (fast release of the blend). NIR was also used for estimation of blend segregation in the bin and for automated analysis of tablets.

There has been a paradigm shift, said Mr Warman, from a laboratory-based approach to a process-based approach.

#### ACOUSTICS

In process analytical technology, an ideal method would be non-invasive, non-destructive, relatively inexpensive, have a short measurement time, and be intrinsically safe. The emerging technique of acoustics had these attributes, said Professor David Littlejohn (University of Strathclyde). In this simple technique a transducer containing piezoelectric material is glued to the outside wall of a reaction vessel and the acoustic information collected and processed. Acoustic measurement could be passive (where the process is the source of the acoustic wave) or active (where the acoustic wave is put into the process and the change in velocity or attenuation is monitored). In an example to demonstrate monitoring of a mixing process, acoustic measurement was shown to give similar results to the established near infrared methods. Additional information could be obtained from the acoustic spectra; for example, at lower frequencies (less than 50kHz), the signals obtained were dependent on the particle size of citric acid added to Avicel, whereas at higher frequencies (50–150kHz) the signal depended only on the amount of citric acid added.

Heterogeneous reaction monitoring is sometimes difficult to monitor with optical

spectroscopic techniques and acoustics could assist in this area by monitoring the consumption or production of particles, appropriate kinetic studies, and end-point detection. For example, in the reaction of itaconic acid with 1-butanol in toluene to give mono- and di-esters, only the itaconic acid is a solid under the reaction conditions. Acoustic emission spectra successfully monitored the disappearance of the acid in real time, comparing favourably with the standard HPLC method for determining the formation of the esters. In work carried out so far — and Professor Littlejohn emphasised this work is continually expanding — it is apparent that acoustics can be used to monitor a wide range of processes, providing complementary information to molecular spectroscopic techniques to give real-time information from product discovery through to full-scale manufacture. The use of multiple sensors appropriately placed around the reaction or mixing vessels would also provide spatial information. The wider use of acoustics for process monitoring will require advances in transducer technology, signal processing, signal interpretation (including mathematical modelling), and most of all a multidisciplinary approach, Professor Littlejohn said.

#### THE REALITY

PATs provide additional tools for manufacturing process development, said Bob Chisholm, of AstraZeneca Engineering. The use of these tools has led to greatly improved process understanding in the pharmaceutical development phase which translates through technology transfer into effective and efficient manufacturing processes. Identified critical formulation and processing factors are monitored and controlled to prevent or mitigate the risk to quality (real-time quality control and quality assurance).

Regulatory policies and procedures will be tailored to recognise such approaches and regulatory scrutiny or inspections appropriately applied. This risk-based approach by the pharmaceutical industry will be mirrored by a risk-based approach to regulation.

The AstraZeneca solid dosage facility in Germany incorporates networked in-line NIR analysers at each unit operation providing the capability to monitor key process variables identified in the risk assessment process. Each incoming raw material in the active and excipient dispensaries is identified and characterised; moisture in the fluid bed drier is monitored and there is continuous on-board monitoring of powder blending. Statistically based in-line monitoring of tablet quality parameters is carried out throughout the batch.

The system includes four NIR analysers with seven spectral inputs and appropriate computer stations. The resulting real-time quality control and quality assurance provides the platform for real-time release of product.

Thus PAT increases process understanding and when used in a manufacturing

execution system is a key component in the toolbox to deliver manufacturing excellence. Through this understanding, PAT is an effective tool to improve robustness of existing as well as newly developed processes, Mr Chisholm said.

#### REGULATORY FACILITATION

For the final paper Dr Ajaz Hussain, FDA, Washington, joined the meeting by satellite link and presented the agency's draft guidance for industry, "PAT — a framework for innovative pharmaceutical manufacturing and quality assurance". Working with existing regulations the draft guidance describes a regulatory framework to encourage the voluntary development and implementation of innovative pharmaceutical manufacturing and quality assurance, said Dr Hussain. There were two components to this framework: a set of scientific principles and tools supporting innovation, and a strategy for regulatory implementation that will accommodate innovation.

Atypically for FDA guidelines, this guidance is written for a broad industry audience in different organisational units and scientific disciplines and it discusses principles with the goal of highlighting technological opportunities and developing regulatory processes that encourage innovation. Companies ready with innovative ideas for implementation should propose to the agency a scientific, risk-based implementation plan and the preferred regulatory path for implementation. The agency is ready to provide a scientific assessment of the proposal before a submission to define the type of data needed to evaluate the proposal and provide a mutually acceptable regulatory path.

PAT is a system for designing, analysing, and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality. It works on the principle of quality by design. The design of manufacturing processes using sound principles of engineering, material science, and quality assurance ensures acceptable and reproducible product quality and performance throughout a product's shelf life. Gains in quality, safety and efficiency will vary depending on the product and are likely to come from: reducing production cycle times by using on-, in-, and at-line measurements and controls; preventing rejects, scrap and reprocessing; allowing the possibility of real-time release; giving increased automation; facilitation of continuous processing; use of small-scale equipment (to eliminate certain scale-up issues) and dedicated manufacturing facilities; improved energy and material use; and increased capacity.

A desired goal of the PAT framework is to design and develop processes that can consistently ensure a predefined quality at the end of the manufacturing process.

The next steps will be to collect public comments, issue the final guidance early next year, and mount workshops on this guidance, said Dr Hussain.