The analysis of inhaled products

At the heart of any review of the key analytical issues in global product approval for inhaled products is the matter of complexity, said Prasad Peri, of the US Food and Drug Administration. The products themselves are complex, with physical interactions between the ingredients and the devices employed. Complexity also occurs in the variable nature of the patient and in the analytical methods used to monitor the systems.

Reviewing regulatory aspects of the analysis of inhaled products, Dr Peri concentrated on the physical chemistry properties of the product rather than on content identity or quality. He said that the analyst needs to consider particle size distribution and dose content uniformity, spray patterns, plume geometry, device robustness and characterisation, and drop testing. The dosage forms could be aerosols (as solutions or suspensions), dry powder inhalers (with or without carriers), nasal sprays, nebulised products or inhalation sprays. The devices could be press-and-breathe metered-dose inhalers (MDIs), breath-actuated MDIs, premetered dry-powder inhalers (DPIs), device-metered DPIs, nebulisers with face masks, nose masks or ventilated systems.

Dr Peri’s review emphasised that quality by design was as important an issue with inhalation products as it was with conventional dosage forms. The FDA proposed to update the draft MDI/DPI guidance accordingly.

Methodology

Reviewing the key analytical issues in expediting formulation development, Philippe Rogueda, of Novartis, emphasised the need for analytical tools for measuring properties to predict product behaviour. These tools need to be rapid and accurate and able to provide predictability.

From the formulator’s perspective, information is needed to help theory and understanding. For solids and dry powder inhalers the favoured method is rheology, particularly in the determination of the flowability of powders. The simple test of measuring resistance experienced by paddles immersed in powders provides a rich source of information on bulk powders. With further advances in the science, rheology is expected to be even more fruitful, said Dr Rogueda.

Atomic force spectroscopy

The end of the spectrum is the application of atomic force spectroscopy (AFM), which gives information at the individual particle level. Discussing this technique, Clive Roberts, from the University of Nottingham, said that structural and chemical analysis at the nanoscale has rapidly progressed in recent years. In particular, the use of AFM has a key role in the increasing demand for nano- and microscale control and characterisation of pharmaceuticals.

AFM has the potential to be a standard multifunctional approach to the analysis of formulations, said Professor Roberts. It provides information at the level of single particles or even molecules and is therefore a flexible platform for studying particle interactions. However, such characterisation can do more than act as a quality controlling procedure and may play a large part in formulation development itself.

Discussing whether nanoscale AFM measurements can be routinely translated to predict bulk formulation behaviour, Professor Roberts said that this is not obvious, or perhaps even likely, because particulate interactions and powder behaviour result from a complex mix of factors, including surface topography, shape, size, size distribution, density, mechanical properties, exposed chemical moieties, environmental conditions and thermodynamic properties such as surface free energy.

This range of factors usually requires the application of a number of analytical approaches, including AFM, inverse gas chromatography, isothermal microcalorimetry, contact angle, liquid penetration of a powder bed, centrifuge-based techniques, modelling, and particle sizing.

The disadvantage of AFM, said Professor Roberts, is that measurements are based on data gathered from small contact areas. It is therefore difficult and time consuming to build up a full view of properties of the whole sample and it is hard to separate errors in measurement from true variation in sample properties.

Nevertheless, AFM has a proven ability to quantify properties such as topography and roughness, surface energy and mechanical properties. Its advantages include the need for only small amounts of material — an important factor in early screening. It is a sensitive technique and will reveal heterogeneity in samples.

The provision of multivariate data from AFM can provide a potentially powerful tool for predicting bulk behaviour from nanoscale measurements, concluded Professor Roberts.

Cascade impaction

Describing the routine use of cascade impaction, Frank Chambers (AstraZeneca) said that the Andersen cascade impactor is the long-established industry standard. It is robust and compact and its performance is well understood. However, sample preparation in situ is impossible, interstage losses can be high, and a high degree of skill, including manual dexterity, is needed to obtain consistent results.

The so-called “next generation” impactor is the first compactor designed specifically for the pharmaceutical industry. However, there have been some initial quality issues. New developments are expected to include abbreviated impactor measurements and a simplified impactor-based approach to the problem of aerosol particle size characterisation in inhalers.

The drive to improve analysis efficiency has led to a new focus on seeking alternative approaches to full impactor testing. An interesting alternative is direct spray mass spectroscopy, said Mr Chambers. Current screening techniques lack specificity to drug components in the formulation. The selectiv-
Laser diffraction
Nasal sprays are combination products and the interaction of the device and the formulation is deemed critical from the regulatory point of view, said Dr Paul Kippax, of Malvern Instruments. There is a need to ensure reproducible delivery and droplet size analysis is used to assess quality (through laser diffraction) and efficacy (deposition location).

The technique of laser diffraction provides access to dynamic information, wide dynamic range measurements, measurements under realistic conditions, and formulation screening capabilities. The technique has to be robust enough to cope with the complexity of the potential products in development.

Examples were demonstrated for the nasal sprays in the presence of viscosity modifiers, determining atomisation dynamics and monitoring performance during the product life. Experiments showed significant time-dependence for the aerosolisation process for spray devices.

Laser diffraction offers a significant and robust aid to device and formulation selection, as reflected in the FDA's guidance for nasal sprays, concluded Dr Kippax.

NMR spectroscopy
Nuclear magnetic resonance (NMR) spectroscopy offers many advantages within pharmaceutical development, said Dave Martin, from AstraZeneca. It provides a unique resonance pattern for all samples, and can be used for identification and full structural characterisation.

Because all protons give equal responses, the technique is inherently quantitative. Multiple tests can be carried out on a single spectrum. The same test can be used for drug substance and drug product, and NMR is widely accepted by the regulators.

NMR has some disadvantages. These include cost and relative insensitivity (typically 1–2 mg is required per analysis). Samples must be fully dissolved in deuterated solvents, and true quantification requires an internal standard.

On the face of it, NMR is not suitable for pMDIs, because therapies in these devices are typically formulated with highly volatile solvents, solutions or suspensions and have no NMR internal standard. Nevertheless the technical challenges are being overcome by techniques such as solvent suppression, where the basic aim is to remove the dominant solvent signal, and selective excitation, where the basic aim is to excite only the desired but weak signal from the analyte.

Examples of both techniques demonstrated the effects of salt form, solvent and excipients on solubility, the success of testing drug substance in drug product, and the identification of common extractables and leachables.

NMR clearly has a role to play in future pMDI development, concluded Dr Martin.

In vitro–in vivo correlations
Testing inhalation devices by in vitro methods assumes that the measurement chosen bears a relationship to the efficiency whereby the drug is delivered to the lung. Hence it is pertinent to establish a relationship between in vitro and in vivo data, said Gary Pitcairn, from Pfizer. The primary interest is the emitted dose and particle size distribution and, in particular, the fine particle fraction. Passive dry powder inhalers require the patient to breathe through the device to generate a powder aerosol.

The effort that patients put into inhaling through a powder inhaler can vary tremendously, depending on age, disease state and the patient's interpretation of the instructions for use. The way patients inhale through the device can significantly influence how much drug reaches the lungs. In vivo assessment can be by radionuclide imaging or by applying pharmacokinetic principles to biological fluid measurements of the drug. Imaging studies can be carried out with clinical doses and they provide data on drug deposition in the respiratory tract. The amount of drug in the device or exhaled, as well as regional lung deposition data. However, radioaerobulbing is technically challenging, there is a risk associated with a radiation dose to subjects, and studies require highly trained staff to acquire and analyse data. Pharmacokinetic studies are easier to perform, with no radiolabelling issues, and it is easier to demonstrate linear dose-response relationships. However, data from urine or plasma is an indirect measure of lung delivery, plasma or urinary concentrations may not be measurable at clinical doses, and they do not provide data on deposition patterns. Establishing a relationship between in vitro and in vivo data for DPIs is challenging, with numerous factors to consider.

Can one use cascade impactor data to predict either the dose or site of lung deposition, asked Dr Pitcairn. We do not have a clear understanding of how impactor data correlate with the amount of drug delivered in vivo. The impactor is used to assess reproducibility of drug delivery, not predict lung delivery. However, the use of a smaller cut-off size for the fine particle fraction may improve the correlation for DPIs. Ex vivo testing (ie, use of patient profiles and standard in vitro testing) is a useful tool for demonstrating or comparing product performance at clinically relevant flow rates. Studies using ex vivo testing and oropharyngeal cast suggest that it may be possible to predict average in vivo lung dose from in vitro tests.

Perhaps we need a new way of measuring and evaluating the aerosol that would allow a fuller characterisation of the small delivered particles rather than just measuring the respirable mass, concluded Dr Pitcairn.

Company collaboration on automation
The analytical testing of inhaled products involves a high degree of manipulation combined with the collection of airborne micronised drug particles in relatively small amounts, said Dave Russell-Graham, of Pfizer, in a joint presentation with Andy Rice, of GlaxoSmithKline.

When the testing is conducted manually in the laboratory the process is time-consuming and open to variability, leading to data that may not truly represent the product under test. On a practical note, the very act of conducting the testing may induce repetitive strain injuries in the analyst. Automation in the laboratory may mean computers to the information manager and the fully mechanised laboratory or just mechanics to those seeking simple laboratory aids.

For testing of inhalation devices, Dr Rice and Dr Russell-Graham identified a knowledge gap — what do we not know about our sample preparation? This included ignorance of ambient conditions at time of dosing, the exact time of day, flow rates at the time of drug capture, how the device was operated, the exact process used to perform the test, and whether the test was carried out correctly.

The challenges in automation were in delivering the right level of automation to match the company's needs and expertise, and to keep manual methods (internal and external) with the right experience and knowledge, and the right breadth of support functions needed to complete the project. The latter would include company IT departments, engineering and maintenance, safety standards, quality assurance personnel, project management and cultural and regulatory differences between the US and Europe.

A case study described involved a dry powder inhaler test for batch release and stability testing. The two companies had similar machines, processing 50 to 100 samples a day with unattended operation. It was concluded that automated integration was possible.

Examples of automation already implemented included joint projects between Pfizer and GSK and between AstraZeneca and GSK. But their development had not been without blood, sweat and tears along the way.

Sample preparation is the source of most method variation and the least understood of the process, the speakers said. Back-end engineering automation onto existing products is fraught with difficulty and is costly. The analytical strategy needs to be created early in product development. Translating manual actions to mechanical operations is difficult. Engineering design is not a core skill for analytical chemists and analytical chemistry is not a core skill for engineers.

Automation delivers product development information, data quality benefits and ultimately productivity but both speakers stressed the need for an automation strategy before obtaining management long-term commitment for costs and resources.