Innovation in analytical tools: More signal and less noise in particle size testing of inhaled products

Improved analytical methods can enhance the speed of device development, device performance and testing productivity

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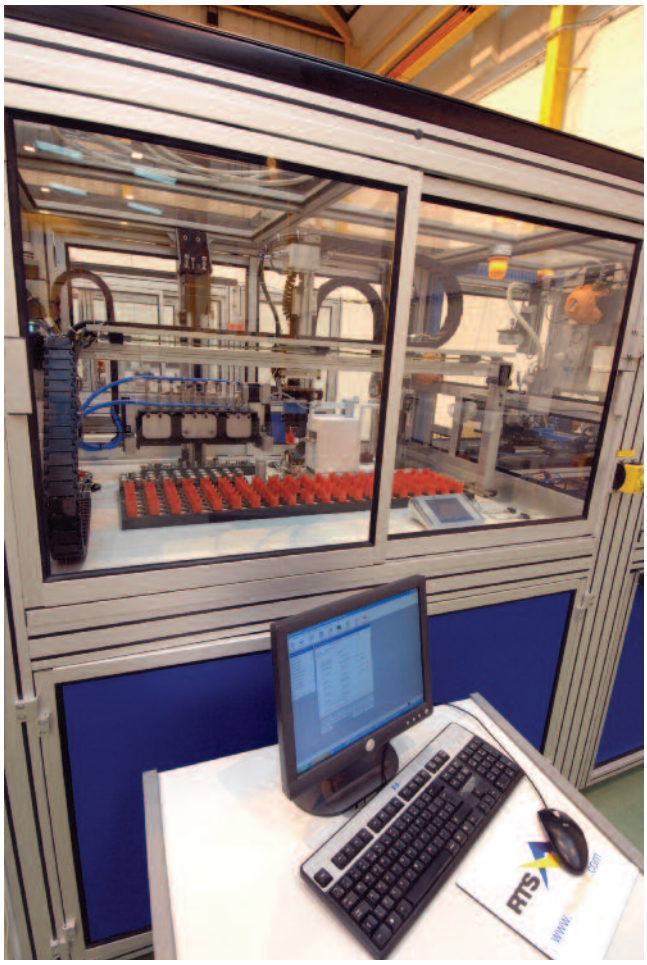
Introduction

The effectiveness of orally inhaled and nasal drug products (OINDPs) is highly dependent on the aerodynamic nature of the drug-containing particles emitted by such devices. During the past decade, the combined need for accuracy, repeatability and speed of analysis has consistently driven new analytical tools to the marketplace. This trend is expected to continue, particularly as the "Quality by Design" (QbD) approach to product quality control is adopted by pharmaceutical companies and accepted by regulators.

Cascade impaction testing (CI) is an *in vitro* technique accepted by industry and regulators for measuring aerodynamic particle size distribution (APSD), and more particularly, for determining the aerodynamic size of the drug-containing particles delivered by OINDPs. The technique enables practical sampling of a complete dose with selective assay of active ingredients as a function of aerodynamic diameter. It also facilitates quantification of the fine particle fraction (FPF), the portion of the drug residing in particles smaller than 4-6 μm that may be deposited in the lung sufficiently deeply to deliver a therapeutic benefit.

Although the APSD test results do not bear a simple relationship to *in vivo* clinical performance,[1] APSD testing is a sensitive analytical probe for product development and quality control, provided analytical processes are appropriately controlled and robust.



This review describes some of the innovations being made in this regard.

The challenges of impactor testing in the context of Quality by Design

Innovations in analytical methods often aim to increase the "signal" to "noise" ratio of the measurement. For OINDPs, the "signals" are changes in APSD profile resulting from intentional or unintentional change to the formulation, the container closure system and the manufacturing process. The "noise" comes from factors external to the product that impact analytical results, including random variability between measurements, laboratories, and equipment and systematic operator bias.

All of the product factors listed in Table 1 are comprised of sub-factors. For example, metering and filling can be defined in terms of the equipment design, metering methodology, fill speeds and pressures. Analytical factors are also related to sub-factors; for example, shaking and actuation is defined in terms of motion profile, duration, amplitude, frequency, dwell time, actuation speeds and forces.

Essentially hundreds of factors can impact the measured APSD of any given inhaler. Given the wide range of attributes and parameters that impact OINDP quality, there are substantial challenges to identifying and quantifying critical quality attributes (CQAs) and critical process parameters (CPPs) that are the cornerstone of the Quality by Design approach.[2-3] The QbD concept is widely practiced in other manufacturing industries, but is relatively new to the pharmaceutical industry, which has traditionally adopted approaches relying on quality by inspection.

Optimizing signal to noise ratio: A justification for automation and better tools

During product development, APSD data are used to evaluate planned product changes and optimize performance in line with existing products or theoretical models. Although cascade impaction testing has limitations, it still provides a reasonable *in vitro* indicator of clinical response and is an excellent QbD tool for exploring the design space of new products.

In a quality control setting, the requirements are different. Here CI testing is required to detect changes that may have impacted product performance. The worst case scenario is an out of specification (OOS) event, which would need to be thoroughly investigated.

In both cases, CI testing can be hamstrung by a poor signal to noise ratio. OOS events and significant changes can be expected to be consistently detected, but subtle changes and trends in APSD profiles may be masked by noise in the measurement system.

In a QbD paradigm, identifying and controlling product CQAs and CPPs cannot be done in isolation. One must also endeavor to understand and control the critical analytical method parameters.[3] Human factors are particularly significant as methods require physical operations that are complex and repetitive. QbD clearly requires tools that allow analytical method parameters to be measured, controlled, explored and understood.

APSD testing as a series of operations

The principles and practicalities of APSD testing are well described in the pharmacopeia and relevant articles and texts,[4-6] however for the purpose of this article, it is useful to consider the process in three main stages:

- **Sample collection:** This is the process whereby an analyst or machine assumes the role of a patient, conditioning the inhaler in a way that a dose can be introduced and delivered into the cascade impactor for subsequent analysis.
- **Sample preparation:** Having fractionated the delivered dose in the impactor, the analyst must prepare samples for analysis. This involves disassembling the impactor, washing components with solvent to recover the deposited drug(s), and collecting samples for analysis.
- **Sample quantification:** Finally the samples are analyzed to "assay" the concentration of active pharmaceutical ingredients and enable the mass of drug deposited on each impactor stage to be calculated. High performance liquid chromatography is the typical analytical finish used with OINDPs.

Table 1

A summary of pMDI APSD analytical factors

Product factors "signal"			Analytical factors "noise"		
Formulation	**Container closure**	**Manufacturing process**	**Laboratory**	**Equipment**	**Operator**
API(s)	Metering valve	Mixing/ homogenization	Temperature and humidity	Impactor variability	Inhaler shaking and actuation
Propellant	Canister	Metering/ filling	Atmospheric pressure	Pump and flow control	Impactor recovery and washing
Excipient/ co-solvent	Actuator	Canister/ valve crimp	Electrostatics	HPLC or equivalent analytical finish	Record keeping and calculation

The following discussion focuses on developments in the area of sample collection.

Better signals: Engineering improvements and better tools

The development of the Next Generation Impactor (NGI) is an interesting case history in developing an analytical tool to be less susceptible to noise.

Historically, most impaction testing was performed using the Andersen Cascade Impactor (ACI). Its use in testing with OINDP pharmaceutical testing was first described in 1973. The ACI became the standard tool for APSD profiling despite challenges such as inherent sensitivity to flow rate variations and stage loading as well as ambiguous engineering specifications.

In the late 1990s, the pharmaceutical industry formed a Next Generation Impactor (NGI) consortium to develop a new impactor more suited to OINDP testing.[6] Development objectives for the NGI project included ensuring more consistent particle cut sizes at a wider range of experimental flow rates and stage loadings, and creating a robust engineering specification for manufacturing and inspection purposes.

In terms of increasing engineering control, the NGI project delivered a clear specification for diameter and geometry of impactor stage nozzles. This contrasts sharply with the historically ambiguous specifications for the ACI as illustrated by the US Pharmacopeia,[4] where specifications for the NGI preceded those for the ACI by three months.

The NGI features a unique collection cup design arranged in a single plane to simplify manual handling, and in theory automation, by allowing the collected particle fractions to be removed as a single unit. Improving usability in this way boosts productivity.

The Next Generation Impactor & Copley TPK Flow Controller

Designing tools that are less susceptible to noise is clearly a successful strategy as evidenced by an almost universal adoption of the NGI in the pharmaceutical industry for new OINDP development.

Laser methods for APSD also have huge potential for improving productivity as they provide near instantaneous results. Laser sizing techniques have largely been restricted to nasal or nebulized products, where emitted particles have a generally uniform drug concentration. Unfortunately in suspension and dry powder inhalers, the relationship between drug concentration and particle size is far from evident and demonstrating a clear correlation between APSD and laser data remains elusive.

Less noise: Machines versus people

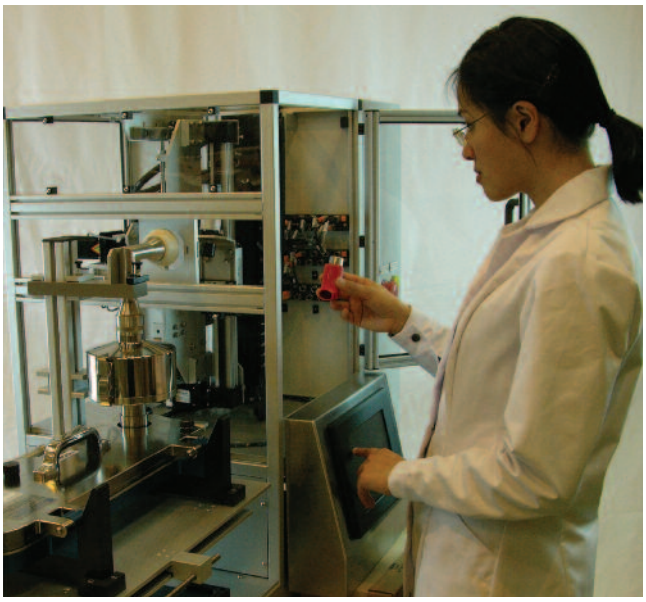
People tend to have a natural error rate of 0.5-1% performing typical routine tasks.[7] Phrased another way, the human process capability tends to be around the four sigma level. It is possible to improve these error rates by introducing secondary checks and peer review, but it is clear for manual work, particularly with transcription tasks and calculations, a 1% error rate should be expected.

If one considers the data recording, transcription and calculation operations involved in calculating stage recovery and mass balance in a typical impactor sample recovery process, the opportunity for error in a manual laboratory workbook process starts to become inevitable. This is another strong driver for automation, systems integration and the use of electronics tools and aids. Instrument integration removes the need for transcription, significantly reducing the opportunity for human error. Software packages, such as CDS, LIMS and the Copley CITDAS software, can remove the need for manual calculation and simplify the reporting process for APSD data with validated software routines.

Automated tools improve device understanding

Automation can help alleviate a key challenge for OINDP product development, namely collecting robust datasets required to understand and document the design space of OINDPs. It is almost inevitable that taking a QbD approach to product development will require more testing and, on that basis alone, the need for automation may be justified. Automation also enables superior control of critical analytical method parameters. This benefit should not be discounted, particularly when the potential impact of better quality data is considered.

As a case in point, during sample collection the analyst or a machine simulates patient usage and actua-



RTS automated sample collection equipment

tion of a device. Device performance is sensitive to manual handling. Using a machine to perform repetitive operations allows handling characteristics to be defined, measured and controlled in terms of critical analytical method parameters. It also allows parameters to be systematically varied and explored. Feedback from analytical testing can then be used to design more robust products and formulations.

Controlling device sample collection is only a single example of one type of automation that can be used in APSD testing. Many automation solutions exist and have their place in the OINDP testing laboratory, from device waste firers, to semi-automated impactor sample recovery systems, to fully-automated inhaler to vial solutions. All can provide significant benefits in terms of throughput and control.

Automation provides a more controlled process and a far more accurate magnifying glass onto product performance; changes that might have been masked by the variability in manual testing are more likely to be exposed. Controlling one set of parameters often leads to greater product understanding, and like peeling an onion, another set of variables may be revealed to be just as important as the ones that were originally targeted. Engineering control in terms of system verification and calibration then becomes of critical importance, especially if multiple automated systems are in use and data need to be compared.

Perhaps the most challenging analytical method parameters to control are those that are born of nature. Environmental and electrostatic effects are increasingly an area of focus in analytical testing. In the automation segment, this has given a healthy focus toward developing solutions with the ability to monitor and control these factors.

Summary and conclusions

APSD testing is still one of the best *in vitro* indicators of expected *in vivo* effectiveness, but from a QbD perspective, analytical variability and increased testing requirements to create robust datasets present a barrier to progress.

Understanding and controlling critical analytical method parameters is fundamental to device performance and the foundation of robust analytical testing. For OINDP testing, better tools, technology, and automated testing equipment are increasingly embraced as routes to improving the speed of device development, device performance and testing productivity.

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