

Regulatory challenges of inhaler testing

The use of orally inhaled and nasal drug products to deliver both locally-acting and systemic therapies is on the increase; however, the regulatory requirements are challenging and in a constant state of evolution. Mark Copley discusses the methods used for DPI testing and the challenges presented by the current regulatory framework.



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What is the regulatory approach for orally inhaled and nasal drug products (OINDPs)?

OINDPs are a class of products that includes dry powder and metered dose inhalers, nebulizers and nasal sprays. Many of the tests suggested by the regulators for ensuring the safety, quality and efficacy of OINDPs are common to all pharmaceutical dosage forms. Tests for leachables, extractables and microbial contaminants, for example, are mandatory for all inhaled products. Of the tests that specifically relate to OINDPs, delivered dose uniformity (DDU) and aerodynamic particle size distribution (APSD) are universally accepted as key parameters in assessing performance.

Performed *in vitro*, DDU testing, which is the first of these tests, collects and measures the total emitted dose of API under well-defined conditions. The test measures a specified number of shots at the beginning, middle and end of the product's life and, in the case of a multi-dose unit, it determines consistency across the lifespan of the product. Assessing multiple devices from every batch produced provides pre-release quality control.

In vitro APSD data can give a broad indication of the likely *in vivo* deposition behaviour of the drug, with a size of 5 μ m or below being widely recognized as an approximate cut-off diameter for penetration into the lung. Regulatory guidance recommends aerodynamic particle size measurement, using cascade impaction, for all OINDPs. Cascade impaction fractionates a sample on the basis of particle inertia, which is a function of aerodynamic particle size. These fractions are easily recovered from collection surfaces within the impactor for chemical analysis, allowing an APSD to be established specific to the API.

It is important to understand, however, that a cascade impactor is not designed to simulate the lung; the deposition properties of which are extremely complex and difficult to replicate *in vitro*. The principal aim of cascade impaction is to obtain a relative measure of APSD for the emitted dose, rather than an absolute measure. Measurements ensure that the marketed product is similar to the product that was tested in the clinic, for which regulatory approval was obtained.

Which bodies are important from the point of view of developing and interpreting regulations?

The ultimate responsibility for the safety, quality and efficacy of medicines and medical devices lies with the various national regulatory bodies designated to safeguard public health. In Europe and the US, this function is performed by the EMEA and FDA, respectively. The principal guidelines relating to OINDPs have been laid down by the EMEA^{1,2} and FDA³⁻⁷. The regulatory authorities are supported in this role by:

(a) the Pharmacopoeia, whose job is to define the standards with which the drug formulation shall comply and the monographs by which compliance will be adjudged, and

(b) in the case of OINDPs, by the International Standards Organization (ISO), whose function is to define the standards and methods relating to the medical device e.g., inhaler, nebuliser, etc. concerned. (see ISO27427:2009⁸ and ISO20072:2009⁹).

In 2002, the FDA launched a new initiative "Pharmaceutical cGMPs for the 21st Century" in which it proposed a new risk-based approach to pharmaceutical manufacturing. This initiative gave birth to PAT, a framework for understanding and improving the processes involved in pharmaceutical development, manufacturing and quality control described in the FDA's Guidance of September 2004.¹⁰ The goal of PAT is to ensure final product quality by understanding and controlling the processes involved in manufacture.

The Quality by Design (QbD) approach was agreed and recently adopted by the EMEA, FDA and the Japanese Ministry of Health, Labour and Welfare in the form of the three quality related guidelines — ICH Q8, Q9 and Q10 — published by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). These guidelines extend the PAT philosophy to all parts of the product cycle from product development, transfer through to manufacturing, and finally the end product. ICH Q8 Pharmaceutical Development describes the suggested contents of a regulatory submission based

on the QbD format. ICH Q9 details a systematic approach to quality risk management as applicable to the pharmaceutical industry. Finally, ICH Q10 describes a new quality management system for the pharmaceutical industry based on the complete product lifecycle and referred to as the Pharmaceutical Quality System (PQS).

How is the regulatory framework changing?

Harmonization is an important trend as the ICH and the Global Harmonization Task Force, a body working specifically on medical device regulation, continue their activities. A potentially transformational change is the implementation of QbD, part of the risk-based philosophy enshrined in ICH Q8, Q9 and Q10. QbD demands that quality is built in to a product from the outset, rather than tested for post-manufacture, and challenges the industry to develop a much greater understanding of both product and process. One important aspect is the requirement for relevant and effective manufacturing controls. QbD therefore dovetails with the PAT initiative, launched by the FDA¹⁰ to encourage the adoption of optimal process analytical techniques and instrumentation.

The evolving environment arising from the adoption of ICH Q8, Q9 and Q10 and the PAT initiative poses particular challenges for OINDP

producers. However, the community is responding and one example of an important development is the introduction of the Abbreviated Impactor Measurement concept (AIM). While traditional multistage cascade impaction methods are highly valuable for the development and QC of OINDPs, they are also time-consuming, labour-intensive, and susceptible to analyst-induced measurement variability. The AIM concept¹¹ addresses these issues, simplifying measurement by reducing the number of impaction stages, and hence size fractions collected, from the seven or eight normally associated with Next Generation and Andersen Cascade Impactors. Suitable for QC and for rapid screening within the development environment, AIM in its simplest form splits the dose entering the impactor simply into a fine and a coarse particle fraction. The coarse particles are collected below the primary impaction stage, and residual fines on a filter, similar to a multi-stage impactor. In the case of DPIs, oversized particles and powder boluses are trapped in a pre-separator before entering the impactor.

Elsewhere, regulators continue to refine and harmonize guidance in very specific areas: new advice relating to nebulizers is especially noteworthy.

Guidance issued by the EMEA and Health Canada in 2006 has changed the regulatory approach for nebulizers in these countries; harmonizing it with the testing philosophy applied to other inhalation products. Historically, nebulizers were classified as medical devices and were used with a range of different drugs, as directed by the prescribing clinician. Consequently they were tested as medical devices, in accordance with the European Committee for Standardisation Standard for Respiratory Therapy Equipment EN 13544-1. The new guidance recognizes that the safety and efficacy of a nebulized product depends on the drug/device combination and is supported by a new harmonized pharmacopoeial draft monograph published in *Ph. Eur. Pharmeuropa*¹² and the

USP Pharmacopoeial Forum.¹³ This defines a testing approach for delivered dose uniformity and aerodynamic particle size distribution for the inhaled drug/device combination. The new standard ISO27427:2009,⁸ which supersedes EN13544-1, also includes this changed approach.

What are the challenges posed by the changing regulatory approach?

While the adoption of new nebulizer guidance is straightforward, implementing QbD in the development and manufacture of OINDPs presents a unique challenge. QbD is significantly more complex for inhaled products than for other dosage forms because, for example:

- Product performance is a function of both device and formulation
- A patient's operating technique may influence the received dose
- Product manufacture and use is influenced by environmental conditions
- There is a lack of relevant real-time analytical tools.

These issues mean that the take-up of QbD for OINDPs may be relatively slow and may also depend on the development of new measurement techniques. One very pertinent issue within this debate is that clear *in vitro*-*in vivo* correlation is often absent. This makes it difficult to target clinical performance and/or demonstrate comparability or bioequivalence in a new or reformulated product. If, for example, a manufacturer chooses to switch to DPI delivery for an API, rather than reformulate a MDI (when a propellant is phased out, for instance), proving clinical equivalence is not straightforward. On the other hand, starting development, as if for a completely new product, is very costly. Identifying new methods for demonstrating bioequivalence is therefore an important long-term goal for the inhalation product community.

Against this background it is fair to say that some companies remain unconvinced that the potential benefits of QbD — which include improved efficiency and greater flexibility, with regard to process changes and a lighter regulatory

The author says...

- Orally inhaled and nasal drug products (OINDPs) include dry powder and metered-dose inhalers, nebulizers and nasal sprays.
- The FDA and EMEA, supported by the pharmacopoeia and International Standards Organization, are responsible for assessing safety, quality and efficacy.
- The introduction of more recent initiatives — PAT and QbD — does, however, pose particular challenges for OINDP manufacturers.
- The evolution towards regulatory harmonization is also proving to be particularly challenging.
- Implementing QbD is very complex for inhaled products, which may mean that take-up could be slow for OINDP manufacturers; however, regulatory bodies may be unforgiving of those who fail to adopt the initiative.

touch — outweigh the effort required to acquire the necessary knowledge for implementation. However, economic pressures on the industry are intense and as the new approach becomes evident in submissions to the FDA, it is possible that the regulatory response to those failing to change may harden. [PTE](#)

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