Testing Inhaled Generics

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New product-specific FDA guidance and USP monographs support the development of popular inhaled products. This article reviews their value in the rapidly growing generic sector

Central to the development of a new generic product is the need to demonstrate bioequivalence (BE) in order to confirm pharmaceutical equivalence to the reference labelled drug (RLD) being replicated. Such evidence is typically supplied in the form of *in vitro* and *in vivo* test data. *In vitro* tests are usually the first step and preferable to the manufacturer from the perspective of ease, cost and speed, but choosing a testing strategy that yields suitable data is also important.

For certain widely used pharma products, the FDA has released product-specific guidance to support the generic submission process; drugs for administration by the inhaled route are no exception. This follows a signalled policy change in June 2010 to actively provide guidance for the demonstration of BE for specific products, rather than simply dealing with requests for information on demand (1). Designed to facilitate generic drug product availability, this guidance helps the generic industry to "identify the most appropriate methodology for developing drugs and generating the evidence needed to support ANDA (Abbreviated New Drug Application) approval" (2).

Keywords

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In addition to this guidance, there are now a growing number of product-specific US Pharmacopeia (USP) monographs for inhaled products, which closely detail appropriate testing for off-patent active ingredients. The FDA and USP are discrete, independent bodies, so there is no obligation to adhere to USP monographs as part of a submission process, even though it is common practice to do so to reduce the risk of inadequate data provision.

Monographs describe the tests required to "ensure the substance is of the appropriate strength, quality and purity" (3), and provide a standard that can be used by the FDA to assess compliance and by manufacturers to guide testing strategies. Product-specific monographs may therefore be helpful to ensure efficient generic development; however, in certain instances, they point to the use of test equipment that is not included in the USP general chapters.

In this article, we examine the drivers for developing product-specific tests and explore the reasons why they may call for the use of unique equipment. A key focus are new USP monographs specified for fluticasone propionate (FP) and salmeterol, plus draft monographs for these two active ingredients in combination. These additions reflect activity to develop generic versions of Flovent®/Flixotide®, Serevent® and Advair®/Seretide® respectively, the latter of which – though now off-patent – has proven notoriously difficult to replicate and continues to command around $6 billion in annual sales (4).

Ensuring Efficiency

The number of generic submissions to the FDA has risen exponentially over the last decade or so, with substantial expansion in the generic sector – in particular in India, where annual growth rates remain in excess of 25% (5). A stated aim of publishing product-specific guidance is to streamline the process of providing support with the design of BE studies, as a way of improving efficiency (1). Furthermore, better quality submissions have the potential to reduce the burden of regulatory assessment without increasing risk.

For generic developers, time to submission is crucial, with the potential prize of a 180-day exclusivity period in certain circumstances (6). Guidance on how to design BE studies is, therefore, valuable in ensuring an efficient development process that will result in data which can robustly satisfy regulatory requirements. While it does not appear that it is mandatory to follow the guidance, the ease and reduced risk of doing so makes it likely that such an approach will be relatively attractive. In summary then, product-specific guidance has benefits for both the regulators and generic developers alike – a happy confluence of interests that perhaps helps to explain the steadily increasing number of products covered by successive guidance releases over the past few years.

Key generic targets in the inhaled area include drugs routinely used for asthma and chronic obstructive pulmonary disease (COPD). As the global incidence of respiratory illness rises, delivering safe, efficacious and inexpensive treatment is becoming increasingly important, with governments seeking to control and contain spiralling healthcare costs. Many generics are destined for home markets in developing countries, but the overall potential export market for generics is sizeable. Overall, across all pharma product types, around 40% of generic drugs and over-the-counter products used in the US are now produced by India, making FDA approval essential (7).

Factors for Testing

The general FDA guidance and USP chapters relating to orally inhaled and nasal drug products (OINDPs) are defined in terms of their applicability to certain product types: dry powder inhalers (DPIs), metered dose inhalers (MDIs), nebulisers and nasal sprays (8,9,10). Key tests include the measurement of delivered dose – the amount of the active ingredient(s) a patient will receive under representative delivery conditions – and the aerodynamic particle size distribution (APSD) of that dose. APSD influences deposition behaviour in the pulmonary system, and is used to assess the likelihood of a drug being delivered successfully to the target region within the lung.

The test equipment and methods defined in the USP general chapters have evolved over a number of years, and represent the view of experts and stakeholders with regard to current best practice. This raises the question of how test methods introduced in the product-specific USP monographs differ and, indeed, why do they do so?

For an ANDA submission, the defining goal is to demonstrate BE to an RLD, essentially reproducing the performance that ultimately led to regulatory approval for the original product. The fact that patents generally expire after 20 years dictates that the development work associated with the RLD is likely to have been carried out some time ago, often prior to the definition of current test methods.

One way of approaching *in vitro* testing within this context is therefore to duplicate the test equipment and method used in the development of the original product, rather than to introduce the complicating factor of comparing results generated using a different set-up. This approach reduces the risk that the data generated – such as delivered dose, impactor drug mass-per-stage or fine particle dose – are influenced by the equipment type or test method used, and hence reduces the burden associated with method validation and specification setting.

Monographs, unlike general chapters, typically include the name of an ingredient or preparation, and their development often begins with the manufacturers of that product drafting a document for consideration by the wider community (3). This heritage is often particularly visible in product-specific monographs, which tend to include hitherto proprietary test methods that are derived in some way from those originally deployed. Although these are broadly similar to those detailed in the general chapters, there are in certain cases some important differences.

The Evolution of Inhaled Product Testing

The use of inhalers to deliver drugs via the lung is far newer than traditional methods of drug delivery, such as oral solid dosage, which means the test methods associated with their development and with quality control are too. The first inhalers were commercialised in the 1950s, 60s and 70s, predominantly by large pharma companies like 3M, AstraZeneca, GlaxoSmithKline and Sanofi (or their predecessors). Ensuring the safety and efficacy of these products was essential for their introduction, so these companies led the way in evolving new test methods, with some designing and manufacturing their own analytical equipment to meet requirements (11-13).

The need to move towards more standardised testing grew with the establishing market, and pharmacopoeial general chapters were subsequently established from the 1980s onwards, supported by expertise within the pioneering organisations. As a result, some proprietary equipment found its way into the resulting chapters, but some did not. Companies remained free to validate their own test methods using preferred equipment, and some continue to do so, even today.

The general pharmacopoeia chapters for OINDP testing continue to evolve, reflecting on-going development and understanding, and the requirements of the market. As a result, all the relevant pharmacopoeias, including the USP and European Pharmacopoeia (Ph Eur), are not fully harmonised. For example, there is an MDI content uniformity apparatus unique to the British Pharmacopoeia for testing pressurised inhalers (14). The additional need to ensure consistent quality during the complete product lifecycle adds to the complexity of refining the general chapters to ensure best practice.

In some areas, unique pieces of equipment are specified

Figure 1: Glass sample collection apparatus is specified in place of the standard dose uniformity sampling apparatus for inhalation powders (left) and for inhalation aerosols (right)

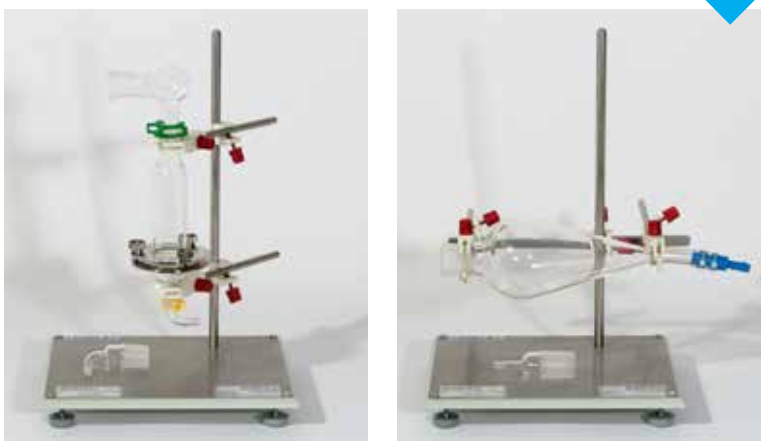

Figure 2: The modified induction port specified for APSD measurement necessitates the use of a modified ACI pre-separator for inhalation powders (left) and a modified ACI inlet cone for inhalation aerosols (right)

Guidance and Monographs

FDA product-specific draft guidance is now available for a number of active ingredients routinely used to treat asthma and COPD. These include salbutamol (albuterol) (15), budesonide (16), FP/salmeterol (17) and, new this year, ipratropium bromide (18). This guidance references test equipment outlined in the general chapters of the USP.

Product-specific USP monographs are in place for FP and salmeterol as follows:

- FP inhalation aerosol (MDI delivery) (2013) (19)
- FP inhalation powder (DPI delivery) (2013) (20)
- Salmeterol inhalation powder (DPI delivery) (2014) (21)

Further draft monographs covering FP and salmeterol in combination, both aerosol and powder, have also been proposed (22,23).

The monographs for FP and salmeterol (and draft monographs for FP/salmeterol combinations) cover both delivered dose uniformity (DDU) testing and APSD measurement. The equipment specified is very similar to that detailed in the general chapters, with the Andersen Cascade Impactor (ACI) specified for APSD measurement. This is one of two cascade impactors routinely used for OINDP characterisation, the other being the Next Generation Impactor.

However, in some areas, unique pieces of equipment are specified, including:

- Glass sample collection apparatus specifically for DDU testing of inhalation aerosols
- Glass sample collection apparatus specifically for DDU testing of inhalation powders
- Modified induction port to be used with the ACI for all APSD measurements
- Modified version of the ACI pre-separator (for inhalation powders only)
- Modified version of the ACI inlet cone (for inhalation aerosols only)

Like the glass sample collection apparatus for inhalation powders, the modified induction port specified in all five monographs for APSD measurement has an inlet geometry similar to that of the Glass Twin Impinger (GTI), indicative of its heritage (13). However, it is manufactured from either aluminium or 316 stainless steel, to match the impactor. Mouthpiece adapters designed for the GTI can be used to interface the induction port with the device, while an O-ring-less tapered exit enables interfacing with the ACI. The modified versions of the ACI pre-separator and inlet cone – for inhalation powders and inhalation aerosols respectively – accommodate the modified induction port.

Product-specific guidance can be extremely helpful in defining *in vitro* test strategies

The new monographs specify the 28.3L/min version of the ACI (Stages 0 to 7, plus filter stage) in all cases, despite the fact that a flow rate of 60L/min is specified for testing powders. 60L/min and 90L/min modified versions of the ACI designed to, among other things, restore the full cut-off diameter range of the impactor at higher flow rates, now form part of the general chapter (24). However, these modified versions of the ACI, although in use for some time now, post-date the equipment available when the initial development of these RLDs was undertaken.

With regard to test conditions, the total air volumes specified in the inhalation powder monographs are:

- 2L for DDU testing, a figure that is widely accepted as broadly reflecting the lung capacity of a typical COPD/asthma patient
- 3L for APSD measurement, a figure most likely to have been specified as a compromise, to achieve adequate volume changes in the ACI

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The need for accurately timed flow control, in order to obtain the above volumes, can be achieved using a fast-acting solenoid valve, as specified in the general chapter set-up for DPI testing, which is also designed to ensure a constant flow rate through the cascade impactor during testing.

A Crucial Role

Product-specific guidance can be extremely helpful in defining *in vitro* test strategies that will robustly demonstrate BE and satisfy regulatory requirements. Product-specific monographs also have a role to play in ensuring the consistent quality of widely used drugs as they transition into generic products. Although some of these call for the use of test methods that differ from those in the general chapters, the equipment required is now readily and commercially available. Its use may be helpful in generic development and in ensuring an ongoing supply of safe, efficacious and inexpensive drug products.

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