Product-specific FDA guidance, and product-specific pharmacopeial monographs, point to the use of test equipment, some of which isn't included in the general USP/Ph. Eur. chapters for orally inhaled products (OIPs). In this Q&A Mark Copley, Sales Director for Copley Scientific, answers questions about the equipment and methods recommended for testing of Fluticasone Propionate (FP) and other popular inhaled generic targets. He also addresses queries about how, and why, product-specific guidance and monographs may differ from those in general use.

Caption: The equipment required for testing Fluticasone Propionate (FP) Inhalation Powder in line with a new product-specific monograph (USP36-NF31).

Q&A with Mark Copley on the implications of the introduction of a new US Pharmacopeia (USP) monograph for Fluticasone Propionate (FP) testing and of product-specific guidance from the FDA for certain asthma and chronic obstructive pulmonary disease (COPD) treatments.

Can you provide some detail about the equipment now specified for the testing of Fluticasone Propionate (FP) Inhalation Aerosol and Powder and the tests included in the new product-specific monograph?

Two new USP 36 Second Supplement monographs for the testing of FP were released in Dec 2013. One relates to the use of FP as an Inhalation Powder[1], that is, as a formulation delivered by a dry powder inhaler (DPI). The other is for FP delivered in Aerosol form, via a metered dose inhaler (MDI)[2]. The monographs cover both delivered dose uniformity (DDU) testing and aerodynamic particle size distribution (APSD) measurement. Delivered dose and APSD are required performance metrics for all orally inhaled products (OIPs) because of their defining influence on the success and consistency of drug delivery[3].

Specified equipment that is unique to the testing of FP includes a:

- Glass Sample Collection Apparatus for DDU testing of Inhalation Aerosols
- Glass Sample Collection Apparatus for DDU testing of Inhalation Powders
- modified induction port to be used with the Andersen Cascade Impactor (ACI) for APSD measurements
- modified version of the ACI preseparator (For FP Inhalation Powders only)
- modified version of the ACI inlet cone (For FP Inhalation Aerosols only).

Two different Glass Sample Collection Apparatus are specified for the DDU testing of FP Inhalation Powders and FP Inhalation Aerosols respectively. A common induction port (throat) is to be used with the ACI for APSD measurements.

Although manufactured from metal (aluminium or 316 stainless steel) the inlet geometry of the modified induction port is similar to that of the Glass Twin Impinger, allowing the use of mouthpiece adapters designed for the latter and giving an insight into its heritage. It also features an O-ring-less tapered exit for interfacing with the ACI. In order for the ACI to accommodate the modified induction port, modified versions of the ACI preseparator and inlet cone are used for FP Inhalation Powders and FP Inhalation Aerosols respectively.

An additional feature of the new monographs is that the 28.3 L/min version of the ACI (Stages 0 to 7, plus filter stage) is used for both powder and aerosol methods. This is despite the fact that the powder method specifies testing at 60 L/min. This is possibly because the original method predates the development of the 60 L/min and 90 L/min modified versions of the ACI, which now feature in the general USP chapter[4] and are designed to, amongst other things, restore the full cut-off diameter range of the impactor at higher flow rates.

Finally, for the FP Inhalation Powder, there is a requirement to conduct DDU measurements for a duration that is consistent with the withdrawal of a 2 L volume of air. This figure reflects the lung capacity generally considered to be typical of an asthma or COPD patient. This value is modified to 3 L in the case of APSD measurements, likely reflecting the need to achieve adequate volume changes in the ACI. The resulting need for accurately timed flow control can be achieved using a fast-acting solenoid valve, as specified in the general chapters of the current USP for testing DPIs. This set-up also ensures a constant flow rate through the cascade impactor during the test. Flow control equipment such as the Critical Flow Controller Model TPK or TPK 2000 (Copley Scientific) is well suited to this job and is widely used already for DPI testing. The simplified Breath Actuation Controller Model BAC 2000 is also suitable, since sonic flow conditions are not specified in this particular method.

What about product-specific guidance for other OIPs? Do they also mean additional test equipment or simply greater emphasis on equipment already referred to in the general chapters of the pharmacopeias?

In the area of inhaled product testing FDA product-specific draft guidance is now available for a number of active ingredients including salbutamol (albuterol)[5], budesonide[6] and FP/salmeterol[7]. These are used globally for the treatment of asthma and COPD and are consequently routine targets for generic development.

Where equipment is specified in product specific regulatory guidance it is generally identical to that described in the general chapters of the pharmacopoeias for OIP testing. Existing dose uniformity sampling apparatus (DUSA) designs, the ACI and/or Next Generation Impactors (NGI) are all specifically referenced. In the case of the ACI and NGI, these are currently the mainstay of cascade impactor testing and with a good number of stages (8 and 7 respectively) they give good aerodynamic particle size distribution (APSD) measurement resolution. However, it is important to note that the USP is an independent organisation and whilst it may, in many cases, reflect US regulatory thinking, it is not obliged to do so.

Furthermore, not all relevant pharmacopeias are harmonised with the European Pharmacopoeia (Ph. Eur.) and USP. Indeed the USP and Ph. Eur. are not fully harmonized themselves with respect to orally inhaled and nasal drug products. This means that other apparatus may be required for certain products or markets. For example, there is an MDI content uniformity apparatus unique to the British Pharmacopoeia which is required to test pressurized inhalations, which has likely been retained for historical reasons. There may also be a need for additional test equipment and modified methods where a product specific monograph or guidance relates back to equipment and methods no longer in routine use, as is the case for FP.

Why are these different methods required? Why are general pharmacopoeial monographs that cover inhaled product testing insufficient for current testing requirements?

The test methods for inhaled products detailed in the general pharmacopeial monographs and regulatory guidance have been refined over a number of years. In the most part they represent current, agreed best practice for the development of new orally inhaled and nasal drug products (OINDPs). However they may differ somewhat from the analytical approaches adopted in the development of originator products that form the basis of today's most popular generic targets.

Generic development begins in earnest as a pharmaceutical product approaches patent expiry. This means that early research work for the reference labelled drug (RLD) may pre-date generic development by a period of close to 20 years. In the field of inhaled product testing the last two decades has marked a period of considerable evolution. New test methods have been adopted, and

new equipment commercialized. Today's understanding of best practice may not therefore reflect the view that prevailed two decades ago. Furthermore, in some instances, research during the innovation of the new drug relied on test methods individually tailored to the unique characteristics of the device and/or formulation.

Inhaler technology is far younger than other drug delivery technologies such as oral solid dosage. The first commercially available inhalers came to market around 50 years ago and it was large pharmaceutical companies such as 3M, AstraZeneca, GlaxoSmithKline, Novartis and Sanofi (or their predecessors) that led the way, evolving new test methods to verify the performance of these innovative products. Some of these companies designed and manufactured their own analytical equipment for inhaled product testing[8, 9, 10].

As inhaler technology developed, and the need for pharmacopeial monographs became more acute, experts from these pioneering companies played an important advisory role in establishing good testing practice. As a result, some proprietary equipment found its way into the pharmacopeias, but other items did not. Companies were at liberty to validate their own test methods using preferred equipment, and some continue to do so, even today.

The success of a generic submission relies on the robust demonstration of bioequivalence (BE) to an RLD. This normally involves, in part, the presentation of *in vitro* test data that unequivocally demonstrate that the generic will perform in a clinically identical way to the RLD. There are multiple ways to achieve this aim but arguably the easiest and least risky way to demonstrate BE may be to present equivalent results using directly comparable *in vitro* test methods and identical test equipment. This approach eliminates any risk of the RLD being particularly sensitive to the type of test equipment used in a certain *in vitro* test. For example, the expected results and/or acceptance criteria applied (e.g. for delivered dose, impactor drug mass-per-stage, fine particle dose or mass balance) may be specific to, or influenced by, the equipment type and test method used.

Generic drug development may therefore be aided by referencing back to the original test equipment and configuration (and possibly published data), and duplicating it as closely as possible, to assess and demonstrate how closely a new generic matches an RLD. Product-specific guidance and monographs would appear, in some cases, to reflect this approach.

In broad terms how does product-specific FDA guidance, or a product-specific monograph, differ from the general advice and testing specifications for inhaler products?

As the name suggests product-specific FDA guidance, or a product-specific monograph, relates to the demonstration of BE for a certain active ingredient, delivered via a specific route. It is more definitive and closely targeted than general guidance and test specifications, which for OINDPs relate to certain classes or types of device: DPIs; MDIs; nebulizers; and nasal sprays.

Most often product-specific guidance relates to a popular subject of Abbreviated New Drug Applications (ANDAs). In June 2010, the FDA signalled a change in process with respect to the provision of information to support ANDAs with a move from an 'on request' approach to a policy of publishing guidance for the demonstration of BE for specific products[10]. The quantity of FDA product-specific guidance has grown substantially over the intervening 3 to 4 years, reflecting increasing activity across the generic sector.

Who is it useful to and why?

The stated aims of the FDA, in publishing product-specific guidance, are to streamline the process of providing guidance on the design of BE studies and to make this process more efficient. Such guidance also provides "a meaningful opportunity for the public to consider and comment on BE study recommendations for specific drug products"[11].

Levels of generic activity have increased exponentially over the last decade or so, substantially increasing the number of ANDAs presented to the FDA. Figures for Jan – July 2013 show that in this period alone the FDA approved 235 ANDAs and the generics sector continues to grow strongly, most especially in India where annual growth rates are running at around 27%[12]. The associated transformation of the submission landscape has clearly stimulated the FDA to revisit and refresh processes in this area. Targeted guidance for the most popular generics may be seen as a way of enhancing productivity.

Happily the needs of generic developers and the regulators are closely aligned in this area, since guidance on how to design BE studies is simultaneously of direct benefit to those working towards an ANDA. It would appear that following the guidance remains a matter of choice and it is feasible to robustly demonstrate an alternative approach. However, by closely defining the test methods and results required for a successful submission, product-specific guidance helps to streamline generic development. At the same time, such guidance removes the risk associated with a less well-defined approval route. The net result is to potentially reduce the time taken to achieve a successful ANDA.

Note: The opinions expressed are the author's own and are not necessarily shared by any regulatory bodies or by the pharmacopoeias.

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