With most orally inhaled products delivering only 10-30% of a drug to the lungs, coupled with the complexity of developing delivery systems for inhaled products,\textsuperscript{1,2} we need to remind ourselves why this seemingly inefficient route of delivery remains an attractive clinical proposition.

• For respiratory indications, inhalation of the drug may be the only route of administration to achieve sufficiently high levels of the drug at the site of the disease. For drugs whose mechanism of action is targeted within the lung, the ability to deliver drugs topically allows for a dramatic reduction in systemic exposure and associated systemic adverse events.

• For other therapeutic indications, the large surface area of the lungs provides rapid and greater absorption of a drug into the systemic circulation, especially when the drug is delivered deep into the lung, potentially providing rapid symptom relief.

• For patients who are afraid of injections, this method of delivery may provide an effective and easy-to-use alternative.

• Inhalation may even offer the most effective method of achieving good absorption of many protein and peptide therapeutics because they are less likely to undergo degradation in the lung.\textsuperscript{3}

In addition to these clinical benefits, innovator companies also may gain a degree of product protection through patents and data exclusivity associated with the inhaled formulations and unique delivery device itself.

DEVELOPMENT AND BIOEQUIVALENCE TESTING FOR INHALED THERAPEUTICS

Here, Stephen Dodds, Manager, Regulatory Affairs, Wesley Hicks, PhD, Senior Medical Director, Global Product Development, and Bill Schachtner, Associate Director, cGMP Labs, all of PPD, describe the regulatory requirements for bioequivalence testing of inhalables, and explain why it is important to select a service provider with capabilities across the board in this regard.

"FOR INHALED PRODUCTS, EQUIVALENCY OF THE DELIVERED DOSE THROUGH DOSE CONTENT UNIFORMITY TESTING AND THE POTENTIAL LUNG DEPOSITION ... ARE CRITICAL COMPARISON PARAMETERS"

In developing generics for inhaled formulations and devices, there can be challenges demonstrating equivalence. Different formulations and device technologies can have a significant impact on the lung deposition characteristics of the drug and potentially on efficacy.

IN VITRO TESTING OVERVIEW

US Center for Drug Evaluation and Research (CDER) \textsuperscript{4,5} and European Medicines Agency (EMA)\textsuperscript{6} guidances outline the testing that is involved for the comparative testing of generic inhalers to reference products. Even though the guidances are for specific products or drafts, the evaluation criteria still are considered appropriate today. For inhaled products, equivalency of the delivered dose through dose content uniformity testing and the potential lung deposition—measured via particle size distribution by inertial impaction testing—are critical compari-
son parameters. Additionally, for DPIs, when comparing devices for aerosol performance, additional testing should be performed under various flow rates and pressure drops, mimicking expected differing patient inhalation ranges.

In addition, for pMDI products, spray pattern and plume geometry testing is performed as well to characterise the performance of the valve and actuator combination to demonstrate equivalence of the spray between the generic and reference products.

All of the comparative testing needs to be performed on each strength of product being considered as the performance of each product can be influenced by changes in drug substance and excipient concentration changes or mass of formulation delivered.

**DEVICE PERFORMANCE**

For inhaled products, not only should the drug product ingredients be formulated within 5% of the reference article, in vitro equivalency only can be achieved if there is equivalency between the devices for aerosol delivery performance. Therefore it is imperative that the generic (test) article matches the delivery system of the reference article as closely as possible. For pMDI products, selecting commercially available valves for equivalency of the valve delivered volume and equivalency of the actuator delivery system with regards to spray pattern and plume geometry in the early product development stages is critical.

For DPIs, the device selection is extremely challenging when considering both the in vitro equivalency requirements, and taking into account the patient interface. It must be remembered that product/device equivalency is the goal. Improved device performance for any measured parameter will not show equivalency and will not meet with regulatory approval.

**MATERIAL SUPPLY, RESERVES AND SAMPLING REQUIREMENTS**

The CDER guidance,7 coupled with the aforementioned inhaler guidance, directs all material requirements and handling for the sampling and reserve storage requirements for all bioequivalence testing. All samples for in vitro testing and retained storage should be sent to the testing facility as a single shipment. The testing laboratory should randomly select the in vitro and reserve samples from the shipment, thus ensuring that the reserve samples are representative of the samples tested. Ten units per lot from three lots each of generic and reference material should be tested for bioequivalence.

It is recommended that the quantity of reserve samples of both the test and reference materials should be sufficient to perform release testing five times. For inhalation products, the number of reserve samples for release testing can be quite large, so the US FDA allows that at least 50 units per batch be retained. This recommendation applies to products that deliver 30 or more doses per unit. The reserve samples must be retained at the study site for five years.

**BLinding and testing design**

For in vitro testing, the identity and lot number of the samples tested should be blinded from the analytical testing personnel. Over-labeling of product to obscure the product name and lot number should be performed. Additionally, full randomisation of the testing—not only by test and reference article, but also by lot number—is recommended and adds further confidence that the in vitro data is an accurate representation of each product. Often test versus reference devices are visually different. Therefore, it is recommended that one analyst should perform the sample collection while a second analyst should process the data. This is particularly important for analytical methods requiring subjective analysis of the data such as manual processing of plume geometry. Manual integration of chromatograms for in vitro testing should be avoided.

**BIOEQUIVALENCe IN VIVO IN THE DEVELOPMENT PROGRAMME**

Clinical bioequivalence can be split into two approaches: 1) lung deposition as determined by pharmacokinetics (PK) or imaging studies; or 2) therapeutic equivalence evaluating a pharmacodynamics (PD) outcome measure.

PK is the most common way to determine lung deposition and has the advantage of being relatively easy to conduct with conventional endpoints and avoids exposure to radiation. The validated analytical methods required for PK analysis must be highly selective and ultra sensitive using state-of-the-art instrumentation to provide reliable results. PK's major limitation is that it lacks detail regarding the distribution of the drug within the airways (central versus peripheral), a detail that is important since receptor distribution is not uniform throughout the lung. Imaging studies provide this detail, but...
are challenging to conduct and interpret. Their greatest limitation is that they are not widely accepted as validated, and tend to be regarded as supportive rather than definitive.

For the development of generic compounds against a reference product, care should be taken to maximise the quality of the in vitro and lung deposition data because it can reduce or obviate the need to demonstrate therapeutic equivalance. Reducing the volume of PD studies will have a major impact on programme timelines and cost. Clinical studies for therapeutic equivalance will vary depending on the class of compound. Inhaled beta-agonists can demonstrate therapeutic equivalance on both safety and efficacy parameters against a reference product with a relatively small and short crossover study. Inhaled corticosteroids are more challenging due to the shallow dose-response relationship. A study powered for non-inferiority on routine clinical outcomes will be slow and costly.

The need to demonstrate bioequivalence for new active substances is also relevant. As longer-term stability data become available and commercial upscaling of the manufacturing process is undertaken, reformulation with different blends of excipients may be required. Additionally, if adverse effects such as cough or pharyngitis are reported in significant numbers of patients in early development, reformulation may be required with an alternate salt. Demonstration of equivalent in vitro and lung deposition data between formulations may allow bridging to the existing clinical data package rather than repeating studies at considerable cost and time.

If spacers are intended for use with a pMDI, additional bioequivalence studies are required.

HEALTHY VOLUNTEER VERSUS PATIENT STUDIES

Early studies with inhaled compounds are normally undertaken in healthy volunteers rather than patients with underlying respiratory disease. Patients with airway hyperactivity may be at greater risk of life-threatening bronchospasms if exposed to a novel entity or formulation. In addition, patients with moderate or severe airflow obstruction may show lower systemic exposure through reduced lung deposition. In small PK studies, even patients with mild airflow obstruction may introduce additional variability into the data and affect the precision of estimates. This becomes more challenging in repeat-dose patient studies due to the day-to-day variability in lung function even in patients with relatively well-controlled asthma. Selection of a healthy volunteer or patient population will depend on the objectives of the study.

PAEDIATRIC CONSIDERATIONS

Delivery systems used in the adult programme may not be suitable for younger children and reformulation may be required (Figure 1). For drugs absorbed from the lungs, modeling systemic exposure in children based on adult data is challenging and can theoretically exceed the maximum exposures that have been evaluated in adults. Modelling does not typically allow for differences in the paediatric oropharynx, breathing patterns and reduced inhalation efficiency.

LOOKING AHEAD

Orally inhaled products should continue to remain an attractive clinical proposition. Although a potentially lucrative market, different formulations and device technologies can have a significant impact on the lung deposition characteristics of the drug and potentially on efficacy. At the same time, establishing bioequivalency of an inhaled therapeutic can be a challenging proposition. For example, the number of inhaled drugs targeting phosphodiesterase type 4 (PDE4) pathways currently in development may be a reflection of the number of systemic PDE4 inhibitors that have failed in development due to systemic toxicity and tolerability issues over recent decades.

There is no one-size-fits-all programme. In vitro equivalence may not predict PK equivalance, and non-equivalent PK might not translate into PD differences. Programmes are designed individually based on regional regulatory requirements, the class of compound under evaluation, and other clinical and pharmaceutical considerations. Companies need to be able to adapt as bioequivalence data in the programme evolves, and they must be able to incorporate additional in vitro or in vivo studies depending on the strength of the data package and agency feedback.

That’s why it is important for pharmaceutical and biotechnology companies to seek out and work with service providers that can address all aspects of drug discovery, development and lifecycle management services. Doing so will help them accelerate the delivery of safe and effective therapeutics like orally inhaled products, and maximise the returns on their R&D investments.

REFERENCES


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