# Demonstrating Bioequivalence

Safe and cost-effective treatments for respiratory diseases are facing a growing demand. The demonstration of bioequivalence within locally acting drugs, such as orally inhaled products, could prove particularly challenging

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The global generic drugs market has experienced rapid growth in recent years, driving the need to address the specific scientific challenges facing the development of generic drug products. The demand for safe, cost-effective, and effectual treatments of respiratory diseases is also growing due to the rising global prevalence of conditions such as chronic obstructive pulmonary disease and asthma.

The development of generics requires the demonstration of bioequivalence (BE) with a reference product. BE studies typically follow on from the characterisation of a reference product and the design of a pharmaceutically equivalent and bioequivalent product. Demonstrating BE in locally-acting drugs, such as orally inhaled products (OIPs), is particularly challenging, primarily because OIP behaviour is a function of the interactions between the patient, device, and formulation. Advances in bioequivalence methodology provide an opportunity to accelerate the development and marketing of generic drugs while also maintaining safety, quality, and efficacy standards.

For OIPs, debate is ongoing as to the relevance of the different BE tests; the FDA and EMA guidelines differ in this regard. From a commercial perspective, reducing requirements for pharmacokinetic (PK) and/or pharmacodynamic (PD) studies is an attractive proposition, since *in vitro* testing is typically the least expensive option. Therefore, there is a focus on

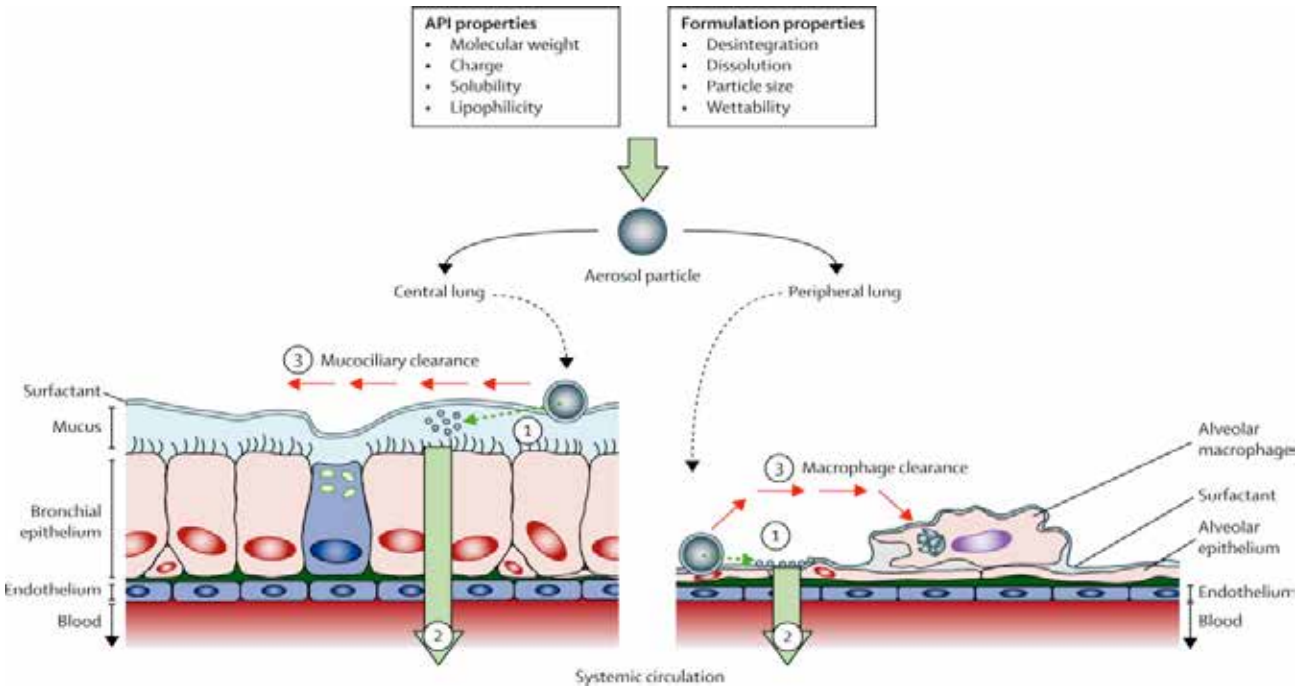
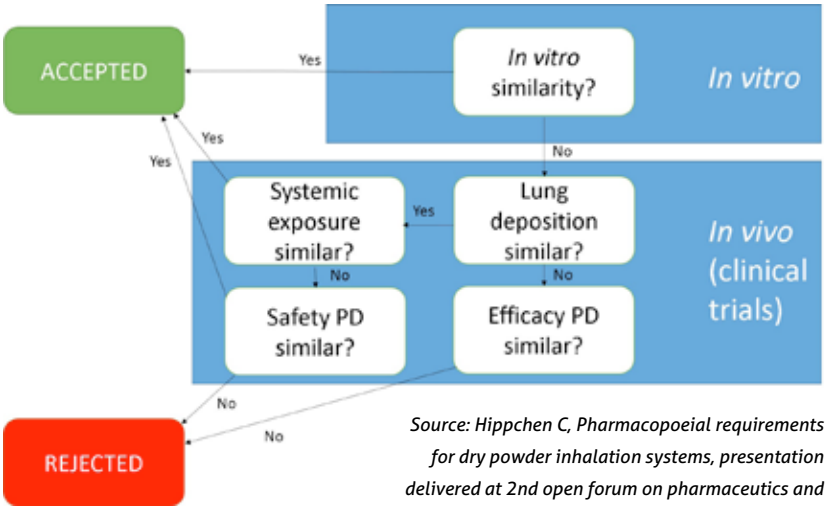



***Figure 1:*** *Inhaled drugs typically deliver localised action via a process of deposition and release of API, dissolution and absorption of the API, permeation into the lung tissue and target engagement, and clearance of the undissolved particle.*

*Source: Ruge CA et al, Pulmonary drug delivery: From generating aerosols to overcoming biological barriers – therapeutic possibilities and technological challenges, Lancet Respir Med 1(5): pp402-13, 2013 (reproduced with permission)*




*Source: Hippchen C, Pharmacopoeial requirements for dry powder inhalation systems, presentation delivered at 2nd open forum on pharmaceutics and biopharmaceutics, Istanbul, Turkey: April 2012*

***Figure 2:*** *The EMA outlines a stepwise approach to testing in support of generic OIP submission*

maximising the clinical relevance of *in vitro* test methods.

This article examines the testing strategies that can be applied to demonstrate the BE of OIPs, their relevance, and the regulatory guidance offered by the FDA and EMA. A key focus is the application of *in vitro* test methods and how these can be modified to improve *in vitro in vivo* correlations (IVIVCs) that are more useful for BE studies.

## Deposition Process of Inhaled Particles

During inhalation, aerosolised particles are drawn from the OIP through the oropharyngeal region into the main airways of the lung and potentially into the deep lung where the upper size limit for penetration is considered five microns. Once deposited in the deep lung, inhaled drug particles dissolve in the fluid lining the lungs, although mucociliary clearance mechanisms simultaneously act to flush the particles from the body. Permeation into the lung tissue brings the dissolved drug into contact with its intended target, facilitating localised binding and therapeutic action. Any drug absorbed through the lung tissue enters into systemic circulation (see Figure 1, page 12). Due to the dynamic and complex nature of OIPs and the combined influence of device and formulation on drug dispersion, ensuring BE by meeting the optical particle size is challenging.

## Testing OIPs for Bioequivalence

For inhaled drug products, *in vitro* BE tests are a crucial aspect of device performance evaluation. A generic product is prescribed interchangeably with the reference product and must therefore deliver closely equivalent clinical efficacy. *In vitro* tests, PK, and/or PD studies are all routinely used to support claims of BE between a test (T) and reference (R) product, but substantially differ in terms of their complexity, practicality, discriminating power, clinical relevance, and cost.

Core *in vitro* test methods include delivered dose uniformity and the aerodynamic particle size distribution (APSD), which is measured using cascade impaction. Other tests may include spray plume and plume geometry measurements, in the case of metered-dose inhalers (MDIs).

Good examples of IVIVC for OIPs are limited due to patient-centred factors such as variability in anatomy/impairment of the lung, device use, and compliance, which make it difficult to secure robust relationships between product characteristics and clinical efficacy. As a result, *in vitro* testing is often supported by *in vivo* studies (PK/PD) for the demonstration of BE, and commercially available products are developed for the improvement for IVIVCs.

## Generic OIPs: The Regulatory Landscape

The complexities of PK/PD studies for OIPs and their application in the

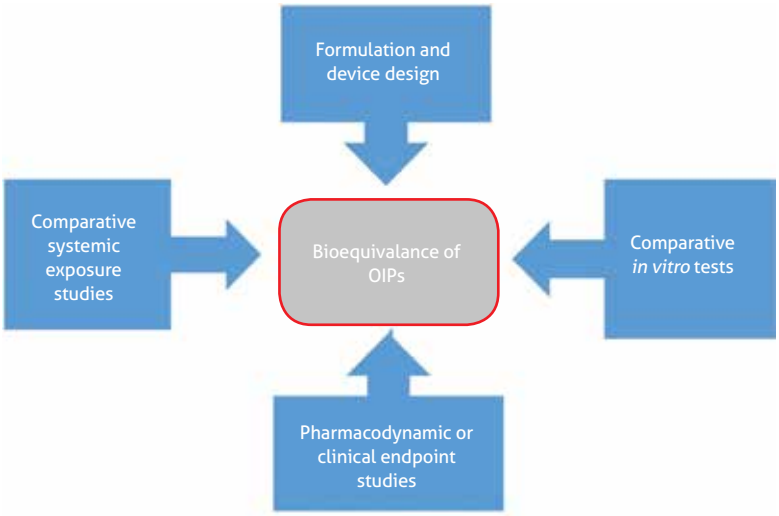



***Figure 3:*** *FDA guidance outlines a 'weight of evidence' approach*

*Source: Hippchen C, Pharmacopoeial requirements for dry powder inhalation systems, presentation delivered at 2nd open forum on pharmaceutics and biopharmaceutics, Istanbul, Turkey: April 2012*

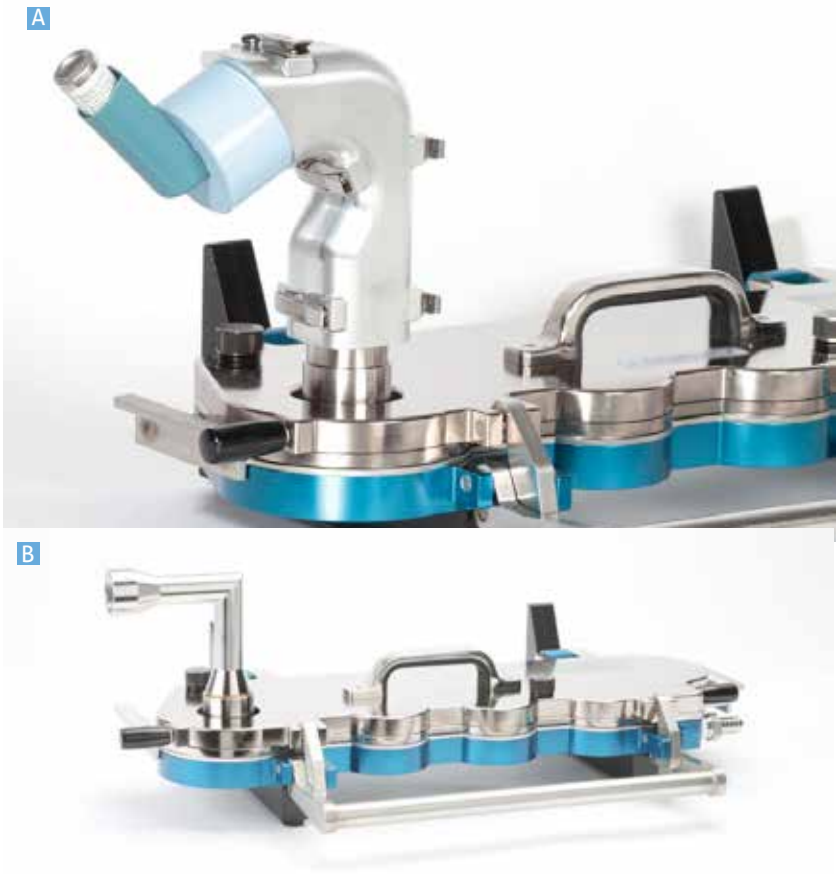



***Figure 4:*** *Idealised throat models (A) more accurately reflects the amount of drug captured in the throat than a standard USP/Ph Eur induction port (B)*

demonstration of BE are perhaps reflected in the different approaches between the EMA and FDA guidances.

The latest regulatory guidance released by the EMA outlines a stepwise approach for a generic OIP submission and indicates that a submission can be accepted without PK/PD testing on the basis of *in vitro* data alone (see Figure 2, page 13) (1).

Despite the cost and time appeal, few products are yet to be approved on this basis. The criteria for demonstrating *in vitro* only BE are demanding and call for the test product to match not only the chemical and formulation characteristics of the reference product, but also for the devices and their behavioural characteristics to be highly similar.

The current regulatory position of the FDA – in place of any formalised guidance – is that most approved generic OIPs have been subjected to some form of *in vivo* testing (see Figure 3, page 13). Such PK/PD studies not only add in time and cost, but may also introduce additional risk, with poor IVIVC data complicating the demonstration of BE. Improving the clinical relevance of *in vitro* methods to access better IVIVCs and enable the greater reliance on *in vitro* methods for BE testing is an important goal for the industry.

## Improving IVIVCs

The primary aim of new models is reflecting *in vivo* predictability, rather than anatomical correctness, where a choice is to be made, while considering ease of use and production (2). Creating a simple model that retains predictability helps achieve this goal. As a result, a number of products that can be used to improve IVIVCs have been developed.

**A More Realistic Throat Model**

New idealised throat models have been developed as an alternative to the standard USP/Ph Eur induction port (see Figure 4), which interfaces with the cascade impactor in the standard set-up for measuring the APSD of an OIP. These models, developed from CT patient scans, have an idealised geometry and can be fully opened for drug recovery, and the internal surfaces can be coated to more closely simulate *in vivo* drug deposition. The USP/Ph Eur induction port has a simple right-angled geometry that allows reproducible drug recovery, but has been shown to capture less of the dose delivered by an OIP than would be deposited in the mouth-throat region during routine clinical use (3-4).

Ten years' worth of experimental data has shown that idealised throat models more accurately quantify deposition than the standard USP/Ph Eur induction port and that it is a prime example of a practical design that delivers enhanced predictability (5).

**More Representative Breathing Profiles**

The breathing manoeuvre of the patient directly influences the drug delivery of many OIPs, including dry powder inhalers (DPIs), nebulisers, and MDIs with spacers/valved holding chambers (VHCs), which are operated with a tidal breathing pattern. Changes to the pharmacopoeial test methods for nebulisers and, more recently, MDIs with spacers/VHCs reflect this with defined breathing profiles now simulating product use by certain patient groups (6-7). Breath simulators enable the investigation of the impact of breathing profiles on drug delivery performance, and their use helps elucidate the differing clinical efficacy of OIPs in different patient groups.

For example, confirming similarity between T and R DPI performance across a range of flow rates supports claims that the products can be used interchangeably by all patients.

**The Use of Face Models**

When testing add-on devices with a facemask, face models are required. Certain patient groups, such as paediatrics, find the coordination required to correctly use an MDI by inhaling immediately prior to actuation a challenge. Add-on devices such as spacers and VHCs are commonly used by such patient groups, eliminating the need for coordination by providing a dead volume into which the dose is aerosolised. However, this can impact both the amount and the APSD of the delivered dose.

In situations where the spacer or VHC features a facemask in place of a regular mouthpiece, interfacing it with the test apparatus presents a significant challenge. The recently released USP Chapter <1602> assesses the testing of MDIs with add-on devices and details highly relevant test methods for the demonstration of BE for MDIs (7).

## Optimising Methods

Improving clinical relevance often involves the introduction of complexity and increased variability. Greater variability translates into lower differentiating power so a test that may be more clinically relevant for the demonstration of BE may be less able to detect a difference between a T and R product.

*In vitro* tests are the simplest of those that can be applied to demonstrate BE, and their rigorous and robust development towards better IVIVCs has much to offer in terms of helping to streamline generic OIP submissions. Much progress has been made in this area over the past decade and current activities will undoubtedly deliver further advances. Optimising the application of *in vitro* methods will help to cut the time and cost of generic development while, at the same time, ensuring the safety and efficacy of new products.

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