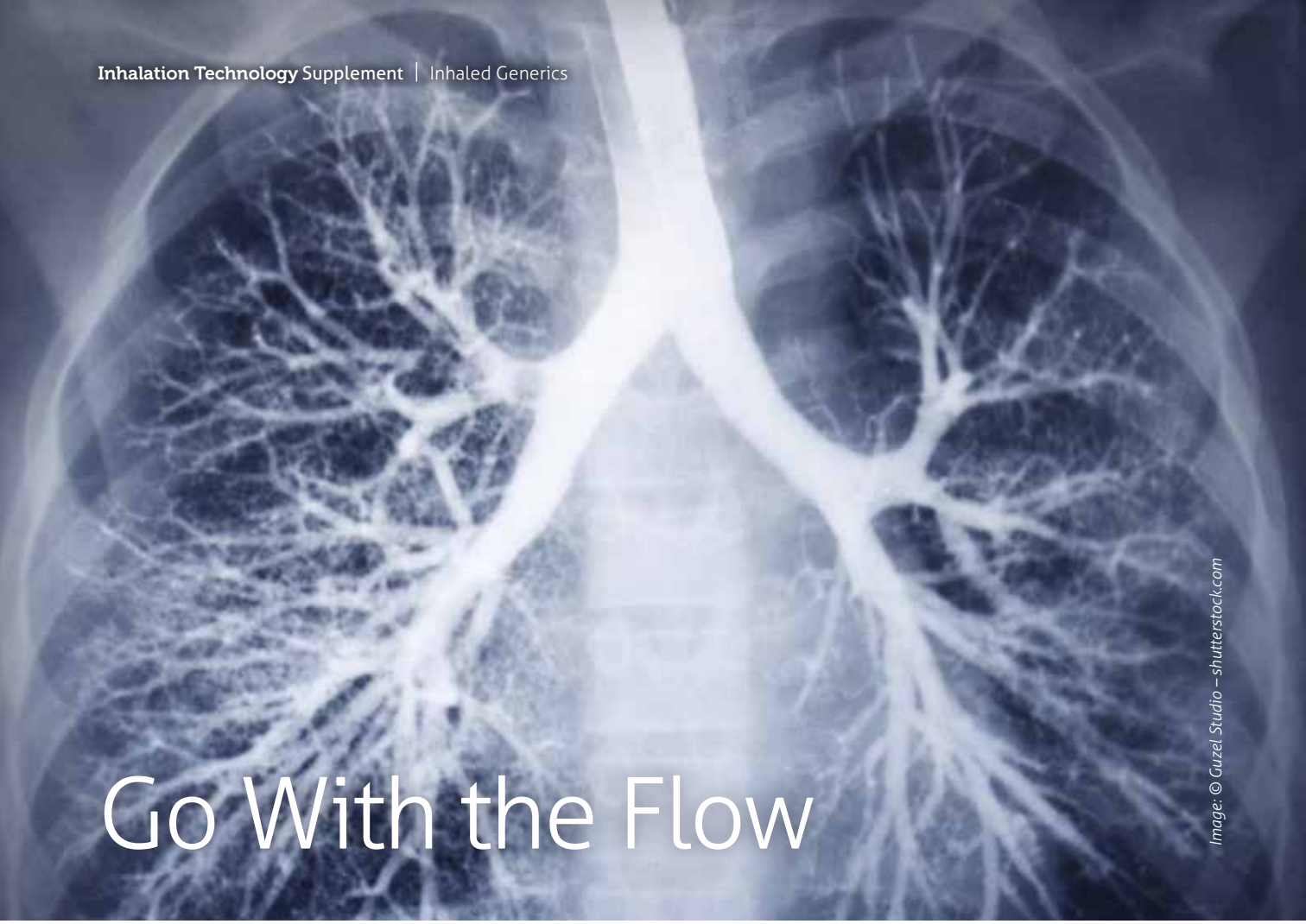

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Go With the Flow

Increasing global requirements for efficacious, inexpensive products to treat respiratory illnesses are driving the development of inhaled generics. *In vitro* methods represent the most efficient way of proving bioequivalence – and can thereby aid a faster time to market

Mark Copley at Copley Scientific

Demonstrating bioequivalence (BE) to a reference labelled drug (RLD) enables safe interchangeable use within the clinical setting. *In vitro* techniques are a cost-efficient way of gathering evidence to support a claim of BE and can minimise, or even eliminate, the need for clinical testing, thereby reducing expense and time to market. Maximising the application of *in vitro* testing is therefore an important strategy for generic development.

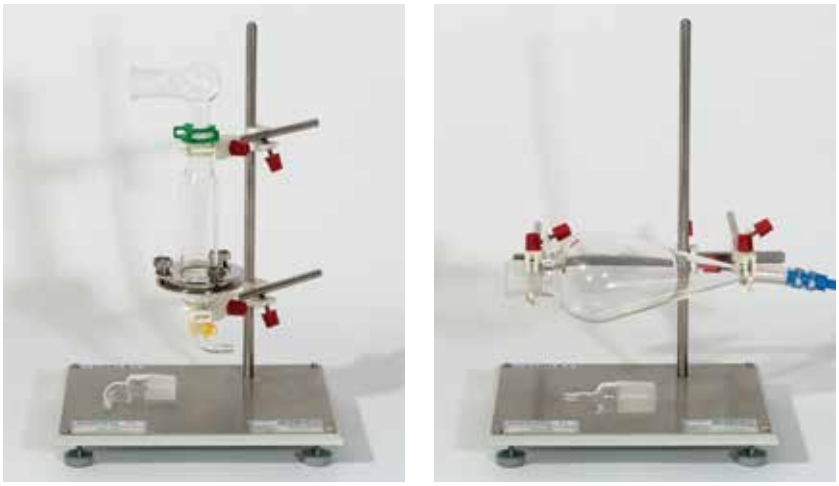
The following examines the application of *in vitro* techniques in inhaled generic product testing, focusing on tests specifically linked to regulatory guidance associated with demonstration of BE or indicated in the product-specific US Pharmacopeia (USP) monographs for popular generic targets.

REGULATORY LANDSCAPE

The most recent guidance from EMA relating particularly to inhaled generics was released in 2009 (1). It implies that BE can be shown through *in vitro* testing alone – without pharmacokinetic and pharmacodynamic (PK/PD) studies – providing a range of stringent criteria are met. Evidence must confirm the following (2):

- The active ingredient is the same, and in the same solid state, as in the RLD – any differences in crystallinity or polymorphic form do not affect solubility
- Any changes to the excipient do not impact product safety or performance, aerosol particle behaviour and/or the behaviour of the patient
- Product handling is similar to the RLD
- The target delivered dose and the inhaled volume needed to deliver is the same as for the RLD (within +/- 15%)
- Resistance to air flow is the same as for the reference device (within +/-15%)

Demonstrating BE through *in vitro* testing, therefore, relies on identifying tests that robustly characterise all these criteria. Currently the FDA does not offer equivalent general guidance for inhaled products; however, it has responded to the growing number of generic submissions with the release of product-specific guidance to support the design of BE studies and improve efficiency (3). In these guidances, *in vitro* testing forms part of a BE strategy alongside clinical trials (PK and/or PD studies).



▲ *Figure 1: Product-specific monographs glass sample collection apparatus for inhalation powders (left) and inhalation aerosols (right)*

DEMONSTRATING *IN VITRO* BE

EMA guidance highlights the fact that inhaled product efficacy derives from interaction between the formulation, device and patient. This determines the dose delivered and its particle size within the dispersed aerosol, which in turn influences deposition behaviour in the lungs. Both the USP and European Pharmacopoeia (Ph Eur) cover general chapters for inhaled product testing, detailing methods for delivered dose uniformity (DDU) and aerodynamic particle size distribution (APSD) measurement. However, product-specific USP monographs are now also available for certain generic targets, including the following:

- Fluticasone propionate inhalation aerosol (metered dose inhaler (MDI) delivery), 2013 (4)
- Fluticasone propionate inhalation powder (dry powder inhaler (DPI) delivery), 2013 (4)
- Salmeterol inhalation powder (DPI delivery), 2014 (5)
- Fluticasone propionate and salmeterol inhalation aerosol (proposed) (6)
- Fluticasone propionate and salmeterol inhalation powder (proposed) (6)

Test equipment and methods defined in the general chapters mirror current best practice and are subject to ongoing refinement. Typically, they are used to meet EMA and FDA requirements. However, in generic development the need to demonstrate BE means researchers are often attempting to mimic performance characterised up to 20 years ago, before current test methods were in place. An alternative to the general chapter methods is to revert back to the tests applied during the first development.

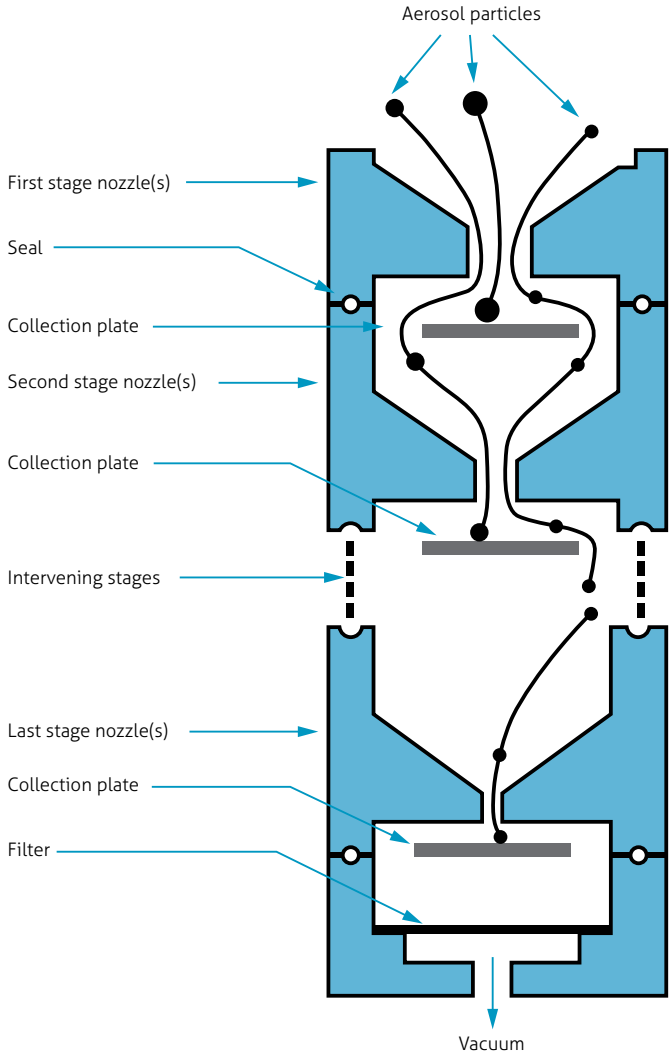
Differences between the methods outlined in the general chapters and product-specific monographs reflect this approach, referencing the RLD's heritage and the sometimes unique test methods utilised during its original development. Their use, whether in product development or for ongoing quality control, is not mandatory, but may reduce the burden of method validation and specification setting by minimising the risk that generated data are influenced by the equipment or test method used.

DDU TESTING

Delivered dose for MDIs and DPIs is usually measured by actuating the device into a dose uniformity sampling apparatus (DUSA). Following EMA guidance, DDU testing is able to verify that the generic delivers a comparable dose to the RLD's label claim. It can also provide supporting evidence that product performance is not adversely affected by excipient choice, and that the inhalation volume required for effective product use is the same as for the RLD. The conditions that are applied during testing vary depending on the type of product (7).

All product-specific USP monographs reference glass sample collection apparatus for DDU testing, which is not included in the general chapters. Two designs are described – one for inhalation aerosols, the other for inhalation powders (see Figure 1). The total air volume for inhalation powders testing is 2L, reflecting the lung capacity of an adult with a respiratory condition and consistent with the volume stated in the revised general USP chapter. However, both apparatus differ substantially from standard DUSAs in terms of their dimensional and operational specifications.

To completely characterise the delivered dose, DDU testing is also used to verify and compare dose uniformity across the life of multiple-dose products. Compendia and regulatory methods recommend assaying doses from the beginning – middle, in some cases – and end of life, indicating the labelled number of doses for the product, and also specifying the number of devices



▲ ***Figure 2:*** *Multistage cascade impactors size fractionate a dose on the basis of particle inertia, by progressively accelerating particles through a number of stages containing single or multiple nozzles and collecting them on a collection surface for subsequent chemical analysis*

Source: Adapted from USP <601>

that should be examined. Testing at a range of flow rates (commonly 30, 60 and 90L/min) may also be required to reflect the traits of the intended patient population. In addition, product-specific FDA guidance calls for population bioequivalance (PBE) analysis of measured dose uniformity data, on a single-actuation basis.

MULTISTAGE CASCADE IMPACTION

The preferred technique for measuring the APSD of all inhaled products is multistage cascade impaction, to infer and compare likely *in vivo* deposition behaviour. Cascade impaction, while not directly simulating the lung, can be used in demonstrating BE to investigate the likelihood of similar *in vivo* deposition properties.

The size of a multistage cascade impactor fractionates a delivered dose on the basis of particle inertia, thus producing a series of samples for subsequent analysis (see Figure 2) (7). Their performance is determined by the flow rate of air entering the impactor during testing, which must be constant. Nebulisers are examined at a constant flow of 15L/min, which is deemed representative of the mid-tidal flow rate of a typical adult user, rather than under tidal (variable) flow conditions – for other orally inhaled products, the flow rates applied are broadly the same as in DDU testing (unless add-on devices, such as spacers, are used).

When comparing cascade impaction data to demonstrate BE, EMA guidance recommends stage-by-stage assessment or comparison of a minimum of four groupings defined on the basis of inferred deposition site within the lung. Such groupings may include fine particle dose – the dose in the one-to-five micron range considered optimal for pulmonary deposition – but must span the full particle size range covered by the cascade impactor.

Additional requirements include the need to test three batches of both the RLD and the generic, with maximum allowable differences calculated to form the basis of a decision justifying BE (8). The variability associated with cascade impaction (especially on stages carrying little drug mass) makes such comparisons arguably the most demanding step in demonstrating in vitro BE. Taking steps to improve the accuracy and precision of the technique can, therefore, be extremely helpful (7).

FDA suggestions for the examination of *in vitro* BE are detailed in the product-specific guidance and are typically based on PBE analysis of impactor sized mass, the provision of individual stage masses and comparison of specific metrics derived from the APSD.

PRODUCT-SPECIFIC USP MONOGRAPH

These mention a modified induction port for cascade impactor testing for inhalation powders and aerosols, manufactured from aluminium or 316 stainless steels to match the

Andersen Cascade Impactor (ACI) specified. It has an inlet geometry similar to the glass twin impinger (GTI), reflecting practice at the time when these products were developed. GTI mouthpiece adapters can be used to connect the induction port with the device, while an O-ring-less tapered exit enables interfacing with the ACI via modified versions of its pre-separator and inlet cone, for inhalation powders and inhalation aerosols respectively.

The introduction of ACI versions designed for testing at 60 and 90L/min post-date the development of the RLDs covered by the product-specific monographs. These specify use of the original 28.3L/min version of the ACI (stages 0 to 7, plus filter stage) with a test flow rate of 60L/min for inhalation powders. The total air volume for APSD measurement of inhalation powders is 3L, larger than is applied during DDU testing – presumably in order to achieve adequate volume changes in the ACI.

ATTRIBUTES INFLUENCING PATIENT BEHAVIOUR AND DRUG DELIVERY

Additional product attributes that can influence patient behaviour and the efficiency of drug delivery are the 'cold Freon' effect and the resistance of a DPI device. The cold Freon effect is the inadvertent response – including coughing and exhalation – to the chilling sensation at the back of the throat following actuation of a propellant-driven MDI. Among the commercial instruments that are used to measure the cold Freon effect is the Plume Temperature Tester Model PTT 1000, which measures temperature as a function of distance from the mouthpiece to produce a temperature profile for the plume. Along with measurements of the impaction force of the plume gathered with an instrument such as the Spray Force Tester Model SFT 1000, these data fully quantify the cold Freon effect, while simultaneously helping to substantiate therapeutic similarity.

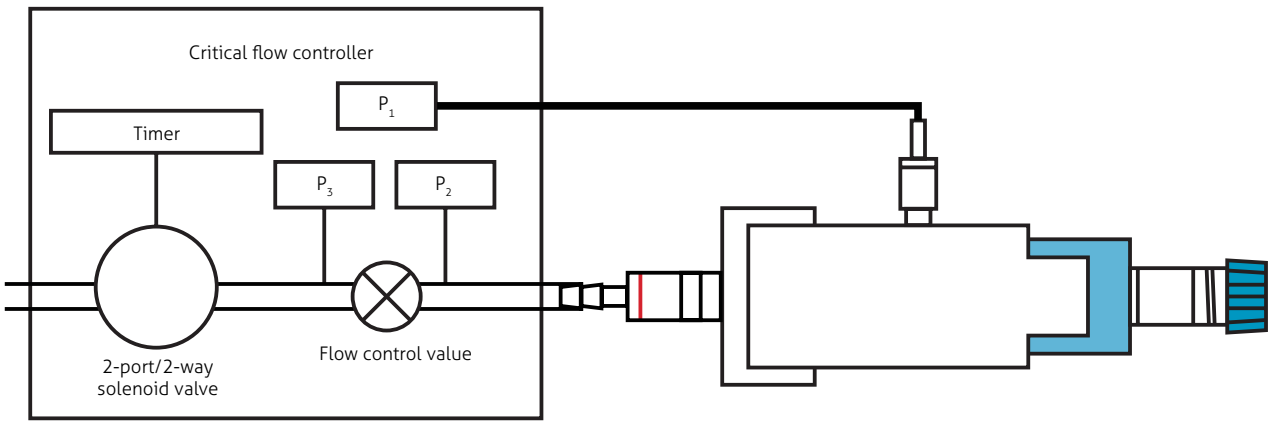
The flow resistance of a DPI device may also directly impact the inhalation manoeuvre of a patient. A device with a low resistance results in a higher flow rate of air passing through the device than one with high resistance, based on the same inspiratory effort. Device resistance can therefore affect aerosolisation performance, delivered dose and patient experience. The test set-up used to determine the flow rate required for DDU and APSD measurements for DPIs, according to the USP and Ph Eur general chapters, is shown in Figure 3 (7). This can be manipulated to gauge the pressure drop across a device at a defined, fixed flow rate to learn and compare the internal resistance of an RLD and generic device. Measurements across a range of flow rates ensure complete characterisation of the device.

ADVANCING *IN VITRO* TESTING

General EMA and product-specific FDA guidance, as well as product-specific USP monographs, provide information to help generic developers substantiate therapeutic equivalence. They highlight the potential scope of required *in vitro* testing arising from the complexity of inhaled pharmaceuticals, the performance of which is subject to far greater variability than drug delivery via oral solid dosage. As correlations between *in vitro* measurements and *in vivo* behaviour are not yet secure, product replication remains challenging, broadening the scope of tests required to ensure efficacy and safety.

Achieving better *in vitro* and *in vivo* relationships is an important goal for

▼ ***Figure 3:*** *The test set-up used to determine the flow rate that generates a 4kPa pressure drop across a DPI, for DDU testing and APSD measurement, can be readily adapted to measure internal device resistance as a function of flow rate*



the inhaled product community, and would strengthen BE studies (9). The use of breathing simulators producing more realistic breathing profiles during testing, for example, is increasingly common practice. Similarly, product innovations such as the Alberta Idealised Throat have been shown to improve conventional APSD testing – instead of using the standard USP and Ph Eur induction port – by better reflecting *in vivo* drug deposition behaviour. *In vitro* dissolution is also an area of increasing interest as developers endeavour to learn more about the fate of particles after pulmonary deposition.

Demonstrating BE through *in vitro* testing is a cost-efficient goal for generic developers, but demands a rigorous and robust testing strategy. Both traditional and evolving test methods have a role to play in bringing new generics to market in a timely and efficient manner.

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"The flow resistance of a DPI device may also directly impact the inhalation manoeuvre of a patient"