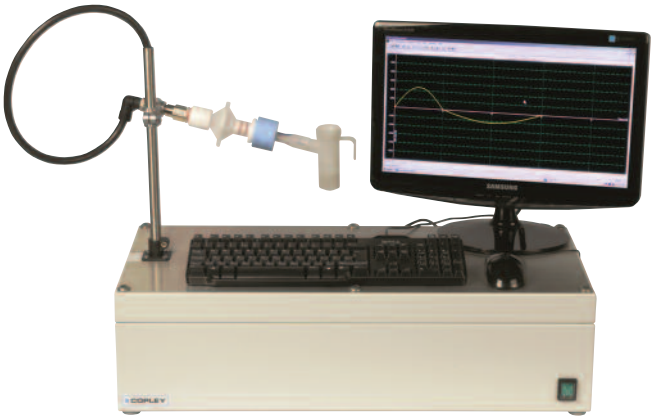
# Assessing the role of breathing simulators in OIP testing

## *Exploring how the application of patient-representative inhalation profiles can improve the relevance of test data*



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Breathing simulators, instruments that generate an inhalation and/or exhalation profile that mimics that of a human subject, have become a routine feature of orally inhaled product (OIP) testing. Recently updated monographs for nebulizers[1,2] and a new draft USP monograph for the testing of pressurized metered dose inhalers (pMDIs) with spacers and valved holding chambers (VHCs)[3] specifically call for the application of representative breathing profiles during testing. In addition to these specific protocols, researchers are employing breathing simulators to more robustly scope and fully understand OIP performance.[4-8]

This article reviews the capabilities of breathing simulators and their application in nebulizer, dry powder inhaler (DPI) and pMDI testing, clearly differentiating between that which is specified by the pharmacopeias and that which remains optional but potentially valuable.The focus is delivered dose uniformity (DDU) testing and aerodynamic particle size distribution (APSD) measurement. Delivered dose and APSD are considered Critical Quality Attributes (CQAs) for OIPs, variables that define clinical efficacy and consequently drive the majority of *in vitro* testing.

## The impact of inhalation

A case can be made for the application of breathing simulators for testing all types of OIPs, with the exception of pMDIs in the absence of a spacer or a VHC. For nebulizers, dry powder inhalers and pMDIs with either a spacer or a VHC, a patient's inhalation profile affects the efficiency of drug delivery.

**Nebulizers:** Nebulizers continuously generate an aerosolized cloud of droplets for inhalation by the patient. The therapeutic dose received therefore depends directly on how effectively the repetitive, tidal breathing cycle draws the droplets into the lungs and on the duration of use.

**DPIs:** The majority of DPIs are passive, which means that the only energy supplied for dispersion and aerosolization of the dose, and subsequent delivery, comes from the inhalation maneuver of the patient. For DPIs, the applied inhalation profile therefore influences the extent to which the dose disperses to a respirable particle size, the emptying of the device and the extent to which the drug is drawn into the lungs.

**pMDIs with spacers/VHCs:** In the absence of a spacer or VHC, efficient drug delivery with a pMDI relies on synchronizing device actuation with inhalation. However, beyond this, the drug delivery and aerosol generation process is propellant-driven and relatively insensitive to the breathing profile applied. The situation changes when a spacer or VHC (Figure 1) is used because they separate the pMDI from the patient. Both eliminate the need to precisely coordinate actuation and inhalation, capturing the dose emitted from the pMDI as a reservoir of dispersed particles that can be inhaled in much the same way as with a nebulizer. In doing so, they make pMDIs suitable for a wider range of patients. However, such devices simultaneously make the efficiency of drug delivery more dependent on the breathing profile of the patient because retention of a portion of the dispersed aerosol is possible within the spacer/VHC.

## Nebulizers: A regulatory requirement for representative breathing profiles

New harmonized monographs for nebulizer testing—Ph. Eur. 2.9.44 and USP <1601>[1,2]—were adopted in January 2012 and August 2011 respectively. These monographs recommend that nebulizers, like other OIPs, are tested as combined products (formulation and device) and include well-defined breathing profiles for this testing that reflect guidance issued by the European Medicines Agency.[9] The new monographs reference four breathing profiles: adult, child, infant and neonate (Table 1).

Breathing simulators that produce these profiles are now used routinely as part of delivered dose uniformity testing for nebulizers to measure two discrete parameters: active substance delivery rate and total active substance delivered. These parameters define the rate at which the drug will be inhaled by the patient and the total dose inhaled over a prescribed timeframe.

Measurements of APSD for all nebulizers are carried out at a constant flow rate, as required for operation of the cascade impactors used for these measurements. The prescribed flow rate for the testing is 15 L/min, a figure broadly representative of the mid-tidal flow of a typical adult user. Nebulizers are essentially active devices so the droplet size they produce is minimally affected by the breathing profile of the patient. APSD measurement under these conditions is therefore deemed sufficiently representative of in-use performance. The Next Generation Impactor (NGI) has calibrated performance at 15 L/min and is particularly well-suited to nebulizer characterization, mostly because of the substantial capacity of the NGI collection cups for liquid droplets generated by nebulizers. This conclusion is reflected in the new monographs which provide useful guidance for its application.

## Dry powder inhalers: A broader scoping of product performance

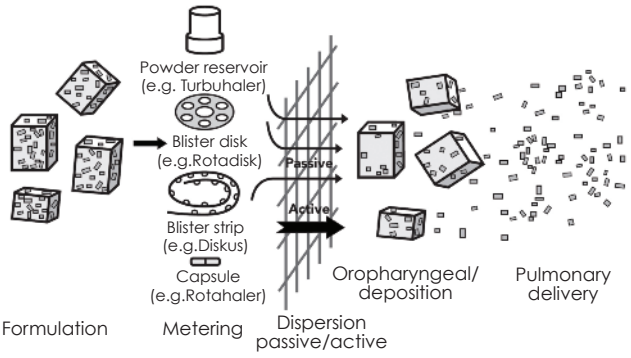
The passive nature of the vast majority of DPIs makes the mechanisms of drug delivery markedly different from those of other OIPs. Figure 2 illustrates these mechanisms, showing how the energy provided by the patient during inhalation influences both the size to which the particles are dispersed and the effectiveness with which the drug is drawn out of the device and into the lungs. This method of operation makes DPI performance more

### Figure 1

**Using a spacer or a VHC (shown) eliminates the need to precisely coordinate pMDI actuation with inhalation, easing product use and increasing drug delivery efficiency. Each VHC has a one-way valve at the patient interface to prevent failed aerosol delivery in the event of exhalation through the device, whereas a spacer is simply a section of open tube.**

### Figure 2

**Air drawn through a DPI, by the patient's inhalation action, aerosolizes the powder bolus, ideally dispersing the drug particles to a suitable size (smaller than 5 microns) for deposition in the deep lung. Adapted with permission from M.J. Telko, et al. (September 2005) "Dry powder inhaler formulation." Respiratory Care, Volume 50, Number 9, pages 1209-1227.[18]**




### Table 1

**Breathing Simulator Specification for Nebulizer Characterization Tests**

| | Adult | Neonate | Infant | Child |
|---|---|---|---|---|
| **Total Volume** | 500 ml | 25 ml | 50 ml | 155 ml |
| **Frequency** | 15 cycles/min | 40 cycles/min | 30 cycles/min | 25 cycles/min |
| **Waveform** | Sinusoidal | Sinusoidal | Sinusoidal | Sinusoidal |
| **I/E Ratio** | 1:1 | 1:3 | 1:3 | 1:2 |

sensitive to variability in the applied breathing profile than any other OIP.

This conclusion is reflected in current pharmacopeial tests for DPIs, which are based on establishing product-specific test conditions. The first step in either DDU or APSD measurement is to determine the flow rate that generates a 4 kPa pressure drop over the DPI; a pressure drop deemed to be representative of that which a typical adult asthmatic or COPD patient will generate during use. This flow rate is dependent on the flow resistance of the device under test, with low resistance devices resulting in a higher flow rate than those that present higher resistance to flow (Figure 3).

Using this derived flow rate (up to a limit of 100 L/min) the test duration is calculated on the basis of a total test volume, specified to represent the total inspiratory volume of the patient during use. The FDA recommends 2 L[10] and the pharmacopeias favor 4 L to better suit the size-fractioning mechanism of cascade impactors.[11] Both can be argued as representative of a typical adult patient, although the former is probably more representative of an asthmatic or COPD patient. This volume is used to define a square wave profile that is applied during both DDU and APSD measurement.

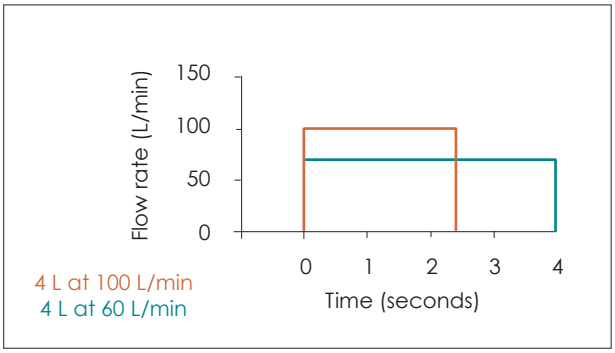
This established method helps to ensure that the critical parameters that drive the aerosolization process during testing are broadly representative of actions that will occur during patient use, within the constraints of the test apparatus. However, it has limitations, most especially for the assessment of DPI performance for:

- weak patients or those with severely impaired lung function unable to generate a 4 kPa pressure drop during product use[12]
- healthy patients with a stronger inspiratory capability using a DPI for systemic treatment[13]
- any patient with a sub-optimal operating technique

These limitations are becoming more problematic as the use of DPI technology is extended to, for example, pediatric and geriatric patients who do not have the lung capacity of a healthy adult and the delivery of systemic therapies such as insulin, antibiotics and vaccines to otherwise healthy patients with unimpaired lung function. Furthermore, as the industry embraces Quality by Design and also seeks ways to show bioequivalence in the case of generic products, there is a broader requirement to fully scope and understand product performance. This requirement cannot be met completely using current testing methodology, which has evolved principally for the QC environment. Understanding the impact of any variability that may arise from, for example, differences in patient physiology or technique, is becoming increasingly important, prompting wider experimentation, often with alternative breathing profiles.[5,7,8]

## Figure 3

**A product-specific, square-wave flow profile is applied during DPI testing, defined from the flow rate commensurate with a 4 kPa pressure drop across the device and an associated inspiratory volume (2 L or 4 L).**




With the existing pharmacopeial test set-up, the physiology of stronger or weaker patients can be assessed by varying the pressure drop used to determine test flow rate or by changing the test duration to investigate the impact of inspiratory capacity. However, air flow rate is essentially either "on" or "off." Breathing simulators, in contrast, enable the application of variously shaped/dimensioned breathing profiles to investigate the ways performance is impacted by:

- a more realistic air flow acceleration rate, from zero to peak flow
- the shape of the breathing profile of specific patient groups (potentially obtained from clinical data)
- exhalation back into the device, i.e., incorrect operation

As previously discussed, in the case of DPIs, both the aerodynamic size of the particles produced (APSD) and the dose delivered can be impacted by the breathing profile. Here, breathing simulators consequently have the potential to bring added value to APSD measurements, as well as to DDU testing. This raises the question of how to impose a defined breathing profile through the DPI while maintaining the constant flow rate through the cascade impactor that is required for its correct and calibrated operation.

A mixing inlet is a device that can be used to address this issue (Figure 4). By decoupling the flow profile applied to the DPI from that which is applied to the impactor, in real-time, a mixing inlet facilitates the application of a breathing profile that reflects the conditions of interest, during DPI testing.[14] The accuracy of APSD measurements is maintained because the flow rate through the impactor remains constant. (See sidebar "An optimized set-up for DPI testing?")

## An optimized set-up for DPI testing?

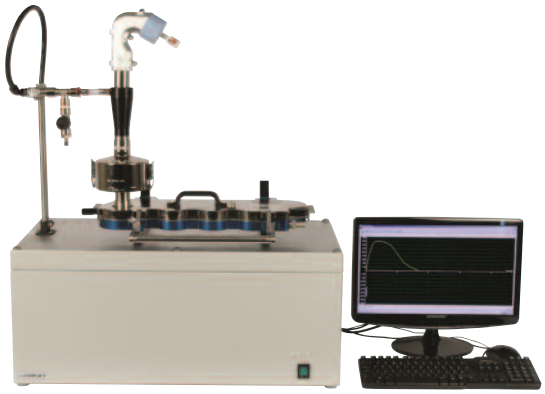
The test set-up in Figure 4 illustrates the way bioequivalence testing can be improved by the combined application of three pieces of equipment that are routinely absent from the standard test set-up: a breathing simulator, an Alberta Idealized Throat (AIT) (in place of the standard USP induction port) and a mixing inlet.

The breathing simulator and mixing inlet together enable the application of a patient-relevant breathing profile through the DPI, while maintaining the constant flow rate through the impactor that is required for accurate APSD measurement. This allows the robust demonstration of equivalent drug delivery performance across a range of conditions that represent the variability associated with the target user group. This flexibility to fully scope variability is far greater than with the standard pharmacopeial test set-up.

The AIT addresses the widely recognized limitations of the standard USP induction port in accurately representing aerosol transport through the upper respiratory tract. Part way between a human throat cast and the simple right-angled tubular design of the USP induction port, the AIT produces data that are more representative of measured *in vivo* behavior, thereby supporting a more reliable demonstration of bioequivalence.[15,16]

**Figure 4**

**A set-up for more patient-representative DPI testing, combining a breathing simulator, an Alberta Idealized Throat (AIT) and a mixing inlet.**



## pMDIs with valved holding chambers (VHC) and spacers: A new USP monograph

The use of a spacer or VHC with a pMDI results in a reservoir of dispersed particles that can be inhaled in much the same way as with a nebulizer. It also allows for the introduction of a time delay between actuation of the MDI and inhalation of the aerosol cloud produced. A new USP monograph, currently in draft form,[3] highlights these facts and brings breathing simulators into the spotlight for the representative testing of this class of OIP.

The approach outlined in the draft monograph draws on experience gained in Canada over the past 10 years, since the publication of an existing Health Canada standard defining clinically-appropriate performance test methods.[17] It closely echoes the strategy employed for nebulizers, providing breathing profiles for DDU testing, and suggesting that APSD measurement be carried out at a fixed flow rate, both of which are broadly representative of the target patient group. Defined breathing profiles are recommended for delivered dose measurement, with test conditions specified for adult and pediatric patients: neonate, infant and child.

The draft monograph also includes a requirement, unique to pMDIs with spacers and VHCs, to assess the impact on delivered dose when actuation and inhalation are not properly coordinated. This reflects the potential use scenarios by the patient: closely coordinate inhalation and device actuation, or device actuation during exhalation prior to inhalation. Testing at the extremes of fully coordinated and fully uncoordinated use, using breathing profiles programmed to start on inhalation or exhalation, helps to fully scope the impact of this source of variability.

## Looking ahead

The availability of cost-efficient, reliable breathing simulators has encouraged their use throughout OIP testing. This technology eases compliance with new pharmacopeia monographs for nebulizers and with a new draft monograph for pMDIs with spacers and VHCs. In addition, breathing simulators enable the more robust scoping of product performance—for both innovator and generic submissions, especially for DPIs. By helping to quantify the likely impact of variability introduced by patient physiology and technique, they bring significant value, whether the aim is to demonstrate the suitability of a new product for a specific patient group or bioequivalence.

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