Using breathing simulators to enhance inhaled product testing

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Breathing simulators, machines designed to generate and apply an inhalation and/or exhalation profile that mimics that of a human subject, are becoming an increasingly routine part of orally inhaled product (OIP) testing. Advances in breathing simulator technology have brought sophisticated, cost-efficient solutions to the industrial marketplace, opening up opportunities to improve the clinical relevance of *in vitro* OIP testing techniques. The application of a range of appropriate breathing profiles is now enshrined in recently updated pharmacopoeial monographs for nebulisers [1,2] but beyond this, researchers are starting to look at the broader value of working with a representative inhalation profile in order to fully scope product performance [3,4]. This is most especially true for dry powder inhalers (DPIs) [3-7] and within the context of Quality by Design (QbD).

In this paper we look at the capabilities offered by breathing simulators and review their application in OIP testing. We clearly differentiate between what is specified by the pharmacopoeias and what is optional; areas where the use of a breathing simulator is not mandatory but is nevertheless highly informative. Nebulisers and DPIs, as well as pressurised metered dose inhalers (pMDIs) used with spacers and valved holding chambers (VHCs), are the focus.

Breathing simulators: evolving to meet industrial needs for testing

The use of all OIPs involves an inhalation manoeuvre by the patient. However the potential for that manoeuvre to impact drug delivery varies depending on the device being used. The value of breathing simulators in OIP testing is therefore similarly dependent on the technology under investigation.

A pMDI, when used without a spacer or VHC, actively delivers the drug dose directly to the patient, using a propellant. With these devices, inhalation must be coordinated with actuation to ensure success, but the shape or characteristics of the breathing profile are unlikely to have much impact on the aerodynamic particle size distribution (APSD) of the delivered aerosol and/or the effectiveness of delivery. This is not the case for DPIs and nebulisers or pMDIs used with spacers. Here the breathing profile of the patient directly influences the efficiency of drug delivery. As a result it can be argued that all these products should be tested under conditions that simulate, to some extent, the breathing profile of the target patient population.

Pragmatism plays an important role in identifying how to design testing to meet this requirement. For example, highly sophisticated electronic lungs have been available for inhaled drug studies for some decades now [6]. These can closely simulate patient breathing patterns and enable the detailed study of how subtly tailored inhalation profiles influence drug delivery. However, they are expensive, difficult to interface with laboratory based analytical test equipment, complex to validate and therefore ill-suited to routine, high throughput testing, either for quality control (QC) or during product development.

A good example of an alternative approach - an intelligent trade-off between close simulation of the breathing manoeuvre and practicality - is provided by the current pharmacopoeial methods for DPI testing. These recognise the need to tailor inhaler testing to reflect the critical parameters of the breathing manoeuvre, but are relatively unsophisticated in how they do so, reflecting the need for standardised, relatively simple testing, tailored to a QC environment. Test conditions are based on an assumption that a standard or average adult patient will generate a 4 kPa pressure drop across the DPI during forced inhalation, and a further assumption is made regarding total inhalation volume. These figures are used to then define a constant test flow rate and duration, and a square wave profile is then applied during dose uniformity and cascade impactor testing.

Efforts to advance OIP technology are prompting increased scrutiny of how established test methods such as these might be enhanced to give improved *in vivo* representation. In the case of generic OIPs where there is a need to demonstrate bioequivalence with the reference product, there is a broad cavern that separates *in vitro* testing, based on established pharmacopeial methods, and clinical trials. Indeed, it is not unusual for equivalence to be demonstrated *in vitro* only to fail during subsequent pharmacokinetic and/or pharmacodynamic studies. Needless to say this can be a costly misadventure and so the desire to try and bridge the gap between *in vitro* and *in vivo* testing is compelling. The concurrent evolution of breathing simulators highlights a potential strategy. As it becomes easier to access cost-effective, but efficient breathing simulator technology, the value of applying more representative breathing profiles during testing is being more widely assessed. For some products, nebulisers for example, this is already a routine part of testing. For others it remains an activity that is reserved for more in depth investigative research.

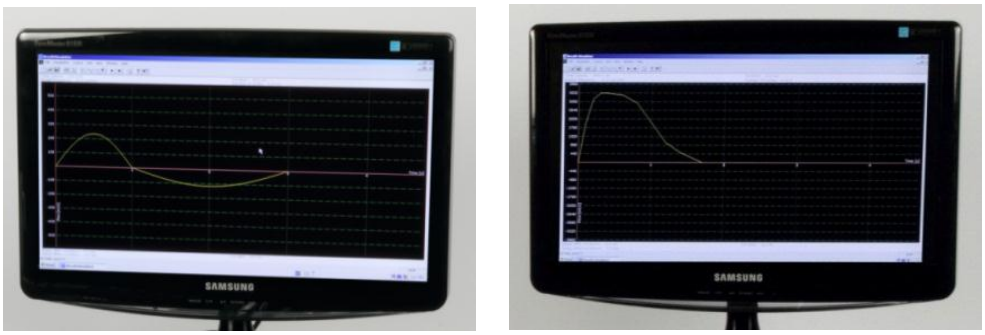

Figure 1: Breathing simulators enable the application of well-defined wave patterns to more closely simulate the inhalation performance of different patient groups

Today's simulators are easily integrated within established OIP testing set ups and make it possible to:

- apply different wave patterns: square; sinusoidal; triangular; or user defined
- alter tidal volume – the volume of each inhalation and/or exhalation
- separately vary the duration of inhalation and exhalation, if required (I/E ratio)
- introduce a delay after inhalation and/or exhalation
- control the number of breathing cycles during each test.

As a result such systems can be used to simulate a range of breathing profiles (see figure 1) and to investigate those features of the inhalation manoeuvre that may change from patient to patient, such as how acceleration to the peak air flow rate is reached during inhalation. These systems therefore support a range of established and evolving test methods for OIPs.

Nebulisers: a refreshed regulatory regime based on testing with defined breathing profiles

Drugs destined for delivery via a nebuliser are formulated as therapeutic liquids. These solutions or suspensions are loaded into the nebuliser, from a nebule, which actively atomises the liquid to form respirable droplets. A number of different atomisation technologies are used [8] but in most cases the device operates continuously once loaded. The user breathes under tidal conditions (at rest), through a mouthpiece or facemask, during treatment. The therapeutic dose received depends on how effectively the repetitive breathing cycle of the patient draws the atomised droplets into the lungs, and the duration that the device is used for.

Until fairly recently nebulisers were classified as medical devices and the prescribing clinician chose which nebuliser to use with each formulation. However changes to the regulatory framework have been introduced to recognise that it is the formulation and nebuliser device in combination that control the droplet size delivered, and hence the efficiency of drug delivery. This brings nebulisers into line with pMDIs and DPIs. Two new harmonised monographs for nebulisers: Ph. Eur. 2.9.44 and USP 1601 [1, 2] came into force in January 2012 and August 2011 respectively, and these provide a useful indication of current regulatory thinking. Nebulisers like other OIPs are now tested as combined products (formulation and device), with well-defined breathing profiles specified for this testing, which is reflected in guidance issued by the European Medicines Agency [9].

The new monographs reference four breathing profiles: adult, child, infant and neonate. Nebulisers require little coordination by the user, making them a popular choice for treating paediatric patients, which is why the new monographs focus on making testing more fitting for these physiologies. The test conditions for each patient group are defined in table 1.

The defined child, infant and neonate profiles are based on significantly smaller volumes, higher breathing frequencies and different inhalation/exhalation ratios.

Table 1:

Breathing Simulator Specification for Nebuliser Characterisation Tests				
	Adult	**Neonatal**	**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

Breathing simulators that produce these profiles are now used routinely as part of delivered dose uniformity testing for nebulisers, to generate results that are specifically relevant to the target user group for any given product (see figure 2). Two different parameters are measured: active substance delivery rate and total active substance delivered. These define the rate at which the drug will be inhaled by the patient and the total dose inhaled over a prescribed timeframe.

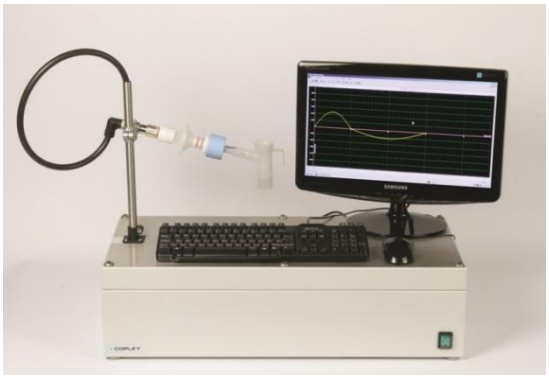

Figure 2: Breathing simulators are a routine part of nebuliser testing, used to produce the well-defined inhalation profiles specified in the monographs for delivered dose testing

Measurements of APSD for all nebulisers are carried out at a constant flow rate (as required for operation of all cascade impactors) of 15 L/min, a value representative of the mid-tidal flow rate of a typical adult user. The NGI has calibrated performance at 15 L/min and is therefore well-suited to nebuliser characterisation; a conclusion reflected in the new monographs which provide useful guidance about its use in this area.

In summary then, for nebulisers the inclusion of breathing simulators for delivered dose measurements is enshrined in the pharmacopoeial monographs. Their use allows the application of a specific adult or paediatric breathing profile, thereby enabling the representative determination of drug delivery rate and total drug delivered for specific patient groups. However, as an active device, the droplet size produced by a nebuliser is not appreciably affected by the breathing profile of the patient. Measuring APSD at a constant flow rate of 15 L/min is therefore considered sufficiently representative of in-use conditions, within the constraints of routine cascade impaction.

Defining OIP performance: delivered dose and aerodynamic particle size distribution (APSD) measurement

Two parameters take centre stage when it comes to defining the performance of OIPs – delivered dose and APSD. Considered as Critical Quality Attributes (CQAs) these are measured for all inhalers and nebulisers and drive the majority of *in vitro* testing.

Delivered dose uniformity (DDU) testing, as the name implies, involves measuring the total amount of drug delivered to the patient during product use and excludes any drug retained by the device under test. An APSD is measured specifically for the active pharmaceutical ingredient to infer where in the lung the dose is likely to deposit and to ensure batch to batch consistency. Particles less than 5 microns in size are preferable for penetration to the deep lung; those larger than this are more likely to be ingested rather than inhaled.

When it comes to the practicalities of testing, delivered dose uniformity is measured using a dose uniformity sampling apparatus (DUSA) which simply captures the dose delivered by the OIP, to enable chemical analysis. APSD measurements are made using a multistage cascade impactor: a precision instrument that size fractionates the incoming aerosol on the basis of particle inertia. Analysis of each fraction enables the generation of a size distribution specifically for the active ingredient. The Andersen Cascade Impactor (ACI) and Next Generation Impactor (NGI) are the most frequently used instruments for this application.

Dry powder inhalers: scoping performance through the application of different breathing profiles

Actuation and operation of the majority of DPIs relies solely on the inhalation manoeuvre of the patient and they are therefore generally categorised as passive devices. As the patient inhales, air is drawn through a powder bolus held in the device (typically contained in a blister, capsule or dosing reservoir) causing it to aerosolise. This aerosolisation process disperses the formulation to a respirable size, producing a cloud of particles that are drawn from the device into the lungs (see figure 3). The mechanisms of drug delivery with a DPI are therefore markedly different from those of either pMDIs or nebulisers. The lack of any active mechanism means that both the size of particles produced, and the extent to which the device is emptied, are breathing profile dependent. The potential for DPIs to be more sensitive to variability in the applied breathing profile than any other OIP is therefore clear.

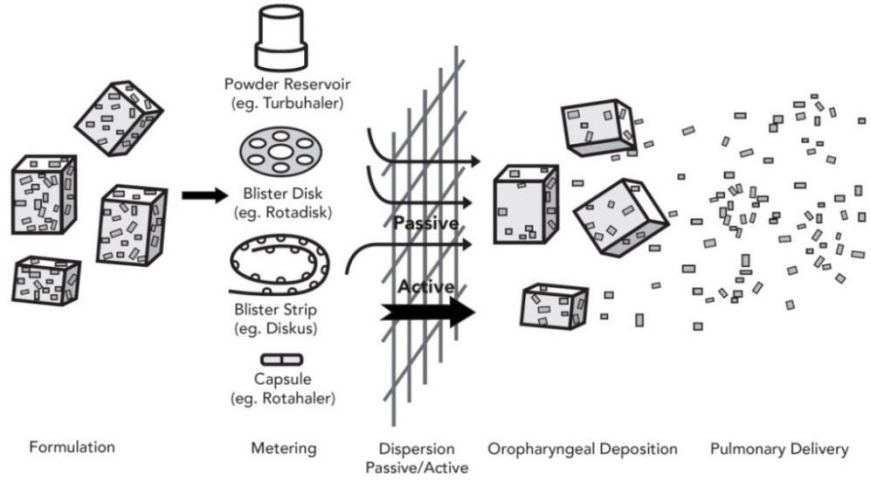

Figure 3: In the majority of DPI formulations small active particles are attached to larger carrier/excipient particles. During operation the active is stripped from the carrier to ensure delivery at a suitable size for pulmonary deposition

[Image redrawn from M.J. Telko et al. "Dry powder inhaler formulation" Respiratory Care, Sep 2005, Vol 50 No 9]

This conclusion is reflected in the current test regime for DPIs, which is based on establishing product specific test conditions. The first step in DPI testing, either DDU or APSD measurement, is to determine the flow rate that induces the 4 kPa pressure drop, deemed to be representative of what a typical adult patient will generate across the device during use. The flow rate that induces this pressure drop is dependent on the resistance to flow of the device under test. If resistance is low then the 4 kPa pressure drop will result in a high flow rate, and conversely if the device resistance is high the flow rate generating the same pressure drop will be lower.

Once this flow rate has been determined (up to a pharmacopoeia imposed limit of 100 L/min) test duration is calculated on the basis of a total test volume of either 2 L or 4 L. The FDA recommends 2 L [10] while the pharmacopoeias favour 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 better representative of an asthmatic or Chronic Obstructive Pulmonary Disease (COPD) patient. This volume translates, via the established test flow rate, into a duration for testing; a square wave profile dimensioned from these parameters is then applied and ensures a constant flow rate, as required for cascade impactor testing (see figure 4).

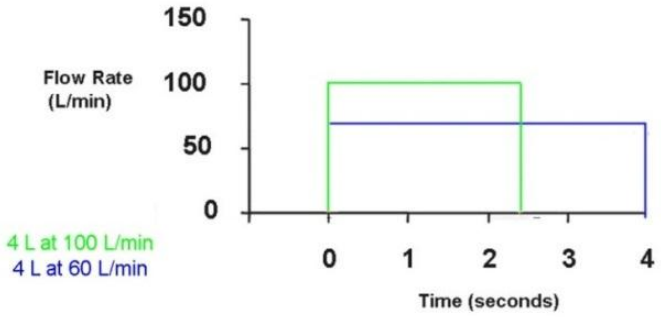

Figure 4: Test duration for a DPI is determined from the established test flow rate and regulatory/pharmacopoeial guidance relating to the total volume of air inhaled during use

This established method, designed principally for application in a QC environment, goes some way to ensuring that the conditions applied to aerosolise the dose during testing reflect what will happen during patient use. However, it is clear that this is by no means a precise simulation. Most especially it has been argued that this method fails to reliably assess how a DPI will perform for:

- weak patients without the strength to generate a 4 kPa pressure drop over the device during use, most especially geriatric and paediatric users, or those with severely impaired lung function [12]
- healthy patients, with much higher inspiratory capability who may have been using a DPI for systemic treatments rather than for the treatment of pulmonary disease [13]
- those whose operating technique is sub-standard and/or unexpected (i.e. mis-use conditions).

These limitations are becoming more problematic as the use of DPI technology is extended to, for example: paediatric 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, the square-wave profile (which is required to ensure constant flow-rate cascade impaction) results in a rapid acceleration of the airflow through the DPI, beyond what could reasonably be expected of a typical patient. Since dose emission, dispersion and aerosolisation normally occurs within the first few milliseconds of the flow profile, it can be inferred that the powder bolus experiences unrealistically favourable test conditions. More generally the industry is also changing the way it approaches research, as a result of QbD.

QbD, the strategy outlined in ICH Q8, is a systematic approach for achieving robustly consistent clinical efficacy from pharmaceutical products. It relies on fully scoping the performance of a product to ensure that all the necessary controls are in place to guarantee consistency. When it comes to DPIs, a QbD approach therefore relies on scoping the potential impact of any variability that may arise from, for example, differences in patient physiology or technique. Wider experimentation, with alternative breathing profiles, helps to procure this knowledge *in vitro*.

With the existing pharmacopoeial test set-up it is possible to base testing on a different pressure drop across the device in order to reflect a stronger or weaker patient and to change test duration to investigate the impact of effective inspiratory capacity. However, air flow rate is essentially either “on” or “off”. There is no facility to, for example:

- investigate whether drug delivery performance is affected by the rate at which air flow rate increases, from zero to the peak inspiratory flow rate
- investigate whether drug delivery performance is affected by the shape of the profile
- look at what happens if the patient exhales back into the device, i.e. operates it incorrectly.

This is where breathing simulators can be extremely helpful. However, their application is more complex for DPIs than it is for nebulisers. With nebulisers there is only a requirement to apply a representative breathing profile during DDU testing, since the droplet size produced is broadly defined by the mechanical atomisation process of the device. This is not the case with DPIs. Here, both the aerodynamic size of particles produced and the effectiveness of device emptying (or overall dose delivery) are defined by the inhalation manoeuvre. To fully scope performance it is therefore necessary to apply a representative breathing profile during both DDU and APSD measurement. This raises the question of how to impose a defined breathing profile across the DPI while maintaining the constant flow rate through the cascade impactor, which, as previously stated, is required for correct operation of the instrument.

Figure 5: An Andersen Cascade Impactor set up with a mixing inlet

Figure 5 shows a mixing inlet. A mixing inlet effectively decouples the flow profile applied to the DPI from that applied to the impactor in real-time [14]. The breathing profile applied to the DPI can therefore be precisely defined to reflect the conditions of interest in any given study, while the flow rate through the impactor is maintained at a constant value, to ensure calibrated operation of the instrument, and the accuracy of the measured APSD. This approach is generally preferable to the use of a large holding chamber/reservoir (in which the fully developed aerosol is retained prior to being drawn into the impactor at constant flow rate) since any delay introduced between aerosol generation and subsequent sampling could cause the aerosol APSD to change and encourage losses due to particle settling.

To summarise, the situation for DPIs is that there is, as yet, no pharmacopoeial or regulatory imperative to apply breathing simulators during testing. However, advancement of the technology and the implementation of QbD are driving their increased use for this important class of OIPs. Breathing simulators can help provide a more complete characterisation of product performance and are therefore valued for those looking to innovate, or indeed to rigorously demonstrate bioequivalence of a generic product within an *in vitro* testing environment.

It is important to note that current pharmacopoeial methods do not require the application of realistic patient profiles to either pMDIs or DPIs, principally due to the associated limitations of APSD measurement by cascade impaction, as described previously. However, there is also no practical reason why breathing simulators cannot be used, without the need for a mixing inlet, to

generate realistic patient profiles through these device types for DDU testing, using existing pharmacopoeial dosage unit sampling apparatus. This could be especially useful for DDU assessment of DPIs, which due to their passive nature, may be sensitive to the patient profile.

An optimised set-up for demonstrating bioequivalence in DPIs?

The test set-up shown below illustrates how new equipment for *in vitro* testing is being exploited to optimise data gathering for demonstrating bioequivalence in a DPI. There are three pieces of equipment present that are routinely absent from the standard test set-up: a breathing simulator; an Alberta Idealised Throat (AIT -in place of the standard USP induction port); and a mixing inlet. It is worth looking in detail at exactly what each element contributes.

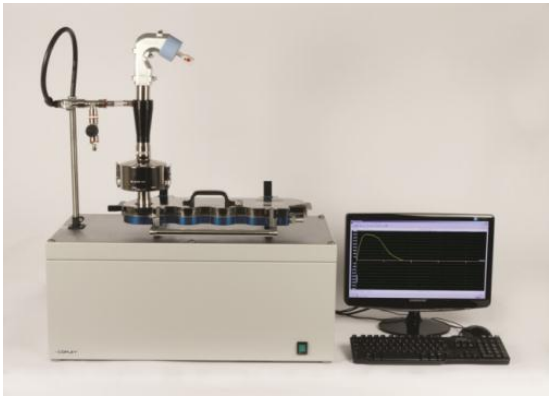

Figure A: Showing a DPI set-up with breathing simulator(s), AIT and mixing inlet (excluding the routine accessories that would also be required to make a fully functioning system)

The mixing inlet decouples the flow profile applied across the device from the flow conditions applied in the cascade impactor. It allows the application of a patient-relevant breathing profile across the DPI while at the same time enabling the cascade impactor to work at the constant flow rate required for accurate APSD measurement.

The breathing simulator enables exploration of the impact of different breathing profiles. In bioequivalence testing it therefore allows the robust demonstration of equivalent drug delivery performance across a range of conditions that represent the variability associated with a target user group. The flexibility to full scope variability is far greater than with the standard pharmacopoeial test set-up.

Finally the AIT addresses widely recognised limitations of the standard USP induction port, which does not provide a particularly accurate *in vitro* realisation of 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* behaviour, thereby supporting the robust demonstration of bioequivalence [15-17]. Furthermore it ensures that the APSD measurement obtained via cascade impaction only occurs on the portion of the aerosol that would likely enter to lungs.

pMDIs with valved holding chambers (VHC) and spacers: a new draft USP monograph puts breathing simulators in the spotlight

Relatively inexpensive and effective, pMDIs remain the 'go to' technology for the relief of pulmonary conditions in many areas of the world. However, the coordination required to synchronise inhalation with device actuation can be an issue for paediatric and geriatric patients, or indeed simply those with poor technique. Although breath-actuated pMDIs exist, this problem is more commonly solved through the use of a spacer or VHC (see figure 6), which separates the pMDI from the patient.

These add-on devices extend the distance between device and patient and provide additional dead volume for the plume to develop. A spacer is simply an open section of tube while a VHC, as the name suggests, has a one-way valve at the patient interface to ensure that uncoordinated use does not result in an exhalation manoeuvre emptying the holding chamber of the developed aerosol. Both essentially provide a reservoir of dispersed particles that can be inhaled in much the same way as with a nebuliser.

Figure 6: Using a breathing simulator to test a pMDI with spacer

Currently there are no pharmacopoeial monographs on the use of these add-on devices but this looks set to change in the near future. A recently published draft USP monograph [18] highlights the fact that the use of spacers and VHCs potentially changes the characteristics of the aerosol cloud released by the pMDI, making it important to assess their impact on the efficiency of drug delivery. The similarities with nebulisers put breathing simulators in the spotlight for representative testing and it seems likely that in the future detailed *in vitro* assessment will be recommended for drug submissions based on this technology.

The approach outlined in the USP document is based largely on experience gained in Canada during the past 10 years, which is enshrined in an existing Health Canada standard defining clinically appropriate performance test methods [19]. It outlines the need to measure delivered dose and APSD, using respectively a breathing profile or fixed flow rate that is representative of the target patient group. There is also a requirement, unique to APSD testing of pMDIs with spacers and VHCs, to assess the impact of the time delay (typically 2 seconds) between actuation of the device and the start of inhalation.

This requirement for time delay testing reflects the fact that with a spacer or VHC the patient may closely coordinate inhalation with device actuation, in which case the time delay will be zero, or use the set-up in an uncoordinated way, in which case inhalation may begin some time after actuation. In this latter case the APSD of the aerosol cloud may change considerably, ahead of inhalation, as certain sized particles may be retained within the spacer or VHC. As an extension to this, in the case of VHCs, the valve is assessed during delivered dose uniformity testing. This is achieved by testing at the extremes of fully coordinated and fully uncoordinated use, using breathing profiles programmed to start on inhalation or exhalation. Again this reflects the potential use scenarios by the patient: closely coordinate inhalation and device actuation, or device actuation during exhalation prior to inhalation. Considering the extreme cases of fully coordinated and uncoordinated use, allows the efficiency of the valve to be measured, with the relevant metric being the ratio of delivered dose obtained in both cases.

Aside from the need to assess the impact of uncoordinated use, the detailed test conditions show close parity with those specified in the latest pharmacopoeial monographs for nebulisers. Defined breathing profiles are recommended for delivered dose measurement, with test conditions specified for adult and paediatric patients: neonate, infant and child (see table 2). For APSD measurements, where constant flow rate testing is required, a flow rate representative of the intended population should be targeted within the calibrated performance constraints of commercially available cascade impactors.

Table 2:

Breathing Simulator Specification for characterising pMDIs with spacers and VHCs [19]					
	Paediatric			**Adult**	
Parameter	**Neonate**	**Infant**	**Child**	**Normal 1**	**Normal 2**
Tidal Volume (mL)	25	50	155	770	500
Frequency (min 1)	40	30	25	12	13
Inspiratory/Expiratory Ratio	1:3	1:3	1:2	1:2	1:2
Minute Volume (mL)	1000	1500	3875	9240	6500

In summary

The availability of cost-efficient, reliable breathing simulators has encouraged their use across inhaled product testing. These systems streamline testing in accordance with the latest pharmacopoeial monographs for nebulisers, where breathing simulators are an essential element of the test set-up and for pMDIs with spacers and VHCs where a revision to the USP is being considered. Elsewhere breathing simulators are increasingly valued for their ability to support the robust scoping of product performance – for both innovator and generic submissions. Using a breathing simulator to assess the impact of different breathing profiles on DPI performance, for example, can help to quantify the likely impact of variability introduced by patient physiology and technique, to more completely map product performance. Such information has significant value whether the aim is to target a specific user group with a new product or demonstrate bioequivalence in the case of generics.

References:

[1] Ph. Eur. Chapter 2.9.44 Preparations for nebulisation: Characterisation.

[2] USP 1601 Products for nebulization: Characterization.

[3] B. Olsson, et al. (2013). "Validation of a General *In Vitro* Approach for Prediction of Total Lung Deposition in Healthy Adults for Pharmaceutical Inhalation Products." *Journal of Aerosol Medicine and Pulmonary Drug Delivery, Volume 26, Number 6.*

[4] B. Olsson, et al. (2010). "Comparing Aerosol Size Distributions that Penetrate Mouth-Throat Models Under Realistic Inhalation Conditions." *Respiratory Drug Delivery 2010, pages 225-234.*

[5] D. Zanker, et al. "In vitro dose delivery performance of glycopyrronium using representative inspiratory flow profiles derived from COPD patients." *Drug Delivery to the Lungs 23, pages 281-285.*

[6] P.K.P. Burnell, et al. (1998) "Design, Validation and Initial Testing of the Electronic Lung Device." *Journal of Aerosol Science, Volume 29, Number 8.*

[7] G. P. Martin, et al. (2006) "Influence of Realistic Inspiratory Flow Profiles on Fine Particle Fractions of Dry Powder Aerosol Formulations." *Pharmaceutical Research, Volume 24, Number 2.*

[8] M. Copley (2008) "Pulmonary drug delivery: Technology, regulation and testing" *Drug Delivery Technology Oct 2008, Vol 8, No 9.*

[9] CPMP (2006) "Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products" to be read in conjunction with – CPMP (2004) "Points to consider on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP)".

[10] U.S. Department of Health and Human Services Draft Guidance Document: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products. *Published 13/11/1998.*

[11] H. Mohammed, et al. (2012) "Effect of Sampling Volume on Dry Powder Inhaler (DPI) - Emitted Aerosol Aerodynamic Particle Size Distributions (APSDs) Measured by the Next-Generation Pharmaceutical Impactor (NGI) and the Andersen Eight-Stage Cascade Impactor (ACI)." *AAPS PharmSciTech, Volume 13, Number 3, pages 875-882.*

[12] M. Copley (2010) "Assessing dry powder inhalers" White paper available for download at: http://www.copleyscientific.com/documents/ww/Assessing%20dry%20powder%20inhalers.pdf

[13] D. Harris (2007) "Testing inhalers" *Pharmaceutical Technology Europe, September 2007, pages 29-35.*

[14] N. C. Miller, et al. (2000) "Aerodynamic Sizing With Simulated Inhalation Profiles: Total Dose Capture And Measurement." *Respiratory Drug Delivery V‖, pages 191-196.*

[15] M. Copley et al. (2011). "Evaluating the Alberta Throat: An innovation to support the acquisition of more clinically applicable aerosol aerodynamic particle size distribution (APSD) data in oral inhaled product (OIP) development." *Inhalation, August 2011, pages 12-16.*

[16] A. Watkins et al. (2012) "Comparative Performance Of Dry Powder Inhalers Assessed Using A Commercially Available Model Of The Upper Human Respiratory Tract." *Respiratory Drug Delivery 2012, pages 877-882*

[17] Y Zhang, et al. (2007) "In Vitro-In Vivo Comparison of Deposition in Three Mouth-Throat Models with Qvar and Turbuhaler Inhalers", *Volume 20, No. 3, pages 227-235.*

[18] In-Process Revision: <1602> Spacers and Valved Holding Chambers used with Inhalation Aerosols, USP Pharmacopeial Forum 40(1), January 2014.

[19] CSA Group Standard, CAN/CSA-Z264.1-02 (R2011) "Spacers and Holding Chambers for Use with Metered-Dose Inhalers."

March 2014
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