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Exploring Newly Introduced Methods for Testing MDIs with Add-On Devices

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The role of add-on devices and how they affect drug delivery with a pressurized metered dose inhaler.

Pressurized metered dose inhalers (pMDIs) are an inexpensive, frontline technology for the treatment of asthma and other pulmonary diseases. Some patients, however, find it difficult to achieve the coordination needed to successfully use a pMDI. Along with novel breath-actuated pMDIs, add-on devices, such as spacers and/or valved holding chambers (VHCs), eliminate the requirement to coordinate device actuation with inhalation and make conventional pMDI technology more effective for a broader spectrum of patients. Globally, the incidence of asthma and chronic obstructive pulmonary disease (COPD) continues to rise, and the use of add-on devices is increasing proportionately. This increasing use is reflected in a new, draft *United States Pharmacopeia (USP)* chapter, issued January 2014, which specifies new test methods for pMDIs with add-on devices (1).

Mark Copley, sales director of Copley Scientific, provides expert insight on why add-on devices are used, how these devices impact drug delivery with a pMDI, and the tests that can be applied to representatively characterize pMDI performance when an add-on device is required.

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Add-on devices and the impact on drug delivery

What is an add-on device and why is it used?

Copley: The 'go to' technology for treating asthma and COPD, pMDIs are small, inexpensive, convenient to use and suitable for the delivery of a wide range of drugs. When actuated, these products use a propellant to aerosolize a fixed volume of liquid formulation to a respirable size. To ensure that the aerosolized particles are successfully drawn into the lung, the patient must inhale slowly and deeply upon actuation of the device. However, some patients lack the required coordination to synchronize these two events. This limitation curtails the successful use of pMDIs by certain patient groups, such as pediatrics, geriatrics, and even some adults. Breath-actuated pMDIs are one solution but add-on devices are more routinely used to address this issue because they can be retrofitted to a range of pMDIs that are already on the market.

A spacer is an open-ended piece of tubing or plastic cylinder that is connected to the mouthpiece of the pMDI. A VHC is similar but incorporates a one-way valve close to the patient interface. With a VHC, the pMDI can, therefore, be actuated into an enclosed dead space. The valve only opens to release the aerosol once the patient starts to inhale. An important advantage of a VHC is that uncoordinated use of the pMDI/add-on device does not result in the exhalation maneuver emptying the holding chamber of the therapeutic aerosol back through the pMDI actuator, which can be an issue with a simple spacer design.

Both types of add-on device interface with the pMDI at one end, typically via a rubber connection, thereby creating a seal, and have either a mouthpiece or a face mask at the other end to enable easy use by the patient. Either add-on device results in the patient inhaling the drug from a reservoir of aerosolized particles, not dissimilar to a nebulizer, rather than directly from the pMDI. In this way, the add-on devices eliminate the need to precisely coordinate inhalation and actuation, broadening the accessibility of pMDI technology to a wider range of patient groups.

How does the use of an add-on device affect the way in which drug is delivered to the patient?

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Table I: Breathing simulator specification for characterizing pressurized metered dose inhalers with spacers and valved holding chambers (1).

	Pediatric			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

Copley: When a patient uses a pMDI without an add-on device, the drug particles are inhaled almost instantaneously as the formulation is aerosolized. Providing that the patient's technique is correct, the size of particles inhaled will, therefore, be relatively well defined. Delivered particle size is a function of the device design (actuator and canister) and the properties of the formulation, which includes the propellant.

In contrast, when an add-on device is used, the patient inhales drug from a reservoir of aerosolized particles. The additional dead volume provided by the add-on device not only provides an opportunity for aerosol expansion, but also particle impaction, settling, and/or electrostatic deposition, within the add-on device (2, 3). This means that the particle size distribution of the aerosol cloud made available to the patient may change considerably ahead of inhalation. Certain sized particles may be preferentially retained in the spacer and the size distribution of particles received by the patient may now differ from that delivered by the pMDI. Variability in the drug-delivery process is also introduced by the fact that the device actuation may be completely coordinated with the inhalation maneuver, or completely uncoordinated, depending on the technique adopted by the individual user.

Testing pMDI performance

What tests are recommended in the proposed *USP* chapter and how do they differ from the standard tests used for pMDIs?

Copley: The general pharmacopeia tests for the assessment of pMDI performance and for quality control (QC) center on the measurement of two parameters—delivered dose uniformity (DDU) and aerodynamic particle size distribution (APSD). In DDU testing, the pMDI is actuated into a dose uniformity sampling apparatus (DUSA) that captures the emitted formulation on a filter. Subsequent analysis of the captured dose, usually by high-performance liquid chromatography (HPLC), reveals how much active ingredient is present.

APSD measurements are made using a multistage cascade impactor (4). This instrument size fractionates an emitted dose on the basis of particle inertia, which is a direct function of aerodynamic particle size. Chemical analysis of the collected, sized samples enables the determination of an APSD specifically for the active ingredient.

Because the particle size delivered by a pMDI is generally unaffected by the patient's inhalation profile, the test conditions applied for these analyses have been set on the basis of convenience. The first cascade impactors used in orally inhaled product analysis were developed for air sampling and originally designed and calibrated to operate at 1 SCFM (standard cubic foot per minute). This value directly translates to the 28.3 L/min used for APSD measurement today for pMDIs. The same figure has, therefore, been adopted for DDU testing.

The tests set out in the new, draft chapter for testing pMDIs with add-on devices (1) are based on experience gained in Canada over the past 10 years following the publication of a standard for testing by Health Canada (5). The methods reflect that, as with a nebulizer, the amount of drug received by the patient with this type of set-up will be influenced by the inhalation profile of the user. The tests in the new chapter, therefore, call for the application of specific breathing profiles during DDU testing to reflect the physiology of the intended user (see **Table I**).

In DDU testing for pMDIs with add-on devices, the combined product is actuated into a filter housing, thereby collecting the dose in much the same way as a DUSA is used for standard

Fit for the Lung? By Jon Faulkes and Emma J Mickley, Aesica Pharmaceuticals

The key to successful delivery of an API to the lung is the generation of a particle that is sufficiently small to be delivered to the lung. In a traditional asthma dry powder inhaler, the micronized API with a mass median diameter of between 1.1 µm to 5 µm would be blended with a milled carrier material, such as lactose, and filled into a capsule or device. Upon inhalation, the API particle detaches from the lactose carrier and travels through the respiratory system until it impacts on the surface of the lung. Although used for decades, this approach is far from efficient because of the varied particle size distribution produced as well as the disruption caused to the surface chemistry of the API and carrier by the micronization and milling processes. In this article, the authors discuss methods of creating engineered particles for inhaled drug delivery and the advantages of particle engineering.

To read this article in its entirety, visit PharmTech.com/Aesica_FitfortheLung

pMDI testing. However, a patient relevant breathing profile is applied during testing, rather than a constant 28.3 L/min air flow rate. Furthermore, tests are carried out to measure the efficiency of the valve, in the case of VHCs, by comparing the dose received when use is coordinated and uncoordinated with device actuation.

Performance is optimal and directly comparable with a pMDI without an add-on device, if the patient inhales as the device is actuated. This is termed 'coordinated use.' In contrast, the worst-case scenario, in terms of performance, is if actuation coincides with exhalation, (i.e., 'uncoordinated use'). Using a suitable breathing simulator, testing can be carried out under both of these conditions to provide a ratio of drug delivered and hence the efficiency of the valve. For spacers (without valve), testing for co-ordinated use is all that is required. When testing spacers/VHCs with facemasks, these are generally removed, and testing is performed using the integral mouthpiece.

Cascade impactors operate at a constant flow rate so breathing simulators are not applied during APSD measurement. Rather, testing is carried out at a constant flow rate broadly representative of the patient population within the constraints of calibrated commercial impactor performance. The next generation impactor (NGI), which has a calibrated flow rate range of 15 to 100 L/min, is a popular choice for this aspect of testing although other cascade impactors can be used. The particle size range of interest for inhalation to the lung is usually taken as sub-five micron, and this is reflected in the tests that recommend comparison of the sub-five-micron dose (i.e., the emitted fine particle mass) with and without an add-on device.

As with DDU testing, the method specified for APSD measurement has been modified to assess the potential impact of coordinated and uncoordinated use. Testing is carried out with impactor sampling and actuation coordinated and, in the case of VHCs, also with impactor sampling starting after a two-second time delay. This delay provides time for the particle size distribution to evolve inside the VHC and directly quantifies the impact of uncoordinated use in terms of the dose that is likely to deposit in the lung. Testing after five and 10 seconds provides further insight into the residence behavior of the aerosol within the add-on device and is also recommended (5).

Is new equipment needed to test in accordance with the revised *USP* chapter?

Copley: For a laboratory working solely on pMDI technology, it may be that new equipment will be required given that the new draft chapter calls for the application of breathing profiles during testing. However, breathing simulator technology has advanced considerably in the last decade, and cost-effective, compact models are increasingly a standard piece of inhaled product testing equipment.

The Copley Scientific BRS breathing simulator range, for example, includes a number of models specifically tailored to the testing of different orally inhaled products. These systems enable the user to:

- Apply different wave patterns (e.g., square, sinusoidal, triangular, or user defined)
- Alter tidal volume (i.e., the volume of each inhalation and/or exhalation)
- Separately vary the duration of inhalation and exhalation, if required (inspiratory/expiratory ratio)
- Introduce a delay after inhalation and/or exhalation
- Control the number of breathing cycles during each test
- Commence the breathing cycle at the beginning of the inhalation or exhalation maneuver.

The availability of such flexible systems is supporting the application of breathing simulators beyond the scope of the pharmacopoeial test methods to more generally explore the performance of inhaled products in line with quality by design (QbD) (6). At the same time, these units also make it straightforward to test under the conditions specified for pMDIs with add-on devices through the provision of specially developed adapters and filter holders.

To meet the requirement for a time delay between actuation of the device and the start of APSD measurement, a timer-controlled, fast-acting, two-way solenoid valve provides a simple, cost-effective solution. Products, such as the breath-actuated controller BAC 2000 (Copley Scientific), provide near instantaneous starting and stopping of the air flow during testing and have both delay and inhaled time functions (7). Such products streamline testing in line with the new draft chapter, easing the task of gathering the information required to ensure the safety and efficacy of using pMDIs with add-on devices.

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