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Review Article

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Developing Ways to Evaluate in the Laboratory How Inhalation Devices Will Be Used by Patients and Care-Givers: The Need for Clinically Appropriate Testing

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Abstract. The design of methods in the pharmaceutical compendia for the laboratory-based evaluation of orally inhaled product (OIP) performance is intentionally aimed for simplicity and robustness in order to achieve the high degree of accuracy and precision required for the assurance of product quality in a regulated environment. Consequently, performance of the inhaler when used or even misused by the patient or care-giver has often not been assessed. Indeed, patient-use-based methodology has been developed in a somewhat piecemeal basis when a need has been perceived by the developing organization. There is, therefore, a lack of in-use test standardization across OIP platforms, and often important details have remained undisclosed beyond the sponsoring organization. The advent of international standards, such as ISO 20072:2009, that focus specifically on the OIP development process, together with the need to make these drug delivery devices more patient-friendly as an aid to improving compliance, is necessitating that clinically appropriate test procedures be standardized at the OIP class level. It is also important that their capabilities and limitations are well understood by stakeholders involved in the process. This article outlines how this process might take place, drawing on current examples in which significant advances in methodology have been achieved. Ideally, it is hoped that such procedures, once appropriately validated, might eventually become incorporated into the pharmacopeial literature as a resource for future inhaler developers, regulatory agencies, and clinicians seeking to understand how these devices will perform in use to augment ongoing product quality testing which is adequately served by existing methods.

KEY WORDS: clinical relevance; inhalation device; laboratory testing; patient use.

INTRODUCTION

Laboratory methods that are incorporated into the pharmaceutical compendia for the evaluation of orally inhaled products (OIPs) have been developed primarily for the purpose of demonstrating product quality in terms of (a) delivered dose uniformity (DDU), specifically total emitted mass (TEM), and (b) aerodynamic particle size distribution (APSD). Since these parameters represent stakeholder-acknowledged critical quality attributes (1–5). These methods are normative rather than informative in nature. As such, there is very limited flexibility for procedural changes when such testing forms part of a dossier associated with regulatory submissions concerned with product performance in development or for batch release. Furthermore, since these methods may need to be carried out for the same product in multiple laboratories worldwide, their design criteria are strongly influenced by the need for simplicity in execution, yet combined with the capability of being performed time and time again with a high degree of accuracy and precision. For the past 25 years or so, this situation has functioned well, with harmonization being attempted with some success between the different major pharmacopeias worldwide through the Pharmacopeial Discussion Group (PDG) process (6).

However, since the late 1990s, it has become increasingly apparent that these basic methods for OIP performance characterization have some important limitations, which are as follows:

(a) Spacers and valved holding chambers (VHCs) that are widely prescribed for use with pressurized metered dose inhalers (pMDIs), and in the latter instance, contain one or more one-way valves as part of their essential function (7) are not evaluated as they would be used by patients in accordance with manufacturer instructions for these add-on devices (8).
(b) The existing methods that were developed largely for pMDIs and dry-powder inhalers (DPIs) are based on sampling the pMDI-generated aerosol at a constant flow rate, or allowing the flow rate from the DPI-on-test to rise from zero to its final value providing a fixed 4kPa pressure drop across the device or 100 L/min, whichever is lower.

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Neither approach can provide information about how the aerosol emitted by the inhaler interacts with the continuously varying flow rate of a patient who may be tidal-breathing. This consideration is especially important if the inhaler is a nebulizer (9).

(c) Even the testing of DPIs, whose evaluation by the pharmacopeial methods involves a standardized air flow method with a fixed pressure drop across a critical orifice, does not necessarily represent the quite complex flow rate-time profiles exhibited by patients in normal use (10).

(d) The flow rates associated with the pharmacopeial methods have been chosen to represent an "average" adult, whereas users of inhalers encompass neonates through infant, small child and adults with pulmonary performance capabilities ranging from normal to severely impaired in severe disease (11).

(e) pMDI with spacer/VHC add-on devices and nebulizing systems are frequently prescribed for use with a facemask rather than a mouthpiece as the patient interface, a situation that is mandatory for neonates, infants and small children who cannot coordinate inhalation by the latter, as well as by adults with limited manual dexterity or with impaired mental function (12–14).

Some progress has been made with the incorporation of age-dependent tidal-breathing waveforms as part of the newer pharmacopeial-based testing procedures associated with nebulizers (3,5), and with a similar approach that is being adopted in a new informative chapter in the US Pharmacopeia (USP) covering spacers and VHCs (15). However, a strong case can be made for a more comprehensive approach across all OIP classes to address all of the limitations above. The goal of such a re-think would be to augment the existing collection of compendial test methods with those that are designed to be more representative of actual rather than ideal patient use. This article outlines how this process might take place, drawing on current examples in which clinically appropriate testing has already produced a better understanding of the in-use performance of these devices.

INHALER DEVICE DESIGN AND PATIENT USE

Although the design and development of different classes of inhaler products may differ widely from one organization to another, there is a degree of commonality to the process that can be used to illustrate best practices. In 2005, a team of experts from the cross-industry European Pharmaceutical Aerosol Group (EPAG) provided a detailed roadmap as an example of how this process might work for a hypothetical pMDI-delivered drug product in the Quality-by-Design environment favored by regulatory agencies (16). The following steps were identified as being critical to the inhaler design development:

1. Identify critical performance characteristics (variables) for the inhaler;
2. Identify potential inhaler construction material attributes and related process parameters;
3. Perform a risk assessment of the potential material attributes and process parameters;
4. Perform screening experiments to establish the "explored" design space;
5. Undertake design space experiments to define the design space;
6. Establish control space for product quality assessment to be entirely within design space envelope.

Unfortunately, this group did not go further to establish which type of tests (whether the existing compendial methods or procedures that focused on clinical relevance or a mixture of both) would be more appropriate for such a purpose, and the team was disbanded shortly after publishing their suggestions. Nevertheless, the concepts identified provide a logical basis by which quality can be "designed in" and verified in a structured way as presented in Fig. 1.

The design of the delivery device (pMDI, DPI, soft mist inhaler (SMI), or nebulizer), rather than the drug product formulation it will eventually dispense, begins following the innermost loop. This process often begins with initial feedback from the marketplace frequently augmented by clinician input of one or more specific needs that the product developer aims to fulfill. Meanwhile, the development of the drug product formulation(s) intended to be used with the delivery device proceeds in parallel, following the well-understood pathway from screening of candidate molecules for efficacy through phase I and phase II clinical trials. Non-functional "mock-up" devices may be created to illustrate to stakeholders the direction the initial design is taking. The validity of the design output in terms of basic mechanical and/or electronic function is ideally verified shortly after internal confirmation of the commercial and clinical viability of the concept. Early prototype devices that are functional, but operate with placebos instead of active drug product are often created for this purpose. Clinician focus groups can often provide valuable feedback of patient needs at this time, as can user-handling studies with these prototypes. The design output is fed back to refine the initial concept in an iterative process that might involve several passes through this initial loop of the process. However, once consensus has been achieved by stakeholders within the organization that the design meets predefined goals, the process proceeds to the final prototype stage moving outward to the second loop of the process (Fig. 1). At this intermediate stage, patient focus groups are a valuable resource to provide input concerning ergonomics and identify any late-stage handling-related issues that may have persisted. Although performance testing of prototype delivery devices should ideally have taken place as early as possible as part of the finalization of the composition of the formulation, it is possible that devices may not have been evaluated with the finalized drug product until this intermediate stage has been reached. The adoption of clinically appropriate test methods can provide significant added value by identifying and resolving potential patient use-related issues before the design is frozen, ideally before the phase-III clinical trials take place. Once regulatory approval has been given and the production version of the device together with its associated drug product(s) are marketed, the final stage of the development process takes place during post-marketing surveillance, involving the capture of patient feedback (outermost loop in Fig. 1). Although ideally no further development should be needed, in practice, such information is valuable at identifying any outstanding ergonomic and handling issues that may ultimately need to be addressed in a follow-on (Mark-II) version of the device. Again, clinically appropriate testing methods are likely to be

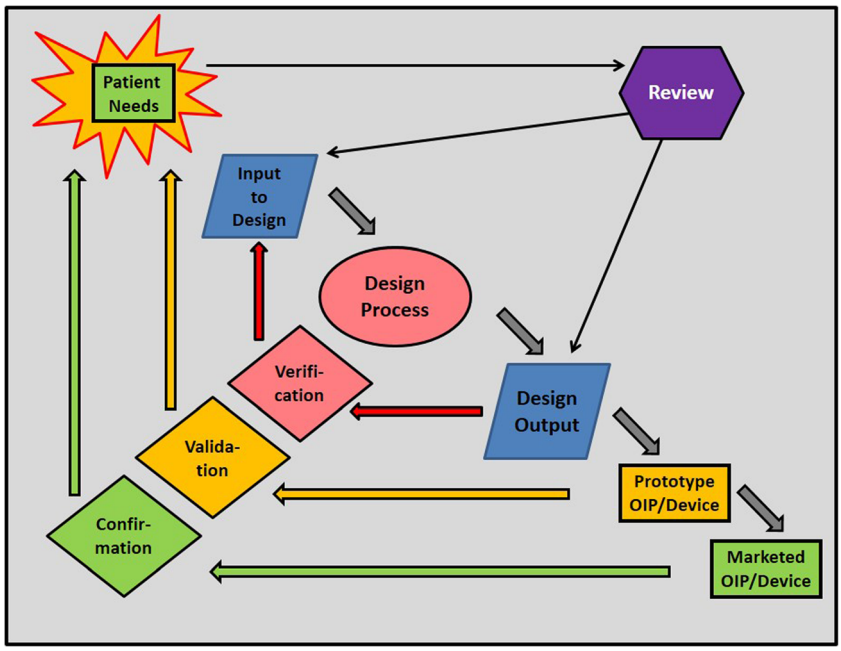

Fig. 1. Idealized life cycle for a medical aerosol inhaler or add-on device such as a spacer or valved holding chamber. **a** The manufacturer bases the design of the new product upon input from perception of market needs augmented by clinician input. **b** Checks are in place to provide assurance that outputs at the various stages meet with patient needs, and the process continues post marketing of the production inhaler

helpful at clarifying the magnitude that non-ideal patient or care giver use of the product might have on the dose delivery efficacy.

The design and development of add-on devices for OIPs, such as spacers and VHCs that are prescribed for use with pMDIs, should ideally follow a similar pathway. However, as these devices are often developed separately by organizations that are not pharmaceutical companies, the precise timing of the performance evaluation of so-called "universal" add-ons that may be prescribed with any pMDI-delivered drug product, may vary from one region to another. For instance, in the USA, the Center for Devices and Radiological Health (CDRH) branch of the FDA regulates the market approval of so-called "universal" add-on devices through the 510(k) pre-market authorization process where a "predicate" device of similar design exists (17). Under such circumstances, the sponsoring organization for the new device need only evaluate it with 3 drug products from different therapeutic classes, making use of a Reviewer Guidance document published in 1993 (18) that advocates testing by multi-stage cascade impactor (CI) following the US Pharmacopeia method (4). The purpose of this testing is to acquire basic aerodynamic particle size-related properties, such as mass median aerodynamic diameter (*MMAD*), geometric standard deviation (*GSD*), fine particle dose (mass) <ca. 5 μm aerodynamic diameter per inhaler actuation (*FPM*) and total emitted dose (mass) per inhaler actuation (*TEM*). However, since 2009, in Europe more stringent testing of the add-on device has been required (19). This testing includes the assessment of drug delivery and aerodynamic particle size distribution (APSD), taking into account patient delays in inhalation following MDI actuation, a common occurrence under normal use (20,21). The provision of such information inevitably necessitates the development of performance measurement techniques that are more clinically appropriate.

STANDARDS RELATING TO THE DESIGN AND LABORATORY EVALUATION OF OIPS

In 2009, the OIP device design process was formalized for the first time by the release of an international standard (ISO 20072) covering DPIs, pMDIs and add-on devices, and SMIs, but not nebulizing systems, referred to as Aerosol Drug Delivery Devices (ADDDs) (22). This standard introduced the concept of a risk assessment-based approach to the design verification process through the development of a device functionality profile (DFP), in which priority had been paid to the assessment of those aspects of ADDD performance subject to the greatest risk of failure (Fig. 2). The DFP is then used to define the *in vitro* performance test requirements from which appropriate test methods can be derived. The committee developing this standard intentionally did not provide prescriptive details of performance tests, as it was understood that users already have a variety of methodologies at their disposal. Furthermore, providing such fixed test methods could possibly stifle future device innovation. The user of this standard is, therefore, left to choose test methods that are based on the existing pharmacopeial procedures or to develop such procedures further to be clinically appropriate as needed. Such testing need not necessarily be undertaken with the finalized drug product(s) for which the ADDD has been developed, since the focus of this standard is on the delivery device (ADDD) part of the overall OIP. It was acknowledged in the process diagram (Fig. 2) that the device design and its evaluation is iterative, as would be expected at this stage of development. Ultimately, however, the goal outlined in Fig. 2

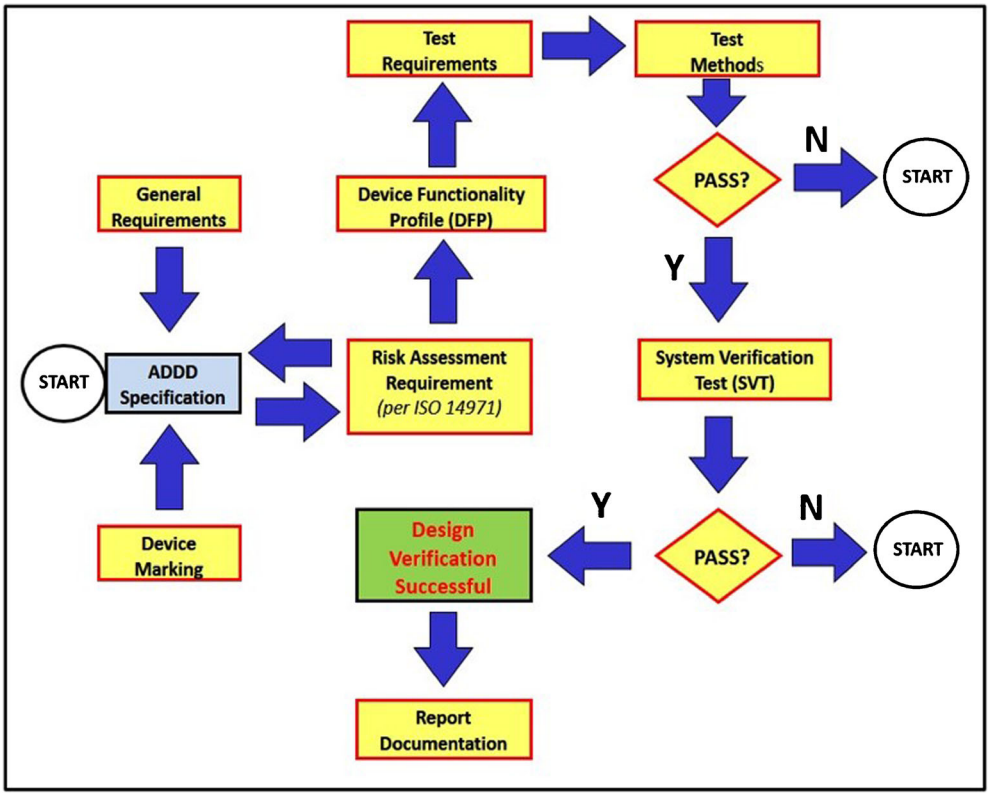

Fig. 2. The Aerosol Drug Delivery Device (ADDD) design process envisaged in ISO 20072:2009; clinically appropriate test methods may be developed to evaluate specific test requirements related to the device functionality profile that has been assembled based on a risk assessment of those aspects of performance that are most vulnerable to failure in use

is to pass these preliminary assessments before going on to verify the *in vitro* performance of the complete OIP filled with its intended drug product through the System Verification Test (SVT).

ISO 20072:2009 was also intended to apply to the design of spacers and VHCs used with pMDIs (22). Here, a predecessor national (Canadian) standard covering the *in vitro* evaluation of these devices had been published in 2002 (23) and updated in 2008 (24), providing prescriptive methodologies for a series of tests that were intended from the outset to be indicative of patient use (25). These developments were driven by recognition of committee members from industry, academia, clinicians and pharmacists that the existing pharmacopeial test methods did not adequately test features, such as the function of the one-way inhalation valve that is a critical component for all VHCs (25). Laboratory studies had shown that there was a real risk that marketed VHCs might fail to deliver medication at all, especially if used by infants or even small children whose suction energy at inhalation was insufficient to open the inhalation valve (26). The publication of this standard, therefore, for the first time provided standardized laboratory test methods for device performance evaluation that introduced the following clinically appropriate attributes (25):

(a) The introduction of a delay between pMDI actuation and the onset of sampling at constant flow rate by CI for determination of aerosol APSD and related properties such as emitted coarse (*CPM*), fine (*FPM*) and extra-fine (*EPM*) particle mass per inhaler actuation to simulate the hesitation with an uncoordinated patient that often occurs before inhalation takes place after the inhaler canister is depressed to initiate release of aerosolized medication into the actuator mouthpiece.
(b) The option to test spacers/VHCs intended for use by infants and small children at age-appropriate flow rates; laboratory work in the late 1990s at Trudell Medical International (London, ON, Canada), in collaboration with MSP Corp. (St. Paul, MN, USA), had developed a low-flow version of the 5-stage Marple-Miller CI that could be used at either 4.9 or 12.0 L/min to approximate inhalation flow conditions associated with infants and small children respectively (27).
(c) Measurement of TEM, connecting the mouthpiece of the VHC to a breathing simulator, simulating fully coordinated (initiate inhalation to sample the emitted aerosol simultaneously with pMDI actuation) and fully uncoordinated (initiate inhalation at the start of exhalation) use; the age-appropriate breathing patterns selected are summarized in Table I, where the terms, V_t, r and *I:E*, refer to tidal volume, breathing rate (number of respiratory cycles/min) and ratio of inspiratory to expiratory time per breathing cycle respectively.

The standardized breathing patterns were based on data from the extensive work at the University College, London, UK, on the development of the human respiratory system (28). In the 2008 update (24), it was acknowledged that the

Table I. Age-Related Tidal Breathing Patterns Used in Canadian Standard CAN/CSA/Z264.1-02:2002 rev. 2008 (Spacers and VHCs), PhEur Monograph 2.9.44 and USP Chapter <1601>

	Patient age group being simulated in the laboratory			
Breathing parameter	Neonate	Infant	Child	Adult
Tidal volume (V_t) in mL	25	50	155	500
Tidal breathing cycles/minute (r)	40	30	25	15
Inspiratory/expiratory ratio[a] (*I:E*)	1:3	1:3	1:2	1:1
Wave form	Modified sinusoidal			

[a] Sometimes reported as duty cycle, based on the percentage of inspiratory time/total time per breathing cycle

development of appropriate model faces with which to simulate the facemask-to-face connection for spacers and VHCs was insufficiently mature for a standardized procedure to be included. However, the door was left open for such developments in the future. A strong case can now be made that research into this aspect of spacer/VHC testing has advanced significantly so that standardized guidance is now possible. The new research arose from a series of papers published following a consensus meeting of experts involved with the development of OIP mouthpieces and facemasks in early 2005 (29–31). A review of the development of model faces for evaluating these devices was subsequently published, in which several viable options were described, including models mimicking the soft tissues of the face and incorporating anatomically accurate representations of the upper airway (32). More recently, the Aerosol Delivery to Anatomical Models (ADAM-III series) developed at Trudell Medical International and incorporating infant, and small child faces with mechanically realistic soft facial tissues, each with an anatomically correct upper airway developed from imaging patients, have been developed and validated (33,34). This technology appears to be equally suitable for the creation of adult versions developed with similar features (10). These developments, associated with an awareness of the increasingly common use of spacers and VHCs, led to publication of a Stimulus-to-Revision article from members of the current "Aerosols" subcommittee of the General Chapters Committee responsible for oversight of the US Pharmacopeia, calling for a new informative chapter to be developed (35). This initiative has been published in January 2014 as an In Process Revision (15), marking the first step towards publication of the new chapter <1602> in the next few years. This chapter takes much of the test methodology from the Canadian standard, making the latter more available world-wide to organizations who test devices using the US pharmacopeia. There are promising signs, based on a request from the British Pharmacopeia in September 2012 to its European counterpart (36), that the approach to testing adopted in chapter <1602> will eventually become incorporated into the European Pharmacopeia (PhEur) as a new chapter.

Although there is fundamentally no reason why nebulizing systems cannot be designed in accordance with ISO 20072, a different ISO committee was allocated the task of developing a standard for these devices. ISO 27427 (37) was first issued in 2009 being based largely on a European (CEN) standard released in 2001 (38). It has since been revised in 2010, and a further revision was published in 2013 (37). Both revisions resulted from stakeholder feedback to make the test methods more user-friendly and clinically appropriate. In contrast with the more flexible approach to test design adopted in ISO 20072, the laboratory test procedures in ISO 27427 are normative, so that there is little discretion to allow the sponsor to adjust the methodology in line with perceived needs associated with new nebulizer design features (*i.e.*, breath actuation) that are not specifically identified as requiring to be tested in the standard (39). Two *in vitro* test methods are part of the normative requirements; the first relates to the determination of aerosol (drug) output (equivalent to *TEM*) and total drug delivery rate (*TEM/min*), and the second test covers the determination of drug mass-weighted APSD by the CI method. Importantly, the CEN standard pioneered the use of clinically appropriate but standardized test methods that were linked to a European Respiratory Society-sponsored clinical guideline (40), with the purpose of overcoming the confusion that had been created by the large variety of approaches that had previously been adopted to evaluate and express the *in vitro* performance of nebulizers. Although ISO 27427 does not provide a formalized roadmap for the design process *per se*, it prescribes tests for total delivered drug mass and rate of delivered drug mass that involve connecting the patient interface (mouthpiece or facemask) to a breathing simulator set to a standard adult tidal breathing pattern inherited from the CEN standard of V_t=500 mL, *I:E* ratio (equivalent to a duty cycle of 50%) =1:1, and r=15 respiratory cycles/minute. It can be argued that even this adult breathing pattern is not representative of normal adult respiration (in which the duty cycle is likely to be closer to 33%), let alone for infants and small children for which nebulizing systems are often prescribed (38). However, this test marked a significant advance from sampling nebulizer output at an arbitrarily chosen constant flow rate, a practice that had hitherto been commonplace. The PhEur first published in 2010 a new normative monograph (2.9.44) relating specifically to the evaluation of the drug products for use with nebulizing systems (3). This monograph therefore augments the device-based focus of ISO 27427. The test methods specified in the PhEur monograph were intentionally aligned with those of ISO 27427, with the exception that a range of different patient age-related tidal breathing patterns were allowed. These patterns had been developed for use with the previously discussed Canadian standard covering Spacers and VHCs (Table I). The USP subsequently published a new informative chapter covering Products for Nebulization <1601> (5), harmonized with PhEur monograph 2.9.44.

In summary, the foregoing developments in national, regional and international standards relating to all classes of

OIPs during the past 15 years or so have been the result of an increasing awareness by all stakeholders of the need to widen the options for inhaler testing. Regardless of OIP class, the ultimate goal is to ensure that all components deemed to have a significant risk of affecting performance in the hands of the patient/care-giver, are properly assessed and remedied, if needed, as early as possible in the design process.

CONSIDERATIONS IN TEST METHOD DEVELOPMENT FOR CLINICAL APPROPRIATENESS

Assessing Potential for Inhaler Misuse

In 2002, the European Pharmaceutical Aerosol group (EPAG) published the results from the first cross-industry discussion about how pMDIs and DPIs might be tested for non-intentional misuse and also in normal operation in the hands of patients (41). Their work was stimulated by recently issued draft regulatory guidance documents concerning the *in vitro* testing of these classes of inhalers for product quality from the EM(E)A (42,43) and FDA(CDER) (44). The main focus of their work was on operational factors such as priming the inhaler before use, multiple actuations at the same time, actuating the inhaler to exhaustion, cleaning of the inhaler and storage in different orientations. However, the underlying purpose of this article was to identify the need for testing pMDIs and DPIs as the patient would use them. They therefore advocated *in vitro* testing for drug delivery efficiency as a function of differing sampling (inhalation) flow rates, reflecting different patient ages and ability of patients to operate the inhaler. Their approach to the simulation of patient use was to evaluate inhaler performance at various stages of life from full to exhaustion of medication, actuating the inhaler at the time intervals that would likely be prescribed in clinical practice. Unfortunately, they did not go further than making use of the existing constant flow rate-based compendial methods developed for determining both DDU and APSD. Such studies, though important in terms of defining how the critical quality attributes for the inhaler might vary in ideal use, do not evaluate how the inhaler might perform in actual operation by the patient with potentially poor coordination, variability in flow rate during inhalation, diseased respiratory tract, etc.

International Standards Development and Clinically Appropriate Methods

Around the same time as the EPAG-based assessment of testing for inhaler misuse was undertaken, a group of European clinical and laboratory testing experts already mentioned in association with a European Respiratory Society clinical guideline (40) identified the need to replace the variety of pre-existing *in vitro* test methods for evaluating pneumatic nebulizing systems with the standardized procedures for total drug mass, drug delivery rate and APSD. This group identified the fact that inherent differences in reported delivered aerosol mass between the variety of nebulizer systems currently available throughout Europe could be more than tenfold. Although some of this variability undoubtedly originated from differences in design, particularly the development of more efficient breath-enhanced nebulizers (45), much of the variability could be traced to differences in testing methods, in particular the choice of sampling flow rate, which was often set at a fixed value rather than using patient age-appropriate tidal breathing to simulate actual use (46). Variability from study to study in controllable factors such as the initial volume fill of liquid containing the drug either as a suspension of particles or in solution, the efficiency by which nebulized aerosol is made available for patient inhalation, and the amount of residual or "dead" volume of drug-containing liquid retained by the nebulizer at the onset of sputtering were also cited as contributing factors (40). The expert committee that developed the ERS guideline therefore advocated the need for a few well-designed test procedures that they hoped would become the standard in Europe (Table II), in each instance providing rationales underlying the normative test methods for drug output (*TEM*), drug output rate (*TEM/min*), and droplet APSD, already referred to in connection with European (CEN) Standard EN13544:2001 (38). Importantly, they identified the need for all types of nebulizer to be evaluated using a common simulated adult tidal breathing pattern when determining *TEM* and *TEM/min*. However, sampling at a low constant flow rate of 15 L/min was retained for droplet APSD determination because it was recognized that it would be difficult to interface the CI (that requires a constant flow rate to function correctly (47)) with the continuously varying flow rate imposed on the nebulizer, had a breathing simulator been present. The expert committee also recognized the limitation imposed by not specifying additional breathing patterns in the CEN standard that would be more appropriate for pediatric users (48) or adults with severe obstructive lung disease (49). However, they concluded in their assessment that the test methods that had been adopted were sufficiently flexible to accommodate additional test configurations. This approach left the door open for sponsors to test at pediatric breathing patterns in cases where the nebulizing system was intended to be used by this population of patients. Since this article was published, a variety of new nebulizers have been commercialized, in particular breath actuated pneumatic devices (50,51), and vibrating mesh and membrane electronic nebulizers (52,53). These newer devices offer some significant advantages to both patient and caregiver that merit consideration for additional clinically relevant laboratory-based test procedures. For example, a standardized method would be useful to demonstrate the ability of both pneumatic and electronically controlled breath-actuated nebulizers to stop delivering medication and at the same time conserve it if the patient removes the mouthpiece temporarily while receiving treatment (anecdotally a common practice among the elderly receiving nebulized therapy for COPD). Likewise, standardized testing to enable comparisons for release of aerosolized medication to the local environment in use would be advantageous for both breath-enhanced and breath actuated nebulizing systems (54). Despite these considerations, the limited number of test methods developed for EN 13544:2001 (Table II) were incorporated without augmentation and with only minor enhancements of the existing methodologies into the current standards applicable to this class of OIPs (ISO 27427, Ph.Eur. chapter 2.9.44 and USP chapter 1601).

Specific Considerations

Delayed Inhalation

The evaluation of the influence of a delay in patient inhalation from pMDI-spacer/VHC combinations when making

Table II. *In Vitro* Test Procedures for Nebulizing Systems Incorporated in ISO 27427[a], Ph.Eur. Chapter 2.9.44[b] and USP Chapter <1601>[b]

Attribute	Test	Comment
Total mass of drug delivered	Filter collection of aerosol captured at nebulizer mouthpiece, with nebulizer operated simulating tidal breathing	ISO 27427 defines one adult breathing pattern (V_t=500 mL, r=15/min, d=1:1); Ph. 2.9.44 and USP <1601> define age-related patterns (see Table I)
Rate of drug mass delivered		Filters collected on minute-by-minute basis to determine delivery rate from start to sputter; many systems offer linear drug delivery profiles and therefore have a single rate of delivery, but non-linearity can occur, especially towards onset of sputter
Droplet APSD and associated respirable dose (equivalent to *FPM*[c])	Cascade impactor	Emitted aerosol sampled from mouthpiece at fixed 15 L/min flow rate; option available to sample all the flow via a Next Generation Impactor or part of the flow (2 L/min) through a Marple model 290 personal sampling impactor

Notes:
[a] ISO 27427 is intended for type-testing nebulizers, so the liquid placed in the reservoir is standardized, either as albuterol 0.1% (*w*/*v*) in 0.9% (*w*/*v*) NaCl aqueous solution or, if allowed or required by local competent authorities, 2.5% (*w*/*v*) sodium fluoride in distilled water.
[b] Ph.Eur 2.9.44 and USP <1601> are intended to characterize the drug product(s) likely to be delivered by a nebulizer, so those product(s) are evaluated rather than a standard test solution
[c] FPM is defined as the mass of drug contained in particles <5.0 μm aerodynamic diameter; there is no lower size limit specified in any of the applicable standards

measurements of emitted aerosol APSD and related sub-fractions (*CPM*, *FPM*, and *EPM*) is a difficult technique. It is necessary to have the flow rate into the CI constant throughout the measurement so as to preserve the fixed stage cut-point sizes in accordance with inertial impaction theory (47), already mentioned in the context of nebulizer testing. It follows that applying vacuum to the CI sampling system after the delay period has elapsed, a practice that had been common before the mid-1990s (55), will result in an unquantifiable bias that is related to the time taken for the vacuum to propagate to the inlet of the sampling system, a process than can typically take several hundred milliseconds with low-resistance DPIs (56), and therefore likely a similar time applies in pMDI testing. Mitchell *et al.* showed in a comparison of a variety of currently marketed solution and suspension pMDI products that *FPM* can fall by as much as 30% in the first two seconds after the inhaler is actuated (57). This decrease is the result of several simultaneous processes, including the presence of electrostatic charge, and gravitational sedimentation, that continuously operate to remove suspended aerosol particles retained by the VHC (58). An apparatus that enables the CI to be pre-set at the desired flow rate before the pMDI is actuated without emptying the VHC was, therefore, developed about 10 years ago at Trudell Medical International in order to overcome this drawback (59,60). This "delay apparatus" (Fig. 3) is first attached to the induction port of the CI system with the shutter in the "closed" position. A slit between shutter and induction port allows unrestricted flow into the CI avoiding the build-up of a vacuum in the sampling system. In use, the inhaler is actuated into the VHC close by, but not yet attached to the delay apparatus, after the flow rate through the CI has stabilized. The pMDI-VHC combination is immediately fitted to the far side of the delay apparatus. A microphone attached to the delay apparatus detects the sound made by the inhaler actuation, starting a timer that drops the shutter into the "open" position after the pre-set delay interval has expired. Sampling of the retained aerosol then proceeds as normal. This type of test apparatus can be easily manufactured, making it possible to investigate the performance of VHCs in accordance with the recommended test procedure for simulating delayed inhalation outlined in both the CAN/CSA/Z264.1-02 (23) and draft USP chapter <1602> (15), as well as exploring in a systematic way how delay-related losses of medication might be influenced by the design of these add-on devices.

Induction Ports

The adoption of a single design of right-angle pipe-bend induction port in the mid-1990s (61) as the universal inlet for measurements of APSD for all classes of inhaler except nebulizing systems and SMIs (not yet invented) by the pharmacopeial authorities in both Europe, the USA, and Japan was itself an achievement in controlling measurement variability introduced by the variety of different options that were in use by various pharmaceutical companies developing pMDI and DPI products (62). Several investigators have since demonstrated that replacing this inlet with either one that is an anatomically correct representation of the oropharyngeal geometry (63–65) or a so-called "idealized" inlet that has internal geometry in which the aerosol deposition characteristics mirror closely reality (66–68) will provide a more accurate measure of the APSD, and therefore, the clinically important sub-fractions, *CPM*, *FPM*, and *EPM* derived from these data. This change alone has been shown from considerations of fluid and particle mechanistic principles to have the potential to improve markedly OIP *in vitro–in vivo* correlations (IVIVCs) (69). On the other hand, cadaver-derived anatomic inlets that were the first to be developed for *in vitro* inhaler testing, are prone to inaccuracy due to the collapse of tissues and dry-out of secretions *post mortem* (70). It is also important that the geometry of the anatomic inlet, derived from whatever source, and its underlying fluid

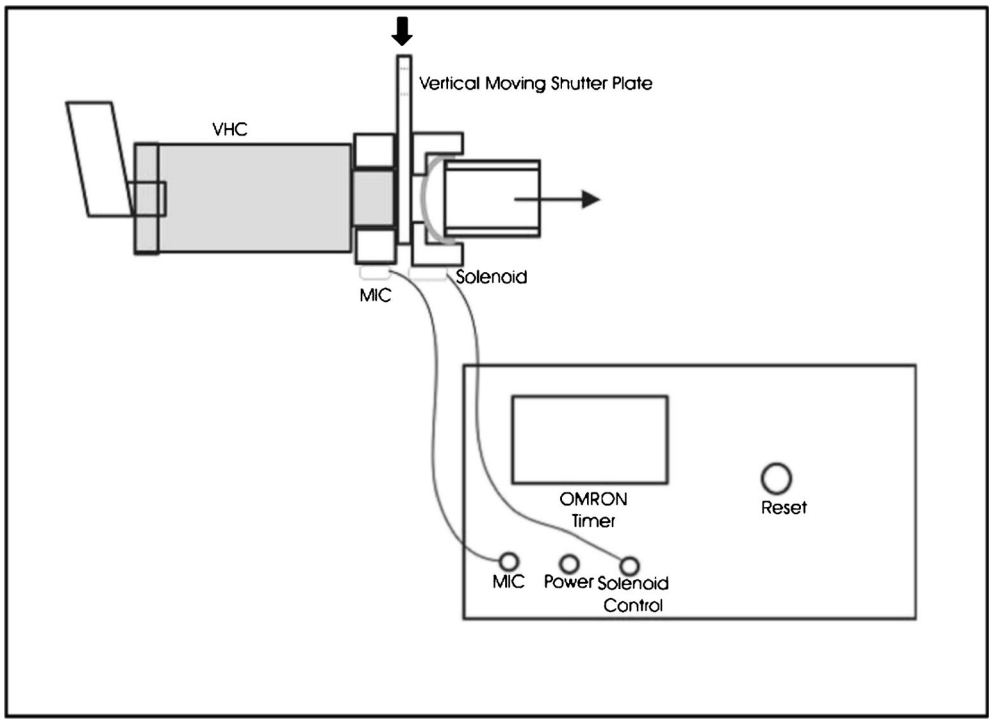

Fig. 3. "Delay" apparatus for use with pMDI-VHC combinations where it is necessary to simulate the effect of imperfect patient coordination on aerosol APSD and related sub-fractions of the emitted mass (CPM, FPM and EPM) in accordance with CAN/CSA/Z264.1-02 or draft USP chapter <1602>; The pMDI-VHC is shown attached to the apparatus just before the shutter drop to the "open" position

mechanics assessment, be age-appropriate for the intended users of the device being evaluated (71). When the use of an anatomic/idealized inlet is combined with patient age-appropriate breathing using a simulator, such as the ASL 5000 (IngMar Medical, Pittsburgh, PA, USA), measures of TEM should therefore be close to reality (72).

Combining Breath Simulation at the Inhaler with Cascade Impactor Measurements

In addition to the selection of an appropriate inlet for the sampling apparatus, a long-term goal for the development of more clinically appropriate measures of APSD has been the reconciliation of the need to satisfy the requirement that a CI should operate at constant flow rate to preserve the fixed stage cut-point sizes (already discussed in terms of delay realization in pMDI-spacer/VHC testing), while simultaneously operating the inhaler by breathing simulator where the flow rate continually varies with time (61). Early attempts involved complex arrangements that were limited in scope by the possibility of introducing transient pressure pulses from flow control devices such as solenoid valves used in flow management to transfer the aerosol from the inhaler to the CI (73,74). Where the aerosol was transferred without valves, careful flow control was required to avoid losing aerosol in transit from the inhaler to the impactor. These systems were also limited to inhalation flow rates that are less than the flow rate required by the CI (75–77).

The advent of a new mixing inlet (Nephele-Miller, Copley Scientific Ltd., UK or RDD Online, VA, USA (Fig. 4)) in the past few years may have overcome these limitations. This inlet brings together the variable flow from the inhaler-breathing simulator merging on-axis with the constant flow of make-up air via a sharp-ended exit nozzle from which the air supply from the inhaler exits. This design thereby mitigates localized turbulence with the "make-up" air stream at the merge-point (78), reducing the risk of attendant losses caused by deposition onto interior surfaces at the exit of the mixing inlet or just downstream before reaching the CI. A formalized validation study with different sizes of monodisperse particles to characterize the transfer efficiency of this inlet as a function of aerodynamic diameter has not been undertaken. However, Olsson *et al.*, using this arrangement (Fig. 5), have more recently demonstrated that highly consistent *in vitro–in vivo* correlations (IVIVCs) are possible for the delivery of the inhaled corticosteroid, budesonide, as aerosol particles delivered by pMDI, DPI and pneumatic nebulizer platforms, in each instance simulating adult use (79). Importantly, they combined the Nephele-Miller inlet with the use of anatomically correct representations of small medium and adult-sized oropharyngeal induction ports as the entry to their sampling apparatus (Fig. 6). These induction ports (Emmace Consulting AB, Sødra-Sandby, Sweden) were derived from output data from the European pharmaceutical industry-sponsored Oropharyngeal Project that took place in the early 2000s (64). This investigation has, therefore, demonstrated the potential for providing more accurate measures of OIP-delivered medical aerosols by the combination of:

(a) use of anatomically accurate inlet(s) as the entry to the CI sampling apparatus;
(b) operating the inhaler by breathing simulator;
(c) careful transfer of the resulting aerosol from the entry of the system to the CI by means of the Nephele-Miller mixer.

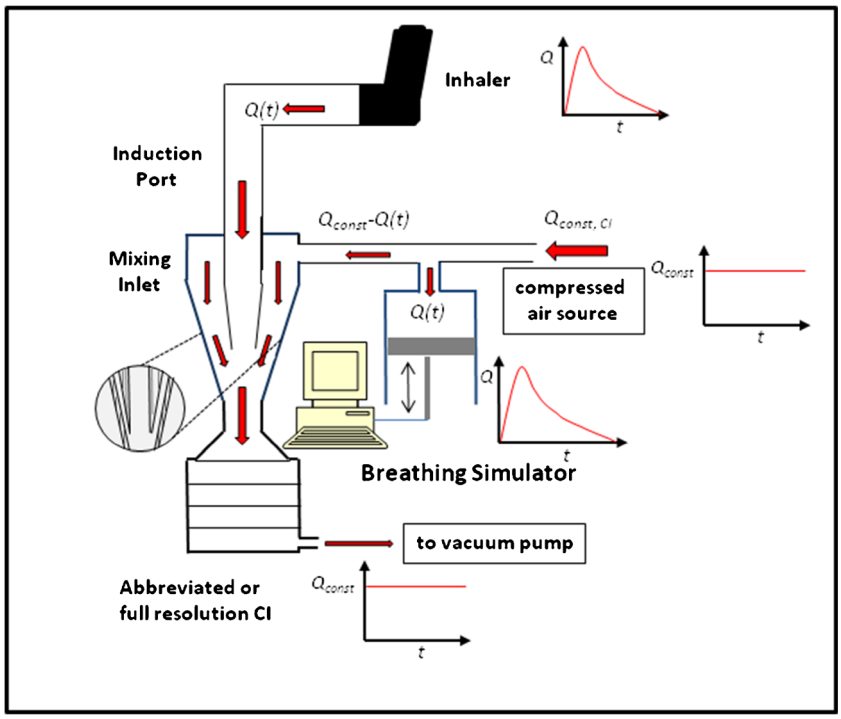

Fig. 4. Nephele-Miller mixing inlet; the variable flow conveying the aerosol from the inhaler (pMDI illustrated, but could be used with a DPI or SMI) converges on axis with the constant flow of clean air supplied to the CI, exiting by a sharp-edged nozzle thereby avoiding turbulence and potential for losses of aerosol to interior surfaces of the inlet

Further work with other therapeutically active molecules (*i.e.* short and long-acting beta$_2$ adrenergic agonists as well as other inhaled corticosteroids) is now needed to confirm whether this approach has more general validity. Interestingly in this context, a similar approach has recently been reported by Below *et al.*, using an "Alberta" idealized child upper airway model (80). This group used actual 4-year-old child inhalation profiles as the basis of its breathing simulation, in their assessment of two different DPIs delivering albuterol. They were able to correlate with a high degree of reproducibility the degree of pulmonary deposition with peak inspiratory flow rates in a wide range from 25 to 51 L/min with one of the DPI devices using these patient-derived profiles, and demonstrate that pulmonary deposition from the other device was flow rate independent. Although further validation studies are needed, preferably with a range of particles whose aerodynamic size properties are known *a priori* by an independent method, this methodology, though complex, has the potential to be developed into a standardized test procedure. Given the work that has already been done to characterize these inlets, it seems that either anatomically accurate or idealized representations of the age-appropriate oropharyngeal airway for the induction port are suitable. Furthermore, all critical components are now available commercially, making it possible to recommend this approach in a pharmacopeial chapter.

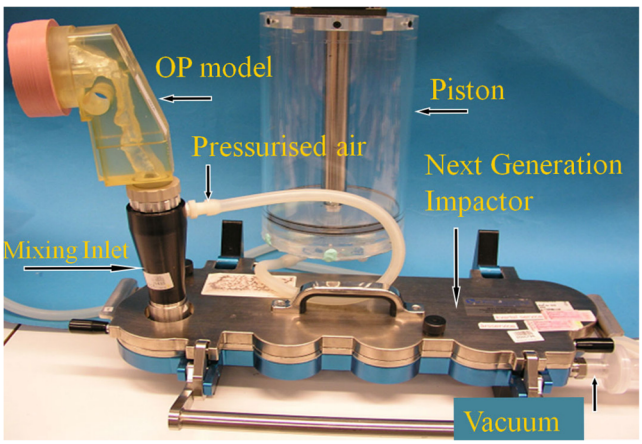

Fig. 5. Complete sampling system used by Olsson *et al.* (78,79) for CI-based measurements of budesonide aerosols from a variety of OIP platforms in their demonstration of consistent IVIVC data [courtesy: Bo Olsson, Astra Zeneca, Sweden]

DPI Testing

In the case of DPI testing, the compendial method restricts the inhalation-flow rate time curve to the profile that is developed when a (4 kPa) pressure drop is applied across a critical orifice at the flow control valve, sampling a fixed volume of 4 L (2,4). Given these constraints, it is difficult to obtain DPI-generated performance data as the patient might use (or misuse) these products. Hence, insight into how a given DPI might fail to meet patient expectations may be missed altogether (81). This limitation has been addressed by several groups involved with DPI development. Thus Chavan and Dalby developed a method to simulate the rise in inspiratory flow rate to investigate powder transfer from the DPI to the CI-based sampling system Fig. 7 (82,83). They simulated different flow rate ramps that were linear with

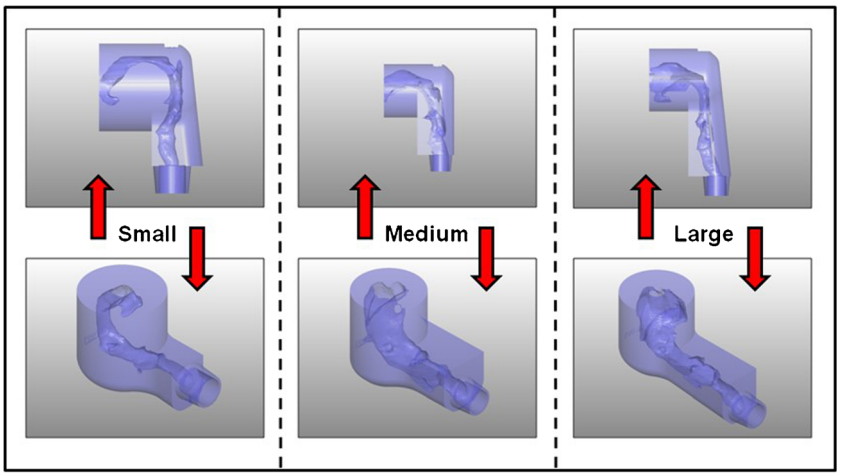

Fig. 6. Small, medium and large anatomically accurate adult oropharyngeal inlet models derived from data obtained by the oropharyngeal consortium (courtesy: Emmace Consulting AB, Sweden)

respect to time, by regulating the air-flow fed via the DPI contained within a small enclosed chamber, by means of a computer-controlled proportionating valve located at the chamber entrance. Their multi-stage liquid impinger (MSLI), which is equivalent to a CI and used to determine emitted aerosol APSD, operated at constant flow rate greater than the maximum flow rate achieved via the DPI, with make-up air coming from an inlet that by-passed the inhaler. Ramps were programmed to reach 30 and 60 L/min over 100 milliseconds; 500 milliseconds; and 1, 2, and 3 s. Chavan and Dalby were able to correlate increases in fine particle fraction from a Rotahaler® DPI (GSK Inc. RTP, NC) with decrease in ramp duration (fastest "inhalation") (83). They attributed this behavior to increased particle de-aggregation and/or the capture of larger aggregates in crevices or regions of low flow within the inhaler at longer ramp durations. Although these flow rate-time ramps were not derived from actual patient data, in principle, the computer-operated inlet valve could be operated using such data.

A group at GSK plc (UK), have developed an alternative approach making use of the so-called "Electronic Lung™" (Fig. 8) with similar objectives. In this apparatus, the DPI-generated aerosol is sampled into a chamber using patient-generated inhalation profiles that operate a computer programmable bellows arrangement (84,85). A CI located at the base of the chamber subsequently samples the aerosol at a chosen constant flow rate after one-way valves are closed to isolate the chamber from the DPI and the inhalation

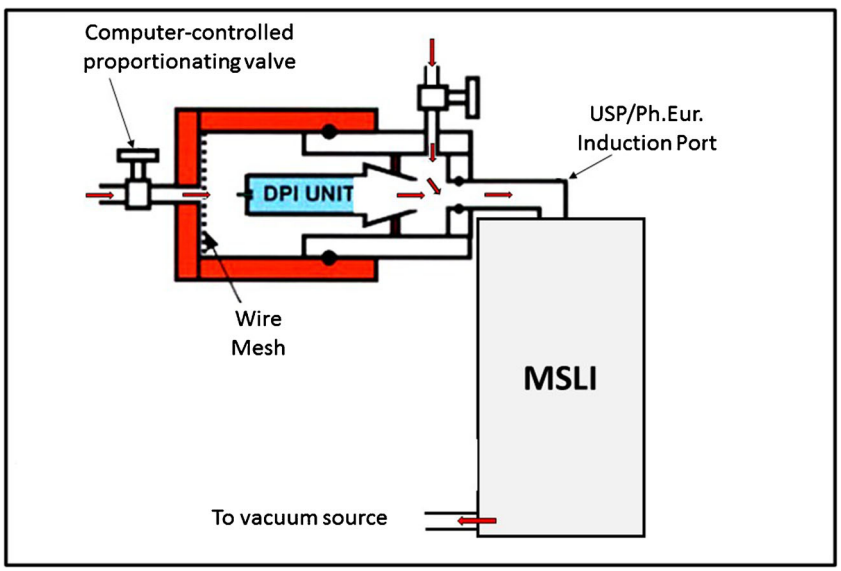

Fig. 7. Test facility for evaluating DPI emitted aerosol APSD developed by Chavan and Dalby (82,83); The DPI on test is contained within a small volume chamber with a computer-controlled proportionating valve at its entrance; operation of this valve controls the flow of air from the DPI Into the MLSI that measures emitted aerosol APSD (courtesy: Richard Dalby, University of Maryland)

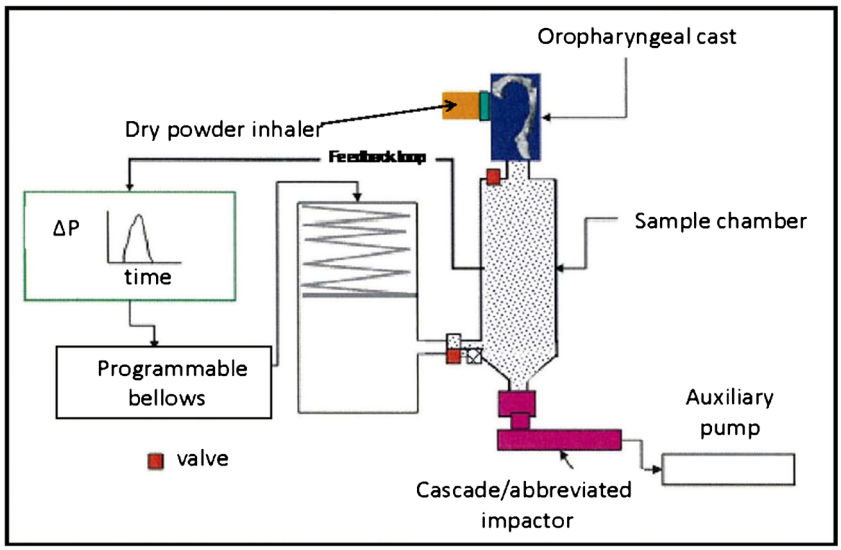

Fig. 8. Electronic lung™ DPI testing apparatus developed at GSK plc, UK (84,85); the DPI is subjected to a patient-generated inhalation flow rate (Pressure Change (ΔP))-time profile using a breathing simulator comprising a computer-programmable bellows; the emitted aerosol passes via an anatomically accurate oropharyngeal cast to be collected in the sample chamber; after closing the valves to the chamber, a cascade impactor samples at a fixed flow rate (courtesy Geoff Daniels, GSK plc)

simulator. The Hydraulic Lung (Fig. 9) is a further refinement that replaces the bellows apparatus using recorded real patient inhalation profiles with "human-like" inhalation profiles that are caused by movement due to gravity of a raised water column in a "U"-tube arrangement (86). The height of the water column can be related to the maximum inspiratory effort exerted by different patient groups, potentially enabling the effect of obstructive disease processes and age to be mimicked in the laboratory. An external pressure source is first applied to raise the column on the right-hand side, and then a valve at the base of the left hand side is closed to isolate the raised water. On opening this valve, the water rapidly returns to the rest position creating a partial vacuum at the inhaler mouthpiece that is attached to the distal end of the column on the right hand side. Prime and Hamilton reported that this apparatus is enabling pressure drop (ΔP)-time conditions to be realized that are close to reality for patient use (86). Both the Electronic™ and Hydraulic Lung apparatuses (Figs. 8 and 9) are potential alternatives to the mixing inlet-based arrangement of Olsson *et al.* (78) previously described. However, the latter has the advantage that aerosol transfer from the DPI to the measurement apparatus is a continuous process without any pauses, as is the case in reality.

Facemasks

pMDI-spacer/VHC combinations and nebulizing systems are often prescribed for use with a facemask rather than a

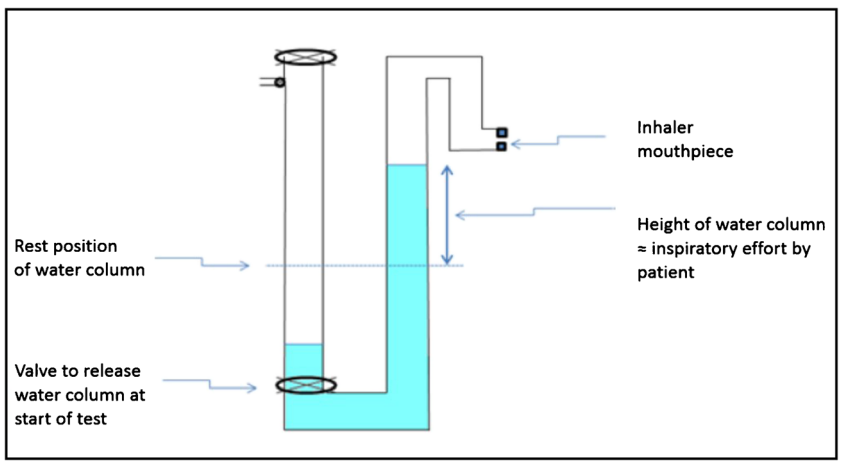

Fig. 9. Hydraulic Lung for generating "human like" inhalation profiles for the evaluation of DPIs using the electronic™ lung DPI testing apparatus (86); the height of the water column can be related to the maximum inspiratory effort exerted by different patient groups potentially enabling the effect of obstructive disease as well as patient age to be mimicked in the laboratory (courtesy David Prime, GSK plc)

mouthpiece as the interface for patients unable to use a mouthpiece because they are too young or do not have the necessary coordination skill (87,88). If the inhaler has a facemask, the use of face models in which the soft tissues where the facemask "lands" on the face is essential in laboratory performance testing in order to achieve realistic measures of either TEM or APSD (32). This is because only in this way can realistic representations be made of the dead-space contained in the often flexible facemask when applied (89), together with assessment of leakage that is particularly prone to occur at the nasal bridge and chin (90). Whereas leakage is not a problem for nebulizers that generate a continuous flow of droplets delivered to the facemask under slight pressure, and may even enhance medication delivery (91,92), there is no such aid to aerosol transport via a pMDI-spacer/VHC once the propellant has flash evaporated. There are currently no

Table III. Considerations for OIP Performance Testing in the Laboratory Using Clinically Appropriate Methods

Pharmacopeial Chapter	**PhEur**	**2.9.18 /2.9.40**			**2.9.18 /2.9.40**		**2.9.44**
	USP	**601**	**1602**	**1602**	**601**		**1601**
ISO Standard		**20072**					**27427**
Test Purpose	**Modification**	**pMDI alone**	**pMDI+ VHC**	**pMDI+ Spacer**	**DPI**	**SMI**	**Nebulizing System**
TEM comparing coordinated and uncoordinated use for spacers/VHCs	Anatomically correct/idealized inlet to sampling system			(N.B. spacers cannot be tested in uncoordinated mode)			
TEM and TEM/min for nebulizers							
APSD by CI for CPM/FPM/EPM		√	√	√	√	√	√
APSD by CI for CPM/FPM/EPM	Imposition of a delay between inhaler actuation and sampling		√	√			
TEM (all aspects) and APSD by CI for CPM/FPM/EPM	Age-appropriate tidal breathing *or* long slow inhalation followed by a breath-hold	Slow inhalation followed by breath-hold may enhance deposition	√	√			√
	Patient-age appropriate inhalation maneuver	Slow inhalation followed by breath-hold may enhance deposition			√	√	May be useful with breath-actuated systems
APSD by CI for CPM/FPM/EPM	CI at constant flow rate with inhaler experiencing breathing simulation	√	√	√	√	√	√
TEM (all aspects) and APSD by CI for CPM/FPM/EPM when facemask is present	Anatomically representative face models	√	√	√	√	√	√

commercially available soft tissue-based face models, a development that will be needed before test methods involving this type of simulation can be adopted into the pharmacopeial compendia. However, the series of Aerosol Delivery to Anatomical Model (ADAM-III) models developed since 2005 at Trudell Medical International (34) have the potential to become standards for OIP-facemask testing. The simulated 7-month-infant face with anatomic naso-pharynx developed at Trudell Medical International has been shown to provide measures of *in vitro* delivered dose to the lungs simulating tidal breathing, that are of the same order as obtained in lung deposition studies with this age of patient (33). The 4-year-old child model face, subsequently also developed with anatomically correct upper airway, appears to provide equivalent data that are consistent with expectations, based on the increase in tidal volume appropriate to this age of child (93).

IMPLEMENTING CLINICALLY APPROPRIATE MEASURES

Table III summarizes by inhaler class a series of considerations concerning the applicability of a matrix of *in vitro* performance testing for OIPs using clinically appropriate methods. The relevant chapters from the PhEur and USP together with the appropriate inhaler-based ISO standards are also shown as a function of OIP class to facilitate identifying where these documents are intended to apply. The purpose of this table is not to suggest replacing these existing compendial test methods, but rather to identify where they could be enhanced with the incorporation of a series of modifications and/or additions that are more clinically appropriate. Thus, those cells identified with a "√" and highlighted in green identify instances in which more accurate measures of TEM or APSD (and related mass subfractions) are likely. In contrast, cells shaded orange indicate where the modification may be less important, but still potentially useful. Note that pMDI-open tube spacer combinations (therefore without an exhalation valve) cannot be tested for TEM simulating uncoordinated use because the act of exhaling will eject all the aerosol contained in the confines of the spacer following inhaler actuation (86). Red-shaded cells identify that the test is inappropriate for the class(es) of inhaler concerned. It should be clear from the foregoing review of laboratory-based methods development that there are several simple measures that can be taken to improve the capability of these procedures to become more diagnostic of how the inhaler may perform in the hands of the patient.

Table IV classifies the options available across OIP classes in terms of the two most important critical quality attributes, TEM and APSD. When using this guidance, it should be borne in mind that the drug product(s) and delivery device must be evaluated as a single system. The suggested

Table IV. Considerations in Developing More Clinically Appropriate Test Methods for OIPs Classified in Terms of Critical Quality Attributes TEM and APSD; The Suggested Improvements May be Applied to Augment the Existing Pharmacopeial Tests for DDU and APSD to Develop the DFP for the System Reflecting Likely Patient or Care Giver Use

Consideration	TEM	APSD
1. Utilize breathing simulation rather than sampling the emitted aerosol at a constant flow rate wherever possible; tidal breathing is the most common mode of use for pMDIs and nebulizers.	Easy to apply by filter collection of the aerosol at the patient interface; care is needed to simulate imperfect patient coordination, and "blow-by" cannot be detected.	More complex to achieve as cascade impactor requires a constant sampling flow rate to operate correctly. A mixing inlet between inhaler and impactor offers potential solution that is robust. The Copley breathing simulators achieve this goal.
2. Continue to evaluate OIP APSD by the constant flow rate CI method, but consider ways in which the inhaler-on-test can be operated simulating age- and even disease-appropriate breathing.		Appropriate when testing spacers or VHCs used with pMDIs, where it is useful to interpose a delay interval between inhaler actuation and the onset of sampling. This approach is less useful for DPI testing.
3. Replace the right-angle bend inlet, most commonly the Ph.Eur./USP induction port, to the aerosol measurement system with an age-appropriate anatomically accurate realization of the upper airway, or with an inlet having "idealized" internal geometry, where available.	Probably the single most significant change that the user can make easily, and that will result in data that are more appropriate as representing patient use. It is important to select an inlet that is age-appropriate for the intended age range of patients that might be prescribed the inhaler. This consideration will likely result in measurements being made with more than one inlet. "Idealized" inlets are becoming commercially available, making them as easy to source as the standard Ph.Eur/USP induction port.	
4. Evaluate OIPs with facemask using a face model, in which the skin surface and soft tissues upon which the facemask "sits" when applied, have comparable mechanical deformation and restoration properties to the corresponding tissues in patients; the model may have an anatomically correct upper airway as a further refinement.	Easy to achieve, but care needs to be taken to ensure that the face model is age-appropriate for the intended user group. Choose between measuring received dose at the lips/nares of the model or dose delivered to the lungs if an anatomic upper airway is part of the model.	Less easy, but not impossible to interface with a cascade impactor. A mixing inlet between face model and impactor offers a potential solution that is robust. The same consideration concerning age-appropriateness of the model applies to APSD measurements.

improvements are intended to augment the existing pharmacopeial quality tests for DDU and APSD to develop the device functionality profile for the system in accordance with the goal expressed in ISO 20072 (22), but also taking into account likely patient or care giver use and even misuse.

BENEFITS TO STAKEHOLDERS

The most obvious beneficiary from the use of clinically appropriate laboratory test procedures will be OIP manufacturers, who will be able to communicate more effectively to clinicians prescribing the products how they are likely to perform, especially in cases in which patient technique is not ideal. In support of this likelihood, Barnes has reported that ease of use together with consistency of medication delivery are key parameters in the optimization of asthma management (94), and the same is likely also true with other chronic respiratory diseases that are managed with OIPs, such as COPD. In the particular case of pMDI-spacer/VHC use, confirmation that aerosol has been created and delivered correctly is seen as important when prescribed for patients with poor inhaler technique/coordination (95). In reviewing the various aspects that patients may consider important in their experience with inhalers of all types, Mitchell has also reported that the interaction between patient and inhaler is crucial to the likelihood of achieving the goal of adherence (96). This interaction is likely to be improved if the prescriber has greater confidence that a particular OIP is likely to perform efficiently for a particular patient, knowing the limitations of that individual in terms of their ability to use the product as intended (97).

The regulatory agencies are also likely to be beneficiaries as the result of improved *in vitro–in vivo* correlations (IVIVCs) that appear to be possible if the sort of measures taken by Olsson *et al.* (79) are implemented more widely across drug therapeutic classes and OIP types. It is well known that the development of reliable IVIVCs for OIP-delivered drugs has been hampered by a lack of understanding about the design of test methods for their *in vitro* evaluation, as well as by the relative complexity of their therapeutic action as topical agents in the treatment of obstructive lung diseases (98,99). It now appears that a few simple-to-implement improvements to the laboratory test methods have the potential to improve the situation markedly from the *in vitro* side of the problem. These are as follows:

(a) use of an anatomically accurate or idealized age-appropriate inlet (78,80,100);
(b) age-appropriate breathing simulation, either by standardized or preferably patient-derived waveforms appropriate to the class of OIP under evaluation (58,78);
(c) simultaneous determination of APSD by CI operated at constant flow rate with the inhaler subject to patient age/disease appropriate breath simulation (79,80).

Reliable IVIVC data should enable regulatory agencies to have greater reassurance about the predictability of laboratory-generated data for clinical efficacy. Such a situation would be highly desirable in Europe, given the cascade approach in which the EMA can potentially allow bioequivalence for a second entry product based on *in vitro* data alone, if the data meet certain defined acceptance criteria (101).

CONCLUSIONS

Although existing pharmaceutical compendial methods for *in vitro* OIP performance are fully adequate for the routine assessment of quality and for registration with the regulatory agencies, there are substantial advantages if these procedures are augmented by methods in which one or more of the modifications identified in this article are introduced with the intention of undertaking measurements that ultimately will be of greater use to clinicians prescribing inhaled medication. This article has set out the current situation with respect to the prospects for so-called clinically appropriate testing, based on the requirements in existing international standards and newly introduced pharmacopeial chapters. A series of modifications to the existing apparatuses for the determination of the critical quality attributes DDU (*TEM*) and APSD has been identified, together with studies that support their implementation. Lastly, guidance has been given as to the potential benefits that are available to stakeholders if more clinically appropriate test methods are added to the list of existing validated procedures.

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