Evaluating the performance of orally inhaled products in the laboratory: Why clinically-appropriate testing is important

Developments in OIP testing that have clinical realism as their prime objective

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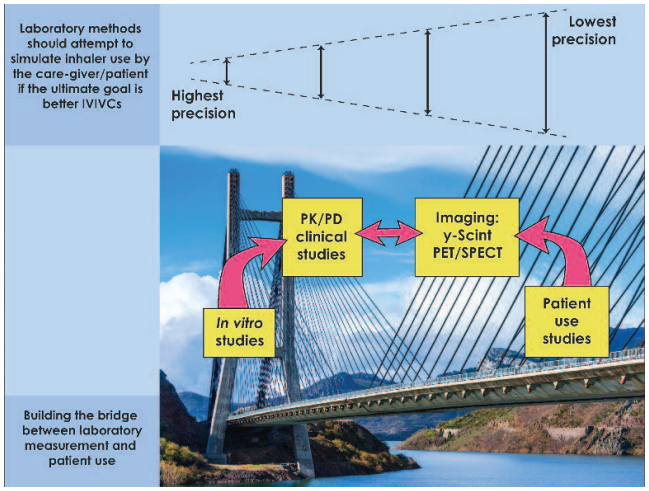
The focus of performance evaluation of orally inhaled products (OIPs) for delivering therapeutic medication has until recently, and with few exceptions, been on quality control and the associated evaluations necessary in development before batches of the product can be deemed acceptably safe and efficacious to be released to market. There is now an increasing understanding by regulatory agencies and other stakeholders, in the interest of patient care, that data derived from such testing is quite limited in scope and application when it comes to informing the prescribing clinician and pharmacist about the way the product is likely to perform in the hands of the patient or caregiver. This article investigates recent developments related to laboratory testing methods that are helping to shape an additional form of robust OIP testing that has clinical realism as its prime objective, rather than test method simplicity.

The two purposes for testing OIPs

Historically, laboratory testing of OIPs was undertaken primarily for the purposes of: (a) establishing the design concept, (b) fregulatory submission in association with licensure and (c) batch release in production. The requirements of such tests as delivered dose uniformity (DDU) and aerodynamic particle size distribution (APSD) are that they be as simple as possible to execute, both precise and accurate, as well as being robust to the inevitable perturbations in the test conditions (Figure 1). Consequently, the resulting methods that are

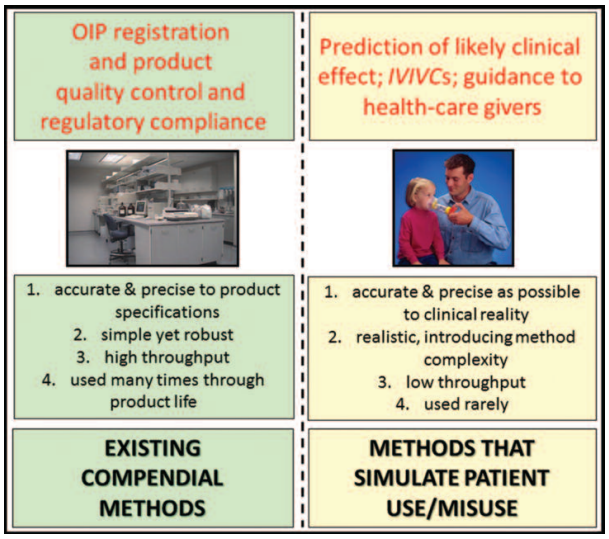


incorporated in the pharmacopieal compendia[1,2] are quite limited in what they can tell us about the way the product will perform in use. For instance, the right-angle bend inlet that is described in the compendia (Ph.Eur./USP induction port) is unrepresentative of the complex geometry of the adult oropharynx,[3] which it is supposed to represent. Laboratory studies sampling both pressurized metered dose inhaler (pMDI)- and dry powder inhaler (DPI)-derived aerosols via cascade impactor equipped with either the compendial inlet or an adult "idealized" induction port in which the flow characteristics more closely mirror anatomic reality have shown that resulting APSDs are shifted to finer sizes with decreased "spread."[4] Taking this example further, there is no provision to test products indicated for pediatric use, using an inlet design that is more representative than the standard geometry. Another example of the limited scope of compendial methods is the lack of simulated breathing, with the notable exception for DPIs, in which the compendial tests for DDU and APSD both attempt to standardize a single inhalation by operating the apparatus at an airflow rate that produces a pressure drop of 4 kPa over the DPI on test, and for a period consistent with the withdrawal of a fixed volume of air (2 L for DDU and 4 L for APSD) from the mouthpiece of the product.[1,2]

In the past 15 years, there has been increasing recognition of the need to develop standardized performance tests that more closely mimic the "in-use" condition for the OIP under consideration (Figure 1).

Figure 1

The two distinct and equally valid methods for comparing OIP performance in the laboratory



The review of Mitchell and Nagel, in relation to the testing of add-on devices widely prescribed to aid in patient coordination when using pMDIs, is an early example of this trend.[5] There have been two distinct drivers for these developments; one has been the desire to respond to criticisms of the lack of relevance of data collected by the compendial methods to patient use,[6,7] the other has been the arrival of an increasing number of generic (second entry) inhaled drug products as the result of innovator products coming off patent protection.[8] In the latter case, both the pharmaceutical industry and the regulatory agencies have been struggling with defining robust non-clinical ways to compare generic (test) with innovator (reference) product, in the absence of well-defined *in vitro/in vivo* correlations (IVIVCs) for this class of therapy.[9] It is proving challenging to bridge the gap that exists between laboratory testing and clinical performance assessments for OIPs (Figure 2).

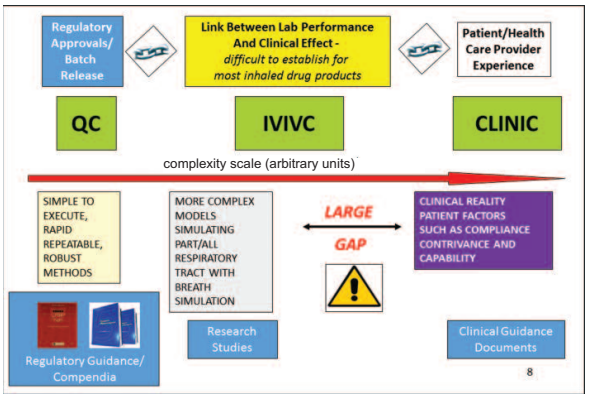
Why add to the already-significant burden of laboratory testing

It is well known that the labor requirements and associated costs for existing laboratory testing of OIPs are high, especially associated with the technically-challenging cascade impactor (CI) method that is the accepted norm for aerosol APSD determinations.[10] Laboratory testing that is associated with product quality control is typically applied to every batch released, so that it is essential to preserve simplicity and robustness while maintaining the ability for a high throughput,[11] which are the chief goals of the pharmacopeial test procedures. Although initiatives, such as the Abbreviated Impactor Measurement (AIM) and Efficient Data Analysis (EDA) concepts have been developed in part to reduce such costs,[12] neither approach by itself is sufficiently realistic to become a surrogate for clinically-appropriate testing.[13]

So why add to this already significant burden? The answer is in several parts, affecting different stakeholders involved with the delivery of inhalation-based therapy. Firstly, it is important to understand that the primary purpose of clinically-appropriate *in vitro* test methods is to establish reliable relationships between the product and its likely performance in the hands of the patient group(s) indicated on the label. In particular, the prescribing clinician needs to know more clearly whether an OIP being introduced into the market is likely to be suitable for a particular patient.[14] Testing, therefore, needs to be related to factors such as patient age (especially for infants and small children under 4 years old). It should also highlight issues where patient/caregiver training is essential, for example, in the correct positioning of a valved holding chamber (VHC) with facemask to avoid substantial loss of medication due to ambient air ingress via the facemask/face contact zone.[15] Secondly, in a licensing submission to a regulatory agency, the manufacturer of a generic OIP needs to have assurance that their product is truly bioequivalent in terms of safety and efficacy, by tests that more closely resemble the way the product will be used.[9,16] Thirdly, if the adoption of more clinically-appropriate methods results in improved IVIVCs, not only will this benefit producers of second entry OIPs, but innovator companies will find it easier to understand the way line extensions to their products will perform in the clinic.[9] Finally, it is most likely that such testing will

Figure 2

The gulf that exists between the laboratory and clinic for OIPs has proven to be a challenge because of the complexity of the processes related to both aerosol delivery and therapeutic action once the drug particles reach their destination in the lungs; clinically-appropriate testing is helping bridge this gap



only need be applied once during the product development process, so that the added burden imposed by making these tests more realistic of use has far less impact than would be the case should such testing be advocated in routine batch release.

Four key elements to clinically-appropriate testing

Four elements should be considered in any approach towards the development of a laboratory test program and are summarized in Table 1, together with their attributes.

1. Introduce breathing simulation

It is self-evident that users of inhalation devices do not breathe at a constant flow rate, however, careful consideration should be given to the choice of breathing pattern that is selected for evaluating an OIP under laboratory evaluation. For all except the DPI class of inhalers, the most likely choice will involve the simulation of tidal breathing, which is the normal mode of respiration. However, passive DPIs (i.e., those that require patient inspiratory effort to function) need to be evaluated mimicking a single inhalation, following the instructions for use, as it is well known that the characteristics of the inhalation maneuver control the quality of the emitted dose by dispersing the powder into aerosol in the optimal manner.[17] The choice of one or more age-appropriate breathing patterns is a further important consideration, and the chosen flow/rate/time waveforms should reflect the entire age range that is indicated for use on the label. Standardized age-appropriate breathing patterns[18, 19] are useful to compare performance of different OIPs. However, some groups, particularly those involved with the development of passive DPIs, prefer to use patient-generated inhalation waveforms,[20, 21] now that breathing-pattern recording apparatuses are widely available.

Table 1

The Four Key Elements of Clinically-Appropriate Testing Applied to OIPs

	Testing Modality	Attributes
1	Introduce breathing simulation appropriate to the indicated age range for the product	In most cases, the pattern chosen will represent tidal breathing, with the exception of DPIs, where mimicking the inhalation maneuver ideally based on recorded patient data is appropriate. More than one breathing pattern may be necessary to cover the indicated patient age range. Likewise, patterns representing mild, moderate and severe disease may be considered for OIPs intended to treat chronic conditions with exacerbations, such as asthma and chronic obstructive pulmonary disease (COPD).
2	Replace the Ph.Eur./USP induction port with an age-appropriate, anatomically accurate or "idealized" inlet	Consider more than one size of adult inlet to represent small, medium and large cases (such inlets are available commercially). Idealized inlets, such as the "Alberta" series, developed by Finlay and colleagues at the University of Alberta, Edmonton, Canada, have the advantage of being commercially available in materials similar to those used for the Ph.Eur./USP induction port and are well characterized as surrogates for anatomically accurate inlets.
3	Test the patient interface, appropriately, especially if it is a facemask	The use of model faces with soft tissue realization is essential to achieve realistic dead space between the facemask and face for a given applied pressure and to simulate the possibility of air ingress. Currently, commercially available versions for infant, small child and adult are not available, but several peer-reviewed publications describe the essential requirements to create such models.
4	Determine OIP APSD with the inhaler experiencing age-appropriate breathing patterns for the indication on the label	Although the cascade impactor requires constant flow rate conditions to operate in accordance with theory, the use of a mixing inlet, such as the commercially-available Nephele design, can enable the inhaler to experience tidal breathing or just inhalation (for DPIs) simultaneously with the measurement of APSD at constant flow rate.

2. Replace the Ph.Eur./USP inlet (induction port)

It has already been mentioned that the right-angle bend comprising the Ph.Eur./USP induction port is an oversimplification of the human oropharyngeal geometry,[22] thereby resulting in an underestimation of the coarse mass fraction of the emitted dose.[4] Nevertheless, this inlet still has an important role to play in the quality control testing of OIPs, where method simplicity, robustness and high throughput are critical attributes. However, in the context of developing more clinically-accurate methods, it is pertinent to point out that several studies have demonstrated that replacing the compendial inlet, either with one that is an anatomically-correct representation of the oropharyngeal geometry or with an "idealized" design that has internal geometry in which the aerosol deposition characteristics closely mirror reality, will result in a more accurate measure of the APSD.[23-27] It follows that an anatomic or idealized inlet will provide a more accurate assessment of clinically-important sub-fractions, such as fine and extra-fine particle mass, which are derived from these data. Going further, it is necessary to consider testing with: (a) inlet geometries appropriate to the indicated age range for the OIP and (b) small, intermediate and large representations of the adult oropharynx. In connection with the first consideration, it should be noted that most infants are obligate nasal-breathers,[28] so the use of a model nasopharynx is more appropriate for this class of patients. As for the second aspect, recent work by the Oropharyngeal Consortium, a European-based group of academic and pharmaceutical industry researchers studying variability in the adult oropharyngeal airway with inhaler use, concluded that internal volume of the oropharynx is the most influential variable governing aerosol retention, creating small, medium and large oropharyngeal models for their studies.[29] These models are commercially available (Emmace Consulting AB, Södra Sandby, Sweden), as are the "Alberta" adult[27] and child (based on an average of 9 children aged between 6 and 14 years[25]) idealized inlets developed by Finlay and colleagues (Copley Scientific Ltd., Nottingham, UK).

3. Test the patient interface appropriately

In most instances, the OIP will be equipped with a mouthpiece and, under such circumstances, there is little to be done, other than to ensure on-axis alignment with the inlet using a flexible coupler, thereby mimicking normal use. The situation, however, is quite different when a facemask is present, as will be the case with products intended for use by infants and young children less than 5 years of age, or by the elderly with mental confusion or a physical mobility condition, such as severe arthritis, that prevents mouthpiece use. DPIs are not indicated for these groups, so that this recommendation is largely concerned with the use of nebulizers and pMDIs, the latter usually being used in conjunction with a VHC/facemask. The positive gas pressure generated by pneumatic jet nebulizers, that typically operate at flow rates between 6 and 10 L/min, will drive the aerosol towards the patient's face, whether or not the facemask has leakage pathways. There may therefore be merit, particularly when inhaling anticholinergics to treat COPD, to have cut-outs in the facemask so that droplets are directed away from the eyes, thereby minimizing the risk of glaucoma.[30] The situation with vibrating mesh/membrane nebulizers that are more dependent upon the breathing pattern of the patient for medication delivery efficiency is less clear, but it is likely that they should be tested in the laboratory in the same way as pMDI/VHC/facemask systems, ensuring that a leak-free interface exists between facemask and face. Esposito-Festen et al., showed that for the pMDI with VHC/facemask situation, even small leak-paths in the facemask-to-face connection, typically occurring at the chin or near to the bridge of the nose, result in near complete loss of medication to the patient.[15] This outcome arises because once the propellant has flash-evaporated, typically within milliseconds of pMDI actuation, there is no pressure source to open the valve of the VHC and direct the aerosol to the patient.[31] It follows that these devices must be evaluated with a model face representative of the indicated age group, if correct sealing is to be verified. Furthermore, the flexibility of the soft tissues of the cheeks should be imitated,[32] so that the correct dead-space is developed between facemask and the lips/nares of the patient when the VHC is applied with a clinically-appropriate force.[33] An added feature is the inclusion of an anatomically-correct oropharyngeal or nasopharyngeal airway, enabling delivered mass to the carina to be estimated.[32, 34] The Aerosol Delivery to Anatomical Models (ADAM-III series) represent the current state-of-the-art in realizing the necessary features for testing OIP/facemask combinations.[35] However, the development of facial/upper airway replicas meeting these requirements has not yet reached the stage at which a suite of age-appropriate models is commercially available. Nevertheless, there is already sufficient technical information available in the peer-reviewed literature for a newcomer to have such model(s) constructed for their testing purposes.

4. Determine OIP aerosol APSD at constant flow rate by cascade impaction, with the inhaler simultaneously coupled to a breathing simulator

The cascade impactor (CI) was designed to operate at constant flow rate, since the cut-point sizes for the fractionating stages are determined by the magnitude of the volumetric flow rate as well as by the number of nozzles and their effective diameter.[36, 37] This limitation has, until recently, restricted the assessment of OIPs either to sampling at a fixed flow rate

or to resort to complex arrangements by which flow rate to the CI is kept separate from the variable flow rate required to mimic patient use of the inhaler under evaluation.[38] Testing at constant flow rate with a simple apparatus at the induction port that opens after the delay interval is all that is needed to evaluate pMDI/VHC combinations,[39] where it is necessary to comply with current regulatory guidance in Europe for these products by simulating delayed inhalation following inhaler actuation in order to mimic the poorly-coordinated user.[40]

The development of the Nephele mixing inlet (Copley Scientific Ltd., Nottingham, UK or RDD-Online, Richmond, VA, US) has greatly simplified the situation with clinically-appropriate APSD measurement, enabling all types of OIPs to be evaluated by breath simulation, with the CI supplied independently with a constant flow rate of air for its operation.[41] The use of tapered surfaces of the inner tube containing the aerosol stream from the inhaler at the merge with the make-up air for the CI avoids particle losses to internal surfaces of the mixing inlet due to turbulence. As a result, one group has achieved remarkably good IVIVCs for budesonide delivered from pMDI, DPI and nebulizer platforms by mouthpiece to small, medium and large adult oropharyngeal models, mimicking appropriate patient-derived breathing patterns.[42] The mixing inlet approach has been successfully used by other researchers comparing laboratory with clinical data for OIPs.[21]

Concluding remarks

This article has set out the reasons clinically-appropriate testing needs to be a key part of the design and development processes for OIPs. It has identified four key elements that should be considered in the design of such a testing program and what may be accomplished by each, in terms of improving the understanding of inhaler performance in the hands of the user. The approach identified is in harmony with current regulatory agency initiatives, especially the Human Factors Engineering approach recently advocated by the FDA as appropriate for the design and development of medical devices. It is likely that more general application of these principles will become the norm in future OIP development programs, now that most of the necessary equipment with which to undertake clinically-appropriate testing is commercially available.

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