Merging pharmacopeial and clinically relevant oral inhaler testing streams: All or nothing or is there a middle way?

How we might progress the current debate

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Introduction

Inhalers are tested in the laboratory for several purposes, including product development, quality control and support to the clinical programs [1, 2]. A large gap exists between the relatively straightforward robust methods in the pharmacopeias, which have been developed primarily for product release, and the more elaborate approaches that have been researched over the years to assist in understanding how inhalers are likely to perform in the hands of the patient or caregiver [3]. As a result, *in vivo/in vitro* correlations and relationships (IVIVCs/IVIVRs), in which markers of lung deposition are compared with measures of fine particle mass fraction derived by pharmacopeial methods, have consistently been shown to systematically overestimate whole lung deposition for a wide variety of orally inhaled products (OIPs) [4, 5]. In the example illustrating this type of bias, fine particle fraction was related to particles less than 3.0 µm aerodynamic diameter [4].

In 2013, Olsson, et al. [6] showed that unbiased IVIVCs based on comparisons of whole lung deposition compared with fine particle mass fraction exiting adult anatomic oropharyngeal models are achievable for three different inhaler classes (pressurized metered dose inhaler (pMDI), dry powder inhaler (DPI) and nebulizer) delivering the same active pharmaceutical ingredient ((API) budesonide). In their study, they replaced the standardized United States/European Pharmacopoeia (USP/Ph. Eur.) inlet with a model adult anatomically correct oropharynx and simulated patient inhalation at the inhaler. Based on their success, in 2014, we explored the feasibility of "bridging-the-gap" between laboratory methods for the performance evaluation of orally inhaled products for product quality control (QC) and those for development and clinical support [7]. However, much of the equipment available to enable such studies was still at the research stage. More recently, the rapidly improving availability from commercial suppliers of key components that contribute to clinically pertinent sampling systems has made practical the routine use of such methodologies in the laboratory.

Options for improving clinical realism in testing have continued since 2014. There is increasing interest in mimicking living lung airway tissue [8], as well as standardizing the testing associated with the dissolution of the API at the site of deposition [9, 10] in order to improve understanding of the in-depth action of the API(s) concerned with the appropriate receptors in the lungs [11, 12].

Despite these promising developments, there remains a reluctance to adopt even simple adaptations to the existing compendial apparatuses for product performance testing, especially in the context of regulatory submissions and in subsequent QC testing. Part of this hesitancy is likely the valid concern about reduced method robustness associated with increased apparatus complexity, especially by going too far in the direction of clinical realism. We propose that there is a middle way forward, in which a few simple-to-implement changes are made to the measure-

ment technique. We believe it is possible to retain robustness in methodologies, while achieving significant gains in clinical realism.

What the pharmacopeial methods can and cannot do

The USP and Ph. Eur. compendial methods of relevance are those that provide delivered dose uniformity (DDU)/dose content uniformity (DCU) and inhaler aerosol aerodynamic particle size distribution (APSD), as these measures define the burden of medication and the likely deposition profile in the respiratory tract [13-15]. Additional chapters relate to similar testing for products/preparations for nebulization [16, 17] and spacers and valved holding chambers (VHCs) used with pMDIs [18]. If undertaken by trained operators in accordance with the instructions given in the relevant chapter/monograph, these procedures are generally recognized by regulatory agencies as having the required capability to support product authorization requests and subsequent product quality assessments [19, 20], because they can provide the highest degree of measurement precision and accuracy. The high degree of standardization associated with these methods is also important to the pharmaceutical industry so that they can be readily transferred and validated from one laboratory to another [21].

The dose uniformity sampling apparatus (DUSA) described for DDU captures the entire mass of medication ex inhaler directly into a cylindrical cartridge containing a filter and sampling takes place at a constant flow rate. This equipment is also used to determine product content uniformity throughout the lifetime of the inhaler from initial use to exhaustion. Inhaler aerosol APSD is determined by a multi-stage cascade impactor with or without its pre-separator, depending on the need to avoid carry-over of larger carrier particles into the impactor in the case of the many dry powder inhalers that utilize this technology to disperse the API(s) upon inhalation by the patient. A standardized right-angle bend induction port is used as the inlet, thereby providing a greatly simplified model of the adult oropharynx. The aerosol ex inhaler is sampled at constant flow rate (an important requirement for stable size-fractionating stage cut-point sizes) except for DPI testing, when a simplified inhalation maneuver is simulated with control over the flow rate/rise time profile with a fixed 4 kPa pressure drop maintained across the inhaler [13-15].

The limitations of these methods are significant when compared with the reality of the patient inhalation experience, arising mainly because of their intrinsic simplicity compared with the complexity of the physiological and biochemical processes associated with the function of the human respiratory tract during the respiratory cycle [22]. Their straightforwardness therefore creates an unavoidable deficiency when attempting to discover how a given inhaler will perform in clinical trials with trained patients/volunteers. Further, it should be remembered that pharmacopeial testing, even with modifications to be described, can provide only limited insight about how the inhaler might perform in the hands of patients with varying airways disease [23], who may often have less than ideal compliance with the instructions for use [24].

Looking at the situation more closely, firstly, it is self-evident that the right-angle bend USP/Ph. Eur. induction port that precedes the aerosol sampling train and therefore "conditions" the aerosol before size characterization is a poor realization of the complexity of the human oropharynx. Further, it cannot be adjusted in size to reflect infant or small child inhaler use. At least one study has demonstrated that APSDs emitted from a pMDI measured with this inlet are shifted to coarser particle sizes compared to measurements made under identical conditions with an inlet having idealized adult oropharyngeal geometry [25]. This bias results in an underprediction of oropharyngeal deposition when the compendial inlet is used compared with the situation when an adult patient uses the inhaler [26]. In consequence, there is an overprediction of the mass fraction likely to reach the lungs. Although a similar bias has been demonstrated comparing pMDI- and DPI-generated APSDs obtained with a USP/Ph. Eur. induction port with those determined using an idealized child inlet [27], the corresponding discrepancies compared with oropharyngeal deposition for small children and infants are largely unknown.

Secondly, for most inhaler classes other than OIPs, sampling the aerosol at constant flow rate does not recreate the continuously varying flow rate regime that is associated with normal respiration. Pharmacopeial methods for evaluating pMDIs also do not provide for a breath-hold after inhalation, a maneuver that has been shown to be important for improving lung deposition from this class of inhaler [28]. Apart from the informative chapter in the United States Pharmacopeia that addresses the testing of spacers and valved holding chambers used as add-on devices with pMDIs [18], these procedures also do not mimic delayed inhalation or exhalation instead of inhalation, both of which can occur with patients who cannot coordinate the inhalation maneuver. This issue is especially significant with pMDI [29] and with soft mist inhaler (SMI) actuation, where some degree of hand/breath synchronization is required [30]. In the case of DPI testing, mimicking a highly standardized inhalation maneuver is unlikely to capture the range of performance that the inhaler might expect to encounter in use [31], especially the effect of airway disease [32].

Table 1

The Three Streams for Inhaler Testing

ATTRIBUTE	ADDITIONAL CONSIDERATIONS	EXISTING QUALITY CONTROL METHODS	AUGMENTED QUALITY CONTROL METHODS TO IMPROVE CLINICAL REALISM	FURTHER ENHANCEMENTS TO OPTIMIZE CLINICAL RELEVANCE
Method Capability		Indicative data for respiratory tract deposition	Improved realism of respiratory tract deposition, but may not provide perfect correlation with clinical outcomes	Possibility of closest relationship with clinical outcomes
Applicability		Product QC	Product development and potentially QC	Early phase product development?
Regulatory Considerations	Recognition	Recognition by regulatory agencies; methods in the pharmacopeias	Limited recognition by regulatory agencies but being researched by these organizations	Not recognized by regulatory agencies
	Compatibility	Compatible with current product registration requirements	May requires bridging studies	Will almost certainly require bridging studies
	Ability to provide additional benefits, such as providing insights into patient use-misuse	Methods adequate for product registration but of limited value in predicting effects of patient age/ disease/use-misuse	Better IVIVCs/IVIVRs (important with second-entry products); potential for improved understanding of performance across intended patient profile	May be able to enable influence of disease processes affecting aerosol transport/deposition to be quantified
Management Considerations	Compatibility with current regulatory practices	No change	Involves a break with methods for previous product registrations	Involves a large break with methods for previous product registrations
	Cost Implications	Perceived as acceptable	One-time costs associated with new inlet options and breath simulation but costs to operate are low	Higher costs associated with apparatus/model acquisition with likely higher operating costs
	Method Transferability	Acceptable without additional effort from the norm	More complex apparatus configurations may require additional effort to achieve transferability	Methods are presently different from lab-to-lab with non-standard configurations making transferability difficult
	Familiarity	Likely unfamiliar in many QC test environments	Method improvements are well understood and easy to adopt	Specialized training needed to implement and therefore likely impractical in QC environment
Analytical Considerations	Equipment Set-up	Simplest option for new/existing labs	More complex set-ups but off-the-shelf solutions are available commercially	Still a research environment with little or no standardization of methods
	Method Robustness	Offers the highest degree of robustness by well-understood methods	Can be made analytically robust and capable of being validated with minimal development	Lack of standardization for methods makes it difficult to achieve robustness
	Data Utility	Provides data representative of ideal patient use and optimum inhaler performance	Can provide realistic assessment of performance under patient use-misuse with minimal development	Largely research tools—large learning curve, data may require specialist interpretation

Differentiating three streams for OIP testing

A wide selection of options has been researched during the past 15 years that are claimed by their sponsors to improve clinical realism in laboratory-based inhaler testing. The increasing arrival of second-entry products as innovator inhalers come off-patent protection is a major stimulus [2]. Here, testing for *in vitro* bioequivalence is important and is linked with the desire for improved IVIVCs that has already been mentioned. Other drivers are a response by those wanting to understand more clearly the limits to inhaler performance with patients of all ages presenting with differing degrees of chronic lung disease as well as the desire to assess how inhalers perform in situations of misuse [3].

Beyond such improvements in clinical realism, there are those who wish to push the boundaries of mimicking the process that take place after the medication particles reach the target regions of the lungs. Such developments have involved advanced models that can incorporate cellular tissues as well as surrounding fluids to simulate the dissolution and absorption processes that take place in both normal and diseased airways [9-12, 33].

Rather than simply separating methodologies into pharmacopeial and clinically relevant groupings, the ways that OIPs can be tested have been divided into three separate streams, as summarized in Table 1:

a. existing quality control methods in the pharmacopeial compendia,
b. augmented quality control methods aiming to improve clinical realism,
c. procedures involving further enhancements to optimize clinical relevance

We have broken down each category into the following attributes that help define the scope of each approach. These are as follows:

1. **Method capability**, or the ability of the technique to achieve the fundamental purpose of providing data that are predictive of the clinical effect resulting from deposition of the medication at the receptor sites in the lungs.
2. **Applicability**, that relates to the actual and potential purposes of the measurements.
3. **Regulatory considerations**, subdivided into: (a) current recognition by the major regulatory agencies; (b) compatibility with current product registration requirements; (c) ability to provide additional benefits, such as providing insights into patient use/misuse.
4. **Management considerations**, subdivided into: (a) compatibility with current product registration practices; (b) cost implications; (c) method transferability; (d) method familiarity.
5. **Analytical considerations**, subdivided into: (a) apparatus set-up; (b) method robustness; (c) data utility.

A summary of each approach to the laboratory testing of OIPs, together with the strengths and limitations, is provided in Table 2.

Further identifying the middle way for OIP testing

Key to our "middle-way" approach (Table 1) is recognition that potentially large gains in clinical relevance are achievable by adopting one or more of the following *simple* enhancements that should be possible to standardize, as takes place with the pharmacopeial methods:

1. Replace the USP/Ph. Eur. inlet by an age-appropriate, anatomically correct oropharynx, such as the small, medium or large inlets, based on the work of the Oropharyngeal Consortium [34] and available from Emmace Consulting AB, Sweden (https://www.emmace.se/products).

   Alternatively, make use of the small, medium and large oropharyngeal inlets developed at Virginia Commonwealth University, Richmond, VA, US [35] and available from RDD Online (https://www.rddonline.com/rdd/rdd.php?sid=105). A further option is to use either an infant, child or adult idealized oropharynx based on the "Alberta" series of models developed by Warren Finlay and colleagues at the University of Alberta, Canada [36], and available from Copley Scientific Ltd., Nottingham, UK (https://www.copleyscientific.com/product/alberta-idealised-throat-ait).
2. Replace constant flow rate sampling with age-appropriate breathing simulation, at least for the inhalation portion of the breathing cycle [3]. The use of a "Nephele"-type mixing inlet [37] to enable the inhaler to be operated with breath simulation while sampling to the cascade impactor takes place at constant flow rate [6] is especially important for APSD measurements, as the impactor can then operate as designed [38]. This mixing inlet is available commercially from both RDD Online and Copley Scientific Ltd.
3. Introduce delayed inhalation for inhalers such as pMDIs and SMIs, where the aerosol is generated by the inhaler than by the patient. This approach is described in informative Chapter <1602> of the USP [18], and equipment to support delayed inhalation measurements is available from Copley Scientific Ltd. (https://en.calameo.com/copleyscientific/read/006693220fa76cad62867?page=179).
4. Use age-appropriate face models when testing inhalers/add-on devices with a facemask patient interface. This approach is essential to be able to mimic potential aerosol leakage pathways around the chin and nose that can greatly reduce aerosol transport

to the patient [39], thereby providing assurance that a given OIP-facemask is fit-for-purpose. Again, commercially available models are available from Copley Scientific Ltd., in which a filter holder can be located immediately behind the lips to capture the total mass of API reaching the oral cavity (https://www.copleyscientific.com/inhaler-testing/improving-ivivcs/facemask-testing/).

5. Consider standardized age-appropriate breathing patterns to enable comparisons between different device platforms/formulations. Such patterns are already available in the pharmacopeias (monograph 2.9.44 [16] of the Ph. Eur/Chapter <1601> of the USP [17] for nebulizers and Chapter <1602> of the USP [18] for spacers and VHCs).

Concluding remarks

We maintain that the benefits of improving clinical realism outweigh the relatively small investment in method development and added complexity. By opting for one or more aspects of the middle approach for routine product testing, appropriate for the OIP indication, it should be possible to avoid sacrificing method robustness significantly. If this proposed way is adopted for the testing of OIPs, the use of standardized breathing patterns will capture general trends in performance associated with the chosen age group(s) specified in the instructions for use. However, if going beyond standardized breathing patterns, it is important to be aware that the influence of intrinsic breathing parameter variation within the chosen patient grouping will require more detailed studies involving exploration within each parameter range to capture the natural variation within that patient population. Looking at the bigger picture, it would be interesting to compare the probability of success in achieving a target clinically relevant outcome using both pharmacopeial and augmented streams following part or all the suggested middle way. Such a study

Table 2

The Three Streams for the Laboratory Testing of Orally Inhaled Products

Features	Existing Pharmacopeial Methods	Augmented Methods to Add Clinical Realism	Methods that Maximize Clinical Relevance
Description	• DDU by sample collection tube with no inlet • APSD by cascade impactor with USP/PhEur inlet (induction port) • Laser diffraction with inhalation cell for aqueous inhalers (nebulizers) • All at constant flow rate	• DDU and APSD with either age-appropriate anatomic or idealized inlet • Mixing inlet for APSD testing to enable cascade impactor to operate at constant flow rate simultaneous with imposition of age-appropriate inhalation profile at inhaler patient interface • "Delayed inhalation" apparatus/modification to inlet of sampling apparatus to mimic hold-up at inhaler actuation • Age-appropriate face models for testing inhalers/add-ons with a facemask patient interface • Standardized age-appropriate breathing patterns enabling comparisons between different device platforms/formulations	• Patient-generated respiratory waveforms • Dissolution simulations at model airway epithelium renderings • Use of cell cultures to add further realism • 3-D airway renderings of larger airways, including flexibility to mimic better respiration mechanics • Simulations of airway clearance mechanisms including coating of airways with mucus layer • Renderings of airways enabling tissue remodeling (emphysema) to be simulated • "Lung-on-a-chip" approaches involving microfluidics
Strengths	• Analytically robust • Repeatable • Transferable • Familiar to users • Recognized by regulators	• Simple to implement • Well researched and understood • Capable of being made robust and transferable • Ability to mirror patient use-misuse • Potentially better IVIVCs	• Close realism to the biological as well as physico-chemical environment in the lung
Limitations	• No attempt to distinguish between infant/small child/adult/geriatric adult • No attempt to assess performance changes brought about by respiratory function decline associated with disease	• Additional effort needed to implement in the laboratory • Effort needed to convince stakeholders, including regulators • First to make change away from pharmacopeial methods	• Relatively complex to implement in the laboratory • Still in research phase • Not likely to be recognized by the pharmacopeial or regulatory authorities in the foreseeable future

would be challenging, but might be undertaken by an industry consortium and could form a persuasive argument in favor of the augmented route.

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