Taking the Evaluation of Orally Inhaled Products in the Laboratory to the Next Level: Introducing the Patient Experience into the Picture

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Summary

Despite significant advances in the technology associated with the administration of all forms of inhalation therapy, patient adherence in the management of chronic conditions such as asthma and chronic obstructive pulmonary disease (COPD) is poor. The focus of laboratory testing of orally inhaled products (OIPs) has largely ignored the way in which the patient interacts with the device, paying attention instead to requirements for data obtained by methods that are simplified to achieve the necessary degree of robustness. Although such testing is clearly essential in the context of asserting product quality, regulatory agencies are beginning to recognize the need for additional information about performance that relates to the intended user experience. In this context, the drug product and delivery device, including add-ons such as spacers and valved holding chambers (VHCs) used with pressurized metered dose inhalers (pMDIs) have to be treated as a single entity. Laboratory methods simulating age-appropriate breathing patterns, poor coordination of inhaler actuation and inhalation, and the possibility that the patient interface may be a facemask rather than a mouthpiece are therefore needed. It is hoped that such approaches will eventually become incorporated into the suite of compendial methods, once validated satisfactorily. Evaluations of inhalers simulating patient use can be very useful in product design and development phases, where increasing emphasis is being placed on a risk management approach. In this way, the patient adherence problem can be better addressed with the next generation of 'patient-friendly' inhalers.

Introduction

For many years, aerosol-based drug therapy has been recognized as an effective modality for managing commonly encountered obstructive respiratory conditions such as asthma [1], COPD [2] and cystic fibrosis [3]. However, the clinical literature is replete with articles in which poor adherence is reported with prescribed therapy, in spite of training of both prescribers and patients in correct use [4-6]. Although factors such as patient choice of inhaler and optimization of technique for effective use have been identified as ways to improve management of patients [7], it is clear that from the patient's perspective, there is a positive link between perceived satisfaction with the treatment being delivered and both adherence and persistence in inhaler use [8]. Crompton cited several criteria that may improve patient adherence with dry powder inhalers (DPIs); importantly in the context of this article, he mentioned ease and convenience of device use, and feedback that drug release has occurred, even at low inspiratory flow rates [9]. Confirmation that aerosol has been created and delivered correctly is seen as important with pMDI-VHCs prescribed for patients with poor inhaler technique [10]. In illustrating the inter-relationships between the patient, drug therapy and delivery device, Barnes noted that ease of use together with consistency of medication delivery are key parameters in the optimization of asthma management [11]. More recently, Mitchell reviewed the various aspects that patients may consider important in their experience with inhalers of all types [12], showing that the interaction between patient and inhaler (Figure 1) is crucial to the likelihood of achieving the goal of adherence.

How Do More Clinically Appropriate Test Methods for OIPs Fit Into the Picture?

Currently, pharmacopeial test methods are intended to be applied in product registration and quality control post approval. As such, they have been developed to provide robust data such as dose content uniformity and aerodynamic particle size distribution (APSD) by methods that are of necessity simplified to minimize bias and optimize precision [13, 14]. Thus, features such as breathing simulation are absent as measurements are made at fixed flow rate(s). Advanced breathing simulators are available from several sources, including IngMar Medical (ASL5000) and Copley Scientific Ltd (BRS 2000 and 3000 models) that can provide such capability. The inlet for aerosol APSD determinations is a standardized right-angle pipe-bend that is only a rudimentary representation of reality. In the case of DPI testing, the compendial method restricts the inhalation-flow rate time curve to the profile that is developed when a (4kPa) pressure drop is applied across a critical orifice at the flow control valve, sampling a fixed volume of 4 L. Given these constraints, it is difficult to obtain data from as the patient might use or misuse the OIP, so that insights into how it may fail to meet patient expectations may be missed.

What can be done to obtain More Meaningful OIP Performance Data Pertinent to Patient Use?

Fortunately, there are several simple measures that can be taken to improve the capability of laboratory methods to become more diagnostic of how the inhaler may perform in the hands of the patient. Table 1 provides a guide; bearing in mind that drug product and delivery device must be evaluated as a single entity.

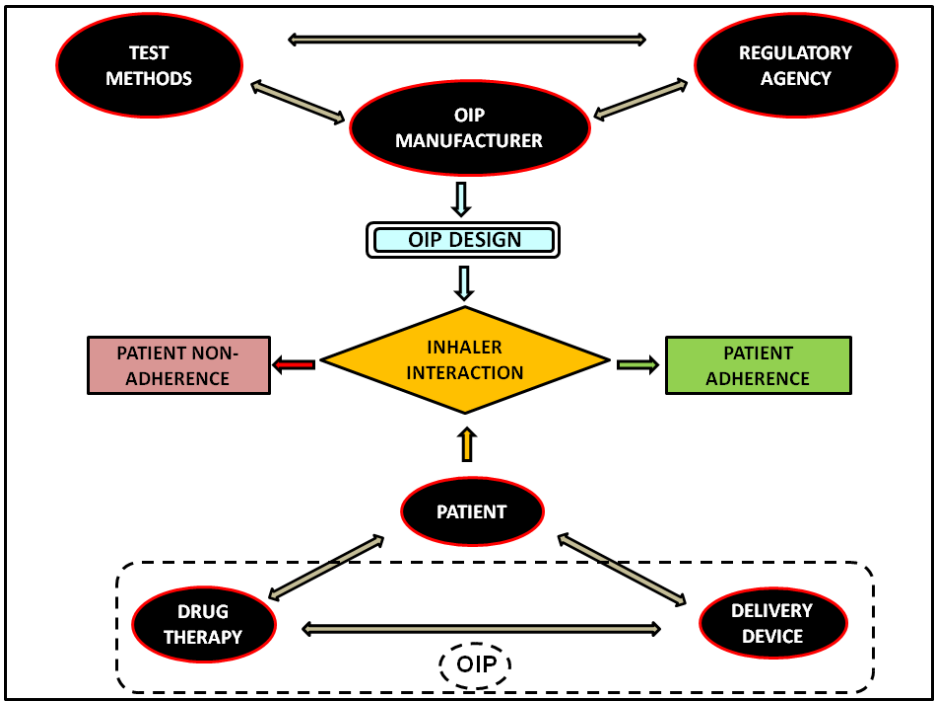

Figure 1: The patient's interaction with the inhaler is central to the achievement of adherence

Table 1: Considerations in Developing More Clinically Appropriate Test Methods for OIPs

Consideration	Emitted Dose	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.

A strategy that incorporates some or all of these considerations should be successful at achieving the desired goal. The simplest and highly effective approach is to replace the compendial inlet with either one that is anatomically correct [15] or a so-called "idealized" inlet that has internal geometry in which the aerosol deposition characteristics mirror closely reality [16, 17]. This change 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) [18] When combined with patient age-appropriate breathing using a simulator, such as the ASL 5000 (IngMar Medical, Pittsburgh, PA, USA), measures of emitted dose should therefore be close to reality [16]. Tidal breathing is appropriate for the evaluation of pMDIs nebulizing systems and soft mist inhalers that do not require simulating the inspiratory effort of the patient. However, it is more appropriate to utilize patient-generated flow-time waveforms to mimic the single inspiration that is needed to actuate a given DPI and disperse the aerosol for inhalation [19, 20]. In the case of APSD measurement, the operation of the inhaler is ideally separated from the constant flow rate requirement of the cascade impactor, a process that can be accomplished using the Miller-Nephele mixing inlet [21] (RDD OnLine, Richmond, VA, USA). This approach has recently been used to develop IVIVCs for delivery of budesonide aerosols to adults with remarkable consistency across pMDI, DPI and nebulizer platforms [22]. If the inhaler has a facemask as the patient interface, the use of face models in which the soft tissues where the facemask 'lands' on the face is essential to achieve realistic measures of either emitted dose or APSD [23]. Only in this way can realistic representations be made of dead-space in the often flexible facemask [24] together with assessment of leakage particularly at the nasal bridge and chin [25]. There are currently no commercially available models. However, the Aerosol Delivery to Anatomical Model (ADAM-III) 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 [26]. The 4-year old child model face, subsequently developed also with anatomically correct upper airway, appears to provide equivalent data that are consistent with expectations, based on increased tidal volume appropriate to this age of child [27].

How do we apply Clinically Appropriate Testing to Aid in Improving Patient Adherence?

Laboratory methods that evaluate OIP performance in clinically appropriate ways have the potential to provide insights into patient misuse as well as simulating the hoped-for optimum interaction with the OIP, and this advantage is becoming recognized by stakeholders, in particular the regulatory agencies. For example in the European regulatory environment, testing of VHCs with a delay between inhaler actuation and the onset of sampling is understood to be a more appropriate way for their evaluation in comparative performance assessments [28]. A recently introduced International Standard covering the design of most types of OIP indicates that patient interaction with the inhaler be taken into account in risk assessments as a key part of developing the Device Functionality Profile [29]. Finally, increasing attention is being paid by the pharmacopeial authorities to testing inhalers in patient-use relevant ways. For example, a new informative chapter <1602> is proposed for inclusion in the United States Pharmacopeia covering spacers and VHCs, in which simulations of delayed inhalation at constant flow rate, user-age appropriate tidal breathing and evaluation of the facemask patient interface with face models that have soft tissue rendering will be described [30].

Conclusions

The development and validation of a suite of clinically appropriate laboratory test methods for the determination of emitted dose and aerosol APSD from all types of OIP is becoming an urgent task for those involved in the improvement of the pharmacopeial armamentarium of methods. It is to be hoped that the use of such procedures in OIP development will enable devices to be produced that more closely meet patient needs, and thereby contribute towards an improvement in adherence with their use in a prescribed therapeutic regimen.

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