Addressing the patient-device use interface: Why patient-friendly features are important

A new approach to OIP development can result in simple-to-use, patient-friendly devices that are more effective at maintaining and improving patient compliance

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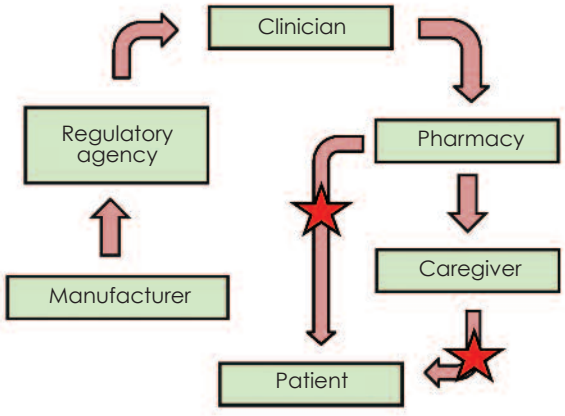
The adoption of concepts, such as Quality-by-Design, with the development of orally inhaled drug products (OIPs) and associated devices marks a significant development in understanding inhaler performance. However, independent assessments of the management of inhaled therapy continue to report poor compliance, even after training. This article investigates why greater consideration of the patient-device use interface is urgently needed.

The OIP and related device life-cycle

In North America and Europe, the OIP life-cycle (Figure 1) begins when a pharmaceutical company perceives a demand for an inhaled drug therapy that is economically sustainable for an acceptably long period of time. The drug product is currently most likely to be delivered by pressurized metered dose inhaler (pMDI), dry powder inhaler (DPI), soft mist inhaler (SMI) or nebulizing system. In contrast with the other forms of OIP in which the drug containment closure comprises much of the device component, in the case of nebulizing systems, the nebulizer itself is the device that is often designed and manufactured separately from the drug product, and into which the drug is placed by the patient or caregiver immediately before use.

Figure 1

The OIP-device life-cycle, showing the link between stakeholders involved in the delivery of inhaled therapies to the patient; the correct use of the inhaler is most vulnerable at the locations indicated by the stars



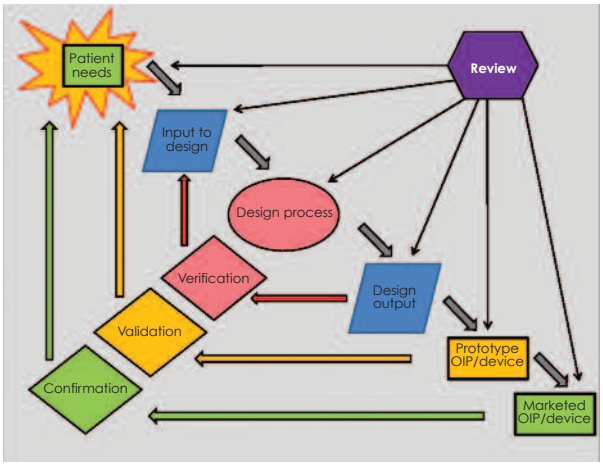
At this early stage, specialist respiratory clinicians are often consulted to provide insight into the therapeutic gap that is being filled by the new offering. This prelimi-

nary stage provides an excellent opportunity to begin consideration of the ways a patient will use the inhaler. The pharmaceutical company, frequently in collaboration with a device manufacturer (if an add-on component is present such as a dose counter or valved holding chamber (VHC)), then goes about developing the product.

As the design processes for drug product and device components proceed, they often each involve further input from opinion-leading specialist clinicians. At this stage, it is critical that handling of the complete package that the patient will use is considered. This process quite frequently includes patient-handling studies of the inhaler, where the opportunity is taken for direct end-user feedback. One leading pharmaceutical company has for some time advocated a so-called "Voice of the Customer" approach through both an initial assessment of user needs, involving a cross-section of likely patients, followed by validation once the device has been designed.[1] Such a patient consultation-based approach can also easily be integrated into post-marketing surveillance activities, thereby providing confirmation that end-user needs have been fully met (Figure 2). If such a process throughout the OIP/device life-cycle was to be adopted as the norm, "patient-friendly" products could be anticipated to follow as a natural consequence. Yet, recent clinical experience has not always been satisfactory in terms of patient compliance with correct OIP usage,[2, 3] suggesting that more needs to be done to improve the patient experience. This article therefore explores some of the principles concerned with integrating a patient-friendly approach as an intrinsic part of inhaler design, with illustrative examples taken from the perspective of an OIP device manufacturer, Trudell Medical International.

Figure 2

A 'Voice of the Customer" approach to OIP design (developed from reference 1)



Regulatory and clinical aspects in OIP and related device development

Regulatory agency involvement is an essential part of the OIP and related device development processes, almost from their inception. In this context, recent regulatory agency- and international standards-based initiatives, such as Quality-by-Design[4, 5] and risk analysis-based testing[6] have deepened the overall understanding of the nature of the many physico-chemical factors that influence *in vitro* OIP performance profiles. However, these initiatives have not had much to do with comprehending patient-handling related factors, which can also have a major impact on OIP performance. Put simply, however well the inhaler has been designed, its effectiveness will be jeopardized if mishandled by the patient or caregiver.[2, 3]

Fortunately for the OIP/device developer, there is now the potential to garner, during the design stage, a better understanding of potential vulnerability to mishandling, abuse and adverse environmental conditions for storage and use by application of the risk assessment-and-evaluation principle espoused in a recently published International Organization for Standardization (ISO) standard covering most inhaler formats.[7] However, once the inhaler has been developed and authorized for sale, it is placed in the hands of primary care clinicians and pharmacists (Figure 1). These professionals very often have little prior knowledge of its capability, other than in general terms through the required Summary of Product Characteristics (SmPC) in Europe or the Prescribing Information (PI) insert in North America. Therefore, their advice to the patient in terms of correct use may be rudimentary in nature. Recently Yawn, in a comprehensive review of literature associated with asthma control,[8] recommended that at regular patient assessments, the patient be questioned on each visit to respond to the challenge: "What kinds of problems do you have using all of your asthma medications daily?" *Furthermore, inhaler technique should be reviewed on each occasion by having the patient bring his or her inhalers and demonstrate technique with each device.*

The clinicians' role is to act as first-line caregivers in the diagnosis and treatment of respiratory disease. In such practice, there is often little time to do more than prescribe one or more OIPs for patients to use either directly, or quite commonly via a caregiver, especially if the recipient of the therapy is an infant, young child or elderly adult. There is strong evidence from the evaluation of inhaler use, particularly in Europe by the Aerosol Drug Management Improvement Team (ADMIT) of specialist respiratory clinicians[9] and by the International Primary Care Respiratory Group (IPCRG),[10] that mishandling of OIPs of all types is commonplace.[2, 3, 11] Despite efforts to encourage training of clinicians,[12] phar-

macists[13] and patients[14] in correct use at the primary care level, the evidence is strong that patients quickly forget and lapse back into poor technique.[15] Although there are a limited number of training aids that can help teach better inhaler techniques,[8] they are often inhaler-specific, necessitating that the prescriber master several different procedures depending on the OIP types that are needed for the range of inhaled therapies being offered in the practice. Given this unsatisfactory situation, it is worthwhile examining the patient-use interface more closely to see if the OIP and adjunct devices can be made more patient-friendly and intuitive to use, as an integral part of the design process.

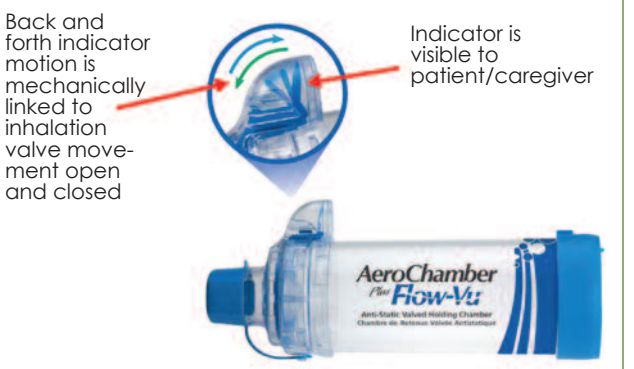
The patient-friendly device: Principles

The examples to illustrate the principles underlying the patient-friendly OIP/device concept are drawn from experience with the pressurized metered dose inhaler (pMDI) and nebulizer; two types of inhaler that are widely prescribed, but often underperform in use. Regardless of the inhaler type, the first and most important principle is that the user interface, however complex, should be both ergonomic and intuitive. If possible, the inhaler, and not individual patient skills, should guarantee correct use.[16] In this way, the end user who may have only minimal training, does not have to struggle to determine the correct way to operate the inhaler. Although the use of electronics may help to aid monitoring of compliance by the prescribing clinician,[17] this benefit often comes with an increase in cost to the patient.[18] Furthermore, caution is advised, since the user may be offered multiple choices in set-up and use, and it is easy to create a situation that is confusing (analogous to problems understanding how to operate some TV remote control units). Overall size and shape (fit in the hand) are important parts of an ergonomic design. Ideally, the inhaler or adjunct device needs to be small enough to handle comfortably and yet sufficiently large and robust to carry out its intended function.

The second principle is that designed-in attributes should be present to prevent possible inadvertent or misuse by the inexperienced patient. It is important to note that such features should not require the patient to do anything specific to enable him or her to operate; the features should be functionally "invisible," but always present. An example of the latter is an in-built audible whistle that signals to the patient they are inhaling from a VHC too quickly.[19] However, as some patients may fail to read the instructions for use and think that the whistle indicates correct inhalation technique, this potential for misuse reinforces the need already discussed[8] for the clinician to instruct the patient in correct use at the first and subsequent visits. A more significant illustration is the use of a visible aid that confirms to a caregiver that the patient is inhaling as well as the optimum time to actuate the inhaler. An example is the Flow-Vu inspiratory flow indicator (IFI) (Trudell Medical International) that is built into the design of the AeroChamber Plus VHC (Trudell Medical International). Its movement back and forth is linked with opening and closing of the inhalation valve and takes place in synchrony with the patient's breathing cycle (Figure 3).

Figure 3

The Flow-Vu inspiratory flow indicator (IFI); movement of this highly visible indicator away from the patient towards the horizontal position takes place as the inhalation valve opens and *vice versa*



Thus, by observing the movement of the IFI, the patient or caregiver can time the actuation of their pMDI to coincide with the onset of inspiration, thereby minimizing delay and optimizing delivery of therapeutically-beneficial fine particles.[20] This feature is especially important if a facemask is used, because the IFI will not operate until a seal exists between mask and face. Thus, it prevents the potential for large losses of medication due to facemask-to-face leakage,[21] by guiding the caregiver or patient to seat the facemask on the face correctly – and at the same time, it indicates the optimum timing for inhaler actuation. The incorporation of a dose indicator or counter for multi-dose OIPs is a further example where the second principle is being applied, as such an aid both confirms dose delivery per actuation and enables the end user to determine when to replace the inhaler. Although such aids have been mandatory for DPIs, their incorporation into pMDIs is still in process, despite regulatory guidance in the United States since 2003, advocating the adoption of this important patient aid.[22]

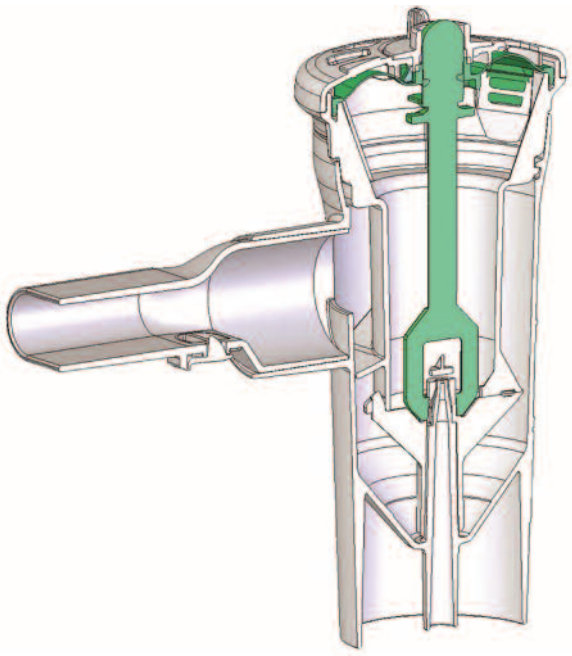
Easy care of the OIP/add-on device is the third principle of patient-friendly design, because patients and caregivers are reluctant to re-use products that become unattractive with reduced performance, due to the accumulation of previously deposited medication[23] and other residues from repeated use. There is also the risk

that the inhaler may have become microbiologically contaminated.[24] Making the product fully cleanable is only the first step in the process. The product should also be intuitive to dismantle and reassemble, because at least one study has reported the frequent occurrence of mistakes in correct cleaning procedure.[25] Today, with the prevalence of automated dish-washing equipment in the home, it is a distinct advantage that the device be at least top-rack compatible.

Going beyond the basics of intuitive and ergonomic design, aids such as some form of indication that shows to the patient or caregiver when the device is delivering medication, not only provides additional comfort at the time of treatment, but may also be used as a coaching aid to obtain optimum inhalation flow rate-time characteristics for deep penetration of fine particles into the lungs. The ability to leverage a patient-friendly feature to train and/or improve inhalation technique represents the fourth underlying principle. As an example of what can be done in this respect, the up-and-down movement of the brightly colored green button located on top of the AeroEclipse breath-actuated nebulizer (Figure 4) (Trudell Medical International) can be used as such a coaching aid, as can the IFI movement previously described with the AeroChamber Plus VHC.

Figure 4

Cross-section through the AeroEclipse-II breath-actuated nebulizer (BAN); the green button that is fully visible to the patient at the start of inhalation moves downwards partly out-of-sight as the breath-actuation mechanism operates during inhalation, returning to the fully visible position at the end of inhalation and during the exhalation phase of each breathing cycle



Both features require no active involvement of the patient beyond observing the indicator and making it move, either in synchrony with their natural tidal-breathing pattern, or in a longer inhalation as instructed by a clinician to improve particle deposition in the airways of the lungs. Importantly, by helping the patient improve their therapy, the risk of an exacerbation of symptoms involving short-term re-hospitalization is reduced, an important consideration in the US for Medicare-funded patients,[26] where there are likely to be financial penalties associated with such occurrences, beginning in the near future.[27]

Finally, the incorporation of toy-like features that are attractive to infants and small children might seem an appealing approach with these patient-age groups. However, caution in the implementation of such measures is suggested, as a recently published study concerning a VHC intended for infant use that contains toy features as an incentive to obtain improved inhalation technique,[28] found that it made no difference to important clinical outcomes such as wheeze-free days, cough-free days, bronchodilator-free days or quality of life.[29] Furthermore, such enhancements can come at significant additional cost that is likely to make the device less attractive for payors. A simpler and therefore lower cost approach is to make the device look less like a medical product by the use of artwork that is visually attractive. This might include the incorporation of animal-related symbols on external surfaces of devices intended for use by infants and toddlers. More abstract themes with clearly masculine- or feminine-oriented coloring may be more suitable for inhalers and add-on devices intended for adolescents, as these groups are often reluctant to take inhaled medication in front of their peers.[30] Finally, the development of training aids, such as the T-haler (Cambridge Consultants, UK [31]) that utilizes an interactive software interface to provide virtual feedback to children receiving pMDI-based therapy, may augment the aid given to users by patient-friendly features of the device itself. In this concept device, reinforcement of correct technique is developed through playing a game in which, during the actuation/inhalation phase, a ball rolls across a makeshift tic-tac-toe board filled with options that indicate incorrect technique, such as inhaling too gently. If the inhalation technique is optimal, the ball rolls down a hole in the middle "winning" the game.

Interchangeability of so-called "universal" inhaler add-on devices: Not such a patient-friendly solution

Interchangeability of OIPs and related devices is attractive to payors as a means to minimize the significant costs associated with inhaled medication therapies and the practice is widespread with the regulatory approval of generic products.[32] However, this practice is to be

discouraged for the following reasons, in the case of spacers and VHCs:

1. The patient or caregiver may become easily confused by the substitution, especially when the user instructions from one device to the other are quite different, as is frequently the case, so the outcome could well be a significant loss of medication delivery efficacy if the correct instructions are not followed;[32]

2. The add-on device substantially modifies the aerosol inhaled by the patient.[33] There is ample *in vitro* evidence that each pMDI–VHC is a unique inhaled medication delivery system, from testing of different VHCs with the same pMDI product[34] and from different pMDI products used with the same VHC;[35]

3. Adequate laboratory-based data, supported if necessary by clinical studies demonstrating equivalence of the substitute, may be absent.

In 2009, the European Medicines Agency (EMA) published a recommendation that for inhaled corticosteroids (ICS): *"Spacers [VHCs] should not be regarded as interchangeable: patients who use a spacer with their inhaler should use the spacer device named in the Summary of Product Characteristics."*[36] This guidance further stipulates: *"Patients whose asthma is well-controlled and who are using a spacer should always use the same type of spacer and not switch between spacers. Different spacers may deliver different amounts of inhaled corticosteroid, which may have implications for both safety and efficacy."* Around the same time, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) provided guidance to clinicians as follows:[37] *(1) "Spacers should not be regarded as interchangeable: patients who use a spacer with their inhaler should use the spacer device named in the SmPC," (2) "Patients whose asthma is well-controlled and who are using a spacer should always use the same type of spacer and not switch between spacers. Different spacers may deliver different amounts of inhaled corticosteroid, which may have implications for both safety and efficacy."* From the foregoing, it is clear that substitution of this class of OIP device would not be a patient-friendly act and may have unintended adverse clinical consequences, at least for ICS. These largely European-driven regulatory developments appear to underlie the recent request from the Inhaled Products Working Party of the British Pharmacopeia to the Ph. Eur. Commission that a general monograph providing information for the testing of spacers, VHCs and facemasks should be developed through the Pharmacopeial Discussion Group (PDG) harmonization process that involves both Japanese and US Pharmacopeias.[38] Reinforcing this need, a Stimulus Article outlining the form that an informative chapter might take in the US Pharmacopeia appeared for public comment in 2011.[39] These developments will hopefully provide developers of both generic and innovator products the opportunity to utilize testing methods that are clinically relevant in the context of adopting a Quality-by-Design approach to the incorporation of the nominated add-on device, at an early stage in the product development process.

Concluding remarks

This article has laid the groundwork for a re-think concerning the ways in which the patient or caregiver is intended to use OIPs and related devices. A case has been made for advocating an approach by all stakeholders in the OIP life-cycle that ultimately results in simple-to-use and "patient-friendly" OIPs and related devices that will prove to be more effective at maintaining and improving inhaler compliance.

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