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*Meeting Report*

*Theme: Current Scientific and Regulatory Approaches for Development of Orally Inhaled and Nasal Drug Products*
*Guest Editors: Lawrence Yu, Sau L. Lee, Guenther Hochhaus, Lana Lyapustina, Martin Oliver, and Craig Davies-Cutting*

# Inhalation Devices and Patient Interface: Human Factors

**Stefan Leiner,[1,4] David Parkins,[2] and Orest Lastow[3]**

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***Abstract.*** The development of any inhalation product that does not consider the patient needs will fail. The needs of the patients must be identified and aligned with engineering options and physical laws to achieve a robust and intuitive-to-use inhaler. A close interaction between development disciplines and real-use evaluations in clinical studies or in human factor studies is suggested. The same holds true when a marketed product needs to be changed. Caution is warranted if an inhaler change leads to a change in the way the patient handles the device. Finally, the article points out potential problems if many inhaler designs are available. Do they confuse the patients? Can patients recall the correct handling of each inhaler they use? How large is the risk that different inhaler designs pose to the public health? The presentations were given at the Orlando Inhalation Conference: Approaches in International Regulation co-organised by the University of Florida and the International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS) in March 2014.

## INHALATION DEVICES AND PATIENT INTERFACE: HUMAN FACTORS

Human factors are defined as '…the application of knowledge about human capabilities (physical, sensory, emotional, and intellectual) and limitations to the design and development of tools, devices, systems, environments, and organizations….' (1). Human factor studies are typically complemented by studies that cover the patient's interfacing and interacting with the device.

The importance of the interface between the device and the patient and the human factors that are relevant for inhalation products was the topic of four presentations given at the Orlando Inhalation Conference: Approaches in International Regulation. First, Orest Lastow (ICONOVO, Sweden) spoke about 'Key Challenges in Device Design and Manufacturing'. He was followed by David Howlett (PharmaDelivery Solutions Ltd, UK) who presented aspects on 'Emerging and Established Inhaler Markets: Can One Size Ever Fit All?', Dave Parkins's (GSK, UK) presentation on 'Patient Factors Consideration' and Stefan Leiner's (Boehringer Ingelheim, Germany) talk 'Is Bioequivalence Just Math? The Importance of Handling Patient Feedback for Bioequivalence Assessment'.

The summary of the talks and of the discussion that arose is presented in this article. The summary does not present each talk separately but combines them with the discussion points to give a comprehensive picture so that it does not necessarily represent the individual views of the authors or their companies.

This paper is part of a series of reports from the Orlando Inhalation Conference: Approaches in International Regulation co-organised by the University of Florida and the International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS) held in March 2014.

### The Importance of Human Factors for Inhalation Products

Inhalation products can be considered to be complex products when compared to an oral-dose product such as a tablet wherein the desired therapeutic outcome is achieved by the patient simply swallowing the product. This contrasts with the inhalation product where it is necessary for the device to deliver the product to the patient in a consistent manner which is a function of the formulation, the device design as well as the patient's ability to use the device correctly. To achieve this, patients may be required to follow potentially complex handling instructions that may include a dose loading step, performing several device operations in a predefined order followed by the correct inhalation manoeuvre. In practice, many patients do not achieve this, with examples in the literature showing that in practice error rates are significant, with rates of 74.6% for metered dose inhalers (MDIs) and 6.8–43.2% for three dry powder inhalers (DPIs) cited in one study (2) and 24% for MDIs and 17–24% for three DPIs in another study (3).

It is therefore important that the needs of the patient and, if appropriate, the caregiver are carefully considered

[1] Boehringer Ingelheim Pharma GmbH & Co. KG, 55216, Ingelheim am Rhein, Germany.
[2] David Jack Centre for R&D, GSK, Ware, Hertfordshire, UK.
[3] ICONOVO AB, Medicon Village, Lund, Sweden.
[4] To whom correspondence should be addressed. (e-mail: stefan.leiner@boehringer-ingelheim.com)

 

during the initial development of an inhalation product so as to ensure the development of a robust and intuitive product. Similarly, this needs to be considered during the life cycle of the product when changes to the product may be required. Patient factors that may require consideration include perception of the colour and shape of an inhaler, ability to perform handling steps, acceptability of forces needed to actuate the inhaler, perception of noise, mechanical robustness and affirmation of the successful inhalation manoeuvre.

The number of inhaler designs, especially that of dry powder inhalers, has significantly increased over the past few years as illustrated in Fig. 1, and this diversity is likely to continue to increase in the future. It is important that we continue to innovate so as to bring in new technologies that will improve the patient's experience of using the product. However, today's level of diversity of powder inhalers with respect to design, operating principles, order of handling steps, exact adherence to the order of handling steps and feedback to the patient does mean that there is significant complexity and the potential to confuse the patient, especially in the situation where the patient is required to use more than a single inhaler type. Such diversity therefore has the potential to impact the effectiveness of the patients' use of their inhalers. Error rates were shown to increase if patients are switched from one inhaler to another one (see Fig. 1).

For inhalation products to be effective, it is necessary for patients or caregivers to correctly complete a number of steps. Besides following the number of actuations and dosing frequency, patients must correctly operate the inhaler by following a predefined series of steps in the correct order followed by the correct inhalation manoeuvres to achieve the desired therapeutic effect.

Figure 2 below illustrates the examples of the diversity of inhaler designs that patients may be presented with. Figure 3 provides examples of the diversity of operating steps that presently exists between different inhaler designs (5–8).

To show that patients can use a new inhaler, it is necessary to conduct human factor studies and/or handling studies with the appropriate patient population during development, the results of which are typically included into a New Drug Application or Marketing Authorisation

**Fig. 2.** Photo showing the diversity in the outer shape of inhalers

Application. These studies are intended to demonstrate that patients understand the operating principles of an inhaler and are able to use it correctly. Often, these studies are supplemented by obtaining inhalers that have been used by patients in clinical trials which can then be checked for any evidence of malfunction or damage that may indicate that the performance of the inhaler in the hands of the patient is not as expected, *e.g.* evidence of excessive forces, clogged air inlets and inability to actuate correctly.

Such studies, however, may be of limited value because, in such trials, subjects tend to receive more detailed training on the use of the inhaler which may not be representative of a real-life situation where patients often receive their medication without specific explanation from a pharmacist and are not regularly monitored. Further, when obtaining patient feedback through handling and similar studies, consideration should be given to evaluating the product in the relevant patient population. Studies reported in the literature show that error rates can be influenced by many factors including patient age and severity of airway obstruction (9) and degree of training (10).

This means in practice that a COPD patient who may be elderly and with a limited inspiratory flow rate, who may not be well trained or monitored and has co-morbidities such as

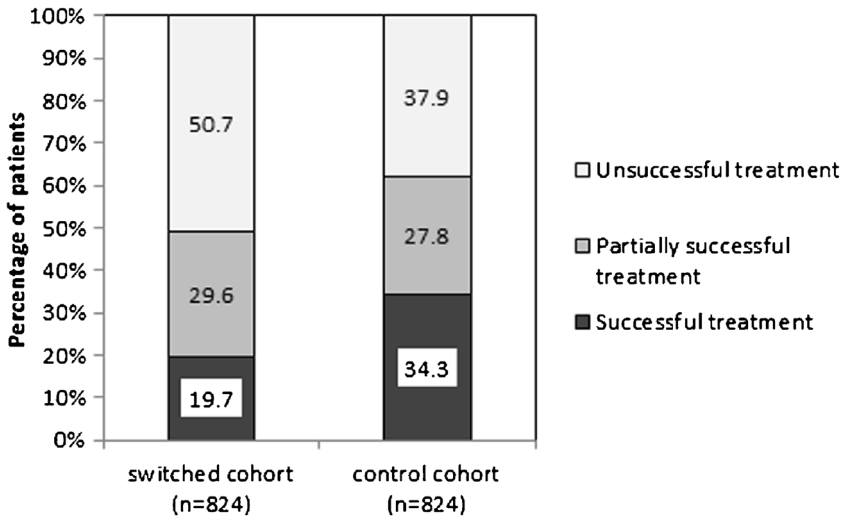


**Fig. 1.** Handling error rates for patients who switched inhalers (*left*) or did not (*right*) (reproduced from (4))

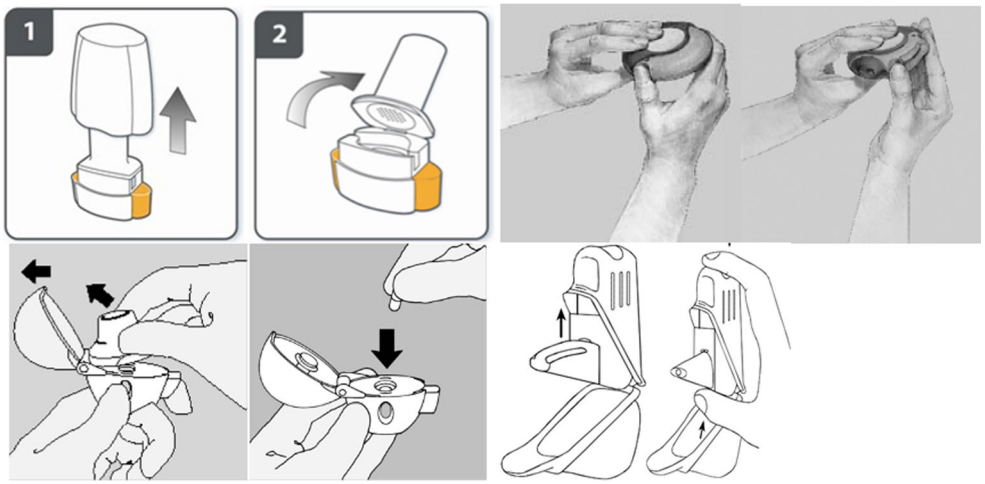


**Fig. 3.** Schematics showing different handling procedures for selected dry powder inhalers: capsule (*upper left* and *lower left*), multi-unit dose blisters (*upper right*), reservoir (*lower right*)

Parkinson's and dementia, may be more susceptible to handling errors for a particular product when compared to a younger asthmatic patient. For paediatric patients, memorising a sequence of handling steps may be especially difficult, and the parents' capability of teaching correct use of an inhaler is important. Finally, such studies generally focus on the inhaler under question and do not necessarily take into account the fact that a patient may use several different devices at the same time or is asked to switch from a device he is familiar with to a new one, which may look like the old one but requires different handling steps. With the increasing number of inhaler designs, this is of critical importance. This means that handling studies do not predict handling situations and the inhaler's susceptibility to handling errors in real life.

Agencies and the pharmaceutical industry have successfully established and applied standards for inhaler moulding and assembly, for the manufacture of inhalation drug products and for quality control. Examples of such co-operation include the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and the Pharmaceutical Inspection Convention/ Co-operation Scheme (PIC/S).

With the increasing number of inhaler designs for the same active ingredient, there is the need for a standard for assuring the correct use of an inhaler. Such a standard may cover the following aspects:

- For a patient who uses two inhalers that have different inhaler designs: How can one ensure that the patient is not overburdened and uses them correctly?
- If a patient is switched from one inhaler to another which delivers the same active ingredient with the same dose and the same particle size distribution, does this assure 'use equivalence' of the inhalers and 'therapeutic equivalence'?
- How close or how different may inhaler designs be before they pose a risk to the public health?

Answering these questions is a key challenge for the next decade. We must take care that innovation does not leave the patient confused. This would achieve the opposite of what innovation is aiming at: improving medication and medication delivery.

The patient needs and patient feedback discussed above can, when analysed, be split into three parts or layers: use, interface and perception. The use is the basic function of the device, *e.g.* dose metering, flow resistance, handling sequence, *etc.* The interface is how the device communicates with the patient, *e.g.* dose counter, graphics to guide the use, intuitive operations, *etc.* The perception is an emotional connection with the device: Does the patient like the device? Does he trust it? Would he recommend it to friends and relatives that need a doctor's prescription? All the patient needs must be collated and analysed to map out the complete user need. When doing so, it is often found that the needs are mutually conflicting and must be balanced and weighed against each other. This is shown schematically in Fig. 4.

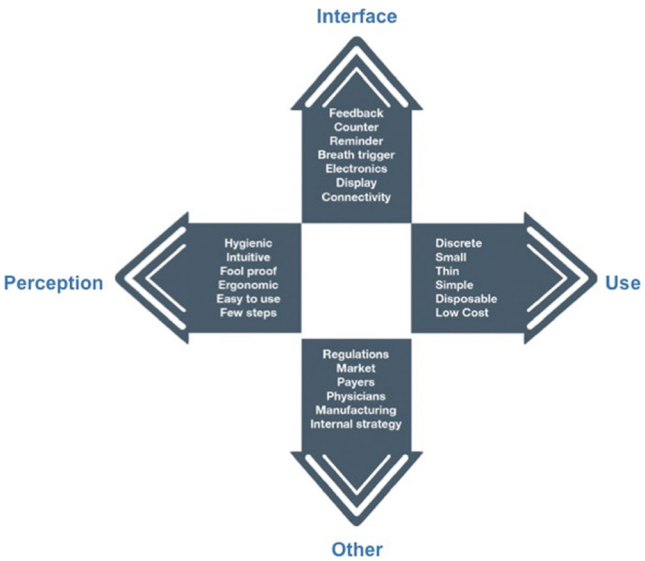


**Fig. 4.** Scheme showing potentially conflicting interests and requirements

## Key Challenges in Device Design and Manufacturing

i) Communications

When the user needs are understood, the product development can commence. This includes the development of the device, the formulation and the filling. The development is full of challenges. The obvious challenges are setting up a good user requirement specification (URS), various technical and intellectual property (IP) barriers, changing timings and changing sponsor needs and expectations. As these challenges are obvious and common, there is often a readiness to handle them. There are, however, many less obvious challenges. An additional challenge is managing the development team. A typical team is very heterogeneous, including skills in medicine, pharmacy, chemistry, physics and mechanics. A challenge is the communication and exchange of knowledge between people with different scientific backgrounds. There are many examples where good communication is of great value but can be difficult because it involves skills too far from each other. Since the different scientific disciplines often have their own culture and terminology, communication with other disciplines can be troublesome. A team with effective and effortless communication between different disciplines will prove more productive and will develop better products.

ii) Formulation development

The development of a formulation typically involves pharmacists and chemists. If the team would involve mechanical engineers and physicists, useful input on process, filling, electrostatics and modelling can be obtained but only if such a team communicates effectively.

iii) Device development

In the development of a device, in contrast, typically only mechanical engineers are involved. Involving a physicist can provide fluid dynamics and modelling capability. The pharmacists can provide formulation and GMP knowledge, the clinicians provide user aspects, the chemists provide materials and stability input, *etc.* Involving more different skills and managing them appropriately will lead to better and more robust products. Focusing an effort on the communication and interaction of people from different disciplines can be very rewarding for the project performance. This is also very evident in the interaction between the pharmaceutical company and the suppliers. For instance, injection moulding requires an understanding of both the requirements and capabilities of both the supplier and the pharmaceutical company. Selecting a supplier is a very critical activity, which requires both strategic and technical expertise and good communication between different skills.

When finishing the development and preparing for industrialization and manufacturing, timing is very critical as different parts of the development are run in parallel. A strategy is needed to manage early performance predictions when the various parts are in different stages of completion (11). When designing for manufacture and manufacturing the product, a right balance must be found between the performance uniformness and robust manufacturing with high $C_{pk}$. A high $C_{pk}$ often means robust manufacturing and a low cost of goods. However, a mechanically robust device can sometimes give a less robust product. A device robust from a manufacturing point of view should, *e.g.* have wide tolerances, few parts, simple processes, *etc.* However, from a clinical and performance point of view, a device with tighter tolerances and more parts could give a more clinically robust product. The bottom line is that a high $C_{pk}$ and low cost of goods do not necessary mean a better and more cost-effective product.

## Device Changes During the Product Life Cycle

The impact of a change to an inhaled product or device is a question that has to be considered throughout the whole life cycle of the product. Changes can arise during the design and clinical evaluation phases of product development in response to user feedback during handling studies or during clinical evaluation. Similarly, changes may be required before product launch in response to robustness testing or during industrialisation as modifications may be required to permit high-speed manufacture and assembly. Once the product is launched, changes may occur for a number of reasons which include, in response to feedback from patients or healthcare professionals, the need to further optimise the manufacturing process, introduction of new suppliers to ensure security of supply or enforced changes in the supply chain.

When assessing the impact of any change, *in vitro* methods and tests can provide important data to support the assessment of that change. The specific methods used for characterisation will depend on the type of inhalation product being evaluated but might include the determination of aerodynamic particle size distribution (APSD), dose uniformity, actuation force, air flow resistance and plume geometry. Additionally, the impact of the change on the robustness of the product may be evaluated through tests such as drop testing and transportation testing. However, it is important to recognise any limitations in the *in vitro* test being used in assessing the impact of the change. For example, cascade impaction testing is widely used to evaluate APSD; however, it is a quality control test which is not intended to mimic the patient; its limitations include being operated under fixed flow conditions with deposition through impaction whereas a patient has a variable inhalation profile and deposition in the lungs can be through sedimentation, impaction and diffusion. The limitation of this specific test has been recognised, and various groups have adapted the methodology in an attempt to better mimic the patient by the use of a more realistic throat such as the Alberta Idealised Throat

**Table I.** Changes During Device Life Cycle: Conclusions and Suggestions

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|---|
| 1. The need to understand the relevance of device changes applies across the product life cycle. |
| 2. It is important to understand the patient interface and relevant populations when evaluating a change. |
| 3. Risk management approaches can be used to identify appropriate studies. |
| 4. There is little consensus on required studies, driven in part by significant diversity in product designs. |

which can be used with patient realistic inhalation profiles (12–14).

Consideration also needs to be given to whether a change might impact the effectiveness of the patient's co-ordination of the device with their inhalation manoeuvre; for example, one needs to be aware of changes that might impact MDI plume velocity which can range from 150 to 500 ms duration (15) or any changes which might result in changes in mouth feel and their perception of dose received. For DPIs, their emitted dose times can vary, changes in the airflow resistance might impact inspiratory effort and differences in powder loading might influence the patient's perception of dose received (16). Consideration should also be given to the impact of changes that could lead to a change in the way the patient handles the device or where a change might alter the feedback (audible or visual) provided by the device to the patient.

When it comes to assessing the impact of device differences, it can be generally considered that with increasing device similarity, the risk of any differences impacting product equivalence decreases (17). A risk management approach as defined in ICHQ9 (18) therefore offers a framework for evaluating risk based on scientific knowledge and ultimately links to the protection of the patient, whilst ensuring that the level of effort, formality and documentation of the quality risk management process are commensurate with the level of risk. However, whilst risk management can be used to help identify appropriate studies, the challenge remains that at present there is significant diversity of views across the industry on what would be required studies for any given situation (19).

From that, the following conclusions and suggestions for changes during the product life cycle are made, as summarised in Table I.

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