The importance of human factors in inhaler development: The making of PowdAir®

This case study highlights the importance of human factors in the development of a novel capsule-based dry powder inhaler

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Introduction

Dry powder inhalers (DPIs) have been widely used in the last few decades in the treatment of asthma and chronic obstructive pulmonary disease (COPD), through orally inhaled drug delivery. The use of inhalation devices is expanding to new therapeutic targets as evidenced by recent product launches (e.g., Novartis with Tobi®, Mannkind with Affreza® and Daiichi-Sankyo with Inavir®). In addition, there is a pipeline of emerging therapeutic applications such as pulmonary arterial hypertension, idiopathic pulmonary fibrosis, pain management, cystic fibrosis, infectious disease, influenza and some neurologic diseases.[1,2] These recent developments have, in most cases, selected DPIs, such as the Dreamboat™ (Mannkind) or the Podhaler™ (Novartis) inhalers, instead of metered drug inhalers (MDIs), which probably reflects the improved performance of breath-actuated mechanisms that eliminate the need for synchronization required when using MDIs.

Still, several studies reveal high failure rates when patients use their own DPIs, showing the importance of instructions for use (IFU) in the reduction of such error rates and providing evidence of strong correlations between device acceptance, age and adherence.[3-5] Inhaler misuse affects treatment efficacy and has been identified as a cause of reduced disease control in asthma and COPD patients.[6]

The US Food and Drug Administration (FDA) has set methodologies to incorporate human factors analysis, testing and validation into medical device optimization[7] and it has become a regulatory imperative to submit such data in drug/device combination applications. Some inhalation products have had programs delayed because of insufficient usability data.[8] In addition, international standards and European regulatory guidance[9,10] aimed at the improvement of device usability and the mitigation of use errors and potential harm to patients have also driven human factors engineering (HFE) to become an increasingly central aspect for manufacturers involved in DPI development.

Human factors driving DPI design

Hovione developed a new capsule-based DPI, intending it to be extremely simple and easy to use by patients comprising a wide range of age, educational backgrounds and different medical conditions across various geographies and, in addition, be produced at a low cost. Human factors are of utmost importance in the development of reusable inhalers employing capsules. These normally require an extensive interaction with the patient during use. Therefore, it is the DPI developer's goal to reduce the number of manual steps from loading of the capsule into the device until capsule disposal, while making the device intuitive, easy to use, easy to carry and convenient so that it can be used by any patient, anywhere. These attributes are also desirably needed from a human factors perspective both to mitigate potential use errors that may affect the treatment's efficacy and to improve the patient's compliance.

However, this objective should ideally be achieved without increasing the number of components or adding mechanical complexity into the device, both of which ultimately result in higher manufacturing costs. At the

same time, the reduction in the number of components and complexity for cost purposes should not be done at the expense of the primary function of the DPI, which is to disperse the unit dose of pharmaceutical powder contained in the capsule and transport it into the desired site of action in the lungs.

This case study illustrates the importance of using HFE principles in identification of patient-centric solutions for the design of certain user-interface attributes, and in the conceptualization of the instructions for use. This article will not discuss aspects of the development process used to ensure that drug product performance remained comparable despite changes in product design in response to results of human factors studies. The authors recognize this is a critical consideration that could be trivial or complex, depending on the particular product.

Initial design

Hovione developed a novel, reusable, capsule-based DPI, suitable for pulmonary drug delivery in both chronic and acute applications, with a design target of extreme simplicity of use and a reduction in the number of operational steps required by the patient. Figure 1 shows the initial design named XCaps®. In use, the patient is only required to perform four movements to prepare the inhaler for inhalation. The patient initially pushes a moveable tray to an open position and loads the pharmaceutical capsule into a chamber. When the patient closes the tray, that movement allows the capsule to be cut open by blades that are integrated in the inhaler's inner walls. A protective cover, designed to prevent the ingress of dust during storage or transport, is then removed and the inhaler is ready for inhalation by the patient through the mouthpiece.

In addition to simplicity, the design was conceived to be highly portable, discrete and of small size, to allow convenient storage by the patient when used in public. Furthermore, the concept integrated plastic blades for opening the capsule in the inhaler's body component. This enabled the device to be made of only three plastic components, produced by injection molding and easily assembled, which results in a low manufacturing cost.

Performance requirements also included the design of a high aerodynamic resistance device providing high dispersion efficiency from flow rates as low as 35 L/min. Unlike currently marketed low resistance devices that achieve maximum efficiency at 100 L/min or more, this requirement has the advantage of allowing maximum performance at flow rates achievable in realistic use conditions by patients with compromised lung capacity.[11]

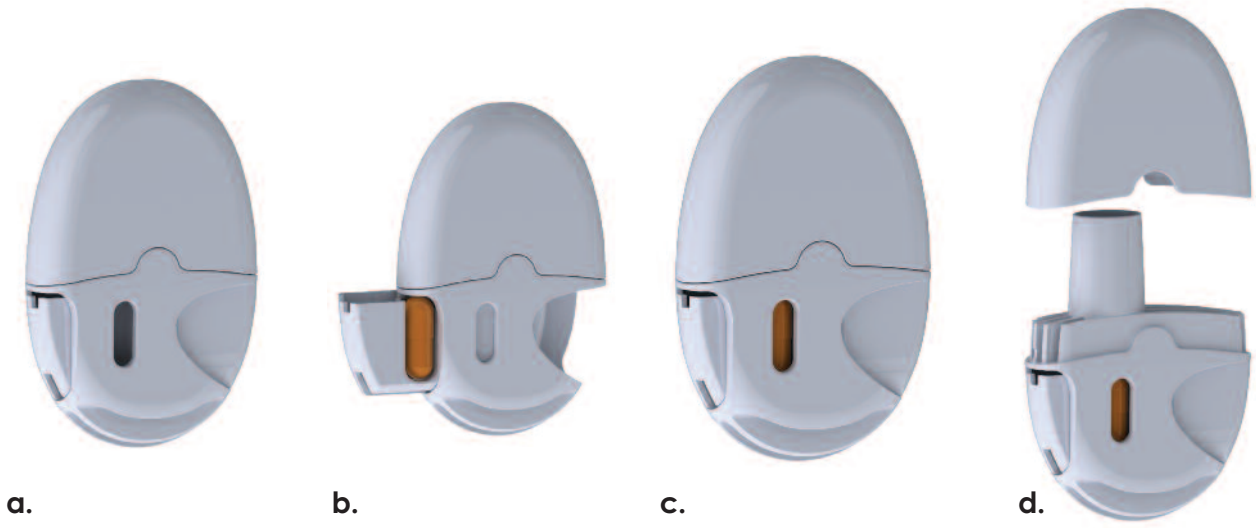
Formative evaluation

A formative evaluation was conducted on the initial XCaps molded prototype to derive information to guide further product development. Despite the intent of broader applicability of the device in multiple therapeutic categories, Hovione decided to undertake a simulated-use testing approach involving use of the device by representative end users with COPD. This disease was selected because it is a condition of older patients who oftentimes have dexterity problems, thereby enabling identification to a greater extent of handling difficulties and need for design improvement.

Hovione contracted an expert in human factor studies to conduct the study and designed a protocol that included 19 COPD patients between 51 and 84 years old. The users were selected to represent a variety of typical patients, including participants experienced with a marketed capsule-based inhaler and naïve participants,

Figure 1

Figure 1a shows the initial device design, the XCaps, in its storage position. Figure 1b shows the step of pushing a moveable tray into the open position for loading of a pharmaceutical capsule. Figure 1c shows the step of closing the loaded tray, which allows the capsule to be cut open. Figure 1d shows removal of the protective cover, which allows the inhaler to be ready for inhalation.



across a range of gender and educational background, as well as elderly users with reduced manual dexterity.

The objectives of the study were:

- Assess the usability of the concept in the hands of representative users and identify and understand opportunities for use errors, confusion or handling difficulties
- Assess the effectiveness and collect subjective feedback on specific design features
- Benchmark the concept against a marketed capsule-based inhaler and collect the participant's overall preference

For this purpose, one-hour sessions were conducted with each participant that included intuitive simulated use of the device and realistic simulated use with the IFU, followed by a root cause analysis and discussion with the participant about use errors or difficulties. Then collection of feedback from a head-to-head comparison between the concept presented and the selected marketed capsule-based device was performed. A range of design features was discussed with each participant including size, overall shape, procedure of use, mouthpiece shape, cover type and ease of capsule insertion, piercing and disposal, and the patients' preferences were collected.

Figure 2 show results from the patients' feedback, which indicates that participants generally preferred the size, shape and use procedure of the new Hovione concept and, in particular, the reduced number of use steps it required. Participants also positively highlighted the capsule opening step which was "automatic" and thus could not be forgotten. This was particularly relevant considering that the demographics of the study sample covered an older population and included participants with dexterity difficulties. However, the patients' feedback also revealed areas where changes would be beneficial, namely: in the type of cover, through provision of a hinged cover to avoid loss; in the design of the mouthpiece, making it wider; and in capsule handling, further facilitating capsule insertion and disposal. Patient feedback also showed that, if these changes were implemented, participants would strongly favor the new concept.

Listening to the patient

Based on the formative human factors findings and patient preferences, Hovione refined the initial concept into the device shown in Figure 3 and created the PowdAir® Dry Powder Inhlaler. The design of the moveable tray was refined to allow easier loading of the capsule from the top after pushing the moveable tray into the open position, as shown in Figure 3c. More convenient capsule disposal was also designed by allowing the capsule to fall by gravity when the device is turned upside down. In addition, a hinged cover was introduced that allows the cover to be permanently connected to the device. Sufficient surface area was provided for user instructions to be printed or engraved to further improve handling through the interface. Figure 3c shows the opening of the hinged cover after the loaded tray has been closed, which allows the device to be ready for inhalation using the mouthpiece. Due to patients' feedback, the mouthpiece was enlarged and reshaped to allow for a more comfortable inhalation. In this refined concept, the hinged cover was formed from molded features integrated in each of the inhaler's injection-molded components. The revised design included only four parts, reflecting the initial design target of utilizing few parts to provide an economic advantage.

Figure 2

Patient preference from a head-to-head comparison of specific design features between the XCaps and a marketed capsule-based device. Comparison included size, cover type, procedure of use, mouthpiece shape, hold shape and capsule handling during use.

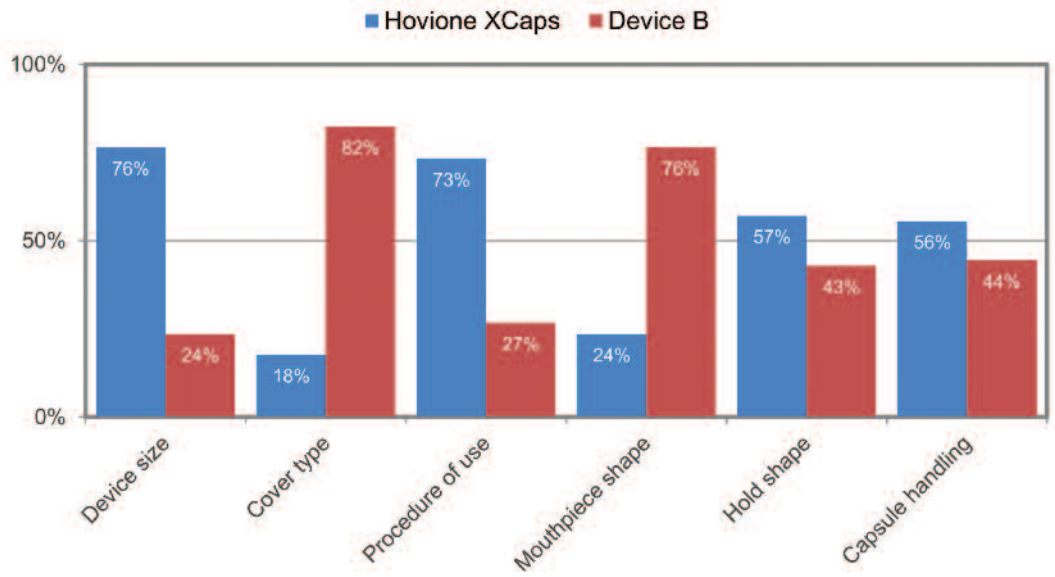


Figure 3

Figure 3a shows the improved design, the PowdAir, in the storage position. Figure 3b shows the step of pushing a moveable tray into the open position for loading of the pharmaceutical capsule. Figure 3c shows the steps of closing the loaded tray, which allows the capsule to be cut open, and opening the hinged cover for inhalation.

Simulated use testing and instructions for use (IFU)

Molded prototypes of the PowdAir were tested using simulated use formative studies conducted in COPD patients with the objective of verifying whether the implemented changes addressed the functional and operational requirements. The protocol included a first study with 18 COPD patients between 36 and 78 years old, followed closely by a second study with 16 COPD patients between 44 and 78 years old. As in the previous study, each new study included participants experienced with a marketed capsule-based inhaler and naïve participants, with various educational backgrounds and elderly users with reduced manual dexterity. The objectives of these two studies were:

- Assess the effectiveness of the design changes and understand potential patterns of use errors or operational difficulties
- Evaluate the comprehension of a new version of the IFU
- Evaluate the usability of alternative quick reference instructions (QRI) to be printed or marked on the cover of the device, as shown in Figure 4, and collect the participant's overall preference

Both studies included intuitive and realistic simulated use of the device in 45-minute sessions with each participant, followed by a discussion about comprehension of the IFU. The first study investigated an initial version of the IFU. Based on usability and comprehension results from that study, changes to the IFU were made and an improved IFU was evaluated in the second study. In addition, the first study evaluated the usability of three different QRI. Each participant was initially provided with a prototype device marked with one of the alternative QRIs on the cover, shown in Figures 4a, b and c. Following the simulated use and discussion, the two additional QRI designs that the participant had not seen yet were shown and the participant was asked for feedback. The order of the QRI marked on the cover initially shown to the patient was counterbalanced during the study. Based on the usability results, changes were implemented to the preferred QRI for evaluation in the second study.

Important findings resulted from these studies. Table 1 shows that modifications to the IFU based on the results

Figure 4

Figures 4a to 4c show the design of three alternative QRI for the inhaler cover, here designated respectively as QRI-1, QRI-2 and QRI-3.

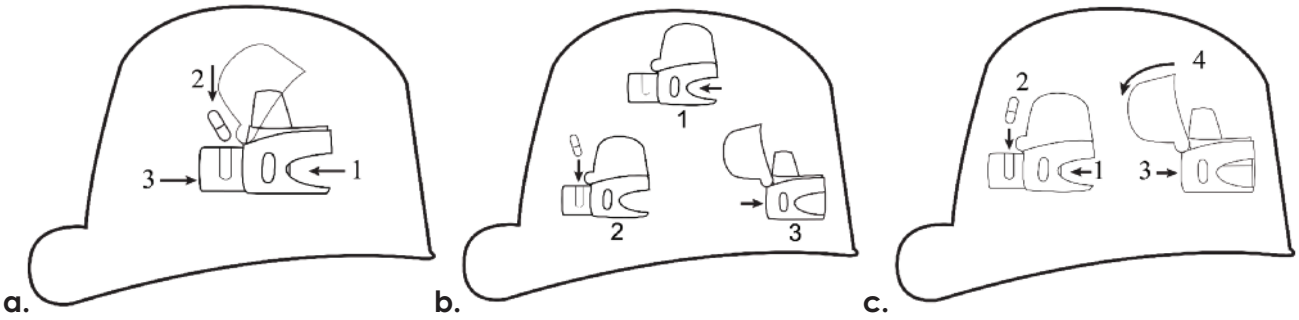


Table 1

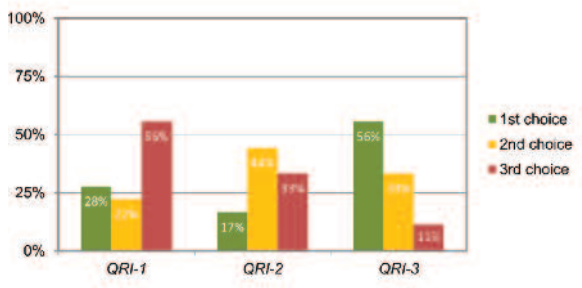
Frequency of participants encountering a use event during the first and second PowdAir simulated use studies. A use event depicts the sum of use errors and resolved difficulties in a given task.

	Use event (n, %)	
	Study 1 (n=18)	**Study 2 (n=16)**
Push tray open until it stops	0	1 (6.3)
Load capsule into tray chamber	4 (22.2)	1 (6.3)
Push tray closed until it stops	0	1 (6.3)
Keep device steady, do not shake	1 (5.6)	0
Open cover completely	0	1 (6.3)
Exhale away from mouthpiece	5 (27.7)	1 (6.3)
Close lips tightly around mouthpiece	3 (16.7)	2 (12.5)
Breath in deeply	2 (11.1)	0
Hold breath	7 (38.9)	0
Leave capsule in tray between doses	2 (11.1)	0
Close cover completely	0	0
Push tray open until it stops	0	0
Rotate device so that used capsule falls out	1 (5.6)	0
Dispose of used capsule in trash	0	0
Push tray closed until it stops	1 (5.6)	0

of the first simulated use study had a positive impact on the overall usability and allowed an overall reduction in the frequency with which participants encountered use events during the second simulated use. Furthermore, during the second simulated use, all participants independently either succeeded or resolved some difficulty with device-dependent tasks, such as opening the tray, loading the capsule, closing the tray or opening the cover. The design improvements in PowdAir thus had a positive impact on the overall device usability.

Figure 5

Patient preference from a comparison among three QRI presented for use on the inhaler cover.



In addition, results shown in Figure 5 revealed that most participants preferred QRI-3 versus either QRI-1 or QRI-2. Approximately 90% of the participants elected QRI-3 as either their first or second choice among the alternative designs. In general, patient feedback was that QRI-3 was clearer with the addition of the fourth use step (Figure 4c), without having too many images or compromising image size.

The PowdAir DPI

Human factors findings and user preferences described in this paper were integrated into the final design of PowdAir to provide a device for future drug/device combination development that responds to patient needs. However, human factors validation testing is still necessary for the intended patient population. Each drug/device combination must demonstrate that the intended users of the inhaler can safely and effectively perform critical tasks in the expected use environments. Such validation testing must be conducted for each disease and intended population.

The new PowdAir DPI from Hovione (Figure 6) addresses key patient needs applicable in different therapeutic indications. The number of steps to inhalation was reduced for easier use. Results from the human fac-

tors studies were effectively utilized in design modifications, such as capsule top-loading and operation of the hinged cover. The need for portability and convenience drove the device to be small size and thin. The delivery performance was designed to be effective for low flow rates. Furthermore, it is essential today to have low-cost devices. Ensuring that a functional device can be built with only four components is an important step in this direction. In addition to the simple use, it is expected that the cover design with integrated instructions will also contribute to better operation and compliance.

Figure 6

The PowdAir DPI device with quick reference instructions on its cover.

Conclusions

This case study presents the methodology followed by Hovione to include human factors engineering principles into device development from the early stages. It illustrates the impact of integrating patient-focused testing during the inhaler device design.

This approach also fulfills a critical regulatory requirement[7, 9, 10] in drug/device combination applications. Human factors engineering has become a central aspect in new DPI development to mitigate user errors and reduce risk to patients. In addition, new device designs are expected to deliver improvements to patients in key product attributes, such as ease and intuitiveness of use, portability and convenience, delivery performance and cost. As shown in the current case study, a human factors-centric approach during DPI development is fundamental for arriving at design solutions that provide such desired improvements for patients.

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