Rethinking Inhaler Systems from a Patient Perspective – the Increasing Challenge of Technology Diversity

The inhalation of dry powders is one of the oldest forms of delivering active substances via the pulmonary route which had been described as early as ~1554 BC. However, the interest remained limited and seemed to become obsolete in the early 1950, when metered dose inhalers (MDIs) using chlorofluorocarbon (CFC) propellants revolutionised pulmonary drug delivery. Even with the introduction of the first capsule-based dry powder inhaler (DPI) product (Spinhaler) in 1970, it remained the only DPI product for many years until the Montreal protocol in 1987 and finally the Kyoto Protocol in 1997 led to a ban on CFC, triggering substantially the interest in DPI as an effective and environmentally-friendly alternative to MDI[1]. The following wave of research and development in the field of DPI formulation and devices led to numerous new products which came to the market during the past 20 years. While the patents started to expire in the last decade, a variety of generic versions and competition reached the markets just a few years ago.

Despite the progress in DPI drug delivery technology, the drug administration with inhaler systems by patients remains a critical factor. Unrecognised administration issues are considered to contribute to poor effectiveness and medication errors. With the increasing number of older and multimorbid patients, as well as emerging regulations to strengthen patient-centric drug product development by focusing on acceptability, usability and real-world evidence, the patient-DPI product interface will become even more dominant.

The Main Patient Population

According to the Global Asthma Report[2], it is estimated that asthma affects as many as 339 million people worldwide. For chronic obstructive pulmonary disease (COPD), the Global Burden of Disease Study published by the WHO estimates the prevalence of COPD to affect 251 million people globally. Asthma and COPD cause a substantial burden of disease, including both premature death and reduced quality of life, in people of all ages in all parts of the world. Asthma symptoms most commonly develop for the first time in early childhood, might persist into adulthood, and predispose people to COPD. COPD generally develops later in life as a result of tobacco smoking and chronic exposure to air pollution.

"The disease in itself because I panic, I'm afraid it'll degenerate, it shows, I'm not clear, unable to focus, I'm desperately looking for my inhaler." Female COPD patient.

Patients with asthma and COPD experience a number of fearful symptoms like dyspnea, cough, and sputum production, and wheezing, chest tightness, and chest congestion. The symptoms are experienced as life-threatening with anxiety and depression as well as breathlessness and a perceived continuous disease progression, with a decline in freedom and social participation[3]. In the situation of sudden breathlessness, panic dictates the behaviour with potentially increasing oxygen demand and very unthoughtful actions trying to overcome the situation. The inhaler will be the first anchor for the patient to get immediate relief and reemphasise the need for effective prevention in form of the long-acting inhalation products. Pressurised metered dose inhaler (pMDI) is still the preferred option for the delivery of short-acting drug (e.g. salmeterol) in an acute asthma or COPD attack, as pMDI delivers the drug in aerolised form independent of the patient inhalation capacity. For preventive treatment, long-acting inhaled glucocorticoids, ß-agonists, anticholinergics and other drugs are being used in combination on a regular basis. Such products are delivered in the form of breath-activated DPI systems. For special patient populations like paediatric patients, nebulisers are being used to administer the therapeutics with the help of care givers (e.g. parents) through an inhalation mask over a few minutes. In addition, spacers are being used for children to allow the inhalation of a single dose by multiple breath cycles. The preventive therapy is performed by the patient on a routine basis and relies on the patients to administer the DPI product "as intended". Beside a clear understanding and recognition of the drug product, minimum cognitive, physical, physiological and sensory capabilities are required by the patient and/or the care giver and/or the healthcare professional.

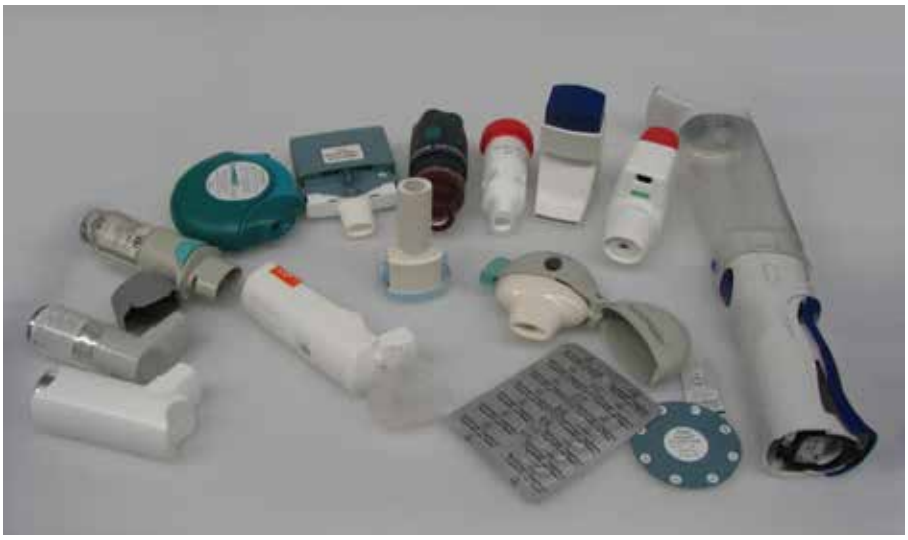
Use of DPI System in Administration of the Therapy

The use of an inhaler device does not differ from the typical use of any other tool or instrument that requires a certain number of operational steps. The first step in the interface with a device is the visual and tangible investigation in order to understand the object and functioning. This assessment is done based on prior experience with similar devices to reduce the level of cognitive demand. The intention is to identify a few dominant visual or sensory cues that fit into any known design model. The use then follows the previous manual proceedings and enables an effortless and intuitive user process. This intuitive user approach bears a high risk of errors or incorrect use that might remain undetected by the patient or lead to short-cuts by skipping steps which might not be seen as necessary for the administration. The issue does not only occur on the patient level, and also affects healthcare professionals or care givers not trained and educated on the devices[4].

Since awareness is growing on the patient as an important part of the intended drug administration process, regulatory sciences have moved towards more involvement of the patients into the device and drug product development process. Human factor design and usability engineering studies into the development of medical devices[5] as well as to consider usability studies in special patient populations provide evidence that the targeted patient population is able to use the product as intended[6].

The Importance of Usability of DPI Products in the Targeted Populations

According to the EMA, usability is defined as "The level to which a medicinal product can be handled in accordance with the product information in the different settings where it may be used, taking into account the variety of patient characteristics, the risk for medication



errors and the burden to the patient and caregiver quality of life." This definition of usability is based on three major elements, which are the handling of the medicinal product according to operation procedures (therapeutic complexity), the environment in which the medicinal product is being used at patient level and the capabilities of the patient populations to handle and operate the medicinal product. For the treatment of respiratory diseases like asthma, COPD and cystic fibrosis, the medicinal product is a combination for the drug formulation and a device, by which the formulation is being administered. Usability of inhalation therapy is a complex interface including a combination of preparative steps and a coordinated inhalation step under the specific disease conditions.

For inhalation therapy, it was found that the rate of correct use of inhalers by patients after at least one month of therapy was very low. The rate of correct usage of DPI was 58.9% whereby pMDI were only used by 31.1% of the patients correctly. Even after educational training on the correct use, the rate increased to 92.6% for DPI and 45.2% for pMDI[7]. The errors in inhaler use were attributed to the device in 50% of the cases, 31% were related to the inhalation technique and 19% were derived from device and inhalation technique[7]. A recent review on medication errors due to problems with the use of inhalers found a statistically significant relationship with patient characteristics such as multi- and co-morbidities, obesity, cardiovascular disease, cognitive impairment and neuropathy[9].

Inhalation errors are associated with worse disease outcomes whereby a reduction in errors over time had improved outcomes for all therapeutic endpoints. Reducing inhalation errors will lead to higher disease control and quality of life for the patients as well as a reduction in the rate of exacerbations, hospitalisations and degree of dyspnea[10].

The Effect of Learning on Inhaler Use

The patients' approach and use of medicinal products and devices is derived from prior learning, intuition and health beliefs. In case of issues with the usability, patients tend to develop their own coping strategies to overcome the issue by their own means and strategies. They generally do this with the best intent or under the impression that it is fully compliant with the instructions for use[11]. The patient information leaflet and instructions for use (IFU), provide patients with the proceedings to use and maintain the inhaler system correctly. Along with, eventually, some training and their own use experience, patients learn to administer the medication through the inhaler system. The routine developed with the use of an inhaler system is then transferred to other inhaler systems intuitively, which means that patients unconsciously apply prior knowledge to a new device that is expected to lead to effective interaction[12]. The intuitive use of patients has been recognised as a potential critical source of errors, when switching from an inhaler product to another, as such generic versions of existing products should not be considered interchangeable unless they are accompanied by intensive patient education programmes to modify the intuitiveness of the patient[13]. After switching patients from one device to another, the rate of unsuccessful treatments increased from 38% to 51%, and the rate of successful treatments dropped from 34% to just 20%[14].

Meeting the Expectations of the Patients

Patients with respiratory diseases are in general requested to manage their inhaler medication themselves. As medical laypersons, they do not feel confident enough with this situation[15]. Education and training play a crucial role in improving patients' capability to administer the therapy as requested by the healthcare professionals[16]. The variety of different inhaler systems and their co-prescription unnecessarily increases the complexity for the patients, as well as the potential sources of errors due to confusion. From a patient perspective, a standard inhaler system would be desirable, which is easy to use, discreet, easy to carry, able to verify that the dose was delivered, providing assurance that sufficient doses remain, as well as being reusable to avoid unnecessary waste. One of the oldest and most commonly used inhalers is the capsule-based Breezhaler, which was optimised a few years ago[17]. In a recent study comparing the six most commonly used inhaler systems, this improved inhaler system was also found to be associated with the lowest error rate by the patients[18] as well as favourable patient satisfaction[19].

Conclusion

Drug administration through inhaler systems remains the most effective therapy to treat respiratory diseases. Compared to oral forms, the administration of inhaled therapeutics is even more dependent on the patients' ability and technique to self-administer the drug product as intended in prevention as well as acute crisis. This requires that patients with a variety of different characteristics can interface with the device and inhaler product more or less intuitively in a correct manner. Intuitive or automatic use is associated with the lowest level of demand from a cognitive as well as handling point of view for the patient preventing errors due to higher complexity. Standardisation and simplicity of inhaler systems should have high priority in DPI product development due to its impact on efficacy and effectiveness. Simplicity of the device will also impact cost of goods and hence accessibility of the medicine in low income countries, as well as contribute to environmental protection by reduced resource utilisation and waste.

As a male COPD patient summarised his expectation very clearly: *"A 'good' inhalation system for me is a system that is efficient, fast acting and easy to use, because when a crisis occurs a state of 'panic' can set in, and so there should be no additional stress with a system that is complicated, and finally it should be correctly dosed and well adapted to the degree of asthma and my pathology."*

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