WHITEPAPER

Why are inhalation devices so difficult to develop?

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Summary

The development of inhalation products is very difficult and therefore seen as time consuming and associated with a high risk. Even though the pharmaceutical companies developing new inhalation products are experienced in the inhalation field, the projects drag out for years due to technical flaws and loop-backs.

The reason for the high cost and long time is the complexity of the inhalation product. A typical dry powder inhaler can be split into four fundamental parts; drug, formulation, manufacturing process and device. The interaction between these four product parts is very complex and their contribution to the performance is inextricable. To this, the operating environment and interaction with the user must be added. Together, these six components give the full performance of the product.

The regulatory requirements on inhalation products are particularly high. An inhalation product must always perform the same way, independently of the user's handling and inhalation effort. Due to the high cost of development, the same inhalation device and manufacturing equipment is often intended for many different inhaled products. This puts another layer of complexity to the development.

Introduction

Today, many conditions are managed with inhaled pharmaceuticals. The route of administration for a pharmaceutical product is determined by the target organ for the drug and other considerations for optimal uptake of the product in the body. The inhaled drug is typically delivered to the nose, airways or lungs using an inhalation device. The main two diseases are asthma and Chronic Obstructive Pulmonary Disease (COPD). The drug is either in a liquid formulation or in a dry powder formulation. There are at present three main device types i.e. pressurized metered dose inhaler (pMDI), dry powder inhaler (DPI) and nebulizers. DPI can come as either a multi dose inhaler or a single dose inhaler. DPI and pMDI are portable inhalers whereas nebulizers are typically stationary inhalers used in hospitals or at home. There are, however, some smaller portable nebulizers on the market. These nebulizers are typically more advanced and expensive, and their market share is, at the moment, relatively small. What all inhalation devices have in common, is that they convert a dose of formulation into an aerosol of respirable particles in the size range of 1-5 micrometer.

The development, manufacturing and registration of an inhalation product is associated with several major difficulties that deter pharmaceutical companies from investing in such development. There are a few major pharma companies that have a strong track record of successful products, but the list is fairly short compared to other dosage forms. This reflects on how the market is structured, with a few major players dominating the market. This is true even though the patents of many major inhaled pharmaceuticals have expired since long, presenting a an opportunity for generic substitution on the market. For a new player, the threshold to enter the market is significant and very few even try. Even major generic companies, with an extensive product portfolio, have great difficulties to build the very eclectic team required to successfully develop an inhalation product and bring it to the market.

Even for an experienced and well-equipped company, such development has proven to be both costly and having lengthy development times. The, perhaps, most significant deterrent is the significant risk of major delays or increased development costs.

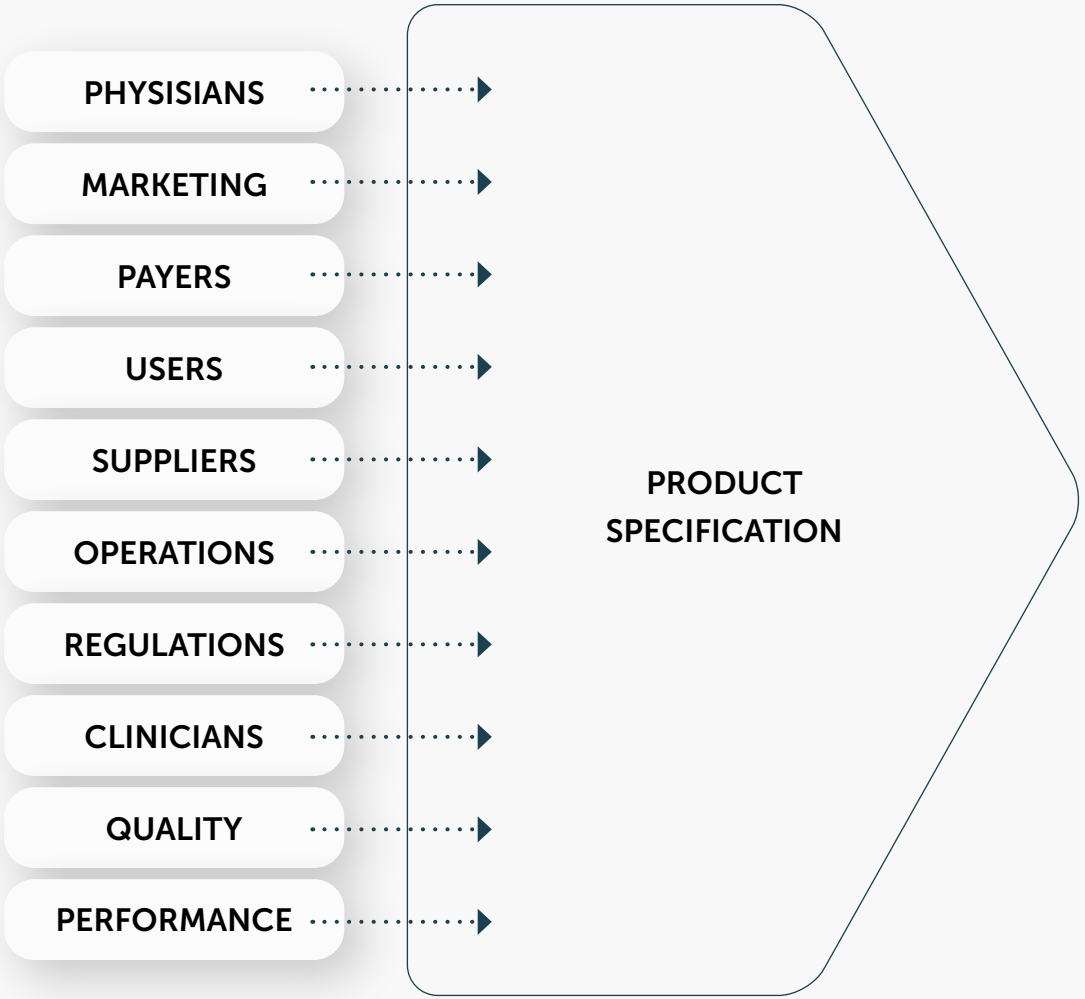
There are four major challenges when developing an inhalation product; conflicting user requirements, product complexity, inextricable performance and the delicate balance between regulatory and manufacturing requirements.

User requirements and conflicting interests

The first key challenge in the development of an inhalation product is to produce a good and balanced specification that voices the demands from users, payers, healthcare and other stakeholders. The specification should be comprehensive and all the requirements must be compatible. All the implications of the requirements should be well analyzed and understood.

There are other important stakeholders in the project than the users, both internally and externally. External stakeholders include healthcare professionals, authorities and payers. Company internal stakeholders and functions should be included i.e. operations, marketing, CMC documentation and the clinicians that will conduct the clinical trials, see Figure 1.

Figure 1
Extended customer definition



The different stakeholders, users and customers will in many cases have very conflicting requirements. Balancing the different needs when compiling a comprehensive specification is very demanding. When a high-level specification is drafted, a number of specific technical questions have to be answered to select appropriate technical solutions. The questions are e.g. dry powder inhaler or pressurized metered dose inhaler, active or passive, electronic or mechanical, pre-metered or reservoir, simple formulation or advanced formulation, large dose or small dose, RH protection or not, few user steps or many user steps, dose counter or dose indicator and many others. These decisions will provide a foundation for future compilation of the specification.

The next step is to map out how the user uses the inhalation product and what drives the different aspects of use. The outcome from user studies typically gives some clear unambiguous results whereas some other results can be mutually conflicting. In some cases, the user has an inconsistent perception of his own personal use and preferences. The highest ranked features are often the various feedback functions. The user requires reassurance from the inhalation device that the dose has

been correctly delivered. It should also be clearly shown exactly how many doses that remain in the device. However, some users perceive too much feedback as complicated and hard to understand whereas others want as much feedback as possible. The device should also be very simple, ergonomic and intuitive to use. It should provide good ergonomics for both to children and the elderly. It should be safe against inadvertent opening or actuation when carried in a pocket or purse but be easy to open and actuated by a person with impaired vision and dexterity. In general, all users agree that the operating sequence should require as few user steps as possibly, ideally open-inhale-close. It should also not be any requirement to clean the device but it should still be simple to clean if so desired.

Another common requirement is that the device should be small, discrete and attractive. This is clearly conflicting with the ergonomics and hygiene requirements. Furthermore, a low-cost disposable device requirement is not compatible with advanced feedback features. A disposable device usually is preferred for simplicity, but the perception of the reusable device is that it is more environmentally friendly. However, a

reusable device is more complicated to use, as it needs reloading and cleaning. A reusable device is also more technically advanced thus more expensive. The overall cost breakeven for disposable vs. reusable device depends on how many times the device is actually reused, which is difficult to predict. The logistics of the refills needs also be factored in. A very important factor is the perception is that the device is safe and reliable. A more clinical and hygienic design comes across as more reliable than a device with a more consumer product like appearance. The clinical and hygienic design is on the other hand less attractive. The device should preferably be attractive to all age groups, from children to octogenarians. A typical market lifetime of an inhalation device is at least 10-20 years, which means that a design should appeal to all ages and sexes over a very long period of time. A typical feature sought after by patients and doctors, is electronic feedback and monitoring. The real benefit of this feature is, however, unclear. The device could remind the patient to take the medicine, monitor e.g. the lung function and automatically upload the data to the prescribing doctor. Although this seems to be a useful feature, it is easy to imagine the patient being annoyed by the constant reminding and seeing the data uploading as an invasion of privacy. Not all doctors can be expected to appreciate the benefit of receiving gigabytes of patient information.

Product complexity

When the product specification has been agreed, the multidisciplinary product development project can begin. An inhalation product is very complex and comprises many fundamental parts that each present their own challenges. The development of the different parts require very different sets of skills and is often done by different teams. The number of parts can of course be debated but in this paper the product has been split into 6 fundamental parts, see Figure 2

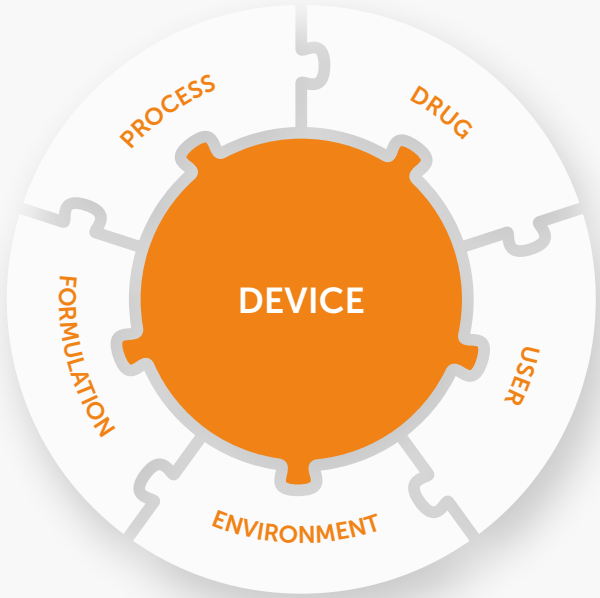


Figure 2
Fundamental parts of an inhalation product
The different parts are intimately interlinked, and all contribute to the function and performance of the product. The device, drug and formulation are physical parts of the product whereas the user, operating environment and manufacturing processes are more abstract parts.

Drug

The main objective of an inhalation product is to deliver the drug to the patient's nose, airways or lungs. Therefore, the drug drives many of the other features and requirements. The chemical and physical properties together with the pharmacodynamic and pharmacokinetic properties of the drug are the key selection criteria when developing the product. These factors also have a strong impact on the formulation type to be used and the most suitable type of device. The potency of the drug drives the dose size and drug content in the formulation. The drug also dictates what kind of protection is required from the device e.g. moisture, light, oxygen etc.

User

Another part is the user or patient. The patient population with diseases that can be treated by the delivery of a drug to the lungs is very heterogeneous and is expected to be even more so in the future. Patients with asthma, who are traditionally treated by inhaled drugs, have been using inhalation devices since childhood. Patients with COPD are, however, often introduced to inhaled therapy at a mature age. When developing inhalation products for this wide and heterogeneous and sometimes multi disease patient population, the patient needs and preferences must be thoroughly investigated and understood. This includes not only hard parameters like inhalation effort, inhaled volume etc.,

but also soft parameters like handling, dexterity, user interface etc. The best way of collecting this type of information is to conduct extensive user studies. Such studies should include both practical tests of usage of different inhalation devices and interviews. The test groups must be sufficiently large and representative in terms of age, gender, disease and prior inhaler experience. The studies should preferably be conducted in all countries where the product is intended to be launched. In addition to patients, also health care professionals, e.g. nurses and doctors should be included to give their perspective. It is obvious that such an extensive study will be very costly and time consuming. The study can be reduced if a body of knowledge is available within the company, which has been gained by long tradition and experience from products on the market. A great deal of information can also be accessed in the literature. However, there is an obvious risk associated with a too retrospective approach when developing new products for new patient groups.

Environment

The inhalation product will be used in many different climates in terms of relative humidity and temperature. The product will also be stored at these conditions for an extended period of time. Many products have a shelf life of two years and in-use life of several months. The drug and formulation must thus be chemically and physically stable during this period of time and the device must provide sufficient protection. The question is whether the device provides sufficient humidity protection or if an additional Al-over wrap is required. There could even be a need for a desiccant in the device or in the Al-over wrap. A critical question is whether the device should be adapted or if the moisture sensitivity can be managed by formulation modifications.

Formulation

The formulation is in a sense the "blood" of the inhalation product. The function of the formulation is to enable the handling and delivery of the drug to the patient. The formulation is very sensitive to the quality of the various ingredients, the composition and the properties of the drug. The development of a formulation also includes the selection of process equipment e.g. mixer and the optimization of all the running parameters. When developing an inhalation product, the ambition is often to use the same type of formulation with many different drugs in the same device. There are many different types of formulations, and they require the appropriate device. The device and the formulation are intimately interlinked and must be developed and optimized together.

Device

The device is what brings all the other parts together. The device should accommodate all the requirements of other parts e.g. ergonomics, performance, stability, robustness and manufacturing. The role of the device is to house and protect the formulation and meter-disperse-deliver the dose. The design of the device is also the user interface and defines the user sequence. Industrial design is used to develop the exterior shape, graphical design, texture, visual expression etc. All the mechanical requirements e.g. tolerances, assembly sequence, manufacturing processes, materials are also defined by the device. It is obvious that a thorough knowledge of all the other five parts is required in the development of the device. Developing a device includes all the traditional mechanical design tasks that are common to all complicated plastic devices. However, in an inhalation device, several tasks and challenges are added. Things like flow resistance, drug retention on the surfaces and a fluid dynamics must be included and addressed. To succeed with such a multi-disciplinary development a very eclectic team must be formed.

Process

When the formulation is filled into the inhalation device, some kind of filling equipment is always needed. The filler must be compatible with the both the formulation and the device. It should also be compatible with variations of the formulation when a different drug is used. The filling and other processes like heat sealing will be a strong contribution to the manufacturing yield and also the manufacturing capacity. The total cost of the product is also strongly dependent on the manufacturing processes and the process equipment. Much of the CMC documentation is related to the various processes that require extensive validation and verification. Due to the high cost of development, the same inhalation device and manufacturing equipment is often intended for many different drug products. This puts another layer of complexity to the development. A major challenge is the journey from simple bench-top technical equipment used during development, to GMP equipment to produce the clinical trial supplies, and the finally a high-capacity commercial equipment. It is a delicate task to balance development risk against financial risk. From a development point of view, it is advantageous to as soon as possible scale-up the process to reduce the risk. From the financial point of view, it is preferred to delay the investments as much as possible to reduce the financial risk.

Inextricable performance

The different parts discussed above interact and together give the performance of the product. The interaction between the physical product parts is very complex and their individual contribution to the performance is inextricable. To this the interaction with the user is added. Pharmaceutical products are highly regulated and the inhalation product must deliver the same performance independently of the user's inhalation effort and inhalation profile. The dose from an inhaler can be described in terms of delivered dose, respirable dose and respirable fraction. To maintain the same respirable fraction, the particle size distribution must be the same for every dose. In order to achieve consistent particle size distribution, the formulation must be consistent and the device geometry variations very small. To have a high delivered dose uniformity, the properties of each individual dose must be the same for each inhalation, each patient and each manufactured batch. It must also remain the same over time, independent of the storage conditions. When an inhalation device is intended as a platform for many different drug products, the performance should be the same for all drugs and all dose strengths. It is needless to say, that it is extremely challenging to meet all these performance requirements and performance testing is the most labor intensive task during development.

Regulatory vs. manufacturing requirements

The regulatory requirements have a strong focus on patient safety and consistency of performance. The patient should always get the same dose irrespective of how the inhalation product is used and how it has been stored. The regulatory requirements drive the complexity and quality standards of the inhalation product. When designing the mechanics of an inhalation device, there are two sets of requirements. One set is the functional requirement i.e. the mechanical function of the device. This requirement has the nature of pass fail, either the inhalation device fits together and works according to specification or not. If the design fails these tests, the product cannot be approved and launched. The mechanical function can be tested and verified without the formulation. The design should be robust enough to be able to accommodate small dimensional variations without failing. The allowed dimensional variations are defined as tolerances. To reach a high yield or process capability, Cpk, which is desirable from a manufacturing and cost point of view, the tolerances should be as wide as possible.

The other set of requirements is performance requirements. Performance requirements must be tested with the formulation and include e.g. delivered dose uniformity, fine particle dose, chemical and physical stability etc. The actual value in the requirement is not absolute and is a matter for clinical trials and discussions with regulatory agencies. There are guidelines to adhere to, but many performance requirements are not covered in the guidelines.

There is a conflict emanating from the two sets of requirements. For instance, some dimensions in the inhalation device require one tolerance for the mechanical function and a different tolerance for the performance. As an example, the functional tolerance could give a high Cpk of e.g. 1.8. This is the process capability of a mechanically functioning inhalation device i.e. no formulation included and no pharmaceutical performance tested. This variation in dimension could, however, lead to a high variability in performance. This could, as an example, be the gap between two parts forming a duct. The duct has no mechanical function but governs the dispersion of the formulation and the inhalation resistance. To achieve acceptable performance uniformity this tolerance must be tighter. The new tolerance will, however, decrease the Cpk to e.g. 1.5. It can be the case, that the uniformity can be improved even more, decreasing the Cpk to 1.0. A low Cpk will lead to a high manufacturing cost. The increased manufacturing cost will in the end reflect on the price and profitability of the product. The higher cost will eventually be covered either by a lower profit margin of the producer or a higher cost for the payer. The sponsor is facing a delicate trade-off between performance and cost.

Conclusion

The development of an inhalation product poses many severe challenges. Most of the challenges have the origin in the complex interaction between the different parts of the inhalation product. In order to keep down the development costs and minimize the project delay, it is important to have a thorough understanding of the inhalation product. This requires good combination of skills including pharmacy, engineering, chemistry and physics. A good understanding of the regulatory requirements together with clinical and pharmacological experience is also very valuable. This required skill-base should be considered when forming project teams. A key challenge is to set up a relevant and comprehensive product specification for the inhalation product. It is time well spent to have a thorough analysis of the various consequences of each requirement. An incompatible or over ambitious set of requirements can have tremendous ramifications on the development. The consequences may not become obvious until late in the development and then lead to extensive redesign and delays.

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Over 30 years' experience inhalation development, mainly from AstraZeneca. Invented more than nine different inhaler devices and been involved in the development of 13 different inhaler devices. More than 40 patent applications and has published several research articles and books. Also co-authored the ISO standard for inhaler devices and is a frequently invited speaker at inhalation conferences. Founder of Iconovo and CEO 2014-2020.

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