DPI development: Understanding the technical challenges

DPIs are challenging to design and should not be viewed merely as "packaging."

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The first commercially-successful dry powder inhaler (DPI), which entered the market more than 40 years ago, was developed by Dr. Roger Altounyan, a former Spitfire pilot, medical doctor and asthma sufferer, who was inspired by the propeller on his fighter plane to develop the Spinhaler, marketed by Fisons Limited. This small DPI used a tiny impeller that drew energy from the patient's inspiration to spin and whirl powder out of a pierced, standard gelatin capsule to create a respirable aerosol, thereby solving the coordination issues experienced by many users of pressurized metered dose inhalers (pMDIs). Eliminating the need for bulky spacers also made the Spinhaler easier to carry and more discreet during use, thereby encouraging greater patient acceptance.

DPI development has moved on significantly since the Spinhaler's launch and the inhaler market continues to grow. Asthma diagnoses are increasing, especially in the rapidly-developing regions of the BRIC countries (Brazil, Russia, India and China), while opportunities for pulmonary delivery are also emerging in various therapy areas, such as chronic pain relief and diabetes management. The DPI also has great potential as a pain free alternative to injection, opening up new opportunities in areas such as mass vaccination, where DPIs could deliver significant cost, safety and hygiene benefits.

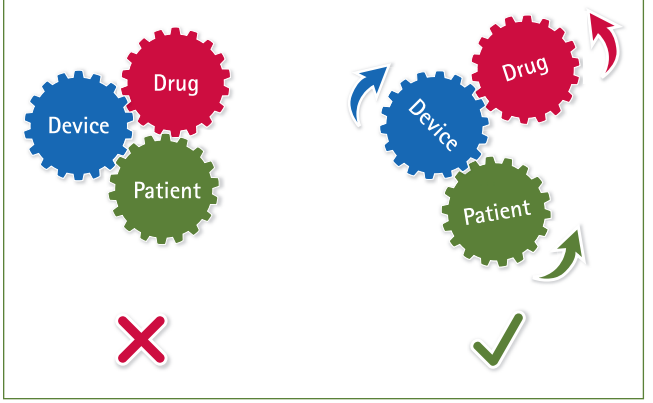
At present, DPIs are used primarily for asthma and chronic obstructive pulmonary disease (COPD) therapies. GlaxoSmithKline's market-leading Diskus device has set the performance benchmark for many years, but the emergence of new markets, together with the imminent expiry of key drug and device patents, indicates that DPI development has gained new impetus. However, despite these commercial opportunities, the launch of a new DPI remains a rare event, and the success rate of a typical DPI development currently stands at around 10 percent. So why is DPI development so difficult?

Varied and diverse challenges

When approaching a DPI development program, R&D teams often appear to be surprised by the wide and diverse range of technical challenges involved. Efficient internal communication between the groups responsible for formulation development, device design, regulatory affairs, marketing and commercialization is absolutely essential. Without it, there is a danger of silo mentality, with each group believing they have sole responsibility for the success of the product. In reality, all aspects must be satisfied; they are equally important. The device is the interface between the user and the drug. The way the user interacts with it almost always affects how well it performs and ultimately how much drug is delivered (see Figure 1).

Figure 1

For the relationship between the user, the drug and the device to work successfully, the device must be considered as a true interface.



Of course, the ultimate DPI would operate 100% effectively for every user. This is an idealized target, but unfortunately not one that the current state of the art is near to achieving. These following challenges must be sufficiently analyzed and understood before a new DPI can enter the market successfully:

Understanding device performance

The complex physics underlying a dry powder inhaler is still not well understood, making new device design a particular challenge. A DPI can be very difficult to model when the relationship between each drug and device is unique,[1] requiring numerous simplifications and assumptions to be made. However, such reduced order modelling is extremely useful in building an understanding of the complex interaction between the patient and the device, as well as between multi-component powder formulations and the convoluted airways or "aerosolization engines" typically found within a DPI. This complexity is underlined by current (and highly successful) DPI efficiency rates of as little as 25% in controlled *in vitro* test conditions and perhaps even lower in real use if the user compromises performance, for example, by inhaling too gently.

The influence of drug formulation

The powdered drug formulations used by DPIs offer many benefits: i) they are easier to manufacture and store ii) once packaged, they are usually more stable and consistent than the fluid-based formulations used in pMDIs. Dry powder also avoids environmental concerns related to pressurized canisters and propellants. However, even though a powdered drug may be easier to handle outside the DPI, moving the drug from bulk storage to device and then into the respiratory tract is not so simple. In a DPI, the correct dose must be delivered every time, irrespective of the environment in which the device is used, the way the patient inhales or whether the dose is the first or last within the course of treatment. Powdered drugs cannot suffer from preferential segregation during manufacture or storage, and once in the device, must not be over sensitive to changes in the environment, particularly at extremes of humidity. The technical challenge required to maintain such sustained control across a broad range of conditions is one that many R&D teams, perhaps unsurprisingly, find hard to meet.

Usability

Usability has always been important but, under new guidance, has now become a regulatory imperative. To gain approval, a DPI must be safe; intuitive and easy to use correctly; and difficult to use incorrectly, a significant challenge in itself, given that users span such a large range of age and ability. Usability will become even more important as new markets open up, for example, where there is no cultural "history" of inhaled therapies or no time for users to develop or practice their technique (e.g. if a DPI is used for a vaccination or to deliver a single dose therapy). As the technical challenge differs for each application, development teams must understand—and in some cases predict—drug, device and user interaction from the start of the development process, otherwise the end result will not meet the usability goals.

Regulatory drivers

As DPI regulation is constantly evolving, a good device design must not only meet current standards but also plan for future regulation by meeting published guidance. BRIC countries and others are also tightening regulatory procedures in the face of both domestic and international pressure, making entry to these huge markets even more challenging. Basing DPI design on existing devices is not always an option, as many current and successful DPIs would not gain regulatory approval if put forward as new products today. Instead, R&D needs to innovate while planning ahead; understanding user's current and future needs while also incorporating new advances in technology where appropriate. Cautionary tales of poorly designed DPIs abound within the sector, but the example of the Ultrahaler, by Fisons Limited, is better known than most. Its innovative technology, relating to both the device and its manufacture, could not keep pace with regulatory change. After 19 years of development and investment, and still no approval, the development program was terminated.

"Only" packaging

Even though the high failure rate in DPI device design underlines the difficulties inherent in the process, many companies continue to see the DPI as "packaging" and consequently treat it with less respect than it deserves, or indeed requires. If this mindset is the starting point for an R&D program, then the process will undoubtedly fail.

Technical challenges can be met

GSK's market-leading Advair Diskus device has remained essentially unchallenged for 15 years, a position of dominance won by a highly innovative, robust and effective device designed to work with specific formulations. Such precision has been rewarded with significant market share, but as key formulations come off-patent, newcomers show that this market can now be challenged.

For example, in 2010, Sun Pharma announced the imminent launch of a new DPI design, the Starhaler (see Figure 2), developed to work with a generic version of an off-patent formulation. Sun Pharma acknowledged the significant technical challenge ahead when it began its development program. It responded by funding a comprehensive, reduced order mathematical model,[2] which allowed the R&D team to run virtual tests and analyses on the design parameters quickly and effectively, and which could also be used in the development of future designs. By innovating rather than replicating,

Sun created a device that meets and exceeds current standards and guidelines. As a result, the Starhaler achieves almost double the efficiency of current market-leading products, but perhaps more importantly, achieves this high performance independently of the quantity of inspiratory energy. If patients have impaired lung characteristics, for example, they will still receive the correct dosage.

Another example of a successful DPI development is the Aptar Prohaler (see Figure 3), which addresses the challenge of usability by achieving an extremely simple usage sequence: "Open, Breathe-In, Close," based on Aptar's "OBIC Technology." Aptar Pharma wanted to develop a multi-unit dose DPI that could meet the requirements of the asthma market and was extremely easy and intuitive to use. It also had to be very difficult to use incorrectly. Consequently, this inhaler was developed with the patient in mind.[3] Formative usability research was undertaken to establish suitably intuitive user-interaction principles, which included a combination of visual and tactile feedback indicating correct use (see Figure 4). A strong visual language for the device played a key part in supporting the three-step operation and would appeal to user groups while being adaptable for potential pharmaceutical partners' varying brand requirements. The result is a compact, distinctive device with an incredibly simple usage sequence.

Scientists and engineers working on the Spinhaler realized that while there is ample inspiratory energy available to create a respirable aerosol, the means to harness this energy may not be obvious. The Spinhaler, and indeed many other capsule inhalers, tend to extend the timeframe during which energy from the patient's inhalation can be transferred into the powder formulation. This is also true of multi-unit dose and reservoir DPIs that use swirling flow to extend particle path lengths and increase residence time, thereby increasing the total quantity of energy imparted into the formulation and improving efficiency. Research into the energy

Figure 2

The Sun Pharma Starhaler is an innovative device that achieves high performance, independent of the patient's inspiratory energy. (Photo courtesy of Sun Pharma Advanced Research Company Ltd. and Cambridge Consultants.)

Figure 3

The Aptar Pharma Prohaler has an extremely simple usage sequence: Open, Breath-In, Close. (Photo courtesy of Aptar Pharma.)

Figure 4

This visualisation of Aptar Pharma's Prohaler was created as part of a color study to explore visual language and brand differentiation. (Photo courtesy of Team Consulting and Aptar Pharma.)

required to disperse and aerosolize several milligrams of typical powdered drug formulation indicates this is several orders of magnitude less than that available from a patient.[4] As collective understanding of the physics in this area grows, it is likely that future passive DPIs will use available energy more effectively and achieve higher delivery efficiencies with greater consistency.

Significant market opportunities

A successful DPI device is one that meets the wide range of technological challenges underpinning efficiency, usability, and regulatory approval, while also interacting effectively with a specific formulation. The breadth and depth of skills required to deliver this level of performance are frequently underestimated by R&D teams. This lack of appreciation is one of the principal reasons so many DPI development efforts fail. Substantial investment is required to develop a DPI which is technically robust, meets current and future regulatory standards, and which patients actively want to use and can use with improved efficiency. However, given the growth of inhaled drug therapies for a wider range of conditions, the commercial and moral rewards are clearly worth the investment.

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