

# DPI Technologies: Time for a Rethink?

By Rob Clayborough and Iain Simpson at Sagentia

Although DPI technology has advanced since its first introduction, effectiveness has been compromised by a poor appreciation of patient need. But with compliance now increasingly important – and huge potential markets emerging – is it time to radically rethink DPI design?

DPI technology – the dry powder inhaler – dates back to the Spinhaler, launched by Fisons in the late 1960s (see Figure 1). This device represented a step change in drug delivery for the control of asthma, and also a catalyst for other DPIs, introduced for the treatment of additional pulmonary conditions such as chronic obstructive pulmonary disease (COPD). A key driver in the development of DPIs was the need to reduce coordination errors frequently encountered with the already existing pressurised metered dose inhalers (pMDIs). Since the Spinhaler, however, technology development has been incremental, often *ad hoc*, and seemingly driven more by regulatory requirements than by patient need. In addition, the drugs used within DPIs (typically bronchodilators and corticosteroids) have changed little during the last 30 years, making inhaler design one of the few ways that a pharmaceutical company can achieve market differentiation.

This has resulted in a landscape where multiple DPIs co-exist, similar in function but different in operation. This causes confusion for prescribing clinicians, and compromises compliance if patients are not taught how to use an inhaler properly. As a result, the compliant use of

DPIs is now causing as much concern as that historically associated with pMDIs.

### TECHNOLOGY TIMELINE & KEY DRIVERS

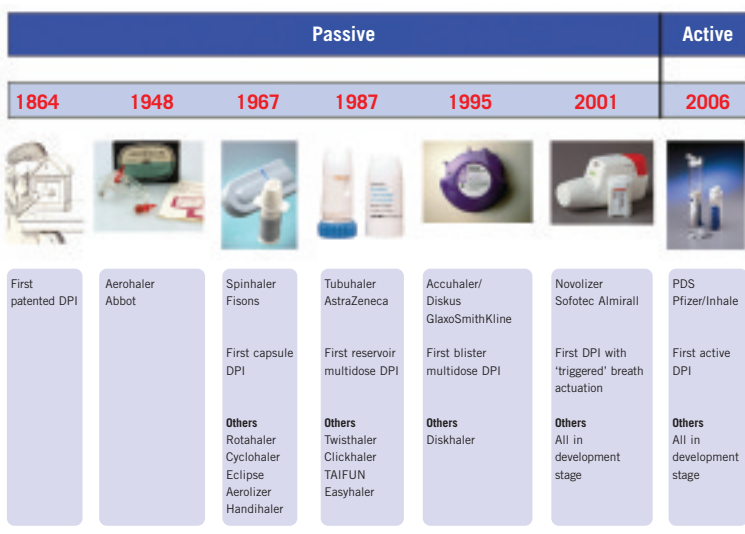
Why was the Spinhaler such a breakthrough? The technology behind the Spinhaler design was a step change because it allowed the delivery of powder formulations to the lung via the use of a capsule containing a relatively large mass of the powdered medicament. The Spinhaler (and subsequent DPIs) minimised the need for accurate coordination by the patient, while also giving manufacturers the opportunity to formulate powders, which had important advantages regarding shelf-life stability. Furthermore, the use of capsules allowed standardised filling technologies to be incorporated into the manufacturing process.

However, DPIs such as the Spinhaler and its successors (such as the Rotahaler, Aerolizer, Eclipse and, more recently, the HandiHaler) are not without issues, such as the requirement for patients to manually load small capsules into the inhaler. Furthermore, in 2008, the US FDA issued further advice, this time regarding the correct usage of capsule-based DPIs, as some confusion had been shown by a small patient population that had been swallowing the capsules rather than loading them into the inhaler.

These technological developments also need to be viewed in the context of regulatory changes and issues of compliance. For example, the Montreal Protocol, enforced on 1 January 1989, prompted the phasing-out of CFC-based inhalers, and their subsequent reformulation into HFA equivalents. This was, at first, expected to be a relatively easy task – in fact, it was much more onerous to undertake this reformulation, borne out by the recent FDA announcement that only now will all CFC-based pMDIs be removed from the US market, a process which will take place over the next 12 months.

Regulation is also focusing increasingly on compliance, especially in the US where reimbursement plays such a

Figure 1: A brief DPI timeline



crucial role in healthcare provision. Compliance is a major factor in the effective management of disease state, and Barnes *et al* estimate that up to 75 per cent of the total cost of treating asthma could be attributed to poor control of the disease, often leading to quality of life issues (1). Drug delivery technologies that can improve compliance are therefore becoming an increasingly attractive option for both patients and healthcare providers. In the case of DPIs, however, user compliance remains a crucial issue, even following the incremental improvements made so far, and resolving this issue is becoming an industry imperative.

### **USER DIFFICULTY**

In 2008, market share for DPIs for the treatment of respiratory diseases was almost 60 per cent, representing sales of \$14,000 million, with annual DPI sales expected to increase over the coming years (2). Yet studies have consistently shown that a significant proportion of DPI users inadvertently misuse their inhalers, struggling either to prepare the inhaler, or to inhale correctly in order to aerosolise the drug and deliver it to the relevant areas of the lung. In addition, users may not store their DPI correctly, or fail to maintain a regular dosing regimen.

This level of misuse rises dramatically with increased disease severity, and with age, with misuse levels highest (even after training) among patients over 60. A study by Weishammer and Dreyhaupt found that for a range of commonly used DPIs the error rate within the 60 to 80-year age group was 41.6 per cent (3). Reasons include cognitive issues, lower dexterity, visual impairment and other related conditions, and these effects are reportedly exacerbated in COPD patients. This is a major concern because the prevalence and diagnosis of COPD is on the increase, and it is predominantly a disease of the elderly, currently mainly treated via the use of DPIs such as Spiriva/Boehringer Ingelheim (\$3,000 million sales, 2008). With new emerging markets and an ageing population with longer life expectancy, there is a real requirement for compliance driven by easy to use and intuitive DPIs.

Similar issues concerning misuse and non-compliance are also found in children, particularly those in the age range of two to six years, where the use of nebulisers tends to dominate as these devices work with normal breathing, rather than a more specific inhalation manoeuvre. However, owing to longer administration times for nebulisers combined with typically short attention spans within the paediatric population, such an approach can be considered to be sub-optimal. Consequently, this could be another opportunity for the development of a 'tailored' DPI.

It is only in the six to 60 age range that it is generally accepted that patients have sufficient physiological capability to use the currently existing DPIs adequately, but only if proper training is provided and is regularly refreshed. Weishammer and Dreyhaupt found that for a range of commonly used DPIs the error rate within the below 60-year age group was 20 per cent which could still be argued as being far too high (3). Furthermore, DPIs designed for adult use may not be well matched to the inhalation capability and throat physiology of children (4).

Inability to use a DPI correctly is not the only patient error encountered. The industry also needs to focus on patient instruction leaflets, for example, where a simple and clear description of operation is provided, perhaps in pictorial form, thereby eliminating subtle differences in language. Furthermore, elderly patients frequently encounter difficulties in opening packaging materials, and so a focus on 'senior friendly' packaging is essential.

Overall, it is clear that current DPI designs fail to recognise the problems many users experience, or the segmentation that exists within the user group (based on differences such as severity of condition, lifestyle, attitude to long-term therapies or even human physiology). In addition, the industry should not just limit usability issues to the inhaler itself in order to address the challenges with patient compliance.

### **WHY PERSIST WITH DPIs?**

With multiple similar but different inhalers actively confusing both the medical and patient communities, and compromising compliance, why persist with DPI technology?

Many advantages – physiological, technical, practical and commercial – continue to make the inhaler the drug delivery method of choice for millions of patients around the world, who form a growing market currently worth around \$31,600 million, \$23,900 million of which is generated from the treatment of respiratory disease (2). The pulmonary route allows access to a target organ that has a large and highly vascularised surface area with the potential for rapid drug uptake to the systemic system, thereby minimising first pass metabolism effects. From a technical perspective, powder formulations offer greater flexibility to the formulator, in addition to eliminating the need for propellants and the associated challenges of formulating stable propellant systems. Inhalation is much preferred to injection, especially for long-term courses of invasive treatment, and it is the non-invasive nature of the DPI (and the pulmonary route as a whole) together with

a non-ballistic aerosol component, that makes the DPI ideal for drug delivery to the lung.

From a commercial perspective, DPIs represent a huge, long-term, and lucrative market – and one that is expected to grow. COPD sufferers, for example, tend to be older people who have smoked, lived in highly polluted environments, or have been occupationally exposed to dusts and chemicals of the type found within the mining, textile, chemical and welding industries. In the West, the causes of COPD are now being controlled, but in emerging economies, such as China, where workplace conditions are often poorly regulated, and smoking increasingly popular, a rise in COPD will undoubtedly occur. As these populations become more affluent, their desire to access better medications will increase, and as such the uptake of DPIs used for the treatment of both respiratory and non-respiratory diseases will grow. The opportunity to self-administer drugs is also a great advantage in regions where access to institutional healthcare is limited.

#### **A RETURN TO PATIENT FOCUS**

There is clearly a need to address the usability issues currently affecting DPIs if users are to fully gain the benefits offered by the technology, compliance issues are to be satisfied, and huge new markets accessed.

One option would be to increase the sophistication of the 'standard' inhaler, in order to meet these challenges. However, would this risk increasing the usability issues of those older patients? Whereas younger users would know how to operate a 'smart phone-like' gadget, older users, often already physically impaired, can be highly resistant to adopting 'new fangled' technologies that they find hard to comprehend, and that would affect their confidence when using the new inhaler. Instead, an opposing, simplified approach may be to return to basics and create a simple, generic platform DPI technology – a standard delivery method using a standard 'aerosolisation engine', incorporating the fundamental principle of ease of use and clear feedback. The caveat is that for a return to basics, the fundamental physics governing the key parameters underpinning its operation are fully understood and appropriately used in the device design.

Specific adaptations could then be made to meet the needs of key target groups. DPIs for older users, for example, would only need limited manual dexterity, and would operate at a lower airflow rate with the aid of an active mechanism that promoted particle dispersion – also very appropriate for paediatric use. More complex

designs could be developed to ensure greater security in the delivery of higher value or controlled drugs, such as opiates, and could incorporate electronics to control parameters such as flow rate and orientation, in addition to feedback mechanisms that would reassure patients that a therapeutic dose had been delivered.

A change in DPI technology could also allow a broader or even a new approach to drug formulation. As particle engineering becomes more sophisticated, there may be the opportunity to administer pure drug only without the need for excipients. Alternatively, improving the physical properties of carrier particles by, for example, increasing their physical size while maintaining their aerodynamic diameter, may improve consistency of delivery, enhancing the fine particle dose and thereby improving bioavailability and possibly causing fewer side effects. Combining the parallel approach of new formulation development methodologies with an improved DPI design – able both to retain the carrier particles and reduce both the flow rates required and the associated flow rate dependence – may benefit both the safety and efficacy of inhalation products.

A DPI using a standardised aerosolisation engine would also offer great potential for the delivery of a much wider range of other therapeutic drugs, not just those designed to treat respiratory conditions. The increased speed of onset of action afforded by the pulmonary route offers great potential for pain management, for example. This speed is highly desirable in the treatment of conditions such as breakthrough cancer pain, as well as for more acute conditions such as short duration lower back pain, or migraine where rapid symptomatic relief is needed. Antibiotics, antivirals, vaccines, insulins, triptans, anti-cancer agents – and more – could also be delivered this way.

#### **FIRST STEPS TOWARDS A BETTER SOLUTION**

Even though a standardised solution may be some way off, immediate changes could still be made to return focus back to the user (while still recognising the need for compliance) and research is already underway in some of these areas.

Improving user feedback, for example, could be achieved perhaps by enhancing the physical sensation accompanying correct usage. A more refined solution may be to incorporate simple and cost-effective sensor technology into the DPI (or alternative pulmonary delivery systems) enabling the inhaler to report accurately on usage patterns both to the patient and clinician. More importantly, such a design would also

provide reassurance to the patient that a dose had been correctly administered, while also giving reimbursement bodies and health authorities the necessary proof that resources are not being wasted.

The ubiquity of the DPI may have led to complacency among users and the pharmaceutical industry, but the inhaler remains a highly effective and low cost means of delivering essential, life-changing therapies. A fundamental re-design, that places the patient first, could challenge the issue of misuse, and therefore compliance, while also improving the quality of life for many more users. With a huge and growing potential market, there is now a real opportunity to make the DPI even more successful.

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