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Direct-Haler: refined thinking that could transform the pulmonary delivery market

The trend in the field of pulmonary drug delivery, driven largely by increasing requirements for performance and patient-friendliness, is for high-tech, high-cost devices which, however easy to use, have increasingly complex designs. Current thinking is that healthcare providers should expect to pay a premium for efficient pulmonary delivery via inhalers with multiple, precision-engineered moving parts, often including electrical and electronic components. The cost of such devices in terms of R&D activity and partnerships determines this and the knock-on effects on market economics are determined accordingly.

To toss into this arena an inhaler with two non-moving, plastic components and negligible manufacturing costs, but whose performance rivals current pulmonary devices, would cause quite a commotion in the respiratory drug delivery community. The business models of pharmaceutical companies that had paid dearly to bring in specialist pulmonary delivery partners, and integrated significant device manufacturing expenses into their budgets, might also need a rethink.

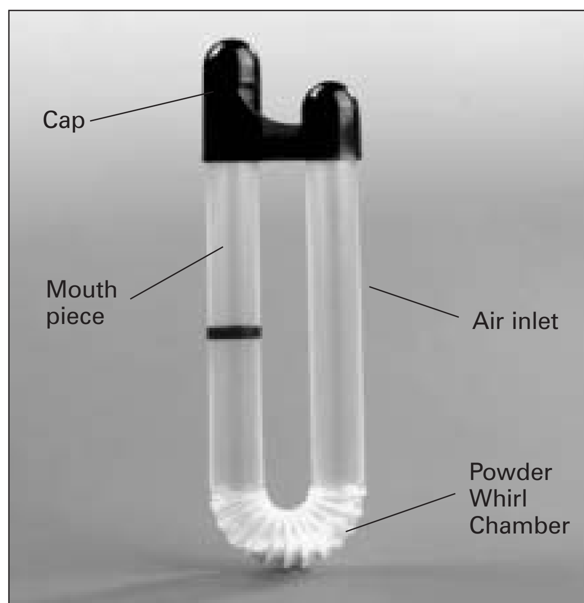

Figure 1. the Direct-Haler pulmonary device

The family-owned, family-funded drug delivery company, Direct-Haler, based in Copenhagen, Denmark, says it is developing such a device. Its founders, Erik Keldmann and son Troels Keldmann have released details of their invention exclusively to *Target*. It is the first time they have presented their technologies in depth outside a confidentiality agreement.

However straightforward the Direct-Haler's design might be, the thinking behind it is sophisticated

Direct-Haler is a prefilled, single-use disposable dry-powder inhaler (DPI). Weighing less than 0.6 g, it consists of two polypropylene parts – a U-shaped tube with a corrugated bend and a double cap that seals each end of the tube (see Figure 1). The powdered dose is contained within the tube and rests at the bottom of the bend. The opening at one end of the tube is the mouthpiece and that at the other end is the air intake. To use the Direct-Haler, the patient takes the cap off the device, puts the mouthpiece in his or her mouth and breathes in.

Even acknowledging that among the fundamental facts of life is that uncomplicated ideas are often the best, it is easy to think that Direct-Haler has taken things to an absurd extreme. But to summarily discount this inhaler, which looks like it has been made by cutting the end off a "bendy" drinking straw like those found in fast-food restaurants, would be naïve.

However straightforward the Direct-Haler's design might be, the thinking behind it is sophisticated, and has taken due note of the many complex considerations of delivery via the respiratory route. The Keldmanns decided on a single-use, dry powder approach. They identified four key functions necessary for such an inhaler to facilitate pulmonary delivery and they developed Direct-Haler in relation to each of these.

The most important factors concern efficient powder delivery. First, the patient-generated air flow must be sufficient to carry the powder into the lungs but slow enough to be comfortable. The diameter of the tube is therefore such that inspiratory resistance is balanced.

Secondly, the inhaler design must ensure that the powder disperses on delivery. Adequate protection against moisture is a pre-requisite and the Direct-Haler's cap achieves this. During inhalation, turbulent airflow is required to disperse the particles effectively. The corrugated section at the bend in the tube – the Powder Whirl Chamber – lies at the heart of the device's effectiveness and forms a key part of its patent protection.

Delivery from a smooth tube results in most of the powder exiting the mouthpiece as one aggregated clump and the rest remaining undelivered, which is useless for pulmonary delivery. However, the Direct-Haler delivers the complete dose gradually over one inhalation as a well-dispersed powder. Figure 2 (see page 20) shows the process. The Powder Whirl Chamber generates recirculation zones – whirls of turbulent air – that force the powder resting at the bottom of the "U" to climb up the inner walls of the chamber from where it is gradually carried off into the airstream. The corrugations have direction: the steep edge provides a barrier to the powder entering the airflow immediately. 11-12 corrugations were found to give optimal powder dispersion.

The third function identified was that the inhaler design must protect the

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oral cavity from drug side-effects. Many inhalers on the market include instructions for users to rinse their mouths after use, but the Direct-Haler's design aims to eliminate this problem.

Again, there is a sense of nagging scepticism but it became clear that the rationale was solid. Troels Keldmann explained that medication exits conventional inhalers near the patient's teeth because of the short and wide mouthpieces, and thus has to travel through the mouth and along the length of the tongue.

In contrast the Direct-Haler's mouthpiece is slim and long.

Its narrow diameter, similar to that of a drinking straw, meant that patients felt comfortable inserting it some way into the mouth, he said. Powder therefore leaves the Direct-Haler nearer the back of the mouth. Furthermore, the design takes advantage of the tongue's reflex of lowering when something touches the top of it. When the Direct-Haler's tube is in the mouth, the tongue is depressed, leaving the already-shortened route to the trachea direct and open.

The final key function was that the device must be easy to handle, and promote compliance. In a similar way to a cigarette, the Direct-Haler lends itself naturally to being picked up and held correctly and the device does not have to be positioned exactly in order to function. Studies have shown little effect on delivery efficiency when the tube, which is flexible because of the corrugated region, is bent to form a wide "U" or a narrow "U" during inhalation.

The device is transparent so that the dose is visible. After use, the absence of powder gives a direct visual indicator that the dose has been administered successfully.

Another important concept behind the Direct-Haler is that, because it is small, cheap and disposed of after one use, the patient does not carry it about in the same way as a multi-dose device. Erik Keldmann used the phrase "multi-place inhaler".
An asthmatic might take a few Direct-Halers for his bronchodilator medication in his pocket, but would also leave some at home, carry some in the car and keep others at work. Mr Keldmann gave the example of a swimmer who, because the devices were small and sealed, could tuck one into his or her bathing costume in case it was needed in the water.

To give a full understanding of Direct-Haler, it is useful to provide some information about how it came into being. In 1987 Erik Keldmann was handed a research thesis by Professor Soeren Pedersen, entitled "Inhaler use in children with asthma", which described a need for improved inhalation devices for paediatric use. Taking up the challenge, the Keldmanns generated many ideas based on what had come before but these became increasingly complex and none of them seemed to give any significant improvement. Erik Keldmann said it was easy to make a complicated device – it was just a case of adding an extra component every time an obstacle was encountered – but such devices were not necessarily commercially attractive products.

Frustrated and close to admitting defeat, they decided on a fresh approach, starting from first principles, to discover what was the essence of an efficient inhaler. They hypothesised that dose storage and metering complicated existing DPIs. They said that these factors often called for intricate design and drove up costs. Subsequently, this made it more difficult for patients to use the devices, and gave rise to the need for a loading procedure, a delivery procedure and even a cleaning procedure – a cleaning brush is supplied with some devices.

Furthermore, each procedure required instructions and demonstrations, making it more difficult for healthcare workers, such as GPs, hospital specialists and pharmacists, to prescribe the medication. The detrimental effects of the need for instruction even spread to the pharmaceutical sales representatives, who had to spend time with doctors explaining how to tackle the problems the device presented to the patient rather than selling its strengths.

It is an interesting insight into the minds behind Direct-Haler that obviating the need for co-ordinated actuation and inhalation, one of the most frequently recounted drawbacks of aerosol-propelled metered-solution inhalers, was not one of the factors considered as key areas for improvement. The Keldmanns believed that the actuation-inhalation limitation had arisen further down the development path because of a "wrong turn" earlier on. In contrast, they were asking questions about inhaler design at the most fundamental level, which would, in effect solve such problems before they arose.

So considering dose storage, they concluded that a capsule containing a powder was a sound starting point.

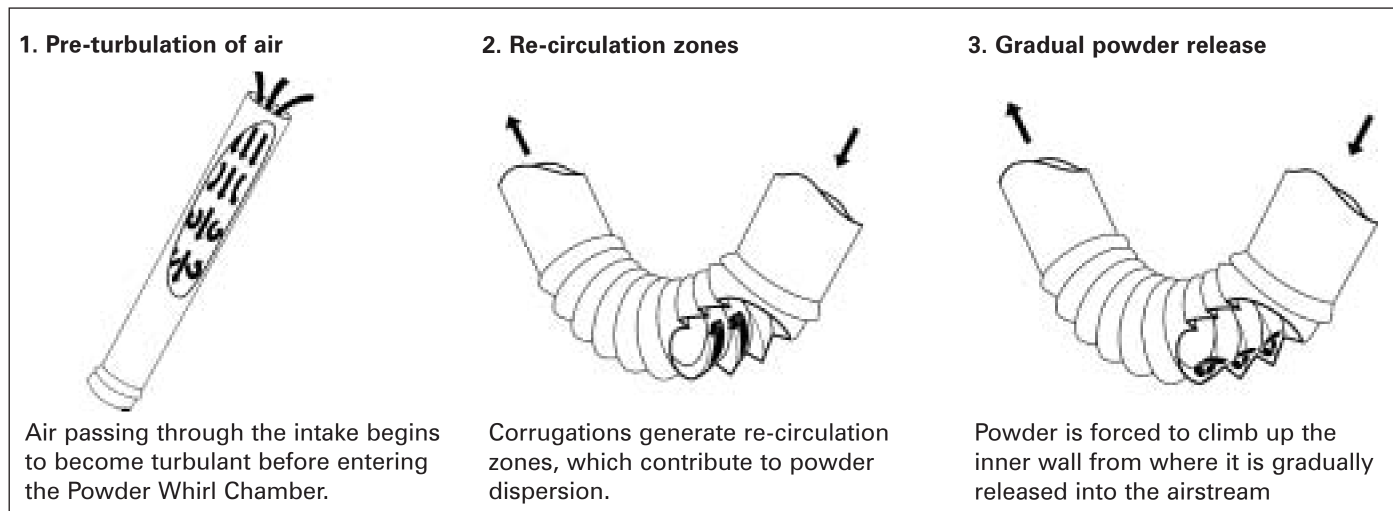

Figure 2. Process of powder dispersion

They then thought about metering and considered whether the capsule itself could be an inhaler, avoiding the need for a metering mechanism. The decision to go for a single-use DPI was already being made.

Initial Direct-Haler design sketches show a straight plastic tube with the two halves of a standard pharmaceutical capsule shell sealing each end. The corrugated area that became the Powder Whirl Chamber was already present in this design. Erik Keldmann said that his background in engineering, specifically climate control, led to its development.

A mechanism for creating turbulence in the air stream was required and he remembered that noise, signalling turbulent flow, was often heard coming from bends in water pipes. The corrugations that make the Powder Whirl chamber are in effect a series of bends, he explained.

The corrugations gave flexibility and the idea of the U-shaped tube followed. It increased the simplicity of the device as bringing the two ends of the tube close together allowing the number of components to be reduced from three (the tube plus two caps) to just two (the tube and the double cap).

proof is in the partnering...

As a virtual company, Direct-Haler will be licensing all applications of its device and progress in this area could be used as an early gauge of success. In 2000 Zambon (Milan, Italy) acquired a one-year option to test Direct-Haler. In late 2001, it licensed global rights to develop Direct-Haler for respiratory indications and around the same time returned to Sheffield Pharmaceuticals an earlier licence to its Premaire inhaler (see *Target*, November 2001, p 14).

The Keldmanns said that Zambon had been impressed with Direct-Haler's performance. In mid-2002, Zambon signed an agreement with Vectura to use the latter's PowderHale formulation technology for the delivery of a Zambon compound, using Direct-Haler, that would be entering Phase I trials.

It is likely that Zambon will itself license out Direct-Haler products to partners since its rights cover a field – all respiratory indications – too large for one company to fully exploit alone.

Direct-Haler intends to find partners for non-respiratory applications of its device. It pointed out that its extremely low cost opened up areas for pulmonary delivery that had previously been ruled out. One example was mass vaccinations, particularly in developing countries, where only a minimally expensive delivery technology could be considered a feasible prospect.

commercial production...

The first area Direct-Haler explored to assess the commercial viability of its inhaler was how easy it was to fill with powder, perhaps because the concept was based on the idea of a capsule. The design was presented to capsule-filling specialist, MG2, which concluded that the device could be filled easily using existing standard equipment.

"The Direct-Haler Pulmonary can match the performance of any marketed DPI device"

Direct-Haler is very cheap to manufacture because the tube is produced by extrusion and roll forming, and the cap by injection moulding.

Rather than being restricted to a few specialist facilities, partners would be able to manage their own manufacturing plants. Expensive specialist equipment is not required so manufacturing could be carried out at several geographic locations, meaning that power remained with the pharmaceutical company rather than the supplier.

Erik Keldmann referred to his invention as "the inhalation pill" since, like the expenditure associated with the tabletting process, manufacture of Direct-Haler was a tiny consideration compared with, for example, the cost of active compound and distribution.

Drawing analogies with the Swedish food packaging system, Tetra Pak, he said that powder filling could be integrated into the manufacturing process. Indeed the cost of Direct-Haler production is more akin to that of packaging than device manufacture.

The extreme simplicity of the device meant that Direct-Haler needed to establish a strong and wide patent estate covering its invention.

The company has patents granted in 35 countries – spanning all the major markets – and a further seven applications are pending. Troels Keldmann said that because Direct-Haler had "opened a new track of development" it had been able successfully to claim broad and complete coverage of the device concept and many derivatives and variations on it. The US and European patent numbers are 5,797,392 and 0805,696, respectively.

but does it deliver?...

Troels Keldmann said that in vivo and in vitro testing, which has been carried out by various companies, including SkyePharma and Vectura, has been extremely positive. More than 90% of the dose was emitted, fine particle fraction was equal to or better than marketed DPIs and dose uniformity was high (standard deviation of about 5% of emitted dose). He said: "The Direct-Haler Pulmonary can match the performance of any marketed DPI device (registered for asthma/COPD therapy)."

He noted that only standard lactose-based, non-optimised formulations had been used so far. Direct-Haler hopes that when optimal formulations have been developed, its inhaler's performance will rival some of those expensive, high-tech devices currently at the cutting edge of pulmonary delivery.

Zambon has conducted successful Phase I/II clinical trials on "a substantial number of patients". However, Troels Keldmann said that the results have not yet been disclosed.

Direct-Haler is a unique company developing a highly innovative device. It is a more basic design than many could have thought possible and this might be the edge that Troels and Erik Keldmann had – they revisited the fundamental issues in inhaler design. Nevertheless, it has a long way to go before reaching the market where it will not be proven until it is accepted by healthcare workers and patients.

In considering whether something so straightforward – after all, it is just a tube – could ever be capable of overcoming the numerous and complicated problems of pulmonary drug delivery, it is worth considering the success of the wheel in transportation. A wheel is, after all, just a circle.

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