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Article

Promising Early Results for New High-Performance DPI

Setting the New Standard for Dry Powder Inhalers

αeolus [ay-oh-luss] is a passive, high-performance, high-consistency dry powder inhaler platform concept that achieves a greater fine particle fraction than that of comparator devices.

The αeolus concept was introduced at a leading inhalation science conference, Drug Delivery to the Lungs (DDL), in 2019. Since then, a collaboration between Cambridge Healthcare Innovations and Kindeva Drug Delivery to develop the technology has produced exciting preliminary results. αeolus promises to set a new benchmark for dry powder inhaler performance.

Current Limitations of Dry Powder Inhalers

Due to the unique benefits of the pulmonary drug delivery route and dry powder inhalers (DPIs), the DPI market is growing both in terms of market share and the number and types of therapies, moving beyond the traditional markets of asthma and COPD.

All DPIs currently on the market are "passive" DPIs, meaning that they are **powered by the patient's inspiratory effort** rather than using an additional power source such as a battery or compressed gas. Passive DPIs have been successful as they are generally cheaper and less complex than "active" DPIs.

However, passive DPIs have struggled to achieve consistent drug delivery performance. This is because, **while the patient provides more than enough inspiratory power**, it is difficult to effectively utilize this power to deliver the drug, resulting in waste and inconsistent dosing.

αeolus is a passive technology but, unlike other passive DPIs, αeolus addresses this efficiency problem through some truly **innovative engineering**.

A New Benchmark

αeolus uses **novel technologies** intended to create a robust and high-performance DPI. This performance offers far-reaching potential benefits, most notably αeolus is designed to improve patient outcomes, reduce product cost, and increase the likelihood of success in clinical studies and in use. αeolus is being developed to be a true platform technology, forming the core DPI "engine" around which any number of DPIs in different formats (single dose disposable through to multi-dose) can be designed.

This report discusses some of the exciting benefits of the αeolus technology, and some of the preliminary performance data from early-stage development.

DRY POWDER INHALERS (DPIs)

Why Dry Powder Inhalers

The popularity of dry powder inhalers is increasing, as evidenced by continued growth in the market and the number of new DPI therapies being delivered and in development. DPIs are expected to grow at a faster rate than pressurized metered dose inhalers (pMDIs) (Xiroudaki, et al., 2021). Behind this rise in popularity are the significant benefits that DPIs provide compared to other respiratory drug delivery technologies:

- *No coordination requirements* — Passive DPIs are inherently breath-actuated, requiring no conscious effort on the part of the user to release the drug at the correct point of inhalation
- *Stability* — The dry powder nature of the formulation makes it inherently more stable than a liquid suspension
- *No additional power source* — Unlike pMDIs or nebulizers aerosolization in passive DPIs is solely reliant upon harnessing a proportion of the **inspiratory energy** provided by the patient
- *As a propellant-free dosage form, it has the potential to have greater sustainability compared with the Global Warming Potential of existing pMDI technologies*
- *High payload potential* — Unlike pMDIs, DPIs are not limited to a maximum active drug payload of a few milligrams per actuation

- *Small size* — Can be designed to be compact for portability
- *Speed of medication delivery* — The full dose is typically delivered in a single inhalation
- *Low device cost* — Compared to soft mist inhalers, nebulizers, or other electro-mechanical pulmonary drug-delivery devices

The Irony of DPIs

Passive DPIs are powered by the patient's inspiratory effort. To date, the performance of passive DPIs can be highly sensitive to the amount of inspiratory power that the patient is able to produce. For example, an Olympic swimmer with optimal lung function will receive a higher inhaled dose than a COPD patient with compromised lung function. The irony of passive DPIs is that it is the COPD patient who most needs the drug. However, the root of this conundrum is not the lack of available inspiratory power, but rather of the ability to apply that power more effectively.

"Power" Struggle

The powder inside a conventional DPI is typically formed of large particles of a carrier fraction (such as lactose) and small particles of an active pharmaceutical ingredient (API) which are stuck to the carrier. The DPI uses the energy provided by the lungs to (1) deagglomerate the powder (detach the tiny API particles off the larger carrier particles), and (2) aerosolize the powder (entrain the tiny, respirable API particles into the inspiratory air flow).

The energy required to do these tasks is a fraction of the quantity of energy that even someone with poor lung function can provide. The problem is that it's extremely difficult to get that power into the powder.

Imagine you're in a car on a flat, icy road, you've only got first gear, and you have bald tires and no traction control. No matter how high you rev the engine, you're going nowhere fast. There may be plenty of power available from your engine, but it's mostly being spent spinning the wheels, not moving the car forward. αeolus does for inhalers what a "gearbox," traction control, and studded tires do for your car.

αeolus aims to solve the problem of getting power into the powder by using two novel technologies: an aerodynamic "**gearbox**" and an innovative deagglomeration mechanism. From the powder's point of view, a patient with **highly compromised lung function could have the inspiratory power of an Olympic swimmer**.

Why Power Matters?

Getting more of the available inspiratory power into the powder brings enormous benefits:

Greater consistency when dosing both between patients and with individual patients.

FIGURE 1. Illustrative schematic of the effect of input energy (E) on fine particle fraction (FPF)

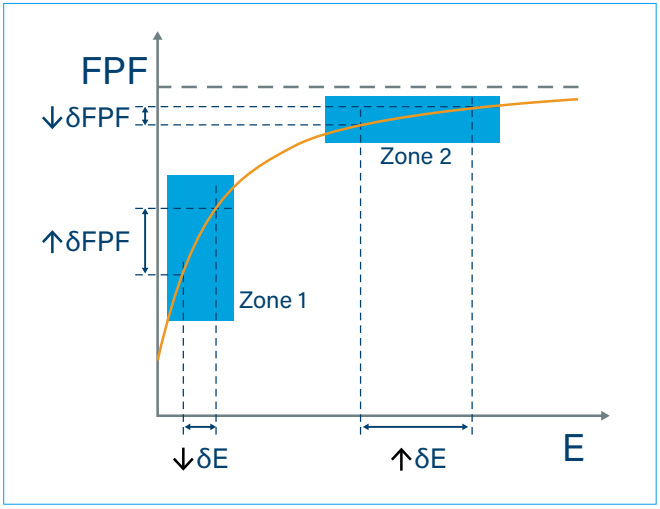


Figure 1 schematically illustrates the effect of energy that the powder sees (E) on drug delivery performance (fine particle fraction) for typical passive DPIs. The performance curve can be considered in two parts — a steep part and a flatter part. **Typically, DPIs channel only a small proportion of the available energy into the powder, so are operating on the steep part of the curve (Zone 1)**. Consequently, a small variation in that energy (δE) results in a large variation in performance. **By channelling a higher proportion of the available energy into the powder**, such that the device is operating in the flatter section of the performance curve (Zone 2), even a large variation in energy results in only a small variation in performance. In this zone, even a **patient with highly compromised lung function will achieve comparable dosing to an athlete** and is likely to achieve a much more consistent dose.

Less Drug Can Be Used

Typical DPIs have an FPF of 20-40% (De Boer & Thalberg, 2021; Newman & Chan, HK, 2020), meaning most of the drug is not delivered to the lungs and can be considered to be wasted. **Figure 1 shows that increasing the energy put into the powder results in better drug delivery performance. Therefore, to deliver the same amount of drug as a typical DPI, less is needed in the formulation**. This could be especially beneficial for expensive next-generation APIs such as biologics.

Reduced Side Effects

Typically, DPIs deposit 40-70% (Baloira, et al., 2021; Danforth, et al., 2021; and Kadota, et al., 2020) of the drug in the mouth and throat. This is a significant, undesirable issue, as not only is it a waste of drug but more importantly it can lead to unpleasant side effects such as candidiasis. **Getting more energy into the powder increases the efficiency of aerosolization, so a higher proportion of drug is inhaled into the lungs** and less is deposited in the mouth and throat. Additionally, the effect of requiring less drug (see above) and aerosolizing more of it compounds to further reduce mouth and throat deposition. For example, doubling the aerosolization efficiency halves the amount of drug required and could reduce mouth and throat deposition by a factor of four.

αeolus — Getting a Grip on Efficiency

The ability of the **αeolus engine** to utilize more of the **patient's inspiratory power** potentially provides:

- **Improved patient outcomes** due to more efficient and consistent dosing and reduced side effects
- **Increased likelihood of success in clinical trials** due to lower variability in drug delivery performance, while providing greater tolerance to formulation variability
- **Lower product (formulation + device) cost** due to less API being used
- **Opening up new areas of therapy** that require more consistent, higher accuracy dosing and/or higher drug payloads such as for lower potency molecules

αeolus

What Is αeolus?

αeolus forms the core technology for a new generation of DPIs. The novel deagglomeration mechanism and aerodynamic "gearbox" are contained within the αeolus device including air and drug flow path. All these components have the potential to be "tuned" to suit the specific requirements of the formulation.

As a true platform technology, a variety of inhaler formats can be designed around αeolus to suit the therapy and user group, e.g., single-dose disposable, single-dose reusable, or multidose.

In April 2021, Kindeva Drug Delivery and CHI began a collaboration to develop and commercialize CHI's αeolus technology. The collaboration leverages Kindeva's inhalation product development, regulatory affairs, and manufacturing capabilities with CHI's DPI technology and device development expertise.

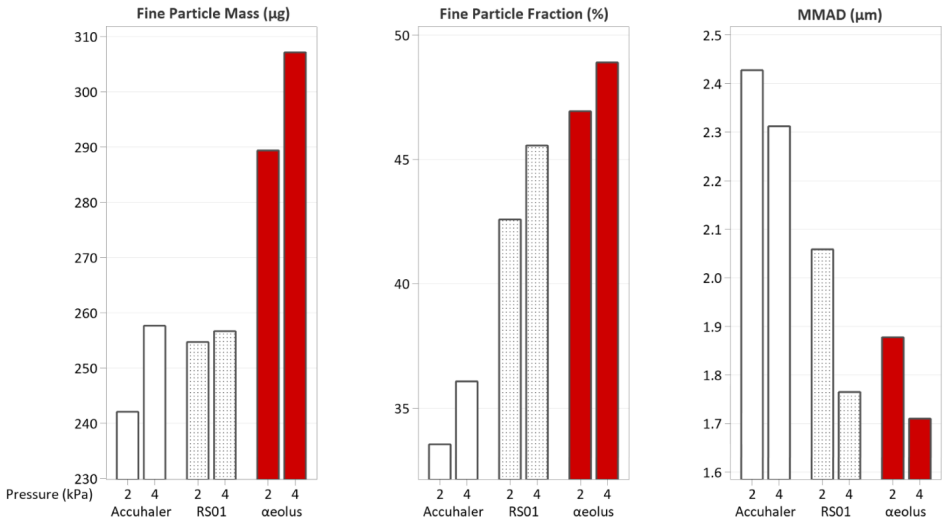
How αeolus Works?

The αeolus technology is simple but clever. The unique mechanisms used within αeolus are covered by two pending patents, and further details will be disclosed upon publication.

How Well Does αeolus Perform?

The pharmaceutical performance of the αeolus technology has been tested at Kindeva Drug Delivery, using an NGI and in accordance with USP 29 <601>, and compared against Ventolin Accuhaler.

FIGURE 2. Fine particle mass (FPM), Fine Particle Fraction (FPF) and Median Mass Aerodynamic Diameter (MMAD) Profile of αeolus Versus Comparator Devices (Ventolin Accuhaler, UHR Plastiape RS01 Monodose and αeolus) at 2 and 4 KPA mouthpiece pressure using ventolin harvested formulation.



The technology is in early-stage development, but the results are already promising.

Fine Particle Fraction (FPF)

FPF is the proportion of emitted dose consisting of particles less than 5 αm in size and represents the percentage of drug that reaches the deep lung to provide the therapeutic dose. αeolus exhibits improved FPF compared with comparator devices using the same starting quantity of harvested formulation, as shown in Figure 2. This increased FPF means more of the drug is depositing in the lung rather than the throat and mouth. Due to the higher FPF, it would be possible to reduce the amount of drug in the formulation (while achieving the same clinical effect) and therefore further reduce the mouth and throat deposition.

What Does αeolus Cost?

αeolus is being developed to be manufactured using standard production techniques and materials. As a platform technology forming the core of the inhaler, the overall manufacturing cost for a device incorporating the αeolus technology will be comparable with existing DPI products.

αeolus as a Platform

αeolus is being developed to be a DPI platform that is intended to be built into multiple device designs aimed at different therapies, users, and dosing regimens. Critically, all DPIs built on the αeolus platform can have identical pharmaceutical performance.

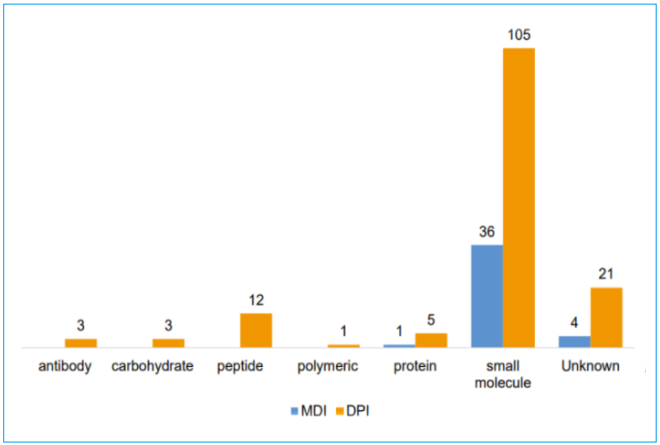
Possible device formats include:

- Single use
  - A low-cost, pre-loaded breath-actuated device. The user simply inhales to receive their dose.
  - Possible uses include vaccine delivery and emergency use therapies (e.g., aspirin, epinephrine).
- Reusable
  - A low-cost, reloadable breath-actuated device. The user simply loads a dose and inhales.
  - Possible uses include pain relief or other nonroutine therapies such as cannabinoids and migraine relief.
- Multi-unit dose
  - Breath-actuated multi-dose device for therapies requiring regular doses. Incorporates a dose counter, with the option for digital connectivity features.

How αeolus Could De-Risk Clinical Studies

In the field of respiratory drug delivery, there are close to 200 inhaled drugs undergoing development today, a large proportion of which are dry powder formulations.

FIGURE 3. Inhaled drugs currently in development globally by molecule type (Pharmacircle, update Feb 21)



Many of these formulations are tested in a capsule-based inhaler, the fundamental design of which is over 40 years old and whose performance is highly dependent on how strongly the user inhales, creating variability in the results and risking the success of the study.

If the company's study is successful, they may not wish to market a new product range in the same inhaler used in the study, and instead they may spend several years attempting to develop an inhaler that meets their requirements with equivalent performance. Alternatively, there may be understandable resistance to changing the inhaler from that which was successful in the study, and the company goes to market with a device that does not meet all their desired product requirements.

The αeolus technology could enable companies to de-risk the clinical to commercial process by:

- **Utilizing an off-the-shelf, rapidly available device that can be converted into a fit-for-purpose bespoke device (e.g., multi-dose) at a later date with identical pharmaceutical performance**. This enables the NCE developer to test their product quickly and cheaply in a high-performance device prior to making the investment in the final device design, with the confidence that the performance will be identical to that seen in the clinical study.
- **Utilizing a device with high delivery consistency both between uses by the same patient and between patients**. This increases the likelihood of clinical study success.

αeolus Enables New Respiratory Therapies

While asthma and COPD are well catered for in terms of the wide variety of drugs available, there are many other therapeutic areas that would benefit from a pulmonary drug delivery solution, but this is not currently possible due to the limitations of the delivery technology.

For example, asthma and COPD drugs typically require doses of a few tens to a few hundreds of micrograms of active drug, and as such, most inhaler technology has been developed to suit this small drug payload requirement. Therapy areas that require much higher doses are not well matched to current inhaler technology, and either are not feasible as a product, or in the best case require multiple inhalations per dose, which can be laborious, time-consuming, and expensive for the patient. Due to the potential of higher payloads coupled with the increased fine particle fraction offered by the αeolus technology, these high-dose therapy areas become achievable.

In addition, most asthma and COPD drugs have a wide therapeutic index, with the body able to metabolize any excess drug delivered and effectively moderate the uniformity of the delivered dose. Current inhaler technology is therefore only really required to deliver "enough" drug product, as there's little danger to the patient who receives higher doses by inhaling more forcefully. However, some drugs have much narrower therapeutic indices and cannot be taken orally, so are almost always delivered by a needle injection system to achieve a sufficiently precise dose. With the greatly improved consistency in dosing that αeolus is designed to provide, many of these injected therapies could become inhaled products, bringing all the benefits of respiratory drug delivery. Examples could include vaccines, insulin, and analgesics.

What Next for αeolus?

αeolus is an innovative technology, and early-stage results demonstrate its capability to significantly outperform existing DPIs. Not only could αeolus improve patient outcomes, but it may also reduce overall product cost as well as increase the likelihood of clinical trial success.

KDD and CHI are excited about the opportunities that αeolus offers to the inhaled drug delivery industry. We are actively seeking industry partnerships to bring NCEs to the market in a device platform that offers several degrees of differentiation compared with existing DPI technologies.

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