PIPELINE TRENDS AND CHALLENGES IN PULMONARY DELIVERY

Here, Gunilla Petersson, PhD, Science & Innovation Director, Inhaled Drug Delivery, AstraZeneca, provides an overview of the inhalables sector from a pharma perspective, covering the three major device types – DPIs, pMDIs and nebulisers. Dr Petersson explains how pharma companies' inhaled product development pipelines have changed recently, and outlines some of the delivery and formulation challenges arising from, and improvements required by, the new drug types now being developed, for new targets, and new therapeutic indications.

THERAPIES USING INHALERS

Marketed inhaled drug products keep growing in number and each year ever more approvals are granted. A review of the PharmaCircle[1] database returned 8/16/24/27 products approved per year (increasing in five-year increments) over the past 20 years. Also, the number of indications these products treat is increasing. Most of them are for local treatment, but more products are also being developed for systemic delivery via the lung (Table 1). Three main types of device are used:

- Dry powder inhalers (DPIs)
- Pressurised metered dose inhalers (pMDIs)
- Nebulisers.

"Standard inhalers, pMDIs, DPIs and nebulisers, are not fully optimised or ideal for all future portfolio demands. A range of improvement opportunities have been outlined."

Large-Molecule Therapies

Looking back, the introduction of large molecules, including biomolecules, into the inhaled drug delivery pipeline has been slow. However, a shift from small-molecule dominance to a significantly higher fraction of large molecules can be foreseen, with Figure 1 summarising active inhalation programmes.[1] Currently, large molecules represent only a tiny fraction, and are based on peptides and proteins only. The clinical pipeline of inhaled products today also includes antibodies, nanobodies, antibody fragments, oligonucleotides, RNAs, vaccines, etc. The diseases related to inhaled large

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DISEASES	Marketed Products	Additional Diseases from Pipeline
Systemic Delivery	Diabetes, acute pain, agitation (CNS related), influenza	Migraine, Parkinson's, vaccines (eg rubella, measles)
Local Delivery	Asthma, COPD, CF (mucolytics), CF (anti-infectives), pulmonary arterial hypertension	Idiopatic pulmonary fibrosis, lung cancer, tuberculosis, bronchiectasis, alpha-1 antitrypsin deficiency, pulmonary alveolar proteinosis

Table 1: Diseases treated via the inhaled route.

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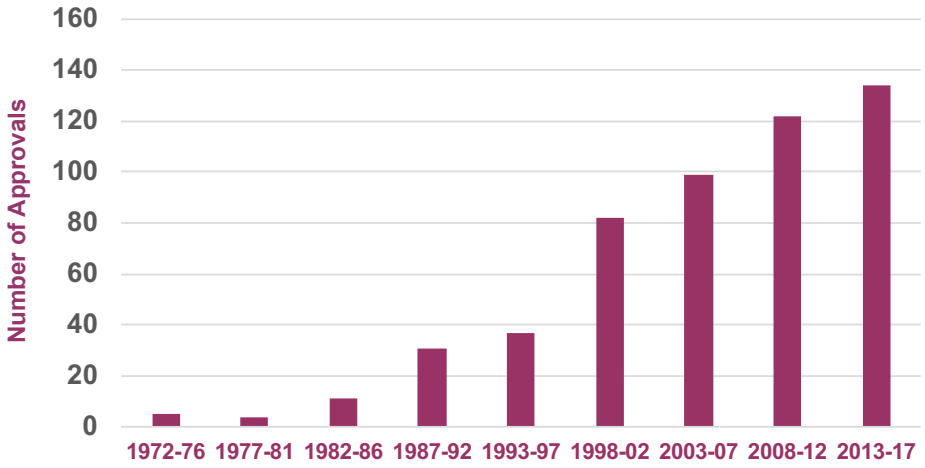

Figure 1: Approvals of inhaled products (1972–2017). (Source: PharmaCircle)

molecules in the development pipeline are more or less exclusive for local treatment. Systemic delivery of biologics has turned out to be challenging, for example due to poor penetration of lung mucus and alveolar lung layer, and there is less appetite seen in this area today.[2]

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IMPROVEMENT REQUIREMENTS FOR STANDARD INHALER PLATFORMS

Standard inhalers, pMDIs, DPIs and nebulisers, are not fully optimised or ideal for all future portfolio demands. A range of improvement opportunities have been outlined to maximise lung delivery for different formulations and patient groups, in order to address concerns such as efficacy, safety, compliance and cost of drug (primarily by minimising drug waste). To address these shortcomings, current devices may be redesigned or combined with new formulation platforms to increase drug load or aerosolisation efficiency. Novel inhaler designs have also been proposed, some of them already on the market.

"The industry has to prepare for higher drug loads and more sensitive drugs and materials, as well as powders with poor flowability and low density."

Challenges Driving A Need For Device Improvements – Portfolio Links

The current development pipeline looks different from that of the past. Not only are new lung targets and new drug classes being explored, but also new diseases. The challenges arising from new types of molecule in the pipeline, and improvements required by pharma companies, are illustrated in Figure 2. The industry has to prepare for higher drug loads and more sensitive drugs and materials, as well as powders with poor flowability and low density, which are also often very moisture sensitive. Fixed-dose combinations are also more common today, which may require separate compartments for two drugs.

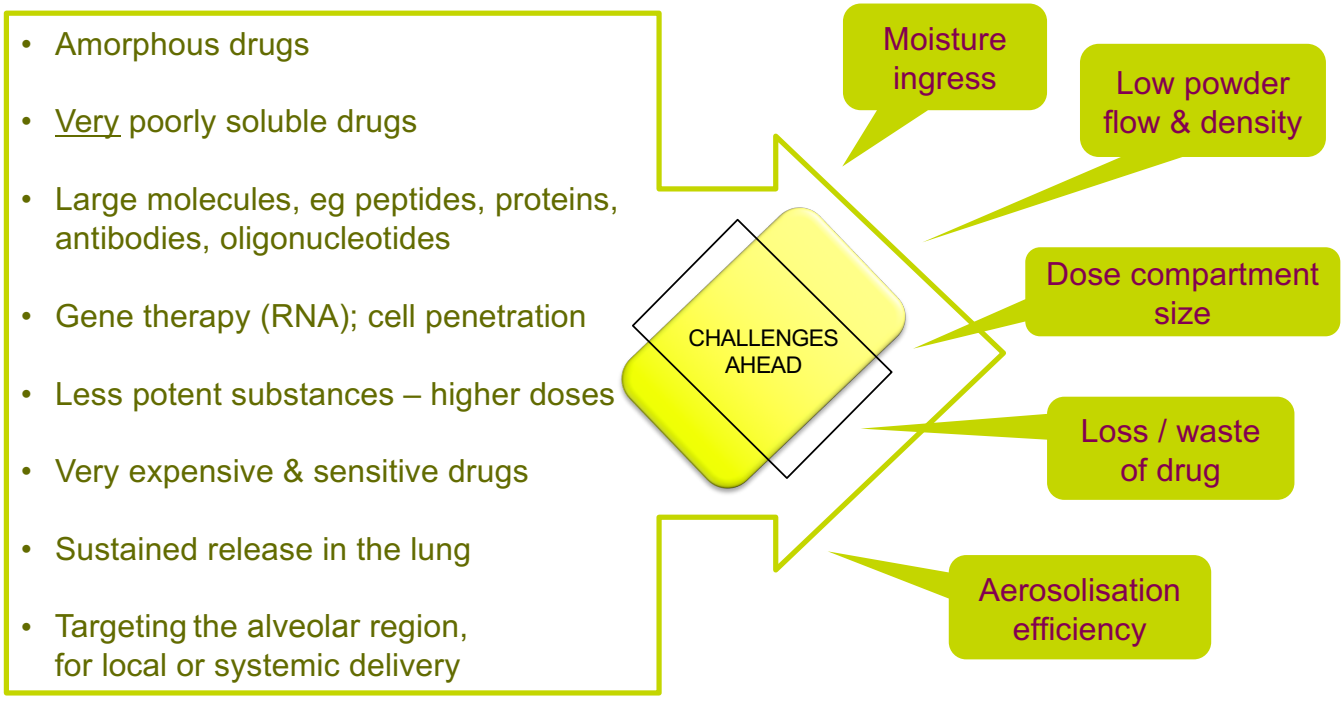

Figure 2: Challenges arising from current pharma pipelines.

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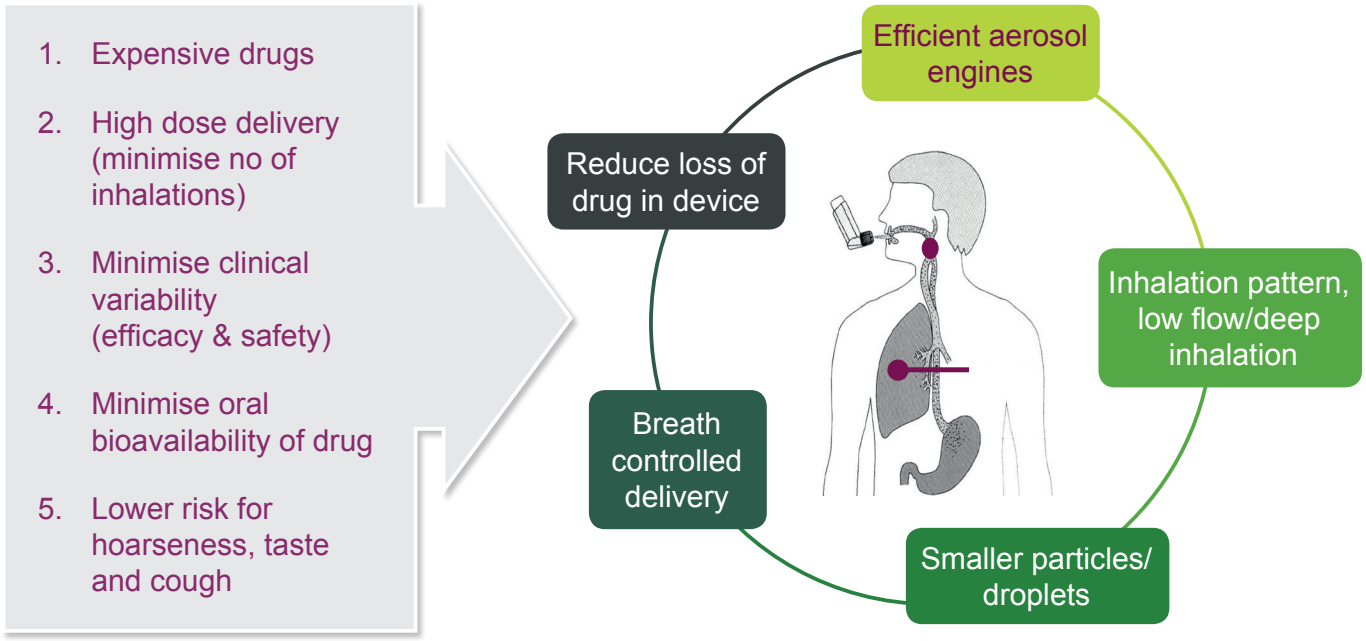

Figure 3: Drivers for higher lung deposited fraction.

Maximise Drug Amount For Lung Deposition

A common theme for a range of improvement efforts is a desire for a higher fraction of the metered drug amount to be deposited into the lung, in some cases also aiming for peripheral lung targeting. The drivers for an increased lung fraction are outlined in Figure 3. New biologics are often very costly and in order to drive manufacturing costs the drug must be used efficiently. For marketed inhaled drugs, a typical lung dose may be around 15–50% of the metered amount, leaving clear room for improvement.

Dry Powder Inhalers

Standard DPIs are designed for crystalline, potent drugs (µg doses) and used with a forced inhalation, particularly so for multidose DPIs. They are not optimal to use for large powder amounts, low density powders with poor flow, moisture sensitive drugs, etc.[3] To partly mitigate this, capsule inhalers with individually sealed powder capsules, i.e. pre-metered doses in moisture protective packaging, have been used when needed. However, these are still "passive" inhalers, meaning that the aerosolisation still relates to the patient's inhalation effort. A high flow rate may aerosolise the powder, but also leads to high throat deposition, limiting the lung-deposited fraction.

Active DPIs have been proposed to assist with powder dispersion. Figure 4 illustrates the difference between passive and active DPIs. The first active powder inhaler was introduced for systemic delivery of insulin (Exubera®), ensuring peripheral lung deposition using a very low inhalation flow rate. However, this device has been registered for more than 10 years and

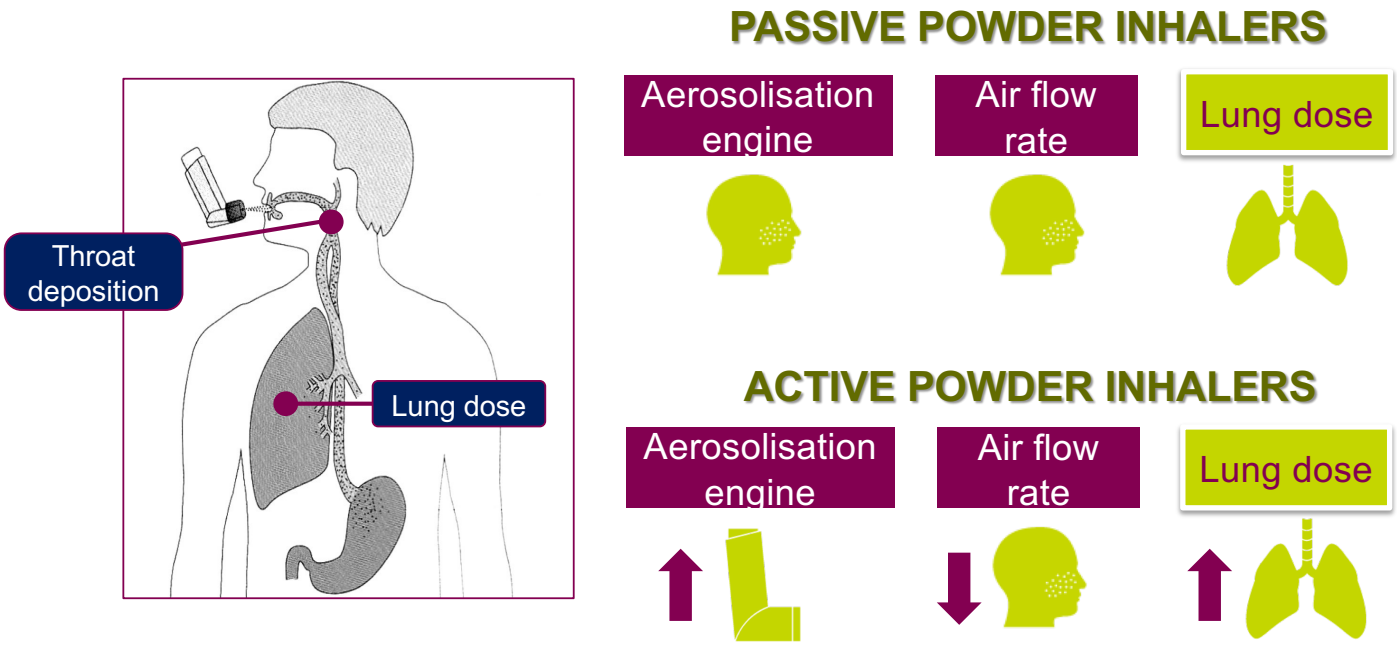

Figure 4: Passive and active DPIs – aerosolisation engines.

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the market is still waiting for more active DPIs, which would also enable use of DPIs for paediatrics, connecting the DPI to a facemask. The advantages of using active DPIs that utilise an active aerosol engine, with a low inhalation effort (low air flow rate), are dependent on the detailed design, and may include:

- Inhalation effort becomes less critical, allowing for disease and age independence.
- Facemask option enables use across all patient groups, including paediatrics (propellant free).
- Slower delivery rate for large powder amounts, avoiding coughing.
- High dose via one large container for applying repeated inhalations (controlled dose titration).
- Increased lung deposition and reduced throat deposition, leading to a low clinical variability, lower cost per dose and a lower safety risk.
- Alveolar/small airway deposition to treat/repair peripheral lung diseases, or for systemic delivery.
- Facilitate dispersion of powders needing a high inhalation force for dispersion.
- More convenient use of nebulisers as "powder nebulisers", which do not need cleaning after each dose or sterilisation of formulation.

Disposable, unit-dose, DPIs for a single dose inhalation are being developed by a range of companies, but so far only two products are marketed: Inavir® (laninamivir, Daiichi Sankyo) in Twincaps® (Hovione) and Adasuve® (loxapine, Teva) in Staccato® (Alexza Pharmaceuticals). Of these, the first inhaler is a two component, low-cost device and the second is a very advanced, breath triggered electronic device. Applications suggested for disposable unit-dose DPIs include:

- High doses/large powder volumes, e.g. via repeated inhalations from a large compartment
- Moisture-protected unit-doses
- Hygienic inhaler, used once, to avoid re-infection
- Refrigeration of doses
- Low frequency use, e.g. weekly treatments
- As needed, on-demand treatment, e.g. pain
- Single use, e.g. vaccines (avoid needles, supply chain)
- Easy to carry for active people.

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Pressurised Metered Dose Inhalers

Standard pMDIs are designed for drugs that can be dissolved or dispersed in a propellant and thereafter stored in a bulk reservoir. The aerosolisation relies on a compressed gas quickly expanding while forming a spray of a small volume metered via a ≈50–100 µL valve. The generated pressure and size of the valve limit the drug load in one inhalation. The low drug load, propellant compatibility (chemical) and shear/spray force sensitivity limit the number of drugs that may be suited for a pMDI. Related to the passive/active DPI discussion is the fast spray and high throat deposition, which limits the lung dose. In addition, to maximise the lung dose there is also a need to co-ordinate device actuation and inhalation, i.e. the patient inhalation manoeuvre affects the lung-deposited dose. These factors may explain why new biologics are developed mainly for nebulisers or DPIs. For those drugs that are delivered via pMDIs and propellants, special inhalers have been in development, so-called "Breath Actuated Inhalers", but so far only a few are on the market. These circumvent the need for patient co-ordination, in order to increase compliance and reduce dose variability.

Nebulisers

Standard nebulisers are still ultrasound and jet nebulisers (requiring an air compressor), although a range of vibrating mesh nebulisers have been developed and are being slowly picked up in the marketplace. The smaller, battery-driven mesh nebulisers are gaining popularity due to their portability, faster delivery rate and lower wastage of expensive drugs[4] and seem to be the preferred device type for drugs in clinical trials, with some drugs also planned to be commercialised in a nebuliser. However, there are still challenges to be solved for the mesh nebulisers. The risk of mesh clogging when suspensions are used is one improvement area, but also sensitive drugs or drug vehicle materials may form aggregates, due to the shear forces applied during vibration.

The majority of nebulisers deliver the drug in a continuous mode, i.e. independent of the patient's inhalation/exhalation cycle, leading to high dose variability and waste of drug into the ambient air. Novel smart nebulisers deliver drug only during the inhalation phase, not during exhalation, and some are designed to ensure a low inhalation flow rate, thus avoiding throat deposition as well as droplet coalescence, the latter resulting in droplets too large for inhalation. The recently developed and marketed FOX® nebuliser[5] (Activaero / Vectura) is an example of a smart device, which senses and adapts to the patient's inhalation effort (resistance to airflow adapted in real-time), ensuring a low inhalation flow in the throat/lung region.

Multiple examples are available where nebulised products have been replaced post-launch (lifecycle management) by improved delivery technologies, driven either by shortening of treatment times, portability concerns and/or cleaning burden. Two examples used for cystic fibrosis related infections illustrate well how improved inhalers can improve both patient convenience and likely adherence. Both lifecycle management examples offered a reduction in dose treatment time of ≈15 min:

- Tobi® (tobramycin, Novartis) via jet nebuliser, later also a capsule DPI.[6]
- Colobreathe (colistimethate, Teva) via jet nebuliser, later also a capsule DPI.[7]

INHALER DESIGNS FOR ALVEOLAR AND SYSTEMIC DELIVERY

Some drug classes need to be deposited in the upper or central airways, as determined by the location of the drug target/receptor. Other drugs are needed in the whole lung. Drugs designed for peripheral lung targets or for systemic delivery should be directed all the way to the alveoli, avoiding deposition in the throat, and upper and central airway to maximise efficiency and minimise side effects. The most advanced concepts proposed for alveolar targeting are

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based on a combination of small droplets/particles and a very low inhalation flow rate, preferably also with repeated inhalations to deliver a full dose. The three known insulin inhalers, of which two have been marketed, explore three different concepts to obtain systemic delivery via the alveoli:

- **Exubera** (Pfizer): an active DPI, standing cloud of powder aerosol, patient instructed to inhale with a low flow rate (special formulation, highly dispersible powder).
- **Afrezza** (MannKind): a passive DPI with a very high resistance to airflow forcing the patient to inhale with a very low flow rate (special formulation, highly dispersible powder).
- **Aeroneb Micro** (Philips Respironics / Dance Biopharm), breath controlled, vibrating mesh nebuliser, only delivering the aerosol as long as the patient inhales at the optimal, low flow rate (solution).

More recent innovations focus on inhalation of very small droplets (sub-micron), similar to e-cigarette delivery, via repeated inhalations from a battery driven (active) delivery device loaded with a solution. Examples are the Nanoaerosol Inhaler from Aerosol Drug Delivery Ltd (Cambridge, UK), and an arm/wrist (portable) inhaler that was designed by a group at Monash University (Clayton, Victoria, Australia), the latter using a standing acoustic wave technology. A marketed product using a liquid for evaporation and repeated inhalations for systemic delivery is Penthrox® (methoxyfluorane) from Medical Developments International (Scoresby, Victoria, Australia), used for acute pain treatment, with up to 30 minutes' worth of inhalations if needed. Patients are instructed to inhale intermittently to achieve adequate analgesia ("titration" for lowest possible dose).

CONCLUSION

A notable evolution is ongoing in the development of new drug classes for new lung targets, but also in designing inhalers addressing accentuated requirements from an increasingly diverse industry portfolio. Competition on the market related to having the "best inhaler" and regulatory focus on human factors are pushing inhaler designers for more creative solutions. Another challenge for all device developers is to consider design flexibility to add or integrate electronics for intel pharma and connectivity. An exciting future can be expected. When designing new inhalers, it is important to keep in mind that some patients have their mind set on "familiarity", where novel features or designs might cause poor adherence.

ABOUT THE COMPANY

AstraZeneca is a global, science led biopharmaceutical company that focuses on the discovery, development and commercialisation of prescription medicines, primarily for the treatment of diseases in three therapy areas – oncology, cardiovascular, renal & metabolism and respiratory. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide.

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