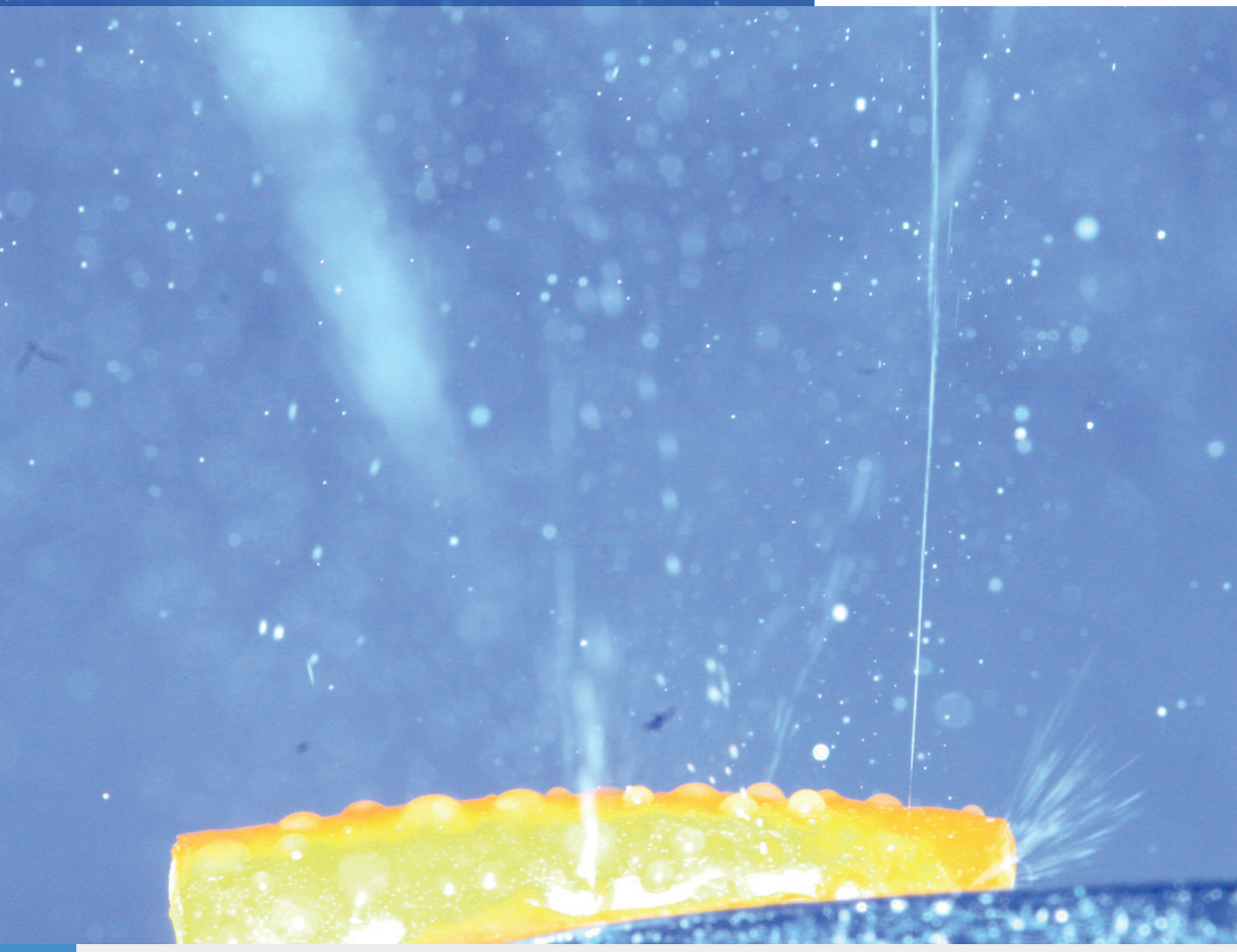
# PULMONARY & NASAL DELIVERY

ON drugDELIVERY



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## PULMONARY & NASAL DELIVERY

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*Front cover image, "Oil jets issuing from a highly bent peel of a navel orange", supplied by Fluids and Structures (FaST) Laboratory, Department of Mechanical & Aerospace Engineering, University of Central Florida, US (see this issue, page 30). Reproduced with kind permission.*


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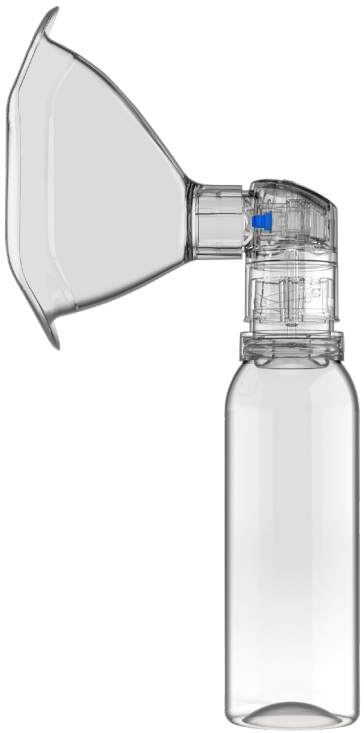

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# PIPELINE TRENDS AND CHALLENGES IN PULMONARY DELIVERY

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

"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."

| 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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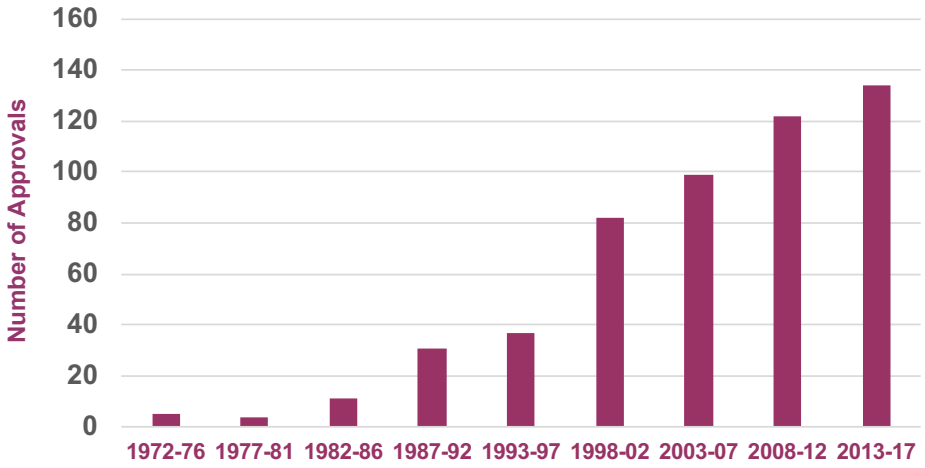


Figure 1: Approvals of inhaled products (1972–2017). (Source: PharmaCircle)

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]

"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."

## 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.

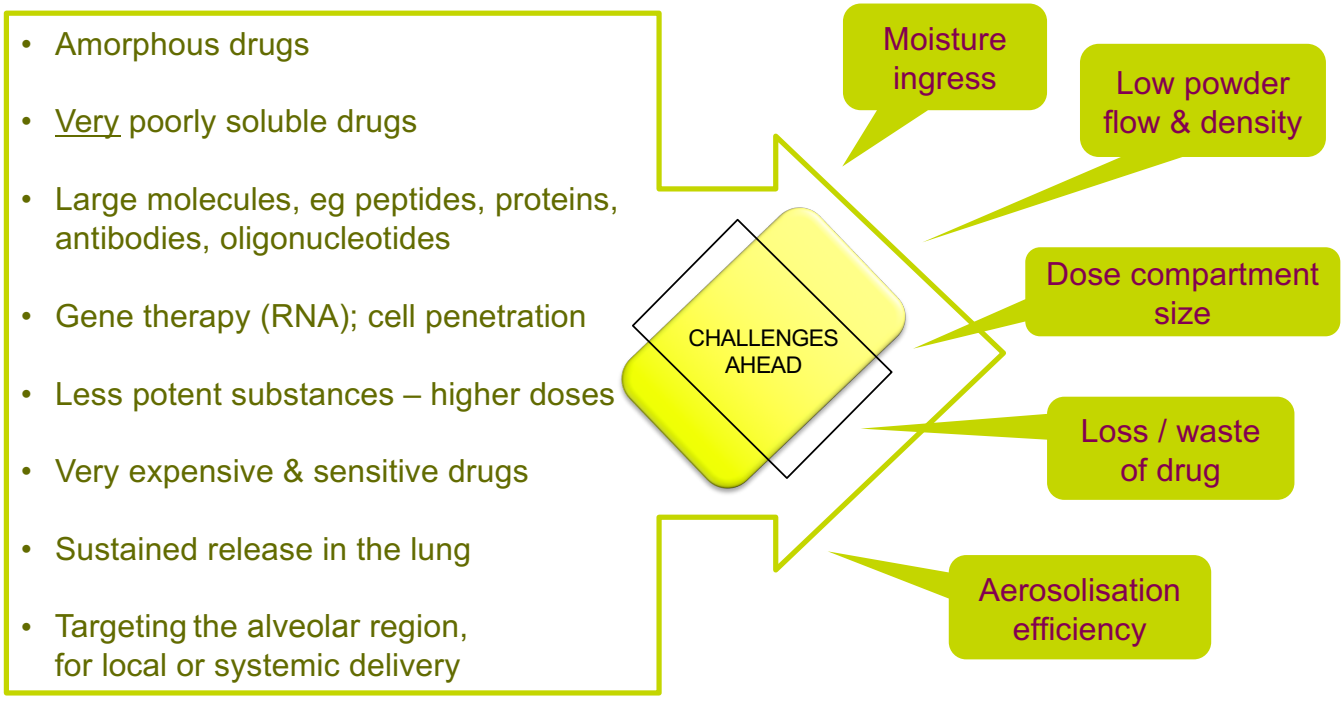


Figure 2: Challenges arising from current pharma pipelines.

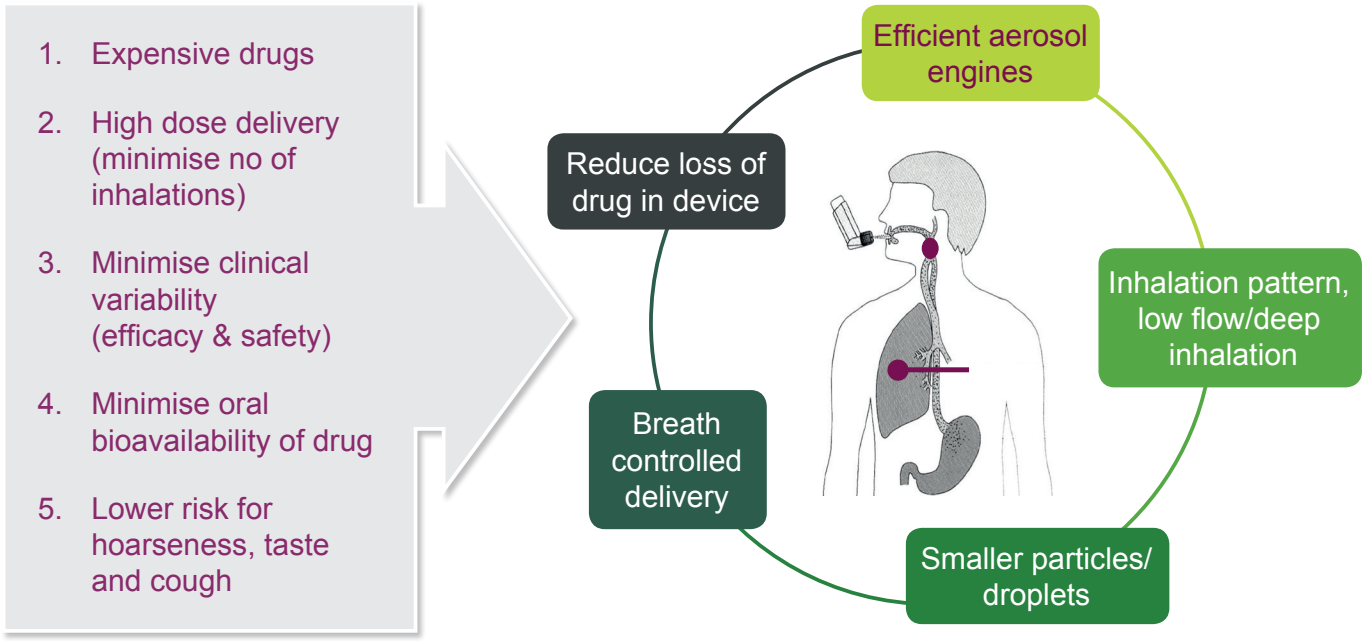


Figure 3: Drivers for higher lung deposited fraction.

### 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

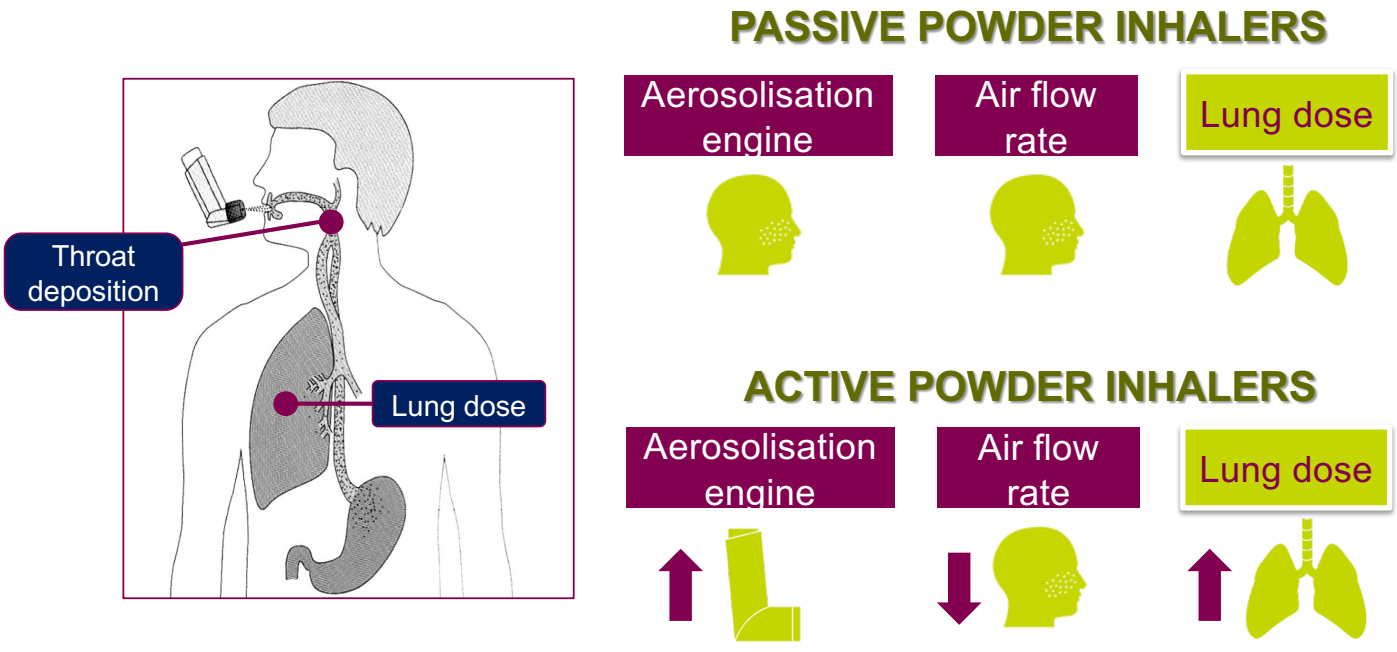


Figure 4: Passive and active DPIs – aerosolisation engines.

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.

> "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."

### 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

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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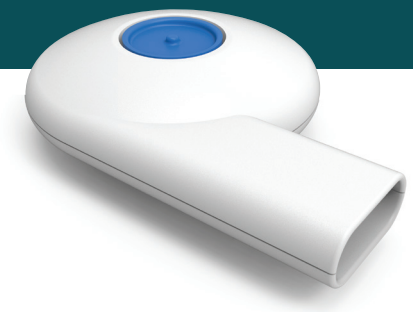

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# NEBULISERS: TIME TO REINVENT THE WHEEL

In this article, John Pritchard, PhD, Director, PMO and Technology, Respironics Respiratory Drug Delivery, discusses the history of the nebuliser, its fall in popularity with the advent of DPIs and pMDIs, and its current resurgence due to the success of the mesh nebuliser, continuing on to how changing the development paradigm to utilise nebuliser technology more effectively can have significant benefits.

## NEBULISED DRUG DELIVERY

Over a century and a half ago, nebulisers were the first widely commercialised devices used for the delivery of medical aerosols to the lungs.[1] Over the intervening period the complexity and efficiency of designs based on the use of a jet of high-pressure air have steadily increased, and jet nebuliser technology has dominated the nebuliser market. However, it was not until the aerosol generation technique employed in nebulisers was successfully reinvented, with the arrival of mesh technology, that the efficiency and features of nebulisation devices began a leap forward in performance.

The popularity of the nebuliser as an aerosol delivery device has been linked with both developments in nebuliser design and other developments in the field of aerosol delivery. The invention of the portable dry powder inhaler (DPI) and pressurised metered dose inhaler (pMDI) in the mid-20th century led to a reduction in the popularity of the nebuliser. Today that decline has been reversed, with the number of doses of medication taken by nebuliser growing faster than either DPIs or pMDIs.[2] This resurgence in popularity is driven by a number of concurrent developments as well as the advantages that nebulised drug delivery provides over other forms of aerosol drug delivery (Figure 1).

The primary advantage that nebulisation has maintained over other aerosol delivery devices has been its universal applicability to all those requiring aerosol treatment, be they very young, very old, severely ill or coping with disability. Other types of aerosol delivery device require specific actions on the part of the user, in terms of the way the aerosol bolus is inhaled in a single breath, whereas nebulised aerosol delivery merely requires the patient to breathe naturally. This universal applicability has come at a cost in terms of the time required to receive a treatment, but the main disadvantage of nebulised therapy over other inhaler therapy has been its lack of portability. The invention of the mesh nebuliser addressed the portability issue, and recent enhancements in mesh nebuliser performance have more than halved the time required for a treatment.[3]

> "Patients with COPD are usually elderly and experience chronic detrimental alterations to their typical breathing patterns, which manifest as reduced PIFs and an extended exhalation phase. Consequently, they are an ideal patient group for consideration for treatment by nebulised therapy."

These developments, along with universal applicability, are opening the window of opportunity to apply the benefits of nebulised therapy past the traditional niche patient groups of cystic fibrosis and pulmonary hypertension into the wider arena of respiratory care. Chronic obstructive pulmonary disease (COPD) is predicted to become the third leading cause of death worldwide by 2030,[4] and nebulised therapy is well placed to provide a key treatment option in the treatment of patients suffering from this disease.[5] Patients with COPD are usually elderly and experience chronic detrimental alterations to their typical breathing patterns, which manifest as reduced peak inhalation flows (PIFs) and an extended exhalation phase. Consequently, they are an ideal patient group for consideration for treatment by nebulised therapy.

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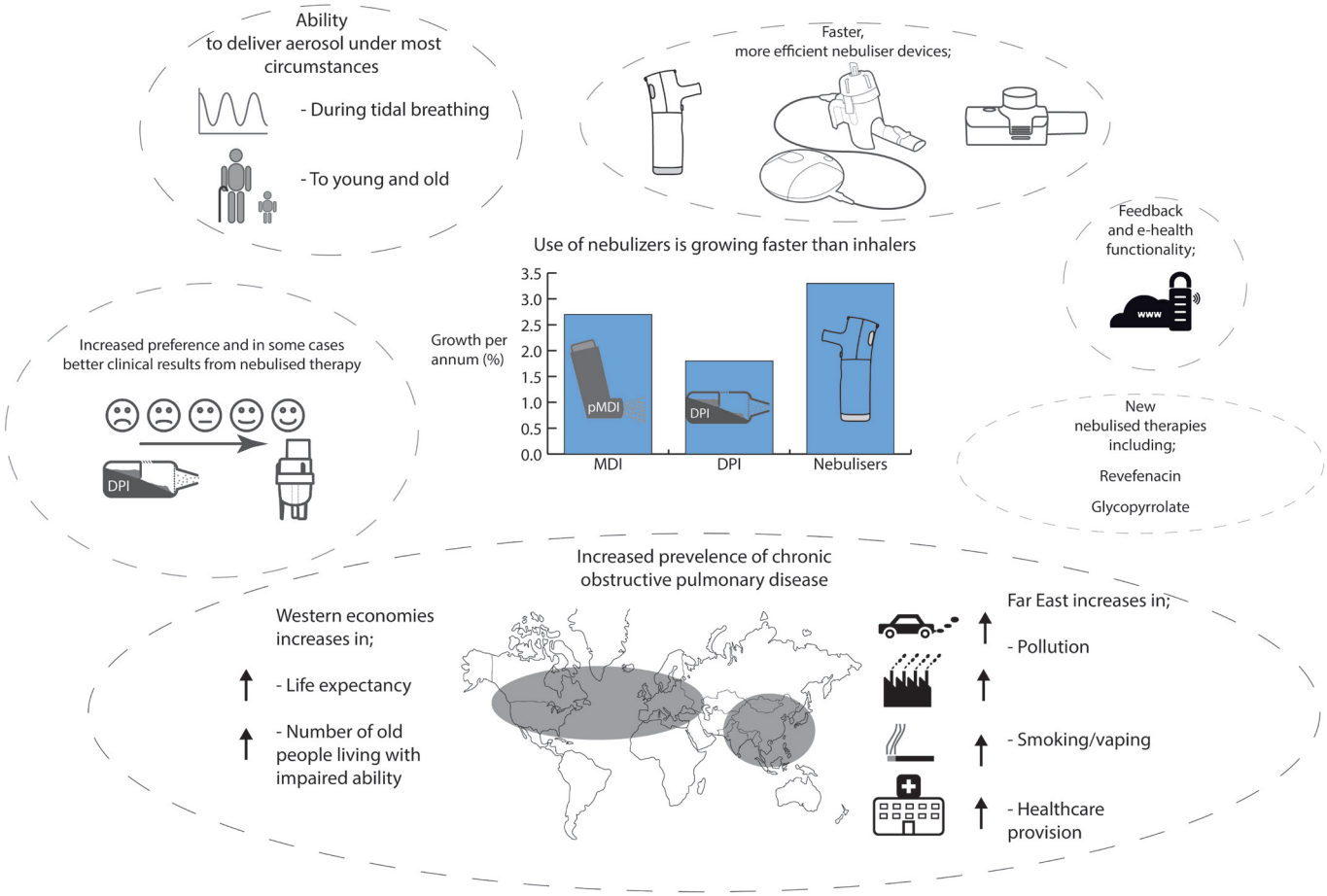


Figure 1: Contributing factors in the resurgent popularity of nebulised drug delivery.

In the US, around 50% of those discharged from hospital can currently be expected to be prescribed nebulised treatment. A recent study in patients admitted to hospital following an exacerbation of COPD raised an interesting difference between sub-groups using different aerosol devices. Patients with PIFs below 60 L/min who were exclusively prescribed a DPI upon discharge from hospital showed higher levels of all causes of COPD readmission compared with those exclusively prescribed a nebuliser upon discharge.[6]

Patient preference for nebulised therapy has long been known, but considering the properties of use of nebulised therapy compared with inhaler therapy as applied to patients with COPD, it is perhaps surprising that this type of clinical effect has not been noticed before. The answer may lie in the low level of commercial and academic interest in nebulised therapy in the years when nebulised therapy was limited to bulky, noisy devices that administered treatment over more than 10 minutes, compared with seconds for an inhaler. The advantages of these new mesh nebulisers for patients with COPD have now been recognised by commercial drug developers. The first drug for COPD, Lonhala (gylcopyrrolate) from Sunovion Pharmaceuticals (Marlborogh, MA, US), developed specifically for use with a mesh nebuliser (Magnair), from PARI Pharma (Gräfelfing, Germany), has now been approved by the US FDA, with others to follow.

> "Addition of a nebulised formulation as a line extension to the existing inhaler formulation offered an increased return on investment, but by far the greatest returns were seen using an entirely new development paradigm that prioritised development of the nebulised formulation right through to commercial launch."

## USING A NEBULISER TO IMPROVE THE CHANCES OF SUCCESS WITH INHALED DRUG DEVELOPMENT

One commercially focused area in which nebulisation maintained a limited but persistent role during the 20th century was in the development of new drug entities.[7] New drug development is a highly financially risky venture with high dropout rates and high manufacturing costs for the small batches of novel drugs produced during early development. In these key early stages, the cost of small batch production can make the drugs as valuable as gold. Therefore quantities are kept as low as possible within the requirement to satisfy the quality and regulatory demands of the required testing programme.[8]

It was recognised that use of nebulised solution formulations in the early stages avoided the need for time-consuming and costly activities, such as:

- Particle size reduction processes
- Overcoming formulation issues with propellant/carrier
- The demonstration of end-of-shelf-life performance.

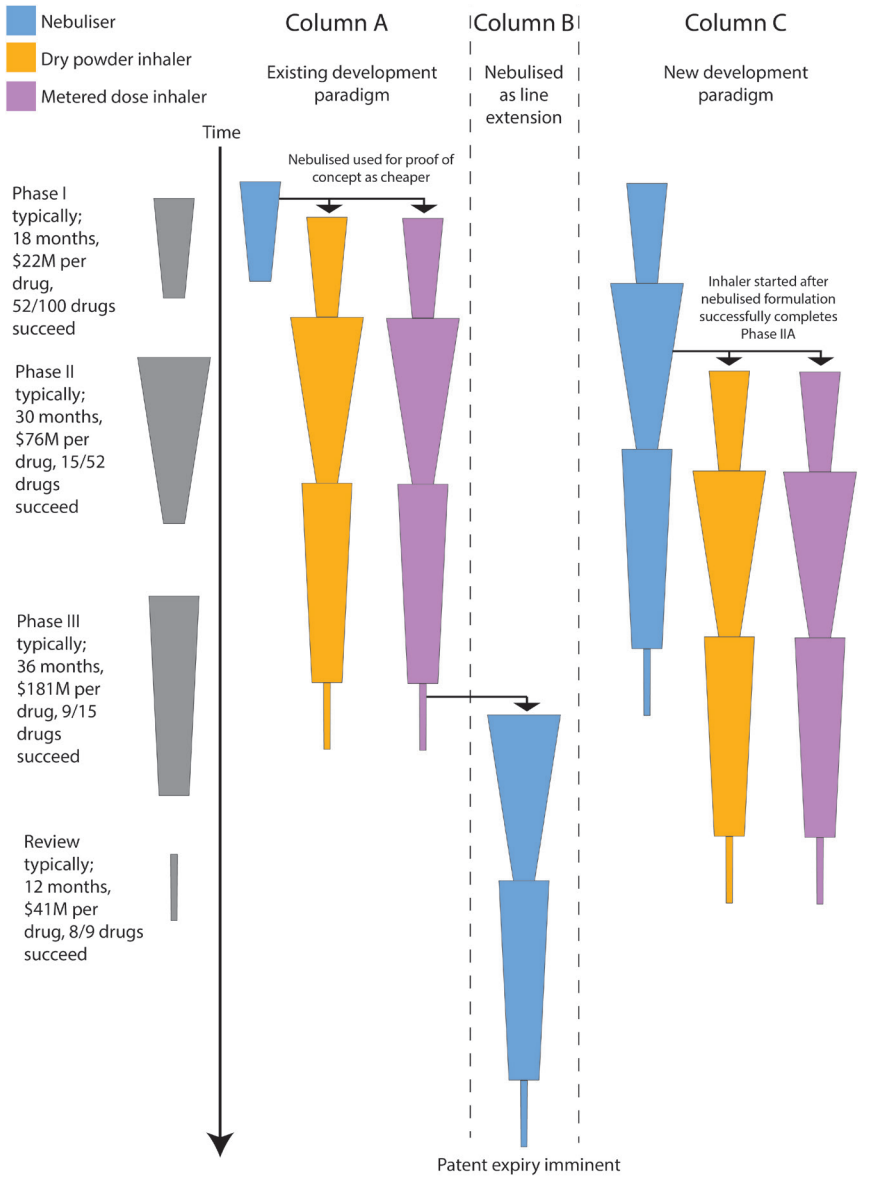


Figure 2: Drug development paradigms.

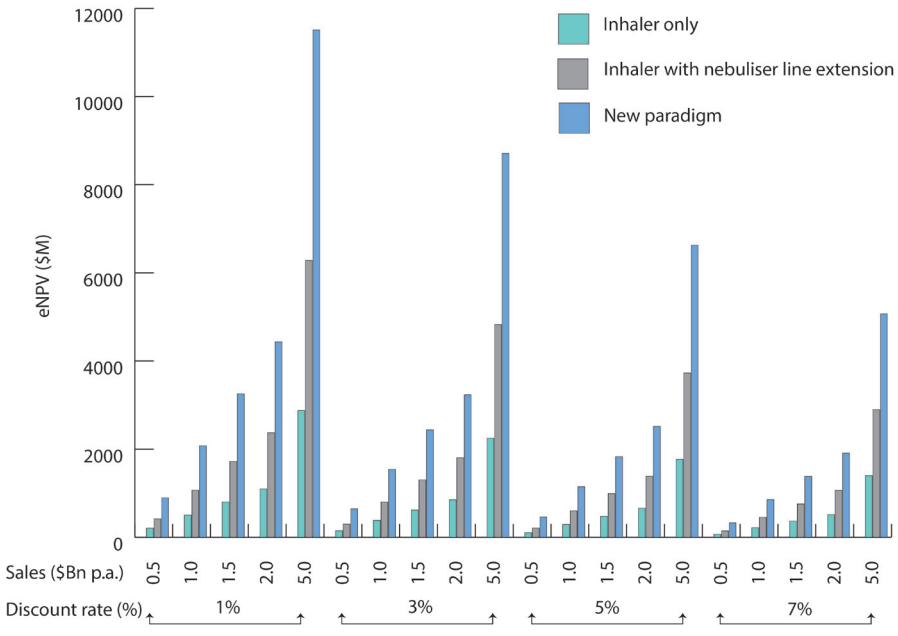


Figure 3: The expected net present value (eNPV) of three drug development paradigms.

Additionally, delivery into tidal breathing and the ability to deliver a wide range of volumes of solution also simplified dose-ranging studies. The savings obtained by using nebulised formulations in the early development stages, during proof of viability, more than offset the additional time required to reset the development programme to the inhaler format required for the end commercial product for successful drug candidates (Figure 2, Column A).

Although the cost efficiency gains to the development programme as a whole were worthwhile, using the traditional development paradigm still led to waste of the initial nebulised development work. The arrival of portable, patient-friendly nebulisers that provide a much lower inter-device drug delivery variability increased the attractiveness of launching new drugs in a nebulised form. Thus the time had come to re-examine and possibly reinvent the established drug development paradigm. A financial model investigating the return on investment of the traditional development paradigm compared with two waste-limiting alternatives showed improvements for return on investment for both.[9] Addition of a nebulised formulation as a line extension to the existing inhaler formulation (Figure 2, Column B) offered an increased return on investment, but by far the greatest returns were seen using an entirely new development paradigm that prioritised development of the nebulised formulation right through to commercial launch (Figure 2, Column C). The model showed that the advantages were present across a range of expected sales values and discount rates that allow for interest rate changes (Figure 3).[8,9]

With a convincing alignment of so many factors falling into place in support of the development and commercialisation of a nebulised drug delivery format in the

> "The main potential for novel drug developments lies in mesh nebuliser designs that provide better drug delivery efficiency in a portable, silent, energy efficient, rapid aerosol delivery and user-friendly package."

arena of modern-day aerosol drug delivery, the question for forward-looking drug developers changed from, "which drug delivery format should the drug be launched in?", to "which nebulisation technology should the drug be launched in?".

## PICKING THE RIGHT NEBULISER

Reinvention does not mean that older designs no longer have appropriate applications. Traditional jet nebuliser technology still provides a cost effective delivery option for generic drugs with wide therapeutic indexes intended to reach as wide a treatment population as possible, and provides a simplified regulatory route to market. Jet nebulisation offers a range of options in terms of delivery efficiency (Figure 4), from conventional constant output jet nebulisers, through breath-enhanced jet nebulisers up to mechanically breath-actuated jet nebulisers, each with its own advantages and drawbacks for the treatment of different patient groups.[10]

However, the main potential for novel drug developments lies in mesh nebuliser designs that provide better drug delivery efficiency in a portable, silent, energy efficient, rapid aerosol delivery and user-friendly package. Modern drug development encompasses a broad range of drug molecules and macromolecules that may be more expensive to produce and require greater volumes of formulation to be delivered. The high delivery efficiency of the mesh nebuliser, with as little as 0.1 mL of drug formulation left behind in the medication chamber at the end of the treatment,[11] provides the potential to minimise the volume contained in the drug nebule and increase the amount of packaged drug that is delivered to the patient.

The electronic platform that the mesh aerosol generator is built on also allows for the incorporation of other features and capabilities to improve both drug delivery and usability.[12] Feedback to the user in the form of automatic detection of the end of the treatment can provide users with added confidence that they have received a complete treatment without spending additional time breathing through the nebuliser after aerosol production has ceased. Breath activation can ensure that all of the intended dose of drug is delivered to the patient regardless of differences in the way that different patients breathe and it can minimise the amount of aerosol wasted to the environment. Breath activation can also be supplemented with additional feedback mechanisms to aid the patient in breathing in a manner to achieve optimal aerosol delivery into the lungs.[13]

The increased number of feedback signals, from basic on/off and end of treatment, to a range encompassing guidance on the best flow rate and how long to inhale for, has resulted in the use of audible, visible and also tactile feedback signals to the user, to ease interpretation of the different signals.

Such guidance on the correct use of the nebuliser to optimise the efficiency of aerosolised drug delivery to the lungs is one of the key drivers of the expectation of better disease control via nebulised drug delivery in the future. However, the top end of the scale of devices for increasing drug delivery efficiency must deal with the issues surrounding adherence of the patient with the prescribed treatment regimen. The electronic basis of mesh nebulisers, with associated feedback mechanisms, allows the seamless integration of connectivity, electronic monitoring and internet-based patient management programmes that are designed to support the patient in their use of nebulised therapy in their daily lives.[14]

> "The electronic basis of mesh nebulisers, with associated feedback mechanisms, allows the seamless integration of electronic monitoring with internet-based patient management programmes that are designed to support the patient in their use of nebulised therapy in their daily lives."

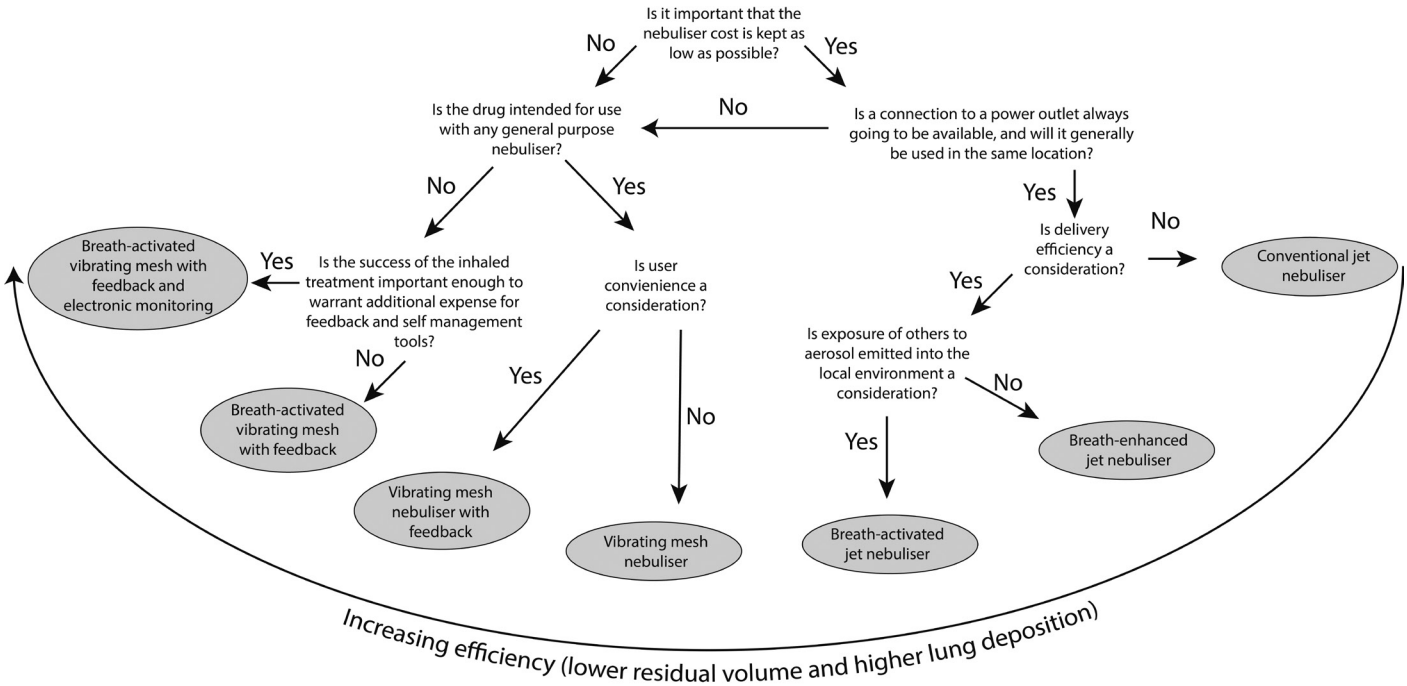


Figure 4: Some factors in selection of the appropriate nebuliser.

## THE INCREASING WORLD OF MESH NEBULISERS

With all the advantages that mesh nebulisers have brought to nebulised drug delivery, their increased use has progressed through the early adoption phase and has begun to move into widescale acceptance. The number of clinical trials sponsored by pharmaceutical companies that use mesh nebulisers now outweighs the number that use jet nebulisers,[15] and as more new drugs are trialled and approved using mesh nebulisers their share of the respiratory market will increase further.

Another driver for increased use of mesh nebulisers is reduced cost; as mesh technology has developed the cost of producing the aerosol generators has reduced, and will continue to do so as new materials and processes are used to create the meshes, which require thousands of holes made to fine engineering tolerances. At one end of the scale nickel palladium alloy mesh designs promise aerosol heads that could last as long as the nebuliser, while at the other end of the scale plastic meshes offer a solution that could be disposable on a weekly or even daily basis. As the costs of ownership decrease, the simpler, more basic models will increasingly take over from jet nebulisers while, at the other end of the scale, systems with advanced feedback may open new markets to nebulised therapy.

The latest advanced systems already include feedback systems to guide the user to achieve the optimal treatment, for example Respironic's own I-neb AAD System guides the patient to an optimised inhalation and the Breelib from Vectura (Chippenham, UK) mesh nebuliser provides an illuminated mouthpiece that indicates when the patient is inhaling with the optimal flow rate. Both these devices can be connected to an e-health application to provide usage information to both patient and healthcare provider.[13]

With so many simultaneous developments in nebuliser performance and capability across the range of simple to advanced devices, the future of nebulised therapy in the treatment of respiratory diseases is looking stronger than ever.

## CONCLUSIONS

Nebulised therapy has been used for the delivery of aerosols to the lungs for over 150 years, but lost favour due to drawbacks and the development of more convenient aerosol delivery systems. New developments in the field of nebulised therapy have prompted a resurgence in popularity, which is only just beginning. New drugs and novel, more sophisticated nebulisers will provide new opportunities to treat both the core user base of the very young, very old and very ill, as well as bringing the advantages of nebulised therapy to a wider range of respiratory patient groups.

## ABOUT THE COMPANY

Respironics Respiratory Drug Delivery (UK) Ltd is a subsidiary of Royal Philips of the Netherlands. Royal Philips is a leading health technology company focused on improving people's health and enabling better outcomes across the health continuum from healthy living and prevention, to diagnosis, treatment and home care. Philips leverages advanced technology and deep clinical and consumer insights to deliver integrated solutions. The company is a leader in diagnostic imaging, image-guided therapy, patient monitoring and health informatics, as well as in consumer health and home care.

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## ABOUT THE AUTHOR


From January 2011 to September 2018, **Dr John Pritchard** was Director, PMO and Technology, for Philips Respironics Drug Delivery, with global accountability for the development of products for the treatment of respiratory diseases. He is now a private consultant specialising in strategic approaches to developing respiratory devices, drugs and digital health. At different stages in his career across three major pharmaceutical companies, he has been associated with the launch of 11 major products and at the Respiratory Drug Delivery (RDD) conference in April 2018, Dr Pritchard received the Charles G Thiel award for outstanding research and discovery in respiratory drug delivery. Dr Pritchard has published widely in the field, as well as having served as a board member on various scientific and industry bodies. He is currently a member of the UN Committee that makes recommendations on the essential uses of propellants.

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# MANUFACTURING DPIS: AN ENGINEERING PERSPECTIVE

In this article, Pietro Pirera, Product Manager, and Stefano Crivellaro, Process Development R&D Laboratory Technologist at IMA Group's IMA Active division, discuss the rising prominence of the DPI in inhalable drug delivery, how this has been facilitated by industrial filling technologies and how dosators in particular provide high-precision industrial-scale filling.

## INTRODUCTION

In 1948, the first commercial dry powder inhaler (DPI) was launched. This first technology seems archaic by today's standards, using a mechanism whereby a deep inward breath would cause a ball to strike a cartridge containing powder and shake the powder into the airstream. Since then, changes in the drug delivery market and regulatory pressures have driven innovation of DPIs forward. Firstly, the introduction of capsules has meant standardised filling technologies can be incorporated into the manufacturing process, thus meeting the need for industrial-scale filling of such devices. With the availability of accurate filling technologies, it is possible to manufacture DPIs on a large enough scale to meet worldwide volume needs at acceptable costs. In addition, the 1987 Montreal Protocol, which called for minimising the use of chlorofluorocarbons (CFCs), diverted market interest away from CFC-propelled metered dose inhalers (MDIs) to DPIs. In the end, healthcare reforms in fast-growing economies did the rest. The availability of low-cost, patient-friendly DPI options also encouraged their use in Asia and Latin America, where MDIs are often still preferred because they are generally considered more cost-effective.

> "DPIs take 50% of the total asthma/COPD market by value worldwide."

It is estimated by the WHO that, worldwide, some 300 million people suffer from asthma and 240 million people suffer from chronic obstructive pulmonary disease (COPD). DPIs take 50% of the total asthma/COPD market by value worldwide. Recent patient-focused studies using DPIs have indicated that the expectations regarding this technology have evolved; patients and pneumologists are now increasingly focusing on convenience and ease of use, favouring a compact design. Indeed, DPIs have shown great promise in their ability to deliver drugs reliably and effectively, and novel designs can ensure that future cost, compliance and safety challenges are overcome.

Some of the performance characteristics essential to DPIs are related to dose delivery, fine-particle fraction (FPF) and performance levels at varying airflows. These characteristics can differ from one powder formulation to another, and some fine tuning of either device, formulation or a combination of both may be necessary to achieve optimal performance. Micro-dosing DPIs takes this challenge to

"DPIs have shown great promise in their ability to deliver drugs reliably and effectively, and novel designs can ensure that future cost, compliance and safety challenges are overcome."

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extremes. IMA Group draws on extensive expertise to provide the most advanced solutions for DPI processing and assembly.

## CASE STUDY: INVESTIGATING OPTIMAL PROCESS PARAMETERS FOR LOW-DOSE DRY POWDER INHALERS

The aim of the study was to explore the best process parameters to achieve a 5.5 mg dose of a powder mix including one type of lactose as the carrier and another (4% in concentration) as an API simulator, using micro-fine lactose. The process was carried out as a first approach in IMA's Minima table-top capsule filling device (Figure 1) and then up-scaled to IMA's Adapta industrial-scale capsule filling machine, with 100% gravimetric fill-weight control (Figures 2 & 3). Two types of lactose were compared from different suppliers: Inhalac 251 (Meggle, Germany) and Respitose SV003 (DFE, Germany). Table 1 shows some technological characteristics of the two kinds of powder mixes.

Figure 1: IMA's Minima table-top capsule filling device.

The target dosage of 5.5 mg was achieved step-by-step after preliminary work on the Minima machine, starting from 25 mg, and then 15 mg, with both formulations. Tables 2 & 3 show the results of this first screening, including machine setting, net weight achieved, tolerances, range between minimum and maximum sample weight obtained and relative standard deviation. It was demonstrated that both formulations gave good results in terms of machinability and tolerance obtained. No significant difference was observed by the operator.


Figure 2: IMA's Adapta industrial-scale capsule filling machine.

The second step of the study was to up-scale the experience gained on the

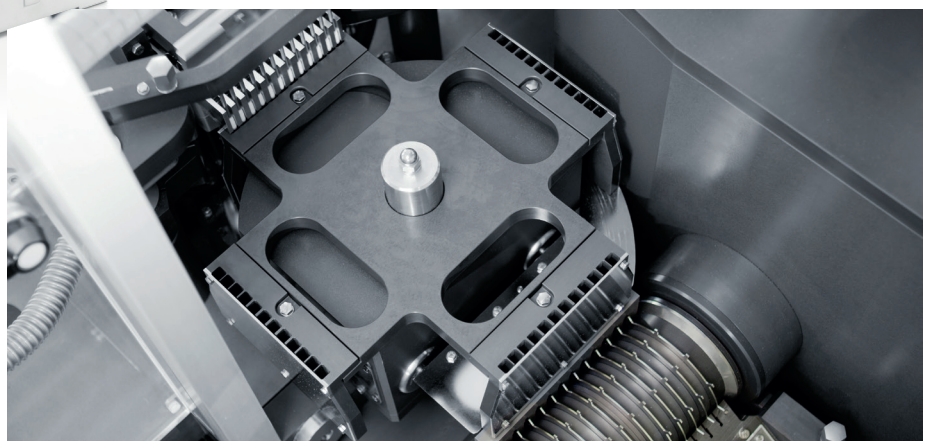

Figure 3: Adapta has 100% gravimetric fill-weight control.

| Powder Mix | Bulk Density (g/ml) | Tapped Density (g/ml) | Carr Index (%) | Loss on Drying (%) |
|---|---|---|---|---|
| Inhalac 251 + 4% lactose microfine | 0.593 | 0.780 | 23.9 (poor flowability) | 0.04 |
| Respitose SV003 + 4% lactose microfine | 0.658 | 0.812 | 18.9 (fairly good flowability) | 0.08 |

Table 1: Inhalac 251 (Meggle, Germany), Respitose SV003 (DFE, Germany).

| Average Net Weight (mg) | Doser Internal Diameter (mm) | Min-Max Weight Sample Deviation (mg) * | Tolerance Obtained (%) * | Relative Standard Deviation (%) * |
|---|---|---|---|---|
| 25.9 | 3.0 | 1.48 | +3.3/-2.3 | 2.03 |
| 14.6 | 2.5 | 0.74 | +1.6/-3.4 | 1.48 |
| 5.4 | 2.0 | 0.70 | +8.0/-6.1 | 3.0 |

Table 2: Inhalac 251+ 4% Lactose microfine, Minima trials. * Values calculated over the gravimetric fill-weight of the 100% of processed capsules.

| Average Net Weight (mg) | Doser Internal Diameter (mm) | Min-Max Weight Sample Deviation (mg) * | Tolerance Obtained (%) * | Relative Standard Deviation (%) * |
|---|---|---|---|---|
| 25.5 | 3.0 | 1.75 | +3.4/-3.4 | 2.24 |
| 14.6 | 2.5 | 0.46 | +1.5/-1.6 | 0.90 |
| 5.5 | 2.0 | 0.67 | +4.8/-8.1 | 2.9 |

Table 3: Respitose SV003 + 4% Lactose microfine, Minima trials. * Values calculated over the gravimetric fill-weight of the 100% of processed capsules.

| Lactose Type | Average Net Weight (mg) | Doser Internal Diameter (mm) | Relative Standard Deviation (%) | Machine Speed (caps/h) |
|---|---|---|---|---|
| Inhalac 251 + 4% lactose microfine | 5.5 | 2.0 | 2.52 | 85,000 |
| Respitose SV003 + 4% lactose microfine | 5.5 | 2.0 | 2.52 | 85,000 |

Table 4: Powder mixes Adapta trials.

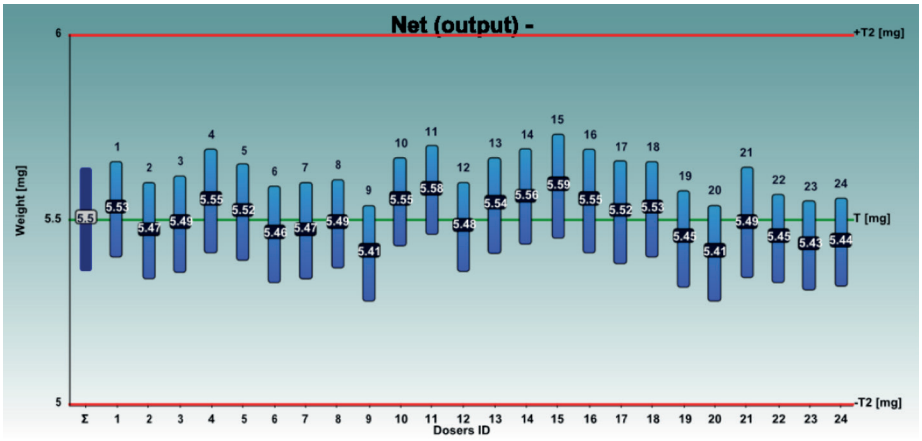


Figure 4: Inhalac 251 + 4% Lactose microfine, behaviour of the 24 dosators on Adapta.

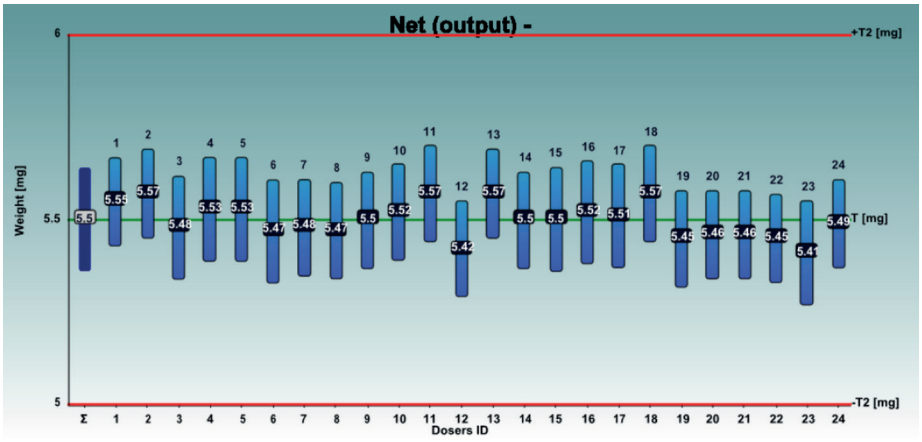


Figure 5: Respitose SV003 + 4% Lactose microfine, behaviour of the 24 dosators on Adapta.

bench-top machine to the production equipment. Since the target dose was 5.5 mg the main work was concentrated on this target with both preparations. Again, both formulations demonstrated good behaviour in the machine without any particular problems (e.g. no seizing, no empty capsules produced). This can be also seen in the final results that are summarised in Table 4, the machine settings for the powder mixes are reported, including net weight achieved and relative standard deviation for an easy evaluation.

It was confirmed that, for 5.5 mg dosing, the range between the minimum and maximum weight value in the table-top capsule filler always came to below 1.0 mg. The results obtained once formulations were tested in the industrial-scale capsule filling machine were even better. For both formulations the relative standard deviation was confirmed to be below 3%. Figures 4 & 5 show the net weights of all 24 dosators of the Adapta.

> "A major advantage of using dosator technology for processing low-dose DPIs is that the system can dose very small amounts of powders into capsules with very high precision."

## CONCLUSION

As shown by this study, a major advantage of using dosator technology for processing low-dose DPIs is that the system can dose very small amounts of powders into capsules with very high precision. This powder dosing technology does not require powder compaction to transfer the powder to the capsule, thus ensuring that the powder within the capsule is less likely to form aggregates and is maintained as a free-flowing powder. Maintaining the free flowing properties of the dispensed powder within the capsule ensures the release of powder from the capsule into

the inhaler when the capsule is pierced, thereby better controlling both the emitted dose and the FPF of the dose discharged from the DPI.

## ABOUT THE COMPANY

IMA Group is a leader in the design and manufacture of automatic machines for the processing and packaging of pharmaceuticals, cosmetics, tea, coffee and food. IMA Active, one of the three pharmaceutical divisions of IMA Group, partners with pharma for each solid dose processing phase: granulation, tableting, capsule filling and banding, weight checking, coating, handling and washing.

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## ABOUT THE AUTHORS


**Pietro Pirera** is Product Manager for capsule filling at IMA Active. He graduated with a degree in Mechanical Engineering from the University of Bologna (Italy), and has been working in the field of solid dose processing and manufacturing for more than 20 years. He is an expert in pharmaceutical engineering and the processing of micro-dosing DPIs.

**Stefano Crivellaro** is Process Development R&D Laboratory Technologist at IMA Active. He graduated in Chemistry and Pharmaceutical Technologies at the University of Bologna (Italy), and has been working in the field of automatic machines for five years. He is involved in product tests for the encapsulation of powders, DPIs, minitablets, pellets and liquids.




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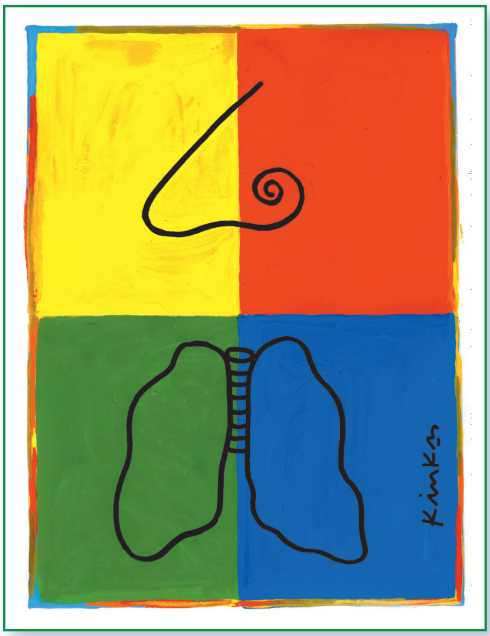

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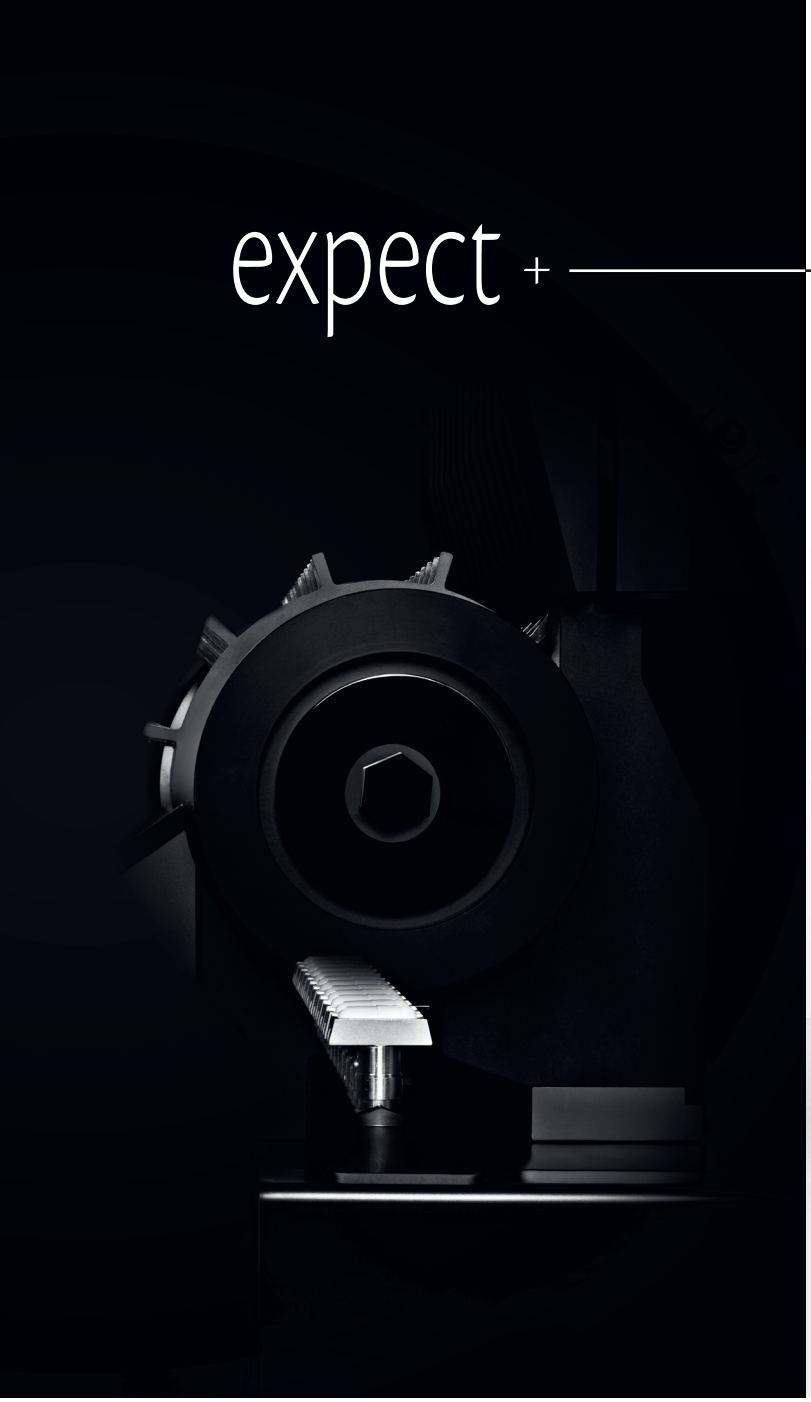

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# BILL WELCH, PHILLIPS-MEDISIZE & JOHN PATTON, DANCE BIOPHARM

**Bill Welch** has over 25 years of contract design, development and manufacturing experience, primarily serving customers in the drug delivery, health technology and diagnostics markets. In his current capacity as Chief Technical Officer at Phillips-Medisize, he leads a global development, engineering, tooling, programme management and validation organisation of over 500 people, with more than 75 concurrent schemes. Mr Welch has been with Phillips-Medisize since 2002.

**John Patton** began Dance Biopharm in 2010 with a carefully selected core team. Previously, he was the co-founder of Inhale Therapeutics (now Nektar Therapeutics), where he helped lead the development and US FDA approval of the first inhaled insulin product. Prior to founding Inhale, Patton led the drug delivery group at Genentech from 1985-1990. Before that time, he was a tenured professor at the University of Georgia. Dr Patton was the founding investor in Halozyme Therapeutics, a co-founder of Incarda Therapeutics and has served as a member of the board of directors of Activaero.

In this exclusive interview with *ONdrugDelivery Magazine*, Bill Welch and John Patton discuss inhaled insulin, connectivity and their two companies' close partnership, under which Phillips-Medisize, a Molex Company, provides manufacturing and large-scale industrialisation services for Dance's inhaled insulin products, also encompassing, under a major expansion of the agreement in December 2017, the provision of connectivity. In October 2018, after this interview was conducted, the companies announced Phillips-Medisize Chief Executive Officer Matt Jennings' appointment to Dance's Board of Directors, thus deepening the relationship still further.

**Q Cutting straight to the quick, Dance Biopharm's inhaled insulin delivery device, Dance-501, comes in the wake of the withdrawal of the (at the time) only approved inhaled insulin product, Exubera, back in October 2007. What is different with Dance-501? Do the same challenges that thwarted Exubera still exist, and how does Dance-501 overcome them?**

JP Dance-501 (Figure 1) is very different from Exubera. Exubera was the star product of the company I first co-founded. It won many technical awards and the Wall Street Journal's medical innovation of the year in 2006, it was as reliable as injection. We were very proud of Exubera. It did have its drawbacks, however, and one of them was connected with the fact that the manufacturing and packaging of the powders was very expensive. One-of-a-kind manufacturing facilities had to be made. The moisture barrier for powders is very technically challenging. Putting it in small blister packs, we had to develop a whole suite of new technologies. Then, powders by their nature can induce cough. This wasn't a major problem with Exubera, but it was a side-effect.

The other thing was that the original device, which was approved, was a large device. It took a lot of abuse online, people called it "the bong", said it was the size of a tennis-ball can, and so forth. Patients didn't really mind it, and we had a much smaller second-generation device in development.

However, while we were developing this powder product we were looking at all of the other inhaled insulin possibilities – the other types of technology. We went to a CRO over in Germany called Profil that specialises in insulin PK/PD studies and asked: "You've tested all types of inhalers, MDIs, DPIs etc. Which type do patients like the best?" Without hesitation the reply was: "The vibrating mesh from Aerogen. It's a soft, gentle mist." That always stuck with me. Then after Exubera was recalled and my company decided not to pursue it, I founded Dance and licensed that vibrating mesh technology for insulin.

> "While you can use drug delivery systems to create numerous products with one molecule, what you cannot do is charge too much. You can't have an expensive drug delivery system for a previously less expensive drug, unless you improve efficacy significantly."

Figure 1: The Dance-501 insulin inhaler uses a vibrating mesh to create a soft mist.

Dance-501 generates a liquid, aqueous mist. The patient loads the inhaler from a sterile, preservative-free insulin dropper. It's a durable inhaler, manufactured for us by Phillips-Medisize.

We've spent a lot of time working on the formulation. We have two formulation chemists, Mei-chang Kuo, PhD, and Blaine Bueche, PhD, and these guys collectively have 37 years of insulin formulation experience, both dry powder and liquid. They've come up with this marvellous high-purity soft mist from which there's virtually no cough.

There was another product approved in addition to Exubera and that's the one that's on the market now – Mannkind's Afrezza. It's also a dry powder, and both Exubera and Afrezza need to be packaged in unit-dose blister packs or cartridges. That means, for most people, they often need to use multiple blister packs to get their dose. These powder devices are like single-shot guns. You have to load the gun (load the cartridge), cock it (puncture the blister pack), fire it (inhale the dose), take the spent cartridge out, put another in, and repeat that process in a serial way to achieve the required dose.

The device that we have is designed to last for at least a year and the patient adjusts their dose by adding the required number of drops of liquid insulin formulation from the drop dispenser into the inhaler (shown in Figure 1). The drops can be placed in a matter of seconds. So it's a much faster, easier device to load. It's silent and low cost. The six-month toxicology that we've looked at is squeaky clean and in preliminary tests in humans we are seeing virtually no cough.

Dance-501 is really very different. It's smaller, far easier to manufacture, and as lung-friendly as we can make it.

**BW** I see three main areas that devices have changed in the last couple of decades. First, the emergence of biologics has driven a need for more devices, including more therapy-specific solutions. This leads to the second area, which is that with more products out there, there's an increased need for innovation to differentiate from numerous other competitors. By this I mean using the device to help differentiate the drug and that really means looking to go beyond the original inhalation devices and patents the device industry has been based on. Third, and I see this as the most important, there is a drive towards smarter and more intuitive devices. That includes connectivity, merging the device aspects of connectivity with full solutions that include digital interfaces and cloud-based database management, with the full intent of driving patient engagement and improved adherence.

Pulling all this together, how does it relate to inhaled insulin today? There's a diabetes epidemic taking place worldwide, not just in Europe and North America. If we take a look at what's happening in Asia, the numbers are staggering. Having better delivery systems that can drive patient engagement and adherence is really going to be the key to improving outcomes for those patients.

**JP** Approximately half of all new medicines are new dosage forms, new delivery systems for old molecules. That's kind of amazing when you think about it, that there are so many different products you can get out of one molecule, using different types of delivery systems. As Bill said, the devices are becoming more sophisticated, connected, cooler I think.

"It's a different world now. It's a new day for inhaled insulin and we think we're very well positioned to take advantage of that."

The need for inhaled insulin remains enormous. Fundamentally, people just don't like sticking themselves with needles. There are a few who do, I guess, but the vast majority do not. They don't like it. Avoiding needles has always been the Holy Grail in drug delivery.

While you can use drug delivery systems to create numerous products with one molecule, what you cannot do is charge too much. You can't have an expensive drug delivery system for a previously less expensive drug, unless you improve efficacy significantly. This is a key element with Dance-501. We have got to be competitive with injection, the same price or lower, unless we can show that our product is so superior medically that it justifies a higher price. One of the reasons Pfizer stumbled and had a poor launch with Exubera was that they felt they could price at a premium, but really there was no justification for it. We take that off the board with Dance. This applies more generally too, thinking in terms of the future of drug delivery, you cannot add too much cost.

Some of the challenges we faced 25 years ago still exist, but others we have really put to bed. For example, the safety and efficacy of inhaled insulin has been studied exhaustively, not only by Pfizer in our Exubera programme but also by Novo Nordisk, Lilly and others. Collectively, the published scientific output from these numerous studies form a unified database on safety and efficacy, with more than 10000 patient years of exposure. We are not being asked to repeat all of that. We do have to show some significant safety data, but the amount of money, time and effort that has already been spent on very good science means we are standing on the shoulders of that. We're able to leverage all of the previous work primarily because we've not added new excipients to our formulation, and the small amounts of excipients we do have in our products are found naturally in the lungs and other inhaled products in large quantities, so there are fewer safety concerns about them. In our ongoing discussions with the EMA and US FDA about our development programme we do not need to repeat everything done before.

The other challenge is that three major pharma companies have dominated insulin product sales in all countries, whether it be with pumps, pens or the old-style vial and syringe, it's all still invasive injected insulin with them. They have considered inhaled insulin but remain resistant to it. But their dominance of the insulin market is crumbling under their feet. With price controls, no non-invasive insulins on the horizon except inhaled, patents expiring, the emergence of biosimilars and other players being able to come into the field, the dominant insulin players will be forced to consider inhaled insulin again or let their markets dwindle.

Overcoming that original challenge has been really hard. If you remember, as soon as Pfizer dropped out, Lily and Novo dropped their advanced inhaled insulin programmes like hot potatoes. The costs of goods in those programmes were not as good as with injections and integrating that into their business was going to be complicated. It's a shame that we have this history, as most patients clearly prefer inhaled insulin over injections. But it's a different world now. It's a new day for inhaled insulin and we think we're very well positioned to take advantage of that.

**Q** **Last December PMC and Dance entered into an exciting, major partnership. Please could you describe the scope and objectives of the deal itself and talk about how the agreement came about?**

JP This is really a marvellous deal that we've struck with Phillips-Medisize. We've been working with them for a number of years. Before partnering, we conducted a thorough diligence project on the other companies that are out there. They were all world class. We ended up with about ten we were talking with and Phillips-Medisize really won us over, hands-down. It wasn't like there were just two or three companies we had to decide upon.

The scope initially was fairly limited, sort of a starter manufacturing relationship, and they performed so well for us that we were very happy to broaden this to Phillips-Medisize being our partner not only for Dance-501 but for future devices, to be our industrialisation and large-scale manufacturing partner.

And now Phillips-Medisize has brought connectivity to us. We always wanted to connect our device but previously it just seemed like it was going to be very complicated and we should "keep it simple, stupid" as they say. We thought let's get the device out there and we'll connect it later. Now, this partnership gives us the opportunity to wade right into this new field. It's very exciting, there is a lot of potential. This is the best partnership we could have for our device and we're very happy.

I don't know how Phillips-Medisize does this but they don't get bogged down with bureaucracy and overdoing things. They just get the things done that need to be done. A lot of large organisations increase the service to try to increase the money that they can make. It sounds counter-intuitive but that's really going in the wrong direction and what you really want to do is keep things streamlined and simple. When you do that, things begin to flow. That's what we have with Phillips-Medisize.

BW We have had a strong partnership on the base device for several years with Dance Biopharm, and Phillips-Medisize has a world-leading position in connected devices, digital interfaces and connected health services. As a reference you can look at the ground-breaking approval of the Bayer Betaconnect device [Betaseron® (interferon beta-1b) for multiple sclerosis] last year.

So, given that existing partnership, and our experience in connected health, it made sense to expand our partnership in this way. We'll be working with Dance on any engineering changes for connectivity, clinical supply and higher-volume manufacturing when that time comes. Additionally we've made significant investments in our connected health offerings and we're very excited to partner with Dance to go beyond the innovative Dance device into digital services that will help Dance's patients.

**Q** **Thinking about the connected device that the partnership will develop, what are the major technical, regulatory and market challenges and requirements that this project will face?**

BW We can divide the technical challenges into two categories – the device itself and the digital interface / cloud-based data management.

On the device itself, we came up with a modular, easy-to-implement approach to adding connectivity to the device. We wanted to avoid impacting anything from a regulatory standpoint, and this requirement drives our approach to how we add connectivity to an existing device. We did not want to disrupt existing firmware or architecture that could cause additional regulatory concerns downstream, so working with Dance on that aspect is critical.

Regarding the the digital interface / cloud-based data management, Phillips-Medisize is at the forefront of this field and in fact we will be announcing a major new development in our offering later this year.

[As this issue was going to press, this announcement was made as Phillips-Medisize launched its third-generation Connected Health Platform (CHP). The CHP is built on technology from the world leader in health data interoperability and includes an advanced analytics package designed for connected drug delivery devices, biosensors and regulated Mobile Medical Applications (SaMD/MMA). This enables customers not only to quickly generate views of their data but also to create a data presentation layer for analytics. The CHP can integrate healthcare data from multiple sources thanks to the enterprise master patient index.]

JP In diabetes, it's a blood glucose challenge. Patients are managing their blood sugar. So our device will be measuring insulin use, and our connectivity challenge and opportunity is to send this information to people's phones and, with algorithms, integrate it with their glucose data to help them better manage their blood sugar. Glucose monitoring and recording technology is moving ahead and changing, there are different players. The big challenge in development is not to build something that is obsolete by the time you get approval. You build into your device the space and capabilities, including for sensors and signalling capability to send and receive data, but you don't build that into your clinical endpoint. You don't need to. The clinical development and the integration of connectivity are done in parallel.

We're building the hardware and capability in our device, and our app, to receive and potentially process glucose data but we haven't partnered with anyone yet. We are leaving that open. Meanwhile, the device we're making is going to have that capacity and the software can change as we wish and as the market dictates. So we're taking our device through the clinical programme. In parallel we're developing the connectivity and building the app and, ideally, they will both come to market as separate products but married to each other.

The other challenge that we have is handling the data. We at Dance are relative "babes in the wood" in this area, and climbing the learning curve, but this is such an enormous area now. New things are happening all the time. We're really grateful to be partnered with Phillips-Medisize, who are on the cutting edge.

A key element is giving doctors back their time. Right now there's an explosion of connectivity work and innovation. Coming soon in the future, the data from connected devices will be processed and brought back to the patients, doctors and other caregivers in such a way that their lives will be made easier and more rewarding. It's going to be a giant boon to the healthcare system, but there are a lot of growing pains. We are repeatedly told that and other healthcare providers don't know what to do with this avalanche of data. It has to be crunched, processed and synthesised into crisp, meaningful insights that make people better at doing their jobs.

Q **Please could you each talk about how this agreement fits within the broader context of your respective organisations' strategies?**

JP Dance has been exclusively focused on inhaled insulin – first, second and third generation products. Even though this is basically an insulin drug product, what everybody sees and everybody holds, the patient interface, is really the inhaler. This is an absolutely critical part of our overall business strategy.

Obviously our insulin partner – Dongbao [Shanghai, China] is our global insulin supplier, and development partner in China – is of strategic importance. As we go downstream we will be entering into marketing partnerships and pharma partnerships also.

In terms of how our relationship with Phillips-Medisize fits within this context, when we go to form any pharma sales and marketing / commercial partnerships we are much, much stronger with a partner like Phillips-Medisize, who we see as the premier medical device company in the world. Having them as our partner is ideal – this is just what we need to advance our business.

BW The relationship with Dance fits with our Smaller and Smarter strategy, and we've advanced our Smaller and Smarter thought processes into the areas of connected health and digital interfaces as well. We remain committed to being a contract development manufacturing organisation serving our customers, and our approach is to be an innovation engine that is going to enable differentiated devices for our customers' drugs and connected devices for their patients. The whole drive behind this, of course, is to bring a device and connected health system together to provide a full connected system to improve outcomes for patients and a leading market position for our customers.

One of the things that is really great about the Dance device is that its life will be one-year minimum. So once you've got an electronic-enabled device, meaning it needs power and a brain, a processor, in order to function, that is a natural platform on which to add on connectivity, to make it a connected device. So the device is a really natural fit for the way the world is headed.

Another interesting aside on this is that when you've got the electronic device, and it's going to be used for many, many doses, that changes the cost profile of how we evaluate the cost of connectivity. It's very difficult today to have a disposable device with electronics on it, just because of the cost of the electronics. To address this, we have a low-cost connectivity electronics solution in development. You've got to find a way to bring down the cost per dose delivered, as John mentioned earlier. Today, key to that is having a device that has a long lifetime, and in this case a long lifetime with electronics in it.

Q **Back at the start of this century the insulin pill was talked about a lot as the natural next step after inhaled insulin. The insulin pill hasn't materialised though and, although not impossible to connect an oral dosage form, it is very difficult. In terms of patient centricity, how does a connected insulin inhaler stack up against an insulin pill?**

JP The dislike of injection is deep and means a pill would be welcome. And you could connect a pill to

> "Especially for diabetes patients, and patients with other chronic diseases, the ability to take control – that empowerment – is the key."

a pill dispenser and it could show on your phone, so it could be a kind of connected system if you wanted it to be. Insulin is a special case though. A pill would be ideal if it could be made but the problem is you have to overcome some major laws of physics and biology in order to do it. These are virtually insurmountable. I spent sixteen years before working on inhalation studying oral drug delivery, particularly oral drug delivery of insoluble molecules and macromolecules. The barriers are formidable. I've spent the subsequent twenty years on inhalation because I know it works.

We're so excited about having our inhaler connected because it's just so much more engaging. My FitBit now analyses my sleep and tells me when I'm in deep sleep, REM sleep etc, for example. Connected devices allow you to get in touch with your body. This can be deeply gratifying, especially when you're managing your health. Clearly, having an insulin inhaler that is connected is much better than having an insulin inhaler that is not connected. Because of the great patient empowerment potential of a connected inhaler you have to connect it if you can. You're stupid if you don't.

**BW** Especially for diabetes patients, and patients with other chronic diseases, the ability to take control – that empowerment – is the key. This is how connectivity can drive patient engagement and hopefully improve outcomes.

**Q** **Finally, I wanted to get personal! Still thinking about the recent partnership between PMC and Dance, and the other recent developments and breakthroughs you've each been involved with, I wondered if you could talk about these as part of your drug delivery stories and careers?**

**BW** Fortunately from a personal standpoint I remain in excellent health and I've never actually needed a drug delivery device, and I'm very grateful for that. However, having family members and loved ones who need devices it does become part of my personal mission every day to figure out how to get better devices on the market.

As a company, we started in this field about ten years ago and we were largely a US-based company. We started expanding our development and electrical engineering expertise within Phillips-Medisize. Then in 2016 we acquired Medicom. That acquisition was made due to their expertise in electrical engineering, embedded software and connected health. Finally, we were acquired by Molex later in 2016 and that rounded us out because we added electronics manufacturing at scale with facilities in Ireland, Mexico and China, thereby providing excellent supply chain management covering three continents and most of the world's population.

**JP** I was hired by Genentech in the 1980s to find a way around the needle for large molecules that cannot go through the gut. At that point the product was growth hormone. That was when we discovered that the lungs were open, the only door that was open in the body to these large molecules. I worked on that project for five years at Genentech, doing all of the preclinical studies showing that it works, that it was safe, looking at formulation and final potency.

I could not convince them that the lung was a good way to go, so I left to found a company, whose principal molecule was insulin and we developed Exubera. I've been working on inhaled insulin for 28 years and it's still unfinished business! As for what the future holds, I want to get this across the goal line and make it stick.

You know, people are dying, because they don't like injections. They refuse or put off injections, they take less insulin than they need, the disease progresses and it's killing them. It genuinely upsets me that this thing is not widely available already with all the work that has been done, all the safety and efficacy studies.

I am involved in a lot of other drug delivery projects; there are many other drugs – indeed many other peptides – that could be inhaled to great advantage, and Dance is now starting to develop some of these and create a pipeline. But I will continue to champion inhaled insulin until it becomes widely accepted.

Returning if I may to our relationship with Phillips-Medisize and Molex, I feel that entering into this partnership really marked a point when the project turned the corner. Bill has believed in what we're doing and without Bill's support I certainly wouldn't have been talking to you today, and we might not have been able to get this thing going at all. Now, with the support we have from Phillips-Medisize, I think we've got a great shot. We're getting some fantastic new people working for the company – a great new CEO, in Anne Whitaker, board members, executives, advisors – we're getting close.

It's kind of a simple story – we have to make this happen.


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# 5 THINGS TO CONSIDER
## WHEN MANUFACTURING CONNECTED DRUG DELIVERY DEVICES

The estimated number of connected drug delivery devices continues to increase and the impact of this trend could be significant, explains Phillips-Medisize, a Molex Company

While digital connectivity or connected health can improve the coordination and delivery of patient care, original equipment managers need to keep these five things in mind when creating connected drug delivery devices:

1. **Development strategy and design consideration**
2. **Situation analysis and patient compliance**
3. **Connectivity ecosystem**
4. **Wireless subsystem**
5. **Security of device and information**

As the Internet of Things continues to become an integral part of people's lives, the opportunity to use it within drug delivery device applications remains promising. The manufacturers and device designers must identify, investigate and overcome these challenges so that the implementation of wireless and other related smart technologies can be achieved. When done successfully, connected systems enable the patient and caregivers to have a 360° view of both the patient and the disease – not only to manage adherence, but to improve results by understanding the effect of the regimen.

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# CITRUS FRUITS INSPIRE THE NEXT GENERATION OF AIRBORNE DRUG DELIVERY

In this article, Andrew Dickerson, PhD, Assistant Professor, University of Central Florida – Mechanical & Aerospace Engineering FaST Lab, discusses recent research undertaken by his team into the mechanics of liquid microjets created naturally by citrus fruits, and how they could be the key to a new design of drug delivery device.

## WHAT WILL CITRUS-INSPIRED TECHNOLOGY ENABLE?

Liquid microjets have been of interest to the scientific community for their use in dermal drug delivery,[2–3] micro-fabrication,[4] and chemical synthesis.[5] Microjet technologies have been made possible by careful control of piezo-electric drivers, microfabrication of precision nozzles and carefully tuned fluid properties. It is critical to control the breakup distance of these jets, so that the drops they produce find the intended location and are of the correct size. Traditionally, technologies which produce tuned microjets require precision-machined parts, pumps and electronic controls, which carry a large cost. While studies of synthetic microjet production and use abound, few have considered the microjets found in nature, which may provide alternative methods for robust jet production through the clever choice of materials and geometry, without the need for cumbersome supporting systems.

> "The microjets which emerge from citrus peels under bending loads may provide the secrets for how to disperse fluid from disposable, single-use devices. Such devices can be easily tailored for dose quantity, rate and droplet size distribution."

In inhalable drug delivery, drug dispersal has been accomplished by atomising fluids by forcing them through a nozzle at high-speed, as is the case with a standard metered dose inhaler (MDI), or by allowing a liquid to transition into an easily inhaled vapour, such as with a nebuliser.

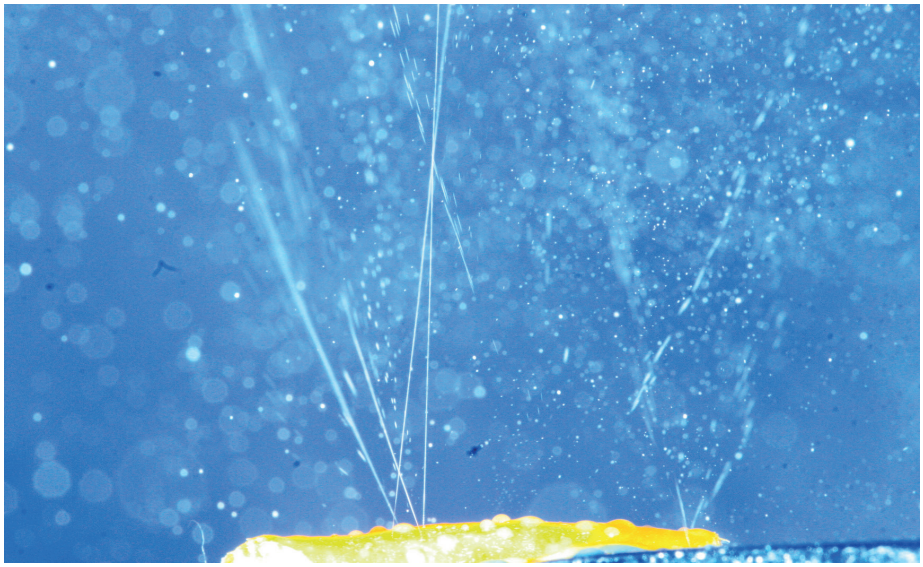

Figure 1: Image of oil jets issuing from sub-surface oil glands in the highly bent peel of a navel orange. The highly unstable jets issue at velocities that produce motion blur in the photo, giving the appearance of jet stability over longer distances.[1]

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The former technique allows inhaled doses to be portable and administered when required. Many patients need inhalers for emergency use and may never consume the many doses available in the device before expiration. The resulting added cost to the consumer and cost-prohibitive dispersion of such devices to underserved populations can be remedied with lower-cost manufacturing and single-use devices.

The microjets which emerge from citrus peels[1] under bending loads may provide the secrets for how to disperse fluid from disposable, single-use devices. Such devices can be easily tailored for dose quantity, rate and droplet size distribution. They will be easy to use, lightweight and appropriate for any fluid, from creams to the lightest and most volatile disinfectants. Applications may range from oral inhalation to dermal and ocular applications.

## WHAT ARE CITRUS JETS?

The avid citrus consumer knows it is impossible to peel an orange and keep your fingers dry, even if the precious fruit inside remains unmolested. Others will have noticed the ephemeral and fragrant mist that is emitted when peels are broken and tiny fluid jets erupt into the air. The ejected fluid has a density about 80% that of water and a nearly identical viscosity. Even with the naked eye, one can appreciate the magnificence of these 100 µm diameter "citrus jets". With a macro lens and high-speed camera, the beauty of this inconspicuous event can become fully realised.[1] One such example is shown in Figure 1. These free jets are best witnessed after a fruit is carefully peeled and by bending the peel such that the zest, or rind, faces outward (Figure 1 & Figure 2a). Oil reservoirs reside in the albedo, a compressible foam-like layer commonly known as the "pith", which fills the space between the fruit locules and the thinner, stiffer flavedo or "zest".[2] The zest caps the reservoirs and shields the

"Even with the naked eye, one can appreciate the magnificence of these 100 µm diameter "citrus jets". With a macro lens and high-speed camera, the beauty of this inconspicuous event can become fully realised."

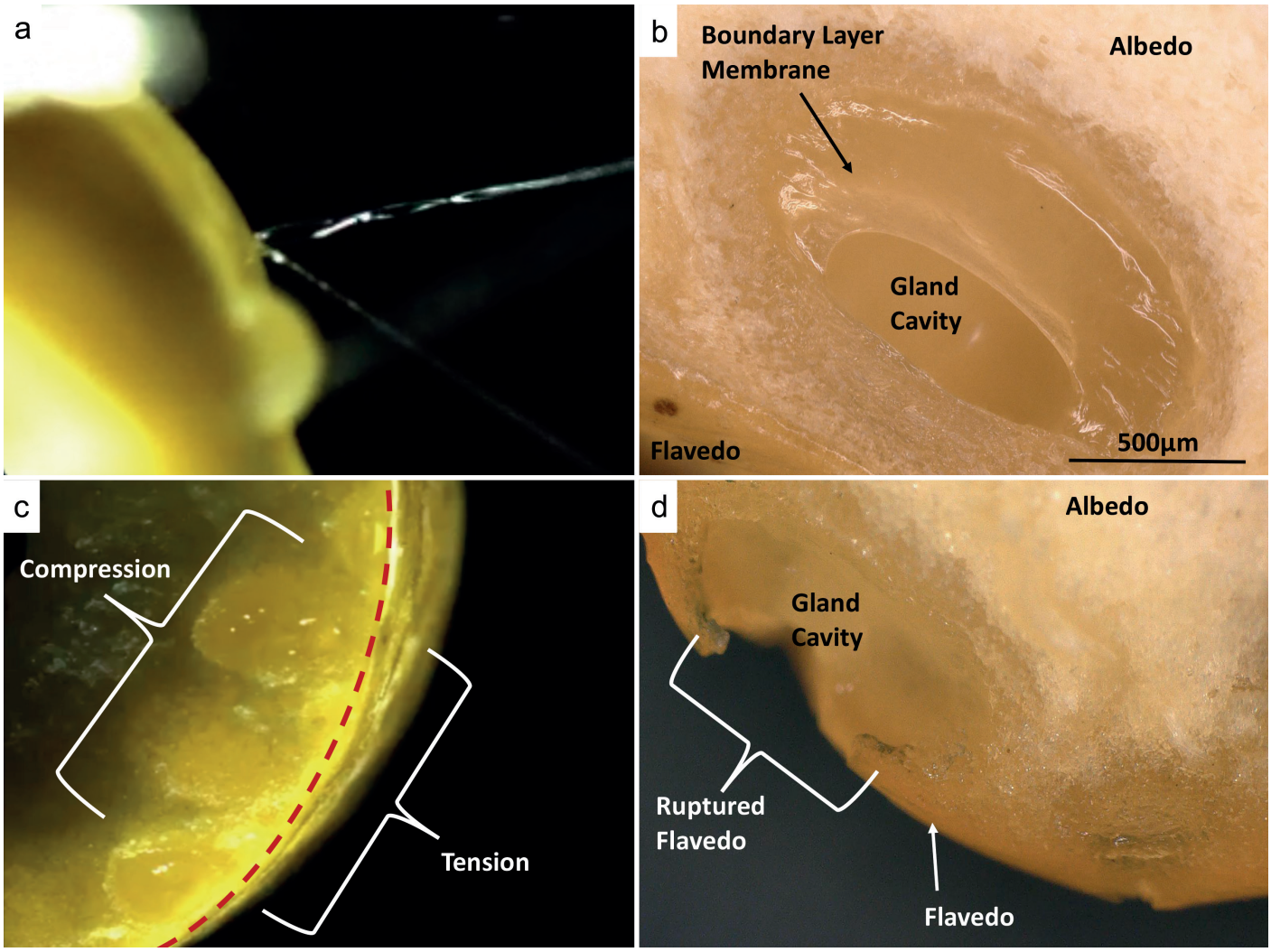


Figure 2: Microscopic images of (a) oil ejection from oil gland reservoir through the flavedo, (b) a cross- sectional view of a singular oil gland with boundary layer membrane partially intact, (c) a group of unbroken oil glands subjected to external bending, and (d) a cross-sectional view of an oil gland after rupture. The gland in (d) appears slightly collapsed due to ingress of the albedo toward the flavedo during rupture.[1]

fruit from the environment. Gland reservoir placement within the peel and relative size can be seen in Figures 2b and 2c. A layer of glossy boundary cells separates the oil in the reservoirs from the absorbent pith, which is clearly shown in Figure 2b, where the window into the reservoir is a fortuitous result of cutting.

It is believed all fruits in the citrus family have been developed by cross-breeding three core fruits in the last 1000 years: the mandarin orange, pumelo, and citron.[6] All citrus fruits tested in our study[1] exhibited oil jetting behaviour but, despite this shared characteristic, there remains no determinate evolutionary function of the oil, and no mention of oil atomisation in the literature to the author's knowledge.

Citrus jets are remarkably fast and very brief. We measured jet exit velocities across all hybrids within two weeks of purchase, finding a singular minimum of 1.58 m/s (mandarin) and singular maximum of 29.65 m/s (navel orange), with an average 8.47 ±4.03 m/s (n=545) across all species.[1]

The internal gauge pressure within the oil reservoirs enabling the average jet speed is about one atmosphere. A greater fluid pressure at the instant of zest failure produces faster jets.

## MECHANICS OF MICROJET PRODUCTION

Bending the peel increases stresses in the zest, with the most perceptible increase in the direction normal to the dashed blue line drawn in Figure 3a-d, and increases pressure in the fluid.[1] The outer surface of a reservoir, as seen looking down onto a zest, can be seen in Figure 3b-d and is outlined by a dashed black ellipse. As the magnitude of bending increases, a failure precursor wrinkle forms on the zest surface atop the oil reservoir, as seen in Figures 3c and 3e. Further bending increases in-plane stress in the zest and fluid pressure below, inducing the brittle fracture seen in Figure 3d. The tear in the zest unveils a channel to the gland reservoir. The crack in Figure 3d begins atop the reservoir and is arrested by stomata surrounding the gland. Stomata are outlined in Figure 3e and are small, nearly circular voids in the zest.

The strength of the zest topping each oil pocket governs how much fluid pressure can build. We also find the strength of the zest is related to its stiffness by applying theory from fracture mechanics.[1] The stiffer the zest, the faster the jets that rocket through it. This mechanism also requires the pith underneath the zest to be soft. In fact, it is two orders of magnitude softer. The zest is similar to acrylonitrile butadiene styrene (ABS) plastic, while the pith is like a foam pillow. Measurements of material stiffness were done with a tensile tester, which measures how much force is needed to stretch a material. Finite-element simulation (Figure 4) shows this contrast in material properties is key for jet creation, allowing the pith to compress while the zest is stretched. The greater the stiffness contrast between these two materials, the greater reservoir pressures bending the peel can accomplish. The final secret to a fast jet is the geometry of the oil reservoir, which is deeper than it is wide. This allows more of the fluid volume to reside in the region of the pith being compressed.

> "Parcels of fluid in the reservoir will experience 5,100 g of acceleration before exit, which is comparable to the acceleration of a bullet leaving a rifle. In nature, this acceleration is outdone only be the mantis shrimp at over 10,000 g and dung cannon fungus at 180,000 g."

## FLUID MICROJET STABILITY

Following emergence from a reservoir at nearly 10 m/s, jets rapidly break up into

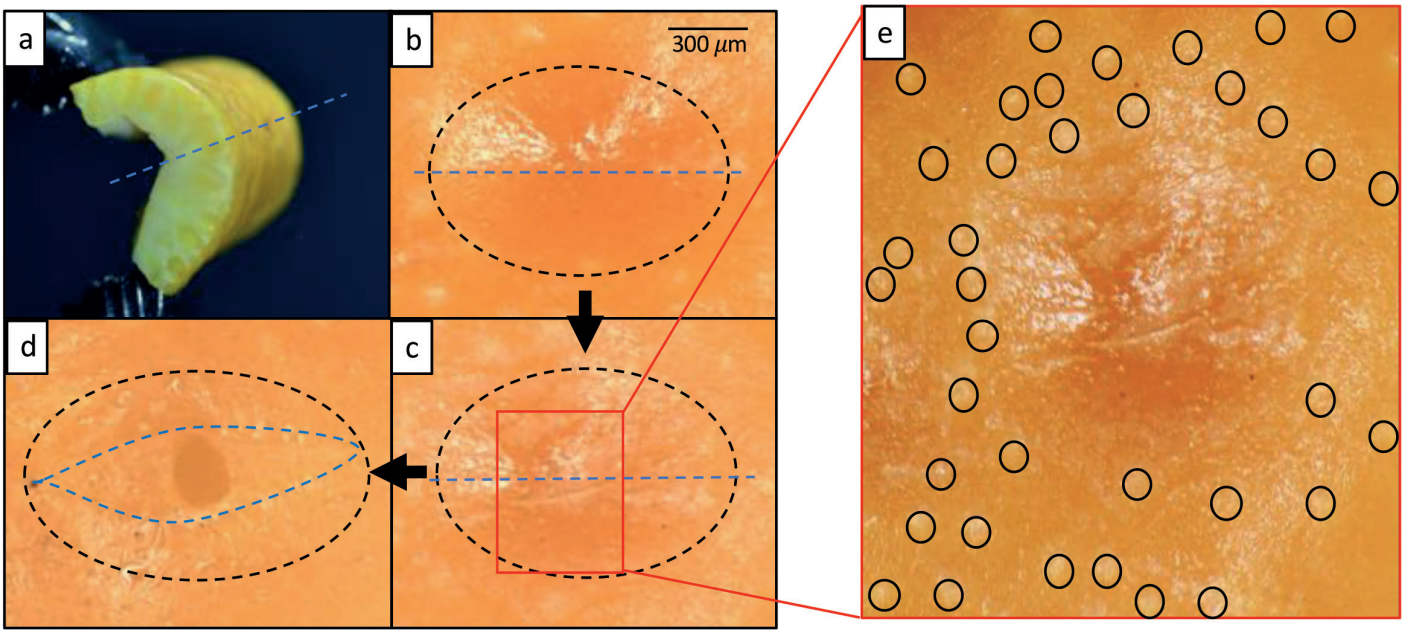


Figure 3: The process of glandular rupture. The process begins with bending a peel (a). From an external view of the flavedo, the unstressed gland in (b) is stressed to imminent failure in (c) and to failure in (d), which shows the channel leading to the oil reservoir. A zoom box of a crack forming prior to failure is shown in (e). Black dashes outline gland extents beneath the flavedo and the blue dashed lines represent the line normal to externally applied stress.[1]

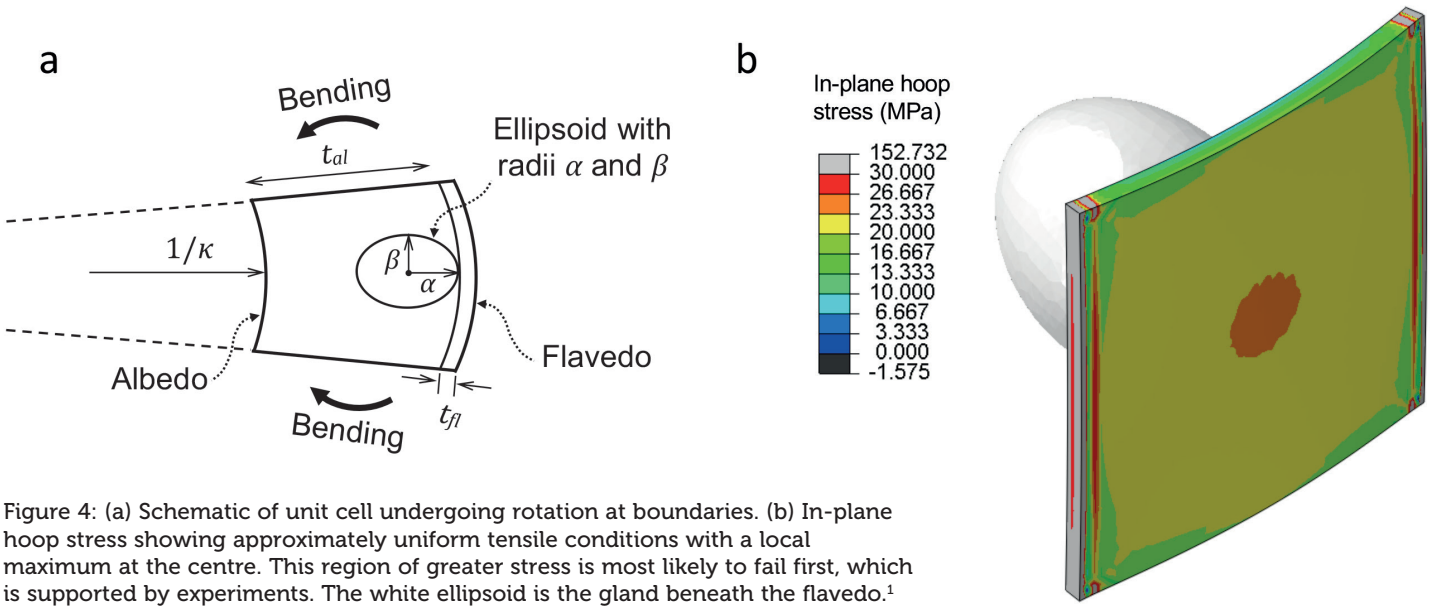


Figure 4: (a) Schematic of unit cell undergoing rotation at boundaries. (b) In-plane hoop stress showing approximately uniform tensile conditions with a local maximum at the centre. This region of greater stress is most likely to fail first, which is supported by experiments. The white ellipsoid is the gland beneath the flavedo.[1]

streams of droplets, losing all streamline velocity in less than 100 ms. The breakup of a coherent jet into a stream of droplets occurs within 2 mm of the zest surface.[1] In citrus jets we witness major-minor axis switching, a perturbation which is the result of eccentric orifices and one that encourages breakup. The orifice geometry through which citrus jets issue is often elliptical in nature, and at times shrouded by irregular edges of the torn zest. This rapid breakup allows the droplets to be advected easily and evaporate quickly.

## DISCUSSION

The size of citrus oil reservoirs and the velocity of oil ejection result in large accelerations by jetting fluid.[1] Liquid at rest in the pockets is accelerated to velocities in excess of 10 m/s over the distance of ≈1 mm. Therefore, parcels of fluid in the reservoir will experience 5,100 gravities (g) of acceleration before exit, which is comparable to the acceleration of a bullet leaving a rifle. In nature, this acceleration is outdone only be the mantis shrimp at over 10,000 g and dung cannon fungus at 180,000 g but is perhaps unmatched in the plant kingdom.

Our results[1] and finite element investigations predict reservoir fluid pressures in agreement with simple fluid theory, but it would appear citrus fruits achieve a suboptimal configuration from the standpoint of achieving even higher pressures by not maximising the disparity between pith and zest stiffness. This material synthesis is likely limited due to the biological origin of the material. Therefore, the system leverages reservoir geometry for enhanced performance (high bursting pressure) indicating the observed elliptical geometries of the reservoirs. Such is a recurring theme in many biological systems where the limitations of material properties are overcome by the geometry or topology of the structure. In contrast, an outer layer with very low strength would not withstand the stresses associated with pressure rise in the small reservoirs and would thus rupture at lower pressures and produce slower, yet more stable jets. This indicates that synthetic devices mimicking citrus peels could be tuned to offer a wide array of jetting behaviours.

> "Synthetic devices mimicking citrus peels could be tuned to offer a wide array of jetting behaviours."

## FUTURE WORK

Now that the physics underlying citrus microjet production are well understood, we must explore synthetic materials which can be assembled into a citrus-like composite structure to perform, or even out-perform, citrus. This notion comes with challenges, but these could be readily overcome with the aid of partners in interested fields. Materials comprising a system mimicking citrus must possess an appropriate stiffness, thickness, be easily cut and machined and be chemically non-reactive.

The process by which two materials are joined will have a large influence on material fracture. Such fracture should ideally be brittle, as ductile fracture could allow cavity expansion and decreased performance. Material properties and desired ejection volume will drive reservoir volume, shape and packing fraction. An effective device must also achieve the desired droplet size distribution and dispersal distance, which are not mutually exclusive. By using stronger or thicker "zest" materials, we may generate higher fluid pressures, but will likely make jets break up more rapidly and have a greater distribution in droplet size. The spectrum of available materials will generate an assortment of orifice geometries, greatly influencing breakup.

Finally, it is critical we explore potential applications for this technology, which could reach asthmatics, the fragrance industry, dental hygiene, skincare and more.

## ABOUT THE COMPANY

Headed by Dr Andrew Dickerson, the Fluids and Structures (FaST) Lab in the Mechanical and Aerospace Engineering Department at the University of Central Florida investigates the physics governing flow at the interface of fluids and deformable solids. The lab's research is inspired by natural systems and combines fundamental fluid and solid mechanics. FaST is excited to work with industry partners to commercialise the discoveries unveiled in the lab.

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## ABOUT THE AUTHOR


**Dr Andrew Dickerson** is an Assistant Professor at the University of Central Florida and holds a PhD in Mechanical Engineering from the Georgia Institute of Technology. He is a fluid dynamicist with expertise in the mechanics of interfaces between fluids such as air and water, and a researcher in the biomechanics of animal locomotion. This research links areas of mechanical engineering, mathematics and biology to make an impact in medicine, robotics and conservation. His work has resulted in publications in a number of high-impact journals such as *Proceedings of the National Academy of Sciences, Journal of the Royal Society Interface, and Physics of Fluids*.

Over the years, his research has also played a role in educating the public in science and engineering. Dr Dickerson has been an invited guest on numerous television and radio shows to discuss his research, including Good Morning America, National Public Radio, The Weather Channel and Discovery Channel.

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# INTERTEK'S CENTRE OF EXCELLENCE FOR INHALED AND NASAL BIOLOGICS

Here, Chris Vernall, Business Development Director, Intertek Pharmaceutical Services, discusses the significance and difficulties of biologics in the inhalables sector, and how Intertek's Centre of Excellence for Inhaled and Nasal Biologics provides valuable services for those developing products in this area.

## THE SIGNIFICANCE OF INHALED BIOLOGICS

Inhaled biologics have been forecast to grow in importance due to the fact that inhalation presents a highly attractive route for the administration of various classes of large molecule, particularly for the treatment of respiratory diseases. The major driver here is the potential for local, targeted delivery to the lung, opening up new treatment pathways for diseases such as cystic fibrosis, asthma and lung cancer. Delivery directly to the lung is likely not only to be more efficacious, but also to require less of the active ingredient compared with other routes of delivery.

Systemic delivery of biologics is also possible via the lungs or the nose. Drug delivery via these routes is more convenient and less painful compared with other routes of administration for biologic drugs, which are generally administered intravenously.

## CURRENT STATE OF THE MARKET

There are a small number of inhaled biopharmaceuticals currently on the market, these being Pulmozyme® (dornase alfa) from Genentech, a nebulised cystic fibrosis (CF) treatment and Mannkind's Afrezza® (insulin) dry powder. There are several others in development including peptides, e.g. Bio-11006 (BioMarck) – a novel peptide chain for lung cancer and ARDS; bacteriophages, e.g. AB-PA01 (Ampliphi BioSciences) – for drug-resistant P aeruginosa lung infections; and oligonucleotides, e.g. AZ1419 (AZ/DynaVax) – for asthma.

> "The complexity of biologics and the difficulty of delivering a drug to the lungs and the nose means that this area of pharmaceutical development is particularly challenging."

## WHAT ARE THE MAJOR CHALLENGES?

The complexity of biologics and the difficulty of delivering a drug to the lungs and the nose means that this area of pharmaceutical development is particularly challenging. Biologic drugs have complex structures fundamental to their function and are much larger than classical small molecules. They are susceptible to a wide range of degradation routes, which can impact the safety and efficacy of the drug.

Protein structures have limited stability and can easily unfold under only mild stress. Aggregation, where the protein self-associates, is one of the most common issues, whereas fragmentation, deamidation, hydrolysis, oxidation, isomerisation, succinimidation, deglycosylation, disulphide bond formation/breakage and other crosslinking reactions can all play their

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"The Intertek Centre of Excellence for Inhaled Biologics deploys a strategic programme of orthogonal analytical methods which aim to fully characterise the biological entity, but also establish whether the device delivery mechanism has adversely affected parameters such as structure, purity and the activity in line with the ICH Q6B Guidance."

part in degradation. In addition to this, inhaled and nasal products require specific testing to assess delivered dose uniformity from the device and the particle size of the drug emitted.

In regulatory terms, inhaled and nasal biologics will require characterisation as per ICH Q6B, as well as the specific respiratory testing outlined in documents such as the EMA guideline on the pharmaceutical quality of inhalation and nasal products (June 2006) or the US FDA metered dose inhaler (MDI) and dry powder inhaler (DPI) products quality considerations guidance (April 2018).

## HOW CAN INTERTEK HELP OVERCOME THESE DEVELOPMENT CHALLENGES?

Intertek has over 30 years' experience in biologics characterisation, from small peptides up to monoclonal antibodies and conjugated species, and has provided contract testing, formulation and clinical manufacturing services for inhaled and nasal drug products for a similar period of time. The Intertek Centre of Excellence for Inhaled Biologics (Figure 1) deploys a strategic programme of orthogonal analytical methods (Table 1) which aim to both fully characterise the biological entity and establish whether the device delivery mechanism (e.g. actuation through an inhaler) has adversely affected parameters, including structure, purity (aggregation, fragmentation etc.) and the activity (potency), in line with the ICH Q6B Guidance.

Figure 1: Laboratory at Intertek's Centre of Excellence for Inhaled and Nasal Biologics.

| Analysis | Methods |
|---|---|
| Structural Characterisation and Confirmation | Amino acid composition (e.g. by AAA)<br>Protein sequencing & terminal amino acid sequencing (e.g. by MALDI-MS and HPLC-MS/MS)<br>Peptide mapping (e.g. by HPLC-MS) |
| Higher Order Structural Analysis | Secondary structure (e.g. by CD, AUC and FT-IR)<br>Tertiary structure (e.g. by NMR, Fluorescence, DSC) |
| Purity and impurities | Content assay and impurities (e.g. A280, SDS-PAGE, LC-MS, CIEF, CE)<br>Aggregates (e.g. AUC, DLS, SEC-MALS) |
| Potency and biological activity | Biological response or *in vitro* model (e.g. cell-based assay, ELISA) |

Table 1: Analytics for biologics.

Intertek's team of expert formulation scientists have extensive experience in product development of nasal or nebulisation solutions, suspensions and dry powders. For biologics, initial formulation work is focused on excipient selection and device compatibility. Liquid formulations will need to include suitable surfactants, anti-oxidants and buffers. If a dry powder formulation is considered, lactose is often not a suitable carrier and a spray dried matrix may need to be considered. Intertek routinely supports this area of formulation development for large molecules, alongside device screening

to support an optimal combination product.

With the expansion of Intertek Pharmaceutical Services' facilities in the UK (Melbourn and Manchester), including increasing the footprint of its laboratories and continual investment in technologies and recruitment, its Centre of Excellence for Inhaled and Nasal Biologics is well positioned to meet the challenges of this growing market. Intertek understands that this complex class of drug products offers multiple potential benefits and have therefore developed the advanced toolset needed across formulation, product characterisation and drug delivery to accelerate development processes.

## ABOUT THE AUTHOR

**Chris Vernall** is the Business Development Director at Intertek Melbourn. He is an analytical chemist by training and holds a Masters Degree from Loughborough University. Mr Vernall started his career at Pfizer, as a Materials Scientist working on novel inhaled compounds, before moving to Nanopharm where he worked in formulation, specifically with DPIs and MDIs. He then made the move to Intertek Melbourn as a Senior Analyst, before taking up a role in Business Development. He started in his Director role in April 2017.

## ABOUT THE COMPANY

With over 25 years of experience in supporting clients' orally inhaled & nasal drug product development, Intertek Melbourn provides product performance testing, method development/validation, stability, CMC support, formulation development and clinical manufacturing capabilities. The company's services are designed to provide the right information at the right time ensuring total quality assurance for products and processes. Intertek Pharmaceutical Services' network of more than 1,000 laboratories and offices and over 43,000 people in more than 100 countries, delivers innovative and bespoke assurance, testing, inspection and certification solutions for its customers' operations and supply chains across a range of industries worldwide.

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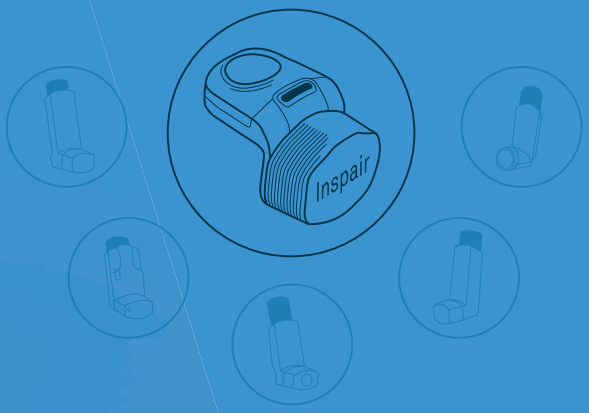


01

## Sensing technology

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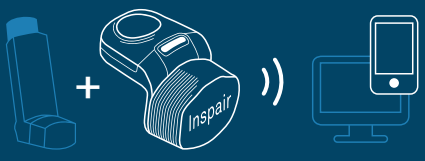


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- Doses Inhaled

02

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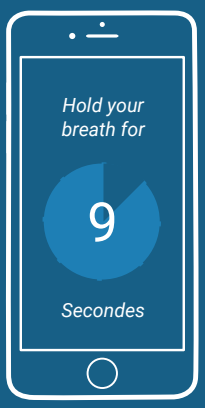


03

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# INHALABLE THERAPEUTIC BIOLOGICS, A PARADIGM SHIFT FOR NON-INVASIVE EFFICIENT MEDICAL TREATMENTS

**In this article, Francesca Buttini, PhD, Associate Professor, University of Parma, and Susana Ecenarro Probst, Director of Scientific Business Development, Qualicaps, discuss the rising prominence of biologics in the pharmaceuticals market and how dry powder inhalers utilising hard capsules are a promising potential delivery method for these new drugs.**

Therapeutic biologics led the top selling drugs in 2017[1] and are expected to experience a gradual growth in the coming years, due to a deeper understanding of some disease pathologies and further developments in biochemical engineering (Figure 1). From recombinant human insulin to interferons and monoclonal antibodies (mAbs), biologics have proved to be very effective therapeutics, improving the quality of life of patients with diabetes, infectious diseases, haemophilia and cancer.

Over 20 mAbs have been approved by the US FDA and the European Medicines Agency (EMA). Since the first approval of adalimumab in 2002, human or humanised mAbs have captured special attention and become a promising growth category within targeted therapeutic agents.[2] The FDA Center of Drug Evaluation and Research (CDER) has regulatory responsibility, including premarket review and continuing oversight, over the following categories of therapeutic biological products:

- Monoclonal antibodies for *in vivo* use.
- Plant, animal, human, or micro-organism-derived therapeutic proteins and recombinant versions of these products.
- Immunomodulators: proteins or peptides that are intended to treat or prevent disease by inhibiting or modifying a pre-existing immune response (non-vaccine and non-allergenic products).
- Monoclonal antibodies, cytokines, and growth factors intended to mobilise, stimulate, decrease or otherwise alter the production of cells *in vivo*.

> "The advantages of pulmonary delivery over the oral route include the avoidance of subjecting the API to the harsh environment conditions and the enzymes in the gastrointestinal tract, as well as first-pass metabolism."

The use of the inhalation route for delivering proteins and peptides is becoming a viable proposition. Investigation into pulmonary delivery of systemic drug therapies is focused on chronic diseases and refractory ailments of both small and large molecules, including engineered macromolecules.

Although it has mainly been used to treat or alleviate local disease conditions of the lungs (asthma and chronic obstructive pulmonary disease), the advantages of pulmonary delivery over the oral route include the avoidance of subjecting the active pharmaceutical ingredient (API) to the harsh environment conditions and the enzymes in the gastrointestinal tract, as well as first-pass metabolism.[3] Additional

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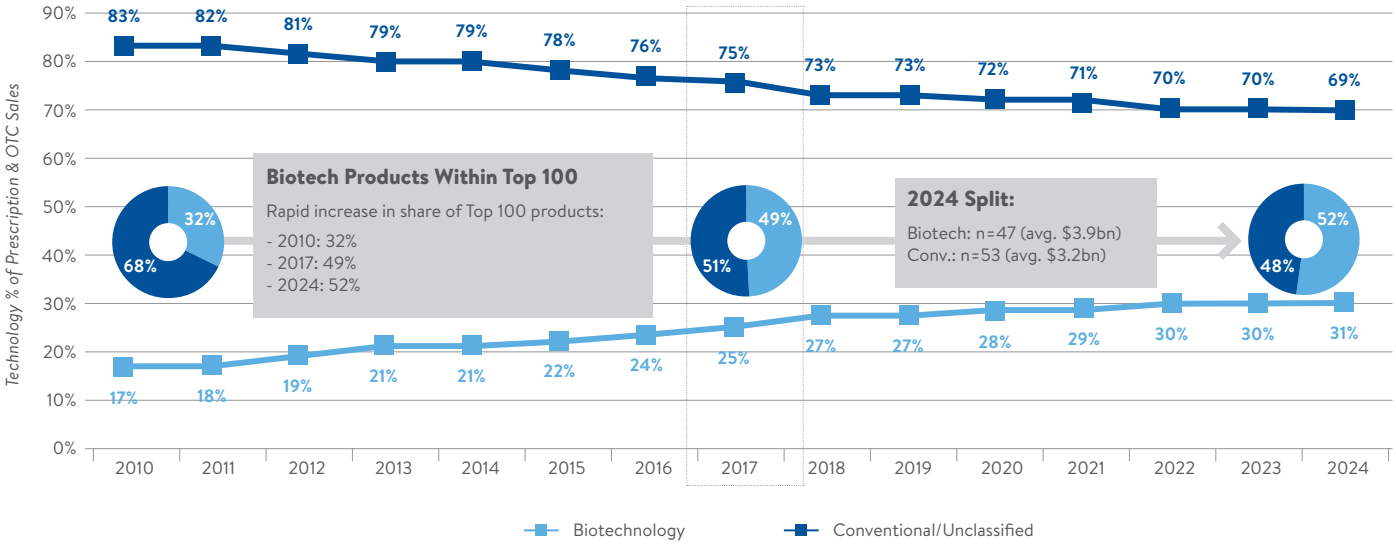


Figure 1: Worldwide prescription drug and over-the-counter (OTC) sales, biotech versus conventional technology.[1]

benefits of using pulmonary administration for therapeutic biologics include:

- Effective targeting allowing for a reduction of the total dose to be given. This reduces the adverse systemic side effects.
- Greater convenience for patients and subsequent improved compliance with the treatment compared with the invasive parenteral route.
- Dry powders for inhalation are stable, and are formulated to avoid the need for cold-chain storage or reconstitution of powders into solutions for nebulisation, which could represent an important advantage for antibiotic therapies or vaccination programmes in tropical developing countries.
- More rapid and higher extent of absorption of drugs compared with other non-invasive routes.

The biomolecules that have been studied are shown in Table 1, which includes a list of proteins/peptides and their target diseases states.

Devices for delivery via the pulmonary route have been used for a long time in their various forms: nebulisers, metered dose inhalers (MDIs) and dry powder inhalers (DPIs).[4] The first two use various solvents, both aqueous and organic, and therefore DPIs offer the best option for stabilising proteins in dry formulations. The DPI consists of unit powder doses packed in either blisters, cartridges or hard capsules. Its action is dependent on the patient's inspiratory flow rate and it is a popular device among users due to the recognised advantages, summarised in Table 2.[6]

| Disease state | Therapeutic protein/peptide |
|---|---|
| Anaemia | Erythropoietin |
| Anticoagulant | Heparin |
| Cancer | LHRH analogues |
| Diabetes | Insulin |
| Diabetes insipidus | 1-deaminocysteine-8-D-argenine vasopressin (dDAVP) |
| Growth deficiency | Human growth hormone |
| Multiple sclerosis | Interferon-β |
| Neutropenia | rhG-CSF |
| Osteoporosis | Calcitonin, Parathyroid hormone |
| Viral infections | Ribavirin, Interferon-α |
| Acute lung injury | Actived protein C |

Table 1: Proteins and peptides proposed for delivery via inhalation. Redrawn from information in references 4 & 5.

| Capsule-based DPI advantages |
|---|
| Breath-actuated and no need to hold breath after inhalation |
| Inhaled dose can be confirmed by the patient due to visibly empty transparent capsule after inhalation |
| Portable, designing the device with the formulation as a separate entity minimises its dimensions |
| No propellant (environmentally friendly) |
| The powder mass in each unit is flexible, permitting use of the same device for both low and high dose volumes |
| Medications requiring high doses are typically delivered by single-dose reusable devices rather than multi-dose inhalers |

Table 2: Advantages of capsule-based DPIs.

The manufacture of protein-based pharmaceuticals needs processes that will not damage them. This requirement has changed the formulation challenges, as these substances, because of their complex structures, are less stable than the small molecules used previously.

Important insights and challenges for inhaled proteins were thoroughly reviewed and discussed in a paper by the Université Libre de Bruxelles (Brussels, Belgium) in 2013.[7] It was highlighted that, of the three major existing inhalation delivery device types on the market, only DPIs do not use liquid formulations. The particle size and shape requirements for dry powders were related to the anatomical features of the lungs. Due to the requirement for particles with a very low aerodynamic diameter (1–5 µm), impaction in the upper respiratory tract should be considered and avoided. This could be achieved by micronisation techniques, as well as by limiting the inter-particle interactions through formulation strategies. The formulated powders must maintain the integrity of the protein and avoid physicochemical degradation, which can lead to loss of biological activity during processing and storage. In this sense, formulation strategies, such as freeze-drying, spray-drying and supercritical fluid drying, and some specific excipients to improve stability, were explained. The systemic absorption of proteins represents another potential challenge due to their high molecular weight. Absorption enhancers may overcome the crossing of the alveolar capillary membrane.

"Among proteins and peptides, insulin has, for some time, attracted the attention of several pharmaceutical companies due to the potential large sales in diabetic treatment."

A recent paper from the University of Chile (Santiago, Chile), and the University of Texas at Austin (US), summarised the challenges and prospects for delivery of biologics through inhalation.[8] For pulmonary development, product pipelines have shifted from a mix of small molecules to include biologics. The key factor for inhalation and deep penetration into the lungs is the aerodynamic particle size of the formulation. Particles with aerodynamic diameters of <3 µm will reach deep into the lungs and be absorbed into the bloodstream to treat systemic diseases. Progress requires a combination of particle engineering and device design to achieve this goal. Currently, over 30 actives are at various stages in the development process, either in preclinical testing or in Phase I and II trials.

Among proteins and peptides, insulin has, for some time, attracted the attention of several pharmaceutical companies due to the potential large sales in diabetic treatment (Table 3). Since injectable insulin was introduced into clinical practice in 1922, other routes of administration have been explored. According to the US *National Diabetes Statistics Report*, 29.1 million people have diabetes mellitus (DM) in the US, approximately 9.3% of the population, with direct and indirect costs totalling US$245 billion (£187 billion) in 2012. Zion Market Research published a report in which it stated that the global human insulin market accounted for $27 billion in 2015 and is expected to reach $43.6 billion by 2021. The market will grow at a $CAGR_{2016–2021}$ of around 8.3%.

All patients with Type 1 DM require insulin therapy. Patients with Type 2 DM may also become dependent on exogenous insulin as their disease progresses.[2] Approximately six million people in the US require insulin therapy.

The history of marketed inhaled insulin products has often been discussed, particularly the problems caused by the Exubera® insulin (Nektar, Pfizer) withdrawal from the market after a single year due to unexpectedly low sales. The failure of Exubera® may have resulted from several factors, including the high cost of the inhaler, dosing in milligrams (which may have confused patients who had been receiving conventional insulin therapy which is measured in insulin units, IU) and finally the large size of the device.

"A collaboration in 2017 between the University of Parma in Italy and Qualicaps Europe studied the chemical stability of pure spray-dried insulin produced using a patented process[11] and filled into inhalation-grade hypromellose capsules."

| | Product | Generic Name | Company | Pharma Class | WW Sales (US$m) 2017 | WW Sales (US$m) 2024 | CAGR 2017-24 | WW Market Share 2017 | WW Market Share 2024 | Current Status |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Trulicity | dulaglutide | Eli Lilly | Glucagon-like peptide (GLP) 1 agonist | 2,030 | 4,622 | +12.5% | 4.4% | 7.8% | Marketed |
| 2 | Ozempic | semaglutide | Novo Nordisk | Glucagon-like peptide (GLP) 1 agonist | – | 4,411 | n/a | n/a | 7.4% | Marketed |
| 3 | Jardiance | empagliflozin | Boehringer Ingelheim | Sodium glucose co-transporter (SGLT)2 inhibitor | 1,139 | 3,510 | +17.4% | 2.5% | 5.9% | Marketed |
| 4 | Tresiba | insulin degludec | Novo Nordisk | Insulin analogue | 1,113 | 3,387 | +17.2% | 2.4% | 5.7% | Marketed |
| 5 | NovoRapid | insulin aspart | Novo Nordisk | Insulin analogue | 3,043 | 2,561 | -2.4% | 6.6% | 4.3% | Marketed |

Table 3: Predicted top five anti-diabetic products worldwide in 2024.[1]

The interest in this administration route remained high, with a second ultra-rapid-acting meal-time pulmonary insulin powder (Afrezza®, MannKind Corporation, US) having been approved by the FDA in 2015.[9] This product contains 18% insulin with fumaryl diketopiperazine used to manufacture respirable microparticles according to proprietary Technosphere® technology. Afrezza® is available in different doses (4, 6 and 8 IU), which are modulated by loading increasing amounts of powder in the device. The product has to be stored at 2-8°C and when the blister foil package is opened, it must be used within 10 days.[10]

A collaboration in 2017 between the University of Parma (Italy) and Qualicaps Europe studied the chemical stability of pure spray-dried insulin (Ins-SD) produced using a patented process[11] and filled into inhalation grade hypromellose capsules (Quali-V®-I). Capsules were semi-automatically filled with 2 mg of insulin powder using an Omnidose TT vacuum drum filler system (Harro Höfliger) and were blister packed using transparent PVC/PVDC films for storage trials. Samples were stored for six months at the ICH conditions 25°C and 60% relative humidity (climatic zone II), and at fridge conditions of 4°C.

The *in vitro* respirability test showed that Ins-SD powder had a high respirability, considering that the delivered dose was >95% and the fine particle fraction (FPF) lower than 5 µm was 91%. The percentage of the degradation products was found to be below the US Pharmacopeia limits in both storage conditions during the six months of the study. The stability outcome has demonstrated that the formulation contained in the hypromellose capsules (Quali-V®-I) together with a PVC-PVDC blister packaging material can offer a stable therapy, less dependent on cold-chain storage.

| Peptides, Polypeptides (up to 50 amino acids in a chain) | Proteins (Enzymes, hormones, etc.) |
|---|---|
| SINAPULTIDE (Synthetic Peptide) Treatment: Respiratory Distress Syndrome | AFREZZA (≈6kDa) (Insulin for Diabetes) |
| CORUSURF (Bovine and Pig Surfactants) Treatment: Respiratory Distress Syndrome) | PULMOZYME (DNAse enzyme, 37 kDa) Treatment: Cystic Fibrosis and mucus clearance |

Table 4: Marketed inhalable biologics. (Soucre: PharmaCircle)

The *in vivo* study was conducted in rats and the glycaemic plasma profile was determined after pulmonary insufflation of Ins-SD and Afrezza® powder. Male Wistar rats received a 1 g/kg glucose injection (time zero) and five minutes later 10 IU/kg of insulin were administered subcutaneously (SC) or intratracheally using a DPI device DP-4 insufflator™ (Penn-Century, Philadelphia, US). The glycaemic plasma profiles after pulmonary insufflation of Ins-SD and Afrezza® were similar, indicating that the two formulations have a similar pharmacodynamic effect. Furthermore, the glycaemic profiles after administration were similar to the plasma profile following SC insulin.

Hormones like insulin could be considered as a promising example of the paradigm shift to new, efficient, non-invasive, and therefore more convenient, medical treatments for patients. Besides the inhaled biomolecules already on the market (Table 4), there are other inhalation programmes in clinical Phase I and II.

As reviewed in this article, there are important challenges and aspects to consider in order to maintain the structural integrity and biological activity of biomolecules during the formulation process, packaging, storage, aerosolisation and in the lung environment. Capsule-based DPIs could enable more stable biologic formulations and help avoid the potential denaturation processes, monomer formation, aggregation and chemical degradation in various forms that could occur with liquid inhalation systems.

The described insulin research study has been successfully completed and provides new perspectives to develop DPI-based carrier-free formulations that could represent an encouraging future in the evaluation of high drug-load formulations with highly dispersible particles.

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## ABOUT THE AUTHORS

**Francesca Buttini** has extensive experience in the field of development of innovative pulmonary products, in particular her main research area is the formulation and testing of DPIs. She is an expert both in particle engineering and in development of carrier-based formulations, as well as in the characterisation of the products and their dissolution. Dr Buttini is Associate Professor at the University of Parma (Italy) and in 2014 she was appointed as Visiting Lecturer at the Institute of Pharmaceutical Science at King's College London (UK). To date, she has published several original papers and patents in the field of drug delivery systems and she recently received the Drug Delivery to the Lungs (DDL) conference emerging scientist award.

**Susana Ecenarro Probst** is Director of Scientific Business Development at Qualicaps Europe. She supports R&D centres within the pharmaceutical industry in new drug development by providing scientific and technical expertise, as well as promoting collaborations with European universities and third parties that focus on the application of state-of-the-art capsule technologies. Prior to Qualicaps, she worked for Schering AG for 18 years, working in diverse QC positions and covering several functions, including analytical development, process validation, technology transfer, and operational excellence projects, amongst others, followed by five years of experience leading an analytical R&D unit at Bayer Healthcare. Ms Ecenarro Probst holds a MBA, and a Bachelor's degree in Pharmacy.

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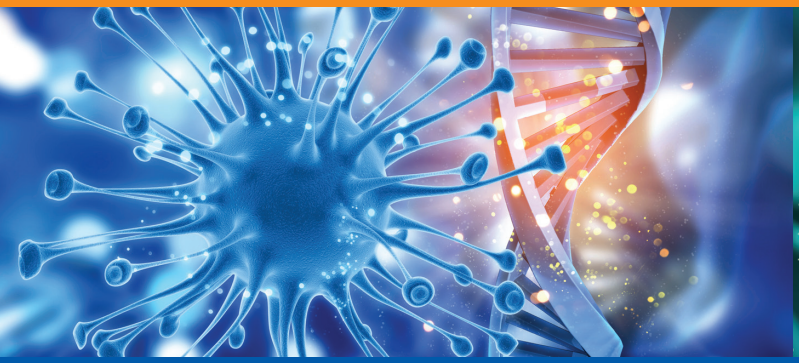

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# NASAL DRUG DELIVERY VIA THE ORAL ROUTE USING A PMDI

In this article, Laurent Vecellio, PhD, Research Engineer, University of Tours, and Scientific Director, Nemera (previously employed by Aerodrug-DTF Medical), Déborah Le Pennec, Research Technician, University of Tours, and Alain Regard, Technology Product Manager, Nemera, discuss a study Nemera has funded into the retronose concept, using a pMDI to deliver to the nasal cavity via the oral route during exhalation through the nose.

## INTRODUCTION

Nasal drug delivery is a non-invasive method that allows for a rapid, high and local therapeutic effect. It offers significant opportunities for new drug development looking to deliver systemic drugs, vaccines and treatments for the central nervous system. A recent study in patients with chronic rhinosinusitis has shown how deposition of corticosteroids in the nasal cavities can have an impact on clinical outcomes.[1] This study demonstrated the importance of the delivery device on drug efficacy.

Standard nasal sprays have limitations regarding the reproducibility and the deposition efficacy in the distal region of interest in the nasal cavities. An alternative, the "retronose" concept (Figure 1) has been proposed as a means to reduce variability and improve drug deposition in specific nasal zones, consisting of drug administration through the buccal cavity during the nasal expiratory phase.

> "The "retronose" concept has been proposed as a means to reduce variability and improve drug deposition in specific nasal zones, consisting of drug administration through the buccal cavity during the nasal expiratory phase."

Using this method, a different nebuliser concept has been developed for better drug deposition in the distal region of the nose,[2,3] without lung deposition. Drug particles enter the nasal cavities through the rhinopharynx, which has a significant impact on drug deposition. Additionally, in a recent study, five asthmatics with rhinosinusitis were successfully treated with an aerosol therapy exhaled through the nose[4] using a similar concept.

In the study funded by Nemera presented here, the use of a pressurised metered dose inhaler (pMDI), as an alternative to a nebuliser, for delivering drugs to the nose via the buccal cavity was explored. Specifically, the study focused on the influence of particle size and the expiratory flow rate on particle deposition in an upper airways model using a standard pMDI.

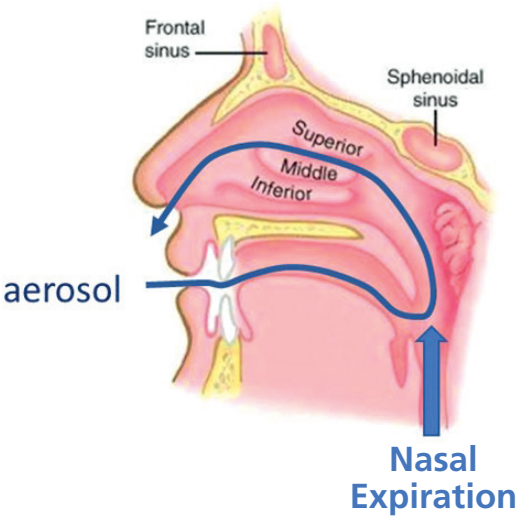


Figure 1: The retronose concept.

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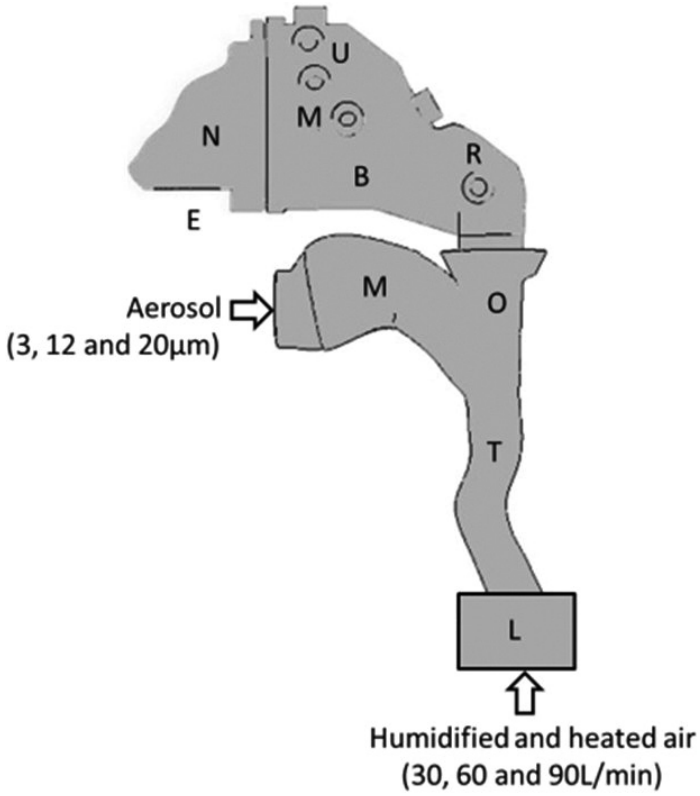


Figure 2: Experimental set up using the VCU upper airways model.

## METHOD

A pMDI filled with HFA 134a propellant (no surfactant) was used with a 90 µL valve system (Inhalia®, Nemera) and an actuator (NM200, Bespak, Germany). Three different particle sizes (3, 12 and 20 µm in terms of volume mean diameter) of a model drug were put in the canisters, resulting in three different pMDI suspensions (pMDI-A, pMDI-B, pMDI-C) delivering 100 µg of drug per dose. Aerosol particle size produced was measured using a cascade impactor operating at 30 L/min (Next Generation Impactor, Copley Scientific, UK).

Aerosol deposition in the upper airways (Figure 2) was studied using an anatomical model[5] developed by the Virginia Commonwealth University (Richmond, VA, US). The trachea model was connected to an absolute filter (L) and a humidified air source at three different flow rates: 30, 60 and 90 L/min. A vacuum pump connected to an absolute filter (E) was located near to the nose model for collecting the totality of the exhaled aerosol from the model. Eight regions of interest were defined in the upper airway model:

- Mouth (M)
- Trachea (T)
- Oropharynx (O)
- Rhinopharynx (R)
- Upper part of the nasal cavity (U)
- Middle part of the nasal cavity (M)
- Bottom part of the nasal cavity (B)
- Nostrils (N).

The active compound was assayed by a spectrophotometric method.

## RESULTS

The aerosol particle sizes produced by pMDI-A and pMDI-B, measured by cascade impaction, were characterised by a mass median aerodynamic diameter (MMAD) as shown in Table 1. The MMAD produced by pMDI-C could not be calculated due to its high deposition in the induction port of the cascade impactor. Regarding the percentage of particle size lower than 10 µm. The results obtained with pMDI-C are consistent with the particle size put in the canister (Table 1).

| | pMDI-A | pMDI-B | pMDI-C |
|---|---|---|---|
| MMAD (µm) | 3.7 ± 1.3 | 14.8 ± 0.4 | N/A |
| Particle size lower than 10 µm (%) | 70 ± 17 | 29 ± 8 | 3 ± 1 |

Table 1: Aerosol particle size data for the three pMDIs.

> "The concept of nasal drug delivery via the oral route using a pMDI in an upper airways model has been demonstrated *in vitro*, with promising results."

An increase of drug penetration into the nasal cavity was observed with a decrease of particle size. No active compound was detected depositing into the filter corresponding to the lung model (L). No statistical difference was observed on the influence of expiratory flow rate on aerosol deposition in the oropharynx, mouth or trachea, and drug penetration into the nasal cavity ($p>0.05$, Friedman test, GraphPad Prism V5) for all three flow rates were examined.

The drug deposited homogenously in all regions of the nasal cavity (Figure 3). An exception was the upper part of the nasal cavity, where deposition was relatively low (less than 2%), independent of particle size or expiratory flow rate. An increase in particle size was associated with a decrease in exhaled fraction. An increase in expiratory air flow rate was also associated with a decrease in exhaled fraction. There was no statistical influence of expiratory flow rate on deposition fraction in the other regions of the nasal cavity, N, U, M, B and R ($p>0.05$, Friedman test, GraphPad Prism V5).

## CONCLUSION

The concept of nasal drug delivery via the oral route using a pMDI in an upper airways model has been demonstrated *in vitro*, with promising results. All anatomical regions, except for the upper part of the nasal cavity, were successfully targeted, with relatively homogenous deposition.

This nasal drug delivery system could be of interest for both local and systemic drug delivery, and for the delivery of vaccines.

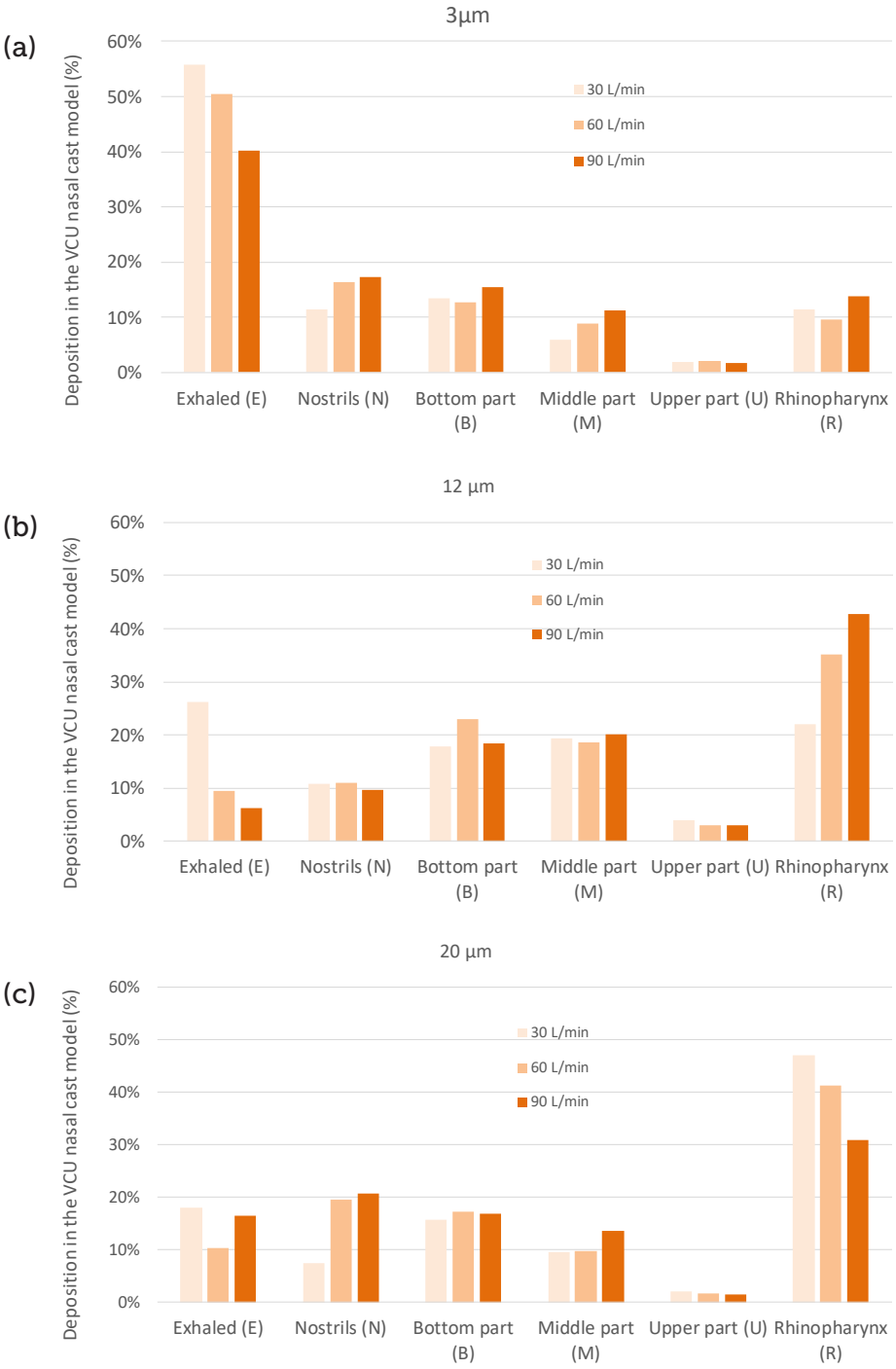


Figure 3: Deposition in the nasal cavity model expressed in term of total drug delivered in the nasal cavity (N+U+M+B+E+R) for 3 µm (A), 12 µm (B) and 20 µm (C) (n=3).

## ACKNOWELDGEMENT

The authors would like to thank Dr P Worth Longest of Virgina Commonwealth University (Richmond, VA, US) for providing the upper airways model.

## ABOUT THE COMPANY

Nemera designs, develops and manufactures nasal, buccal, auricular, ophthalmic, pulmonary, parenteral (passive safety devices autoinjectors, pens, and implanters), dermal and transdermal drug delivery devices for the pharmaceutical, biotechnology and generics industries.

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## ABOUT THE AUTHORS

**Laurent Vecellio** is Scientific Director at Nemera, and research engineer in the Research Centre for Respiratory Diseases at the University of Tours, France. He obtained his PhD in 2002 and his accreditation to supervise university research in 2007. He worked for Aerodrug-DTF Medical in nubulisation from 2000 to 2018.

**Déborah Le Pennec** is a laboratory technician in the aerosol therapy team at the Research Centre for Respiratory Diseases, University of Tours, France. She works on different *in vitro* studies such as aerosol metrology, aerosol deposition, bioequivalence, and scintigraphy, and is experienced in biological and chemical analytical techniques.

**Alain Regard**, Technology Product Manager, Nemera, graduated with a degree in Polymer Engineering and Processing from ESP in Oyonnax, France. After a long experience in design and development in the automotive industry, he joined the company in 2010 as a product development leader. Mr Regard, today one of the key technical experts of Nemera's Innovation Center for Devices (ICD), leads the nasal and dermal developments. He drives some of Nemera's own IP projects as well as working on several customer product developments in the field of nasal and dermal applications.

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# REDUCING VARIABILITY IN TEST RESULTS FOR OINDPS WITH AUTOMATED ACTUATION

In this article, Heli Chauhan, Senior Applications Chemist, and Linda (Lingzhi) Liao, Field Applications Scientist, both of Proveris Scientific, discuss the importance of automated actuation for testing inhalation and spray devices to avoid variability introduced by manual methods, and how Proveris' portfolio of instruments and services can ensure the accuracy and reproducibility of results.

## MANUAL VS AUTOMATED ACTUATION

Inhalation or spray drug-device combination products are notoriously complex and difficult to develop and manufacture. Proper performance of these devices is sensitive to a large number of variables, which must be properly controlled. A lack of sufficient control can adversely affect data quality and reproducibility, which can in turn cause developmental delays or production quality issues. The formulation is often the primary focus of analysis and less attention is devoted to understanding the device usage. However, appropriate actuation and testing parameters are essential for combination products, and any variability will influence the accuracy and reproducibility of the data.

Human actuation of devices is prone to introduce variability, as using hand

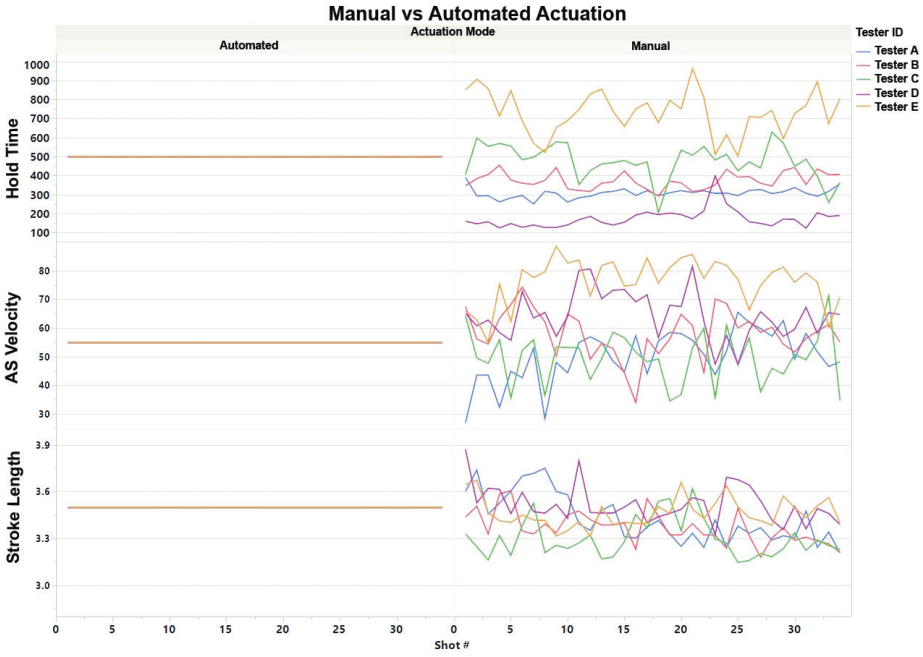


Figure 1: Consistent control over actuation parameters with automated actuation (left) and variation observed with human actuation for pMDI devices (right).

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actuation for testing is neither consistent over time nor between different analysts. The ideal way to conduct testing is automated, mechanical actuation using a defined testing profile (stroke length, velocity, hold time, etc.) derived from human-usage data. This approach reduces variability and improves the correlation between *in vitro* tests and *in vivo* performance. It also makes it possible to avoid the inherent human error that arises due to operator fatigue and other influences when testing a high volume of samples. The result is a significant reduction in the number of deviations/investigations attributed to analyst error, thereby increasing the efficiency of the lab.

The range of variation in hand actuation can be seen in Figure 1. The data is derived from an Ergo™, a Proveris Scientific device which measures and records human-usage parameters. The figure shows the high variability in stroke length, actuation velocity and hold time as recorded from a human actuation (right) compared with the option of controlling parameters consistently with automated actuation (left) for a pressurised metered dose inhaler (pMDI) device. Manual actuation could therefore lead to variability in test results for delivered shot weight, dose content uniformity (DCU) and aerodynamic particle size distribution (APSD). Therefore, it is critical to employ the precise control provided by electromechanical actuation, which enables use of exactly the same parameters across all of the different tests that need to be performed.

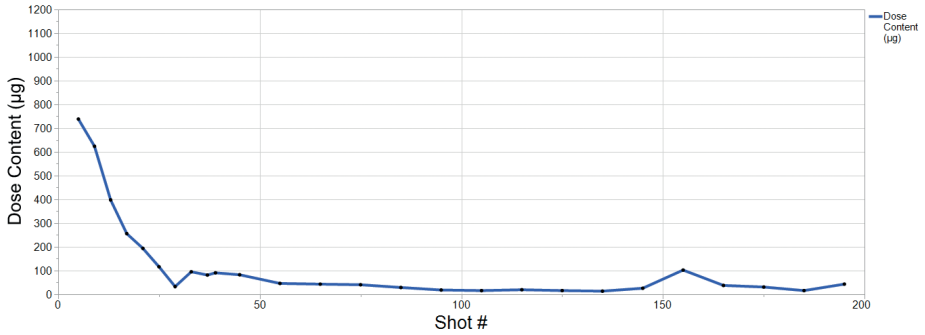


Figure 2: Variable dose delivery from a pMDI device due to lack of shaking.

Controlling testing parameters with automated actuators can help maintain batch-to-batch reproducibility along with ease of regulatory submission. This is valuable when it comes to stability time points for quality control (QC) analysis, where it is important to keep the testing conditions identical over time, thereby minimising the out of trend (OOT) results.

Moreover, the amount of dose delivered from the device can vary greatly depending on parameters such as shaking duration and the time between shaking and actuating the device.[1] Figure 2 shows the importance of shaking a pMDI product. Without adequate shaking, a high amount of drug will be delivered in the initial shots, followed by little to no drug at the end of device life.

Proveris Scientific's Vereo® automated actuators are designed to replicate human actuation of devices, whilst also providing precise control of the actuation parameters. Vereo actuators fit seamlessly into different testing workflows (Figure 3). Furthermore, user defined shaking parameters and a controlled delay between shaking and firing ensure consistent actuation of devices, especially for pMDI devices.

All Vereo actuators run on the Viota® software platform, which has technical controls to enable compliance with 21CFR Part 11 to allow the data created to be used in development submission documents and manufacturing-grade quality records. These controls include the use of electronic signatures, full audit trails, record protection, password controls and multi-level permissions. Viota uses a centralised database and tracks every actuation performed on the Vereo actuator.


Figure 3: Proveris Vereo SFMDx actuator for pMDI products (left); SFMDx with DCU setup (top right) and Anderson Cascade Impactor (bottom right).

## IMPORTANCE OF OPTIMUM ACTUATION PROFILE

For every device type, having an optimum set of actuation parameters is important for consistent actuation through testing. For example, to ensure complete dose delivery of a pMDI device, a fully opened valve is necessary. Figure 4 further highlights the importance of appropriate actuation parameters (actuation velocity, stroke length, hold time). The ideal approach would be to determine these parameters from a human actuation study to ensure the

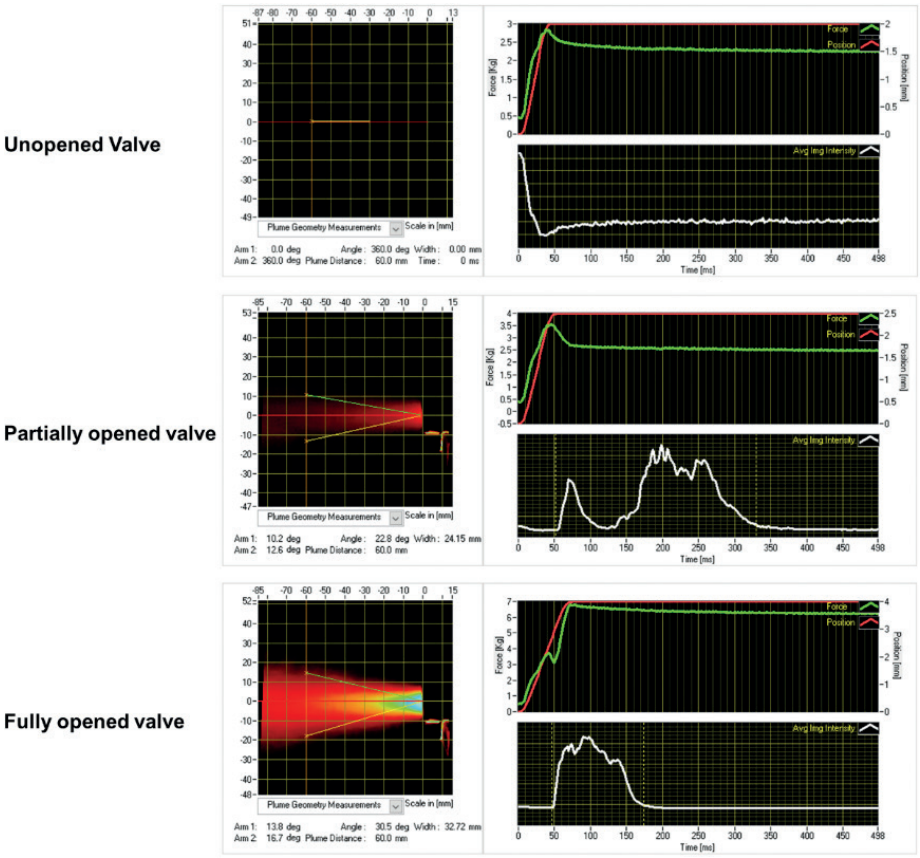


Figure 4: Comparison across plume geometry measurements between an unopened valve, partially opened and a fully opened valve.

values are humanly achievable. As seen in Figure 4, a subpar actuation profile leads to an incomplete opening of the valve, or complete failure to open the valve at all, as visualised by a plume geometry measurement. This may cause non-uniform dose delivery per spray. In contrast, an optimum actuation profile ensures a fully open valve and thus consistent actuation every time.


Figure 5: Proveris' Kinaero High throughput fire-down system for pMDI devices ensures consistent fire-down through device life.

Vereo automated actuators provide user-defined control over parameters such as actuation velocity, stroke length and hold time, as well as return stroke velocity, which could influence the filling of the metering chamber for the next dose.

Critical quality attributes for pMDI devices, such as dose delivery and APSD, need to be tested throughout the life of a device (beginning, middle, end of life stages). To achieve this, the doses between life stages (e.g. beginning and middle) need to be fired down. Firing down represents about 90% of the actuations for each device and introduces the highest source of error in through-life testing if not performed in a consistent and reliable manner. Lack of controlled actuation during fire-down may lead to low end-of-life dose delivery. Using consistent actuation parameters throughout each test, as well as when firing down, ensures uniform testing conditions, resulting in accurate data.

Proveris' Kinaero (Figure 5) is a high-throughput, bench-top fire-down system that provides precise shaking and actuation control with a self-contained evacuation system. Vereo automated actuators, coupled with the Kinaero system, seamlessly integrate consistent actuation parameters into the entire pMDI testing workflow.

## FORCE PROFILES AS KEY OUTPUT FROM VEREO ACTUATORS

Vereo actuators come with time-sequenced force and position feedback that can be used to gain insight into the product, as well as being applied as a tool to monitor device performance in QC. All Vereo actuators provide a force/position vs time graph for every actuation performed. The position profile is pre-defined and kept consistent throughout actuation (as determined by the user-defined stroke length). The force profile

> "Firing down represents about 90% of the actuations for each device and introduces the highest source of error in through-life testing if not performed in a consistent and reliable manner."

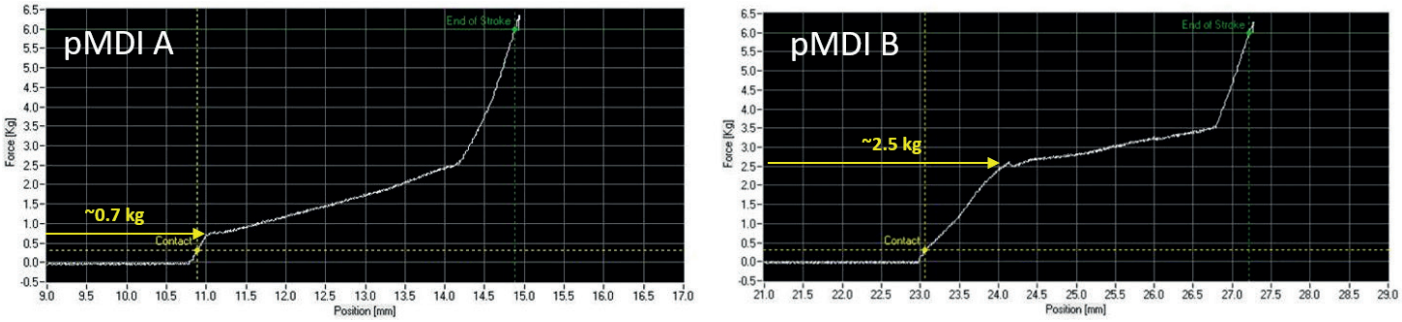


Figure 6: Force displacement graphs from two different pMDI products obtained from Viota software.

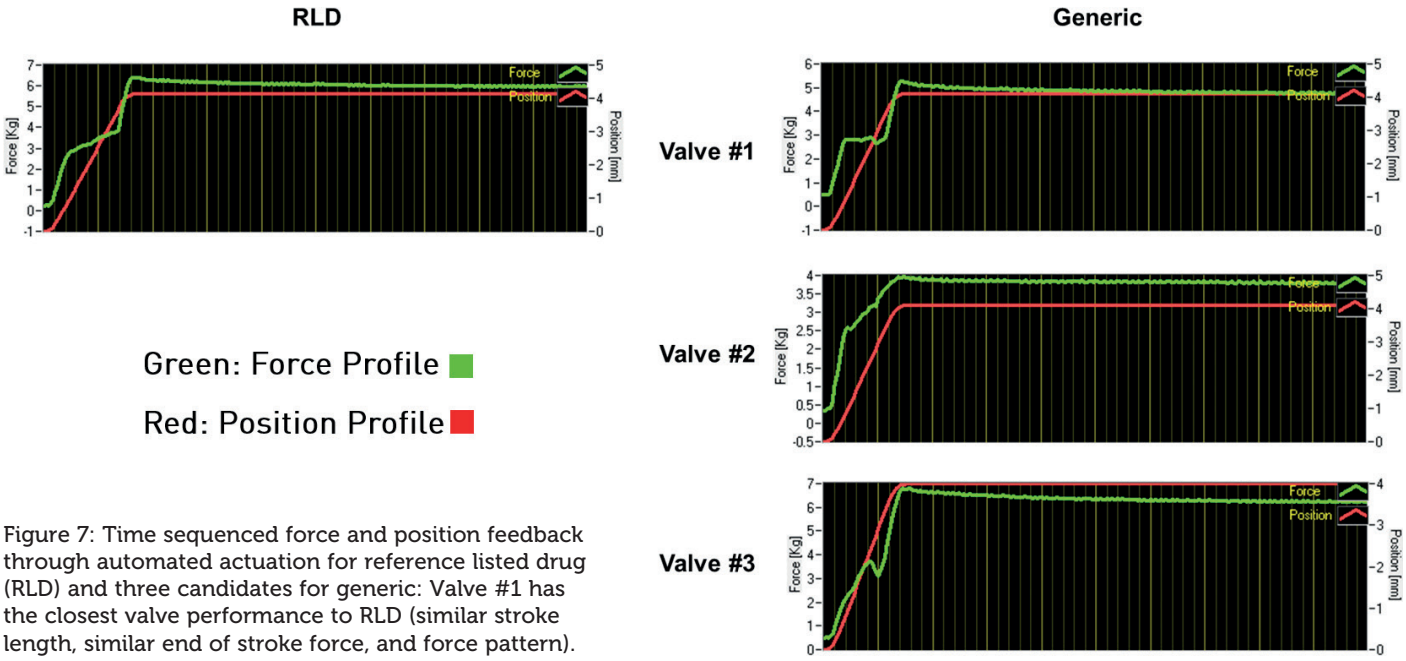


Figure 7: Time sequenced force and position feedback through automated actuation for reference listed drug (RLD) and three candidates for generic: Valve #1 has the closest valve performance to RLD (similar stroke length, similar end of stroke force, and force pattern).

represents the device's resistive force during the actuation. Moreover, this signature force profile for each device type can be used to determine the product actuation force in Viota. The differences in product actuation force across multiple products also help characterise the ease of use for specific patient populations (e.g. children and older patients).

### Force Displacement Graph

Figure 6 shows the force displacement graph obtained from Viota for two pMDIs. The change in force of the middle linear region of the graph indicates the compression of the spring in the device valve.[2] As seen from the figure, a higher force is required to open the valve and ensure complete delivery for product B compared with product A. Insight into the amount of force necessary to drive the valve a specific distance can be very useful during early product development, for characterisation and to select the best valve during device screening. Moreover, evaluation of consistent force feedback from the device across different lots can be used to inspect incoming device components, as well as for further inspections at different points throughout the lifecycle of the product (e.g. during stability testing). The same metric can also be used to perform root-cause analysis in case of out of specification (OOS) results across the entire range of tests that use automated actuation (e.g. DCU, APSD, spray pattern, plume geometry, etc.)

### Force Graph to Evaluate Metering Valve

Shot weight and dose content are critical performance indicators of the metering valve. However, errors could be introduced to such measurements through manual actuation. Alternatively, time-sequenced force/position feedback through automated actuation provides insight into how the valve interacts with the user during actuation.

As exemplified in Figure 7, three candidate valves for a generic product perform differently with the same actuation profile (stroke length, velocity, acceleration, and hold time). Each valve has a different actuation force, end-of-stroke force, and force profile. In this case, Valve #1 has the closest performance to the reference listed drug (RLD) product. Besides metering valve selection, the time-sequenced force feedback can be applied to ensure consistent valve performance across both the product's lifecycle and different lots and batches (release testing). Additionally, it can be used to identify whether the root cause for an OOS measurement is valve failure.

## DIFFERENT DEVICES NEED DIFFERENT MODES OF ACTUATION

The critical quality attributes (i.e. performance metrics) of different device types are influenced by specific actuation parameters. Therefore, specific modes of actuation are needed for particular device types. For example, the shot weight of multi-dose nasal sprays is determined by the stroke length of the device. A lower than optimum stroke length will under-deliver the dose per spray and a higher stroke length might damage the pump components

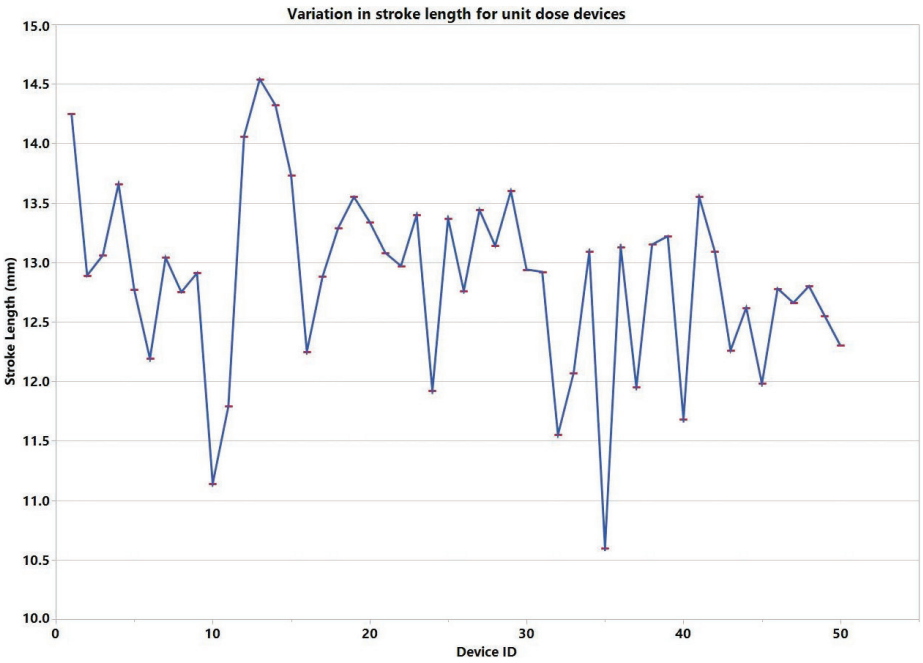


Figure 8: Stroke length differences in unit dose devices from the same lot.

of the device. Therefore, using a consistent stroke length throughout the testing would be advisable. In contrast, unit dose devices have variable stroke length across multiple devices, even from the same lot (as seen in Figure 8). In this case, using a position-based actuation mode would not provide consistent dose delivery. For these devices, a force limited actuation, whereby the device is actuated until the motor detects an end of stroke force, would be ideal, making sure the entire contents of the device are discharged.

### Use with Novel Device Types

With the variety of new device types on the market in recent times, it is more important now to use consistent actuation parameters and to monitor performance throughout testing. Proveris' Vereo actuators can be used with a multitude of device types (Figures 9–11, Table 1) and ensure accurate testing and traceability with Viota software controls in place.

Applications of Vereo actuators include:

- Pump/valve delivery (shot weight)
- Dose/spray content uniformity
- Through-life device testing
- Aerodynamic particle size distribution
- Droplet size distribution
- Spray pattern/plume geometry testing
- Priming/repriming studies.

## STREAMLINING SHOT WEIGHT AND SCU WORKFLOWS

Even with automated actuation, some tasks, such as waste collection or sample collection for spray content uniformity (SCU), can be tedious and labour intensive. Proveris' dose collection holders streamline the process of sample or waste collection (Figure 12). The sample collection accessory eliminates the need for the error prone method of

Figure 9: Range of devices supported by Proveris' Vereo actuators.

*Vereo® Actuator NSx* *Vereo® Actuator SFMDx* *Vereo® Actuator DSx* *Vereo® Actuator SSx*

Figure 10: Different configurations of Vereo actuators: (from left to right) NSx for nasal/oral sprays; SFMDx for pMDIs; DSx for dual sided sprays and SSx for side actuated nasal sprays.

Figure 11: Device specific holders for secure placement in Proveris' Vereo actuators.

| Actuator Configuration | Device types |
|---|---|
| NSx | Vertically actuated unit dose, bi dose and multi dose nasal sprays |
| | Oral sprays |
| | Soft mist |
| | Syringe type nasal spray devices |
| SFMDx | pMDI products |
| DSx | Dual side actuated nasal sprays |
| SSx | Side actuated nasal sprays |

Table 1: Device types suitable for each Vereo actuator configuration.


*Vereo® Actuator NSx with accessory holders*

Figure 12: Dose collection accessories for use with NSx actuator to support shot weight (left) and SCU (right) workflows.

manually inverting the flask for collection of doses for SCU. The hands-free method facilitated by the collection accessory makes it easier to accurately collect the entire dose without any loss or drip-down.

## CONCLUSION

Testing with hand actuation introduces variability into crucial *in vitro* bioequivalence testing and QC results and using a realistic, patient-relevant and optimised actuation profile is essential to accurate testing. Precise control of device performance via mechanical actuation eliminates manual variability and provides confidence in the quality of data. Proveris Scientific's family of Vereo actuators and accessories increase testing efficiency by actuating consistently with user-defined actuation parameters, thereby expediting tedious manual tasks that can be prone to variability.

## ABOUT THE COMPANY

Proveris Scientific delivers innovative technologies, services and deep product knowledge to a worldwide customer base of branded and generic pharmaceutical companies, device manufacturers, CDO/CRO/CMOs and regulatory agencies working with orally inhaled and nasal drug products (OINDPs). Its team of engineers, scientists and service professionals has developed a more complete understanding of the critical quality attributes affecting the performance of OINDPs, and in effectively controlling them from a testing and patient usability perspective.

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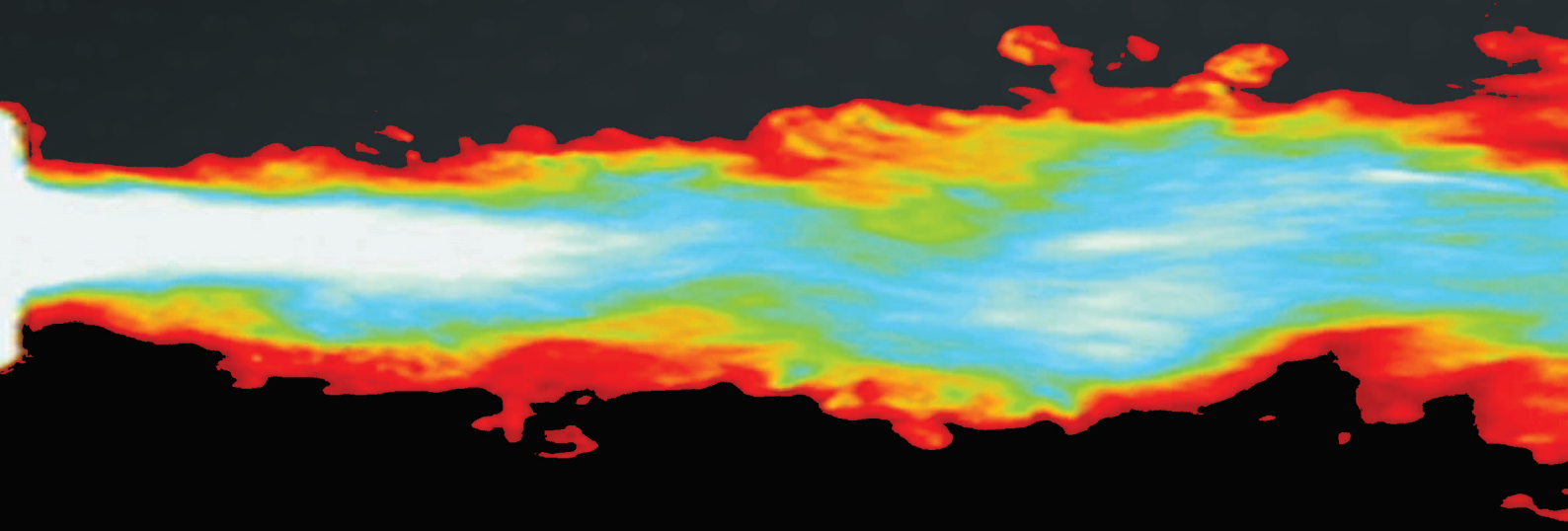

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# VARIABILITY IN CASCADE IMPACTION: SOURCES, IMPACT AND STRATEGIES FOR REDUCTION

In this article, Mark Copley, Chief Executive Officer, Copley Scientific, considers cascade impaction as a method for determining the aerodynamic particle size distribution of orally inhaled drug products, and how techniques to improve air flow control and semi-automation of the process can significantly reduce the variability involved.

The pivotal role of cascade impaction in inhaled product development and manufacture drives ongoing efforts to reduce the variability associated with its use. The delivered particle size of an inhaled drug influences deposition behaviour within the lung and clinical efficacy, making it a critical quality attribute for all orally inhaled products (OIPs). Cascade impaction delivers aerodynamic particle size distribution (APSD) measurements specifically for the active pharmaceutical ingredients (APIs) within a formulation but is a lengthy, predominantly manual technique, prone to variability.

Understanding how cascade impaction works and how to mitigate variability ensures that measured data are robustly fit for purpose. Out-of-specification (OOS) results compromise efficiency and profitability, necessitating repeat testing which reduces productivity and lowers morale. More fundamentally, they make it difficult to identify product variability robustly, eroding a company's ability to safeguard clinical efficacy or progress product development. This article considers the sources and impact of variability highlighting technology that is useful in minimising OOS results, some of which is additionally helpful in delivered dose uniformity (DDU) testing.

> "This comparison underlines the critical point that there is no single cascade impactor set-up or method used in inhaler testing. Variability reduction is a unique task for each application."

## INTRODUCING CASCADE IMPACTION

Cascade impactors separate a sample by particle inertia, which is a function of particle size and velocity. During testing, sample laden air is drawn through the stages of the impactor at a constant volumetric flow rate by a vacuum pump (Figure 1). Each stage consists of a plate with a defined nozzle arrangement and a collection surface, with both nozzle size and total nozzle area decreasing with stage number. At each stage, progressively smaller particles acquire sufficient inertia to break free of the prevailing air flow and impact on the collection surface.

Separation depends on impactor design but for each stage is typically defined by a steep curve (Figure 1). Stage cut-off diameter is the median diameter (D50) from this curve and dependent on:

- Nozzle diameter which is maintained by, for example, regular cleaning and periodic stage mensuration

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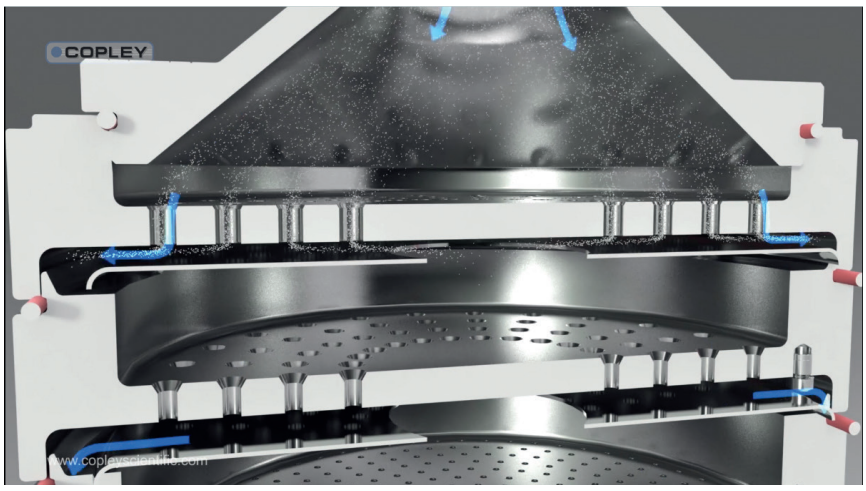
(a)

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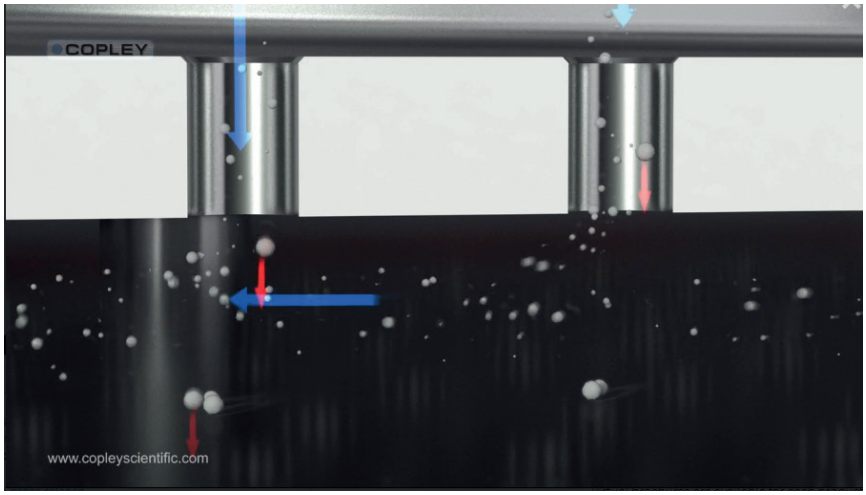


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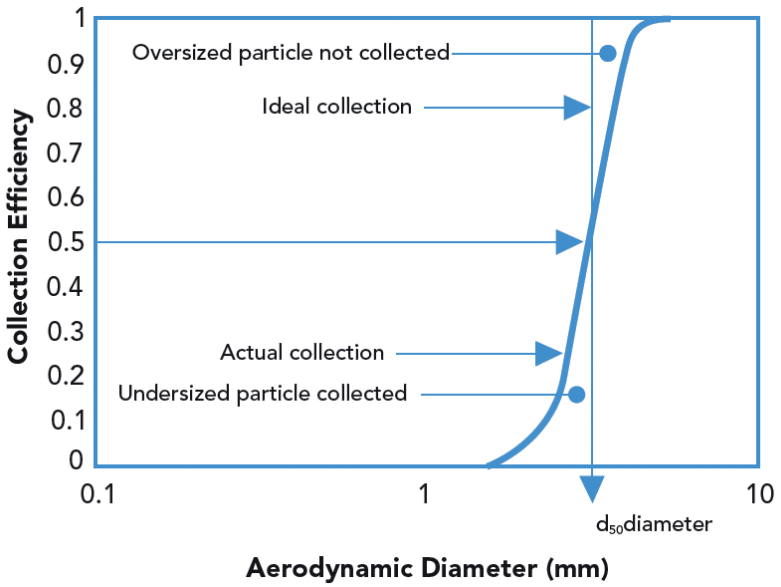


Figure 1: As sample is drawn through the stages of a cascade impactor (a), progressively smaller particles acquire sufficient inertia to break free of the prevailing air flow and impact on the associated collection surface (b). At any given flow rate each stage therefore has a defined cut-off diameter, the D50 of the collection efficiency curve (c).

- Nozzle-to-collection surface distance, although this is of secondary importance
- The flow rate of air through the impactor.

Residual fines are collected on a filter/micro-orifice collector (MOC) and measurement is then completed by rigorous drug recovery from each collection surface, the mouthpiece adapter, induction port, final filter/MOC and pre-separator (where used). The resulting samples are analysed, typically by high performance liquid chromatography (HPLC), to determine APSD data specifically for the drug or drugs, in the case of multi-component formulations.

> "The impact of variability is either a failure to achieve mass balance, meaning not all of the dose is sized, or an erroneous APSD, meaning the dose is sized incorrectly."

## THE PRACTICALITIES OF TESTING

In an APSD measurement set-up the cascade impactor, most usually the Andersen Cascade Impactor (ACI) or Next Generation Impactor (NGI), is used with ancillaries that:

- Maintain a constant, accurately known volumetric air flow rate at the impactor inlet
- Interface the OIP with the inlet (induction port)
- Apply relevant conditions to the OIP during testing.

The apparatus selected depends on the OIP and the purpose of testing. For example, compare an optimal test set-up for quality control (QC) for a metered dose inhaler (MDI) with one tailored more closely to dry powder inhaler (DPI) product development. In QC, the purpose of testing is to detect difference and the test methods and equipment defined in the pharmacopeias[1,2] are usually applied (Figure 2a).

In contrast, in drug development there is considerable value in maximising the clinical relevance of *in vitro* test data, to reduce requirements for more time-consuming and expensive *in vivo* testing and to accelerate progress. The test set-up shown for DPIs (Figure 2b) provides better IVIVCs (*in vitro/in vivo* correlations) by incorporating a:

- More anatomically correct OIP-impactor interface – the Alberta Idealised Throat (Copley Scientific, UK) which generates more clinically realistic throat deposition data than the European/US pharmacopoeias' standard induction port.[3,4]
- Breathing simulator to apply a patient-representative breath profile to the OIP, during testing.

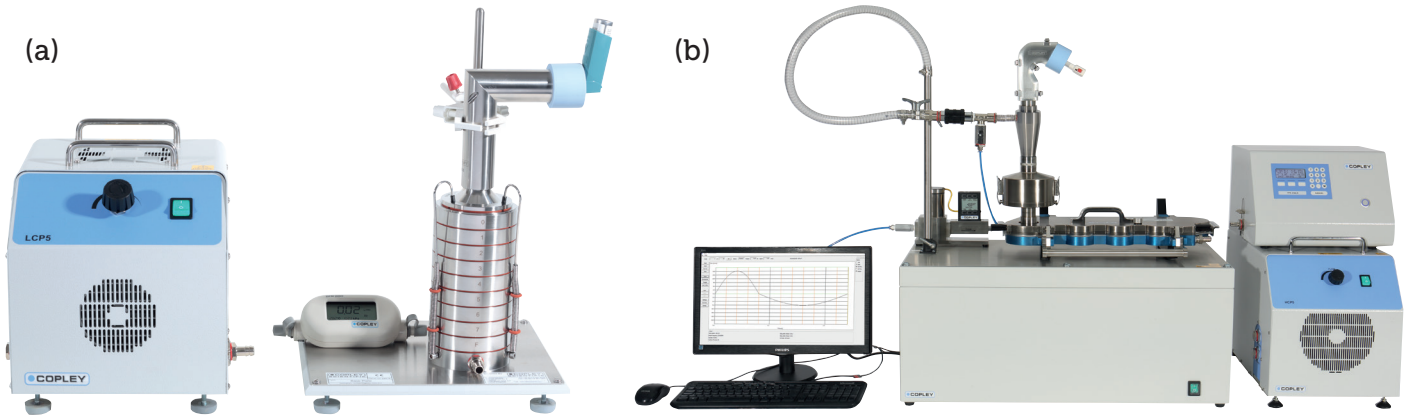


Figure 2: Test set-ups for APSD measurement depend on the purpose of testing such as: a simple ACI set-up for QC for MDIs (a), or an NGI set up for enhanced IVIVCs for DPIs (b).

- Mixing inlet to decouple the flow through the impactor from the flow through the OIP, allowing the maintenance of a constant air flow rate through the impactor.

This comparison underlines the critical point that there is no single cascade impactor set-up or method used in inhaler testing. Variability reduction is a unique task for each application.

## SOURCES OF VARIABILITY AND THEIR IMPACT

There has been significant investigation of the potential sources of variability in cascade impaction (notably a study conducted via the Product Quality Research Institute (PQRI), see Figure 3), which can be helpfully classified as associated with the:

- MANual nature of the analysis
- test apparatus (MACHINE)
- MEASUREMENT method
- product itself (MATERIAL).

This work (Figure 3) provides a foundation for the implementation of good cascade impactor practice (GCIP), the idea that the risk of inaccurate or imprecise CI measurements can be minimised by systematically identifying and controlling all associated sources of variability.[5]

Scrutiny of this list highlights the breadth of factors that must be considered to ensure robustly reproducible APSD measurement, including certain subtle issues unique to the performance of impactors and OIPs such as the:

- Potential impact of the test environment. Temperature and humidity (especially in the case of hygroscopic formulations) may affect an OIP active and must be carefully considered during method development. In addition, for nebulisers, the temperature, or more specifically the thermal mass of the impactor, is a specific issue which can lead to evaporation and the under-sizing of droplets, especially for solution-based products. Impactor cooling, typically to a temperature of around 5°C, is common practice and facilitated by purpose-built accessories such as the NGI Cooler (Copley Scientific, UK).[6,7]
- Influence of electrostatics on particle behaviour within the impactor, which can be exacerbated by low humidity environments. This can cause deposition on the wrong stage or, indeed, between stages, impacting the mass balance. Equipment grounding and the use of static eliminators and metal rather than plastic induction ports/throat models (where adopted)[8] can all be helpful precautions.
- Collection of particles on the wrong stage due to particle bounce and re-entrainment. This is most likely with DPIs and can be resolved by collection surface coating with a thin layer of a viscous or sticky material, such as silicone oil or glycerol.

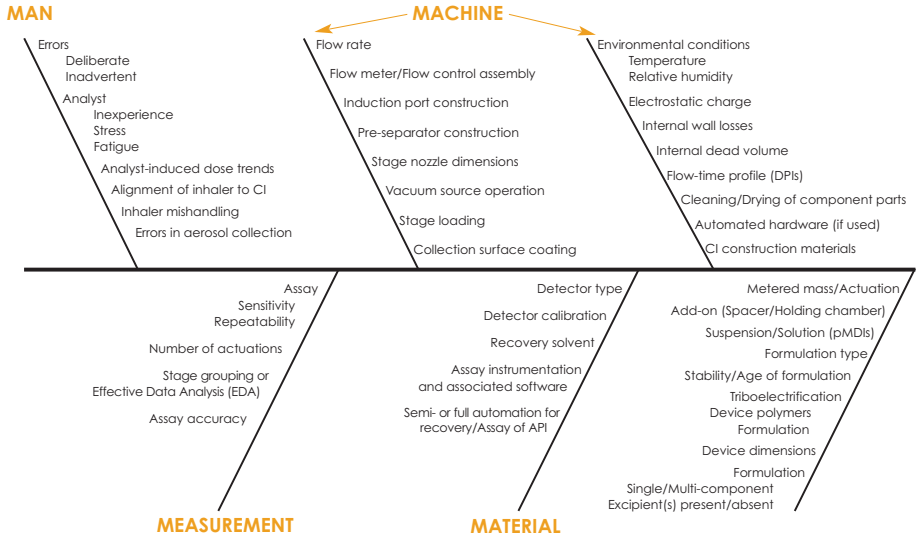


Figure 3: The complexity and manual nature of cascade impaction means that that are many potential sources of variability.[5]

The impact of variability is either a failure to achieve mass balance, meaning not all of the dose is sized, or an erroneous APSD, meaning the dose is sized incorrectly. Criteria for mass balance acceptance include those in the European Pharmacopoeia (EP)[2] which specifies that the total mass of API recovered should lie within 75–125% of the average delivered dose, whereas the US Pharmacopeia (USP) and FDA recommend that the mean amount of API recovered should lie between 85–115% of the label claim on a per actuation basis.[1,9] Ensuring the accuracy of APSD values is more difficult and relies heavily on robust method development.

"While flow control requires appropriate knowledge and understanding, many discrete elements of testing are simply repetitive, laborious and/or time-consuming and are easily automated, in turn reducing variability."

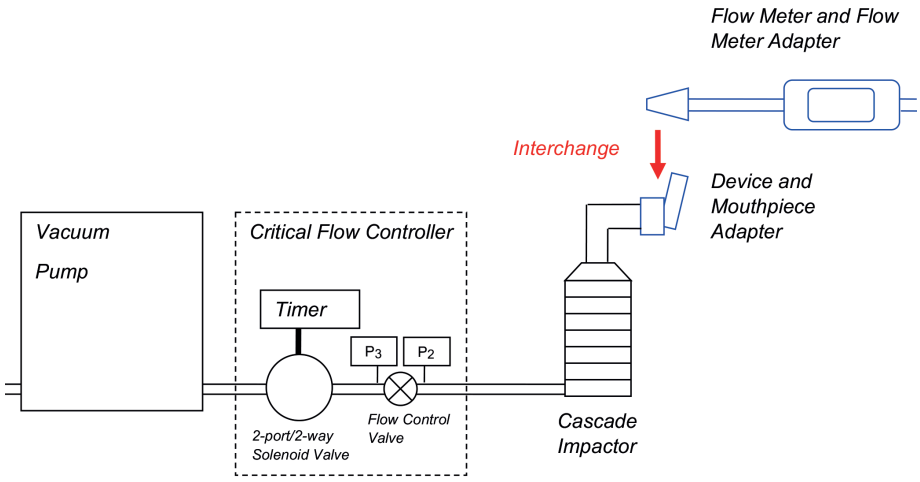


Figure 4: For all OIPs, test flow rate can be determined by replacing the OIP with a flow meter and adjusting the flow control valve. Critical flow across this valve (P3/P2 ratio ≤0.5) is an additional requirement for DPIs, which are most easily set-up using a critical flow controller.

## FOCUSING ON FLOW

Maintaining a constant, accurately determined air flow rate through the cascade impactor is essential for precise APSD measurement, making flow control a primary focus for variability reduction. The pharmacopoeias[1,2] specify that test flow rate should lie within ±5% of the target flow, taking into account errors associated with determining and setting flow, which equates (via Stokes Law) to a variance in stage cut-off diameter of approximately ±2.5%.

Nebulisers and MDIs are both tested at a standard test flow rate of 15 L/min and 28.3 L/min respectively (30 L/min for the NGI, which is calibrated at this flow rate).[1,2,6,7] For DPIs, testing is carried out at the flow rate that results in a 4 kPa pressure drop across the OIP, reflecting the pressure drop generated by a typical adult patient during product use, up to limit of 100 L/min. A total test volume is also specified for DPIs: 4 L per simulated inhalation (2 L for DDU in USP/FDA guidelines). In combination with test flow rate, this defines a square-wave profile that is used for both APSD measurement and DDU testing. To enhance flow stability, the pharmacopoeias also specify that, when testing DPIs, the pressure downstream of the flow control valve, P3, should be less than 50% of the upstream pressure, P2. This imposes sonic flow conditions across the valve, minimising the impact of vacuum pump derived fluctuations in pressure downstream of the valve (Figure 4) and flow resistance changes when switching between OIP and flow meter at the inlet.

For all OIPs, examples of good practice associated with setting up and maintaining the required flow rate through the impactor include[10]:

- Regular leak testing of the impactor, since flow entering by any route other than the inlet will impact data integrity.
- Regular calibration of the flow meter, ideally for exiting flow rate, since this is the entry flow rate to the impactor, though exiting flow rates can be calculated from calibrated inlet air flows when the pressure drop over the flow meter is known.
- Applying suitable correction factors to account for any differences in temperature and pressure between calibration and experimental conditions.

Technology that can be particularly helpful in this area includes the TPK™ 2100 Critical Flow Controller (Copley Scientific, UK), which automates the more complex test set-up associated with DPIs, controlling and documenting all the associated parameters for both DDU testing and APSD measurement. Using an automated flow control valve, this accessory rapidly sets both inhaler pressure drop and test flow rate. An automatic user alert to loss of sonic flow conditions, notification of any failure to meet the acceptance limits associated with set flow rate and leak rate, and the capacity for fully automated leak testing further support rigorous flow control and variability reduction.

### Co-ordination – exploring MDI Performance

While drug delivery with a DPI is triggered and driven by the inhalation manoeuvre of the patient, MDIs provide no automatic coordination, save for a handful of novel breath-actuated devices. Patients unable to synchronise inhalation and actuation therefore often use these products with an add-on device – a spacer or valved holding chamber (VHC). In simple terms, these allow the MDI to be actuated into an enclosed dead volume, from which the patient then inhales.

Issues associated with co-ordination give rise to certain requirements for stop/start timed flow control that are unique to MDI testing in:

- DDU testing, where total test volume – typically 2 L in the US and 4 L in Europe – as well as a volumetric flow rate (28.3 L/min) is specified, so air flow/sampling must be synchronised with actuation and stop after a specific time.
- APSD measurements for MDIs with a VHC[11] which include testing with a time delay of two seconds (longer delays may also be applied) between actuation and the onset of sampling to determine the effect of unco-ordinated product use. This quantifies changes in the APSD of the aerosol prior to inhalation due to, for example, aerosol expansion, particle impaction, settling and electrostatic deposition.[12,13]

In these applications a fast-acting, timer-controlled solenoid valve, such as the BAC™ 2100 Breath Actuation Controller (Copley Scientific, UK), which provides near instantaneous (<25 ms) "stop/start" flow control, has a valuable role to play in reducing variability. This valve can also be used for the automatic actuation of breath actuated MDIs. As with the TPK 2100, all test parameters are automatically recorded.

### Flow Profile Control – Moving Towards Better IVIVCs

The flow control associated with the compendial methods for APSD measurement centres on the application of sharp, square-wave profiles – near instantaneous on/off action, in combination with constant flow. Though essential for cascade impaction these are, of course, quite unlike the inhalation profiles applied by patients. Studies show that "how" you measure, the rate at which flow ramps up during measurement, for example, influences "what" you measure, the value of APSD metrics.[14,15] Measuring the effects of different profiles, flow rates and breathing techniques to scope performance fully and assess variability from patient physiology or technique is therefore increasingly common, within a quality by design (QbD) environment, and to minimise reliance on *in vivo* testing; the associated test set-ups (Figure 2b) bring new flow control challenges.

Breathing simulators are now a core element of the flow control toolkit for inhaler testing. These allow analysts not only to reproducibly generate the standard tidal breathing profiles (neonate, infant, child and adult) specified for DDU testing for nebulisers and MDIs with add-on devices,[6,7,11] but also to apply patient-derived forced inhalation profiles for enhanced clinical realism in MDI and DPI testing. Breathing profiles can be modified by adjusting wave pattern, tidal volume and the number, duration and timing of each breathing cycle. More powerful simulators such as the BRS 3100 (Copley Scientific, UK) are especially useful for studying the impact of ramp rate: the rate at which flow accelerates from zero to peak flow. This parameter is particularly relevant to DPIs because of the correlation between performance and the inspiratory strength of the patient, which drives aerosolisation and dispersion of the powder formulation. The recent introduction of advanced flow control solutions for automatic air flow balancing – a designated, automated compressed air flow controller, in combination with a suitable compressor and appropriately designed manifold – make it significantly easier to achieve the more complex flow control, which is associated with more clinically representative test set-ups, for all OIPs.

## SEMI-AUTOMATION

While flow control requires appropriate knowledge and understanding, many discrete elements of testing are simply repetitive, laborious and/or time-consuming and are easily automated, in turn reducing variability. A prime example is MDI actuation, where automation enables the precise, consistent control of variables such as the shaking profile, actuation force and speed, angle of fire and the length of pauses between shaking and firing, simultaneously eliminating a low-value task for the analyst and the risk of repetitive strain injury (RSI). Suspension formulations, in particular, can be sensitive to these parameters, due to the potential for phase separation, so automated methods can markedly improve reproducibility.


Figure 5: The NGI Assistant is a turn-key solution for automation of the labour-intensive process of sample preparation.

However, it is drug recovery, the most manually intensive part of APSD measurement, that offers most scope for semi-automation of this type, to reduce costs, boost productivity, improve data integrity and reduce the risk of exposure to materials hazardous to health. This is particularly true in QC testing and or where standard compendial methods are being used, since labour-saving devices and automation solutions are especially well developed for the most routinely used pieces of equipment.

Key decisions associated with the drug recovery process include:

- How much solvent volume to use since, an excess can compromise HPLC accuracy, while too little may impact dissolution efficiency.
- The optimal dissolution procedure – contact time, degree of agitation and any requirement for the use of ultrasonics.
- Which equipment to use to minimise sample degradation via sample loss to vessel walls, the absorption of API from solution and solvent evaporation.

The NGI Assistant (Copley Scientific, UK) is a turn-key solution that provides automation from the point of dissolution of the collected samples through to the presentation of sample solutions for HPLC analysis (Figure 5). Up to three complete cup trays, or a combination of cup trays and up to three EP/USP induction ports or three pre-separators can be simultaneously accommodated. The system automatically dispenses solvent to each cup (or accessory), applies a gentle rocking action to dissolve the drug into solution and produces both a primary and back-up sample, in industry-standard HPLC vials, ready for analysis. The latest versions offer even shorter cycle times than their predecessors, freeing up significant quantities of analyst time and effort for greater value-added work.

While requiring appreciable capital investment, compared with full automation these systems provide a lower cost, lower risk solution with a sound return. As a

result, in recent years, companies have taken a more modular approach to automation, focussing on where the greatest improvements can be made, rather than trying to automate the entire process end-to-end. This degree of automation simultaneously eliminates multiple sources of variability, substantially reducing analyst fatigue and stress, the risk of inadvertent errors, and associated requirements for training. As a result, both reproducibility and productivity are significantly enhanced.

Alternatively, simple devices can be used to automate discrete, repetitive rinsing activities in both APSD measurement and DDU testing. The dose uniformity sampling apparatus (DUSA) shaker, for example, automates the internal rinsing of DUSA collection tubes while the sample preparation unit model SPU 2000 performs a similar function for the EP/USP induction port and NGI pre-separator. These devices ensure the consistent wetting of internal surfaces and the controlled application of a defined agitation pattern, thereby offering complete, reproducible dissolution, a minimised risk of RSI and increased productivity. Low cost and easy to validate, they can play a major role in alleviating the operator-related variability associated with drug recovery.

## CONCLUSION

The defining attractions of cascade impaction as a technique for OIP characterisation are widely recognised, but so too are its limitations. Addressing the sources of variability that can compromise measurements is essential for the generation of APSD data that optimally support the development and manufacture of OIPs and there is a wide range of technology that can help, particularly in the areas of air flow control and semi-automation. Choosing ancillaries and labour-saving devices that are well-matched to workflow requirements is a cost-effective way of minimising OOS results, and optimising data integrity.

## ABOUT THE COMPANY

Copley Scientific is widely recognised as one of the world's leading manufacturers and suppliers of inhaler testing equipment and is a major provider of testing systems for other pharmaceutical dosage forms. The company also supplies equipment for detergent testing. Copley Scientific's pharmaceutical product range includes test equipment for all types of OINDPs, with a particular focus on solutions for delivered dose uniformity and aerodynamic particle size distribution measurement. It also includes testers for tablets (dissolution, disintegration, friability and hardness), capsules, powders, suppositories, semisolids and transdermals. Copley Scientific has offices in the UK and Switzerland, and a network of specialised distributors around the globe.

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## ABOUT THE AUTHOR


**Mark Copley** graduated from the University of Bath, UK, in 2000 with a Masters' Degree in Aerospace Engineering. For eight years he was Technical Sales Manager and product specialist for Copley Scientific's range of inhaler testing equipment, before becoming the Sales Director in 2009. He is now Chief Executive Officer for the company. Mr Copley is considered a leading authority in testing methods and systems for MDIs, DPIs, nebulisers and nasal sprays; authoring and contributing to more than 50 published articles. He also provides application support and consultancy and runs focused training workshops for the inhaled drug testing sector of the pharmaceutical industry. An invited member of the European Pharmaceutical Aerosol Group (EPAG) impactor sub-team, he has also made recommendations to the Inhalanda working group, leading to subsequent revisions to EP and USP monographs. As part of Copley Scientific's associate membership of IPAC-RS, Mr Copley participates in a number of working groups with a view to enhancing the regulatory science of orally inhaled and nasal drug products (OINDPs).

# REALISTIC PULMONARY DELIVERY SYSTEM TRAINERS: BENEFITS FOR PATIENTS, PHYSICIANS AND DRUG MANUFACTURERS

The use of training devices has been shown to improve correct inhalation device technique in patients. In this article, Craig Baker, Executive Vice-President, Noble, discusses the prevalence of improper use and how addressing this issue via training devices is of benefit to manufacturers, healthcare providers and patients.

*Based on the article that previously appeared in ONdrugDelivery Magazine, Issue 85 (April 2018), pp 28-31.*

Many treatments for respiratory conditions, such as chronic obstructive pulmonary disease (COPD) and severe asthma, are self-administered through pulmonary delivery systems, including nebulisers, metered-dose inhalers (MDIs), dry-powder inhalers (DPIs) and soft-mist inhalers (SMIs). As this form of targeted drug delivery continues to grow, so too does our understanding of the complexities and challenges associated with this route of administration, particularly those that can result from improper use by patients.[1] The most common failings are related to inhalation timing and force, but this is compounded by the fact that patients are often unaware when they are using improper technique, thus not realising they are not receiving the proper drug dose. This incorrect usage and subsequent under-dosing inevitably has detrimental consequences for patient health.[2]

> "The use of realistic trainers can play a role here by allowing an improvement in the quality of individualised medication self-management programmes initiated by HCPs, which have been shown to increase a patient's medication adherence."

Understanding the need for innovation in patient onboarding and training, Noble has developed a wide range of patented technological advancements to design training devices for pulmonary delivery systems, mimicking the look, feel and operation of the prescribed product and user experience (Figure 1). These training products afford patients a hyper-realistic experience during the onboarding period (defined as the initial 30, 60 or 90 days of delivery system usage), boosting patient confidence and encouraging proper device use, which may ultimately enhance patient health.

Numerous studies suggest the use of realistic trainers in familiarising patients with the operation of pulmonary delivery systems could help ensure that they are being utilised properly. Additionally, the impact of comprehensive onboarding and training can offer benefits to healthcare professionals (HCPs) and drug manufacturers.

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Figure 1: MDI training device designed to replicate an actual MDI's form factor and operation while providing the user with multisensory feedback.

## ENHANCING PATIENT CONFIDENCE AND HEALTH

While there is no question that pulmonary delivery systems can help save lives, patient error is still a concern because it is crucial that actuation and inhalation are performed by the patient in proper sequence with correct timing. This issue is more prevalent than one might expect.

For example, according to a widely reported study published in the *Annals of Allergy, Asthma & Immunology*, only 7% of inhaler patients follow proper technique when using their device.[3] Additionally, a pair of studies from Rice University (Houston, TX, US) concluded that the users of MDIs may be limiting their medication's effectiveness by getting only half the medication they need, again as the result of device misuse. The vast majority of the time, between 70–90%, patients commit errors resulting in only a fraction of the medication, usually less than 40%, actually reaching their lungs, as reported in *COPD News Today*.[4]

A solution to this problem lies in the latest generation of pulmonary delivery system trainers, incorporating an array of both mechanical and "smart" features, such as realistic actuation simulation. To ensure proper sequencing, calibrated whistles have been incorporated as well. As long as the patient is inhaling at the proper rate, a whistle will sound during the process but will stop sounding if the drug intake is occurring improperly.

Additionally, "smart" features on Noble's pulmonary delivery system trainers are designed to monitor the key steps involved in usage of these devices and can give the user feedback in real time. If the patient does not perform the proper sequence of steps or is not inhaling at the proper rate, these errors can be detected immediately and reported to the patient through the use of light or sound effects. Depending on the specific configuration requested by a drug manufacturer, this feedback can be conveyed both via the trainers themselves and in tandem with an app that runs on a smart device, such as a smartphone or tablet. The latter configuration allows the use of interactive videos that can further educate patients on proper use of the trainers.

> "In one study, 94 patients with COPD were observed using a pulmonary delivery system; although 96% self-reported that they utilised the proper inhalation technique, a successful first inhalation attempt was performed by only 30% of patients."

## HELPING HCPS PROVIDE BETTER INSTRUCTION TO PULMONARY PATIENTS

Enhancing patient confidence may also help HCPs to ensure a prescribed treatment is working as intended for a patient, thereby mitigating complications and resulting in an overall better quality of care.

Part of the problem in the pulmonary space is that studies have indicated that only a minority of HCPs are familiar with the proper way to use aerosol devices.[5] At the same time, studies have shown a strong correlation between poor adherence to prescribed inhaled medications and risk of hospital admission due to exacerbations, as well as increased healthcare costs. These studies also spotlight the importance of HCPs taking extra steps to promote patient adherence to these medications, including improving patient education on how to use these medications properly. Studies suggest it is important for HCPs to demonstrate proper use of pulmonary delivery systems to improve the effectiveness of therapy.[5]

The use of realistic trainers can play a role here by allowing an improvement in the quality of individualised medication self-management programmes initiated by HCPs, which have been shown to increase a patient's medication adherence.[5] For example, in one randomised, controlled study of subjects with moderate-to-severe asthma, researchers reviewed the effect of an individualised self-management education programme on medication adherence and markers of asthma control over a 24-week period. It was concluded that subjects who

received such individualised sessions had higher medication adherence compared with a control group.[5]

It is evident that the patient onboarding process is just an initial concern for HCPs. Because whether or not a patient is using their pulmonary delivery systems properly is such a critical factor in the efficacy of a treatment, it becomes a challenge for the HCP to evaluate the drug's effectiveness once the patient is sent home, leading to reliance on patient self-reporting. If patients believe they are utilising their pulmonary delivery systems correctly when in fact they are not, this can throw off the analysis of the medication and disease management. Evidence suggests this is a substantial and current issue. In one study, 94 patients with COPD were observed using a pulmonary delivery system; although 96% self-reported that they utilised the proper inhalation technique, a successful first inhalation attempt was performed by only 30% of patients[6] (Figure 2).

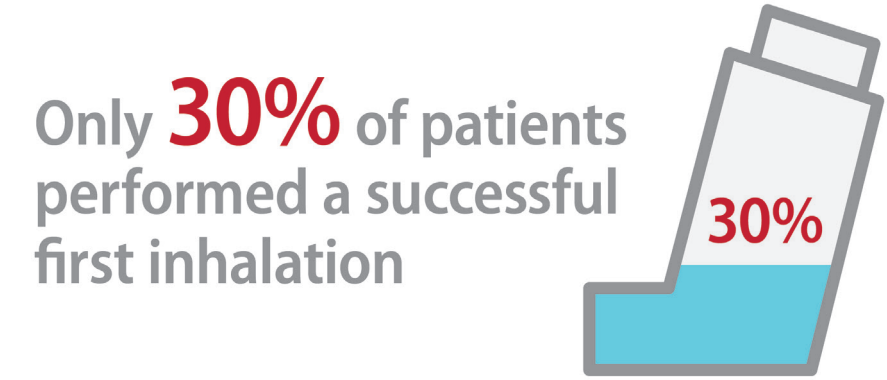


Figure 2: Study finding – 96% of patients self-reported correct inhalation technique, although observations revealed only 30% of participants actually performed a successful first inhalation attempt.

Given the evidence of disparities between patient self-reporting and actual pulmonary delivery system use, advanced training technology can serve a twofold benefit for HCPs. Firstly, a patient who practices with realistic trainers is more likely to adopt proper technique from the start of their treatment and continue to do so when self-administering at home, ensuring more effective drug delivery. Second, certain advanced trainers are capable of generating feedback that patients can share with their physicians and other HCPs in order to verify that the devices are actually being used in the proper manner.

## WHY PHARMACEUTICAL & DEVICE MANUFACTURERS TURN TO TRAINING

Finally, manufacturers stand to benefit from the new generation of realistic pulmonary delivery system trainers, as proper administration resulting from training may positively impact the device's perceived effectiveness. This can be the case not only when starting a new therapy, but also when switching to a new brand or class of treatment. Additionally, manufacturers should realise that patients and their physicians, given a choice between competing therapeutics, might select a brand that can be simulated by a realistic trainer over a competing brand for which no realistic trainer is available.

Of additional interest to manufacturers, whilst Instructions for Use (IFU) have traditionally been included with devices, research suggests that these are not always effective in conveying proper pulmonary delivery system technique to patients. Research demonstrates that many patients who self-administer medication do not fully understand, or even read in some instances, the IFU that accompanies their device (Figure 3). A study conducted by Noble and researchers from Auburn University (Auburn, AL, US) surveyed more than 700 patients and found more than half did not read their device's IFU prior to beginning treatment.[7] Noble has the capability of working with manufacturers to produce training IFUs specifically for pulmonary delivery system trainers, incorporating user-friendly literacy level messaging, multiple language options and simple, step-by-step written and visual instructions. While still an important part of the device package for manufacturers in this area, IFUs can be usefully supplemented with realistic trainers. Noble can work with manufacturers to simulate the attributes of real MDIs, DPIs and SMIs; these are available both as off-the-shelf and customised platforms.

"Given the level of precision built into Noble's production process, manufacturers can be assured that the finished product will precisely simulate their actual device."


Figure 3: Study finding – IFU alone may be insufficient for patients to learn correct administration technique.

Aside from pioneering the technology behind the trainers themselves, Noble has developed processes and systems to optimise the development and commercialisation of training devices. Given the level of precision built into Noble's production process, manufacturers can be assured that the finished product will precisely simulate their actual device. Noble can also work with a drug manufacturer during the global launch of a specific pulmonary delivery system to ensure that trainers are made available in the necessary quantities at locations worldwide in a timely manner.

It is clear there is a multitude of benefits

that pulmonary delivery system trainers can provide to patients, HCPs and drug manufacturers. Especially compelling are the studies illustrating the need for these training devices, which might be able to raise the percentage of users who correctly utilise their devices up from the 7% noted in the *Annals of Allergy, Asthma & Immunology* study, and consequently raise the amount of medication that is actually inhaled above the average of less than 40% noted by *COPD News Today*. As a result, the innovative design and production of Noble's sophisticated, patient-centric trainers may have an impact on the overall quality of healthcare administration.

## ABOUT THE COMPANY

Noble® works closely with the world's leading pharmaceutical and biotechnology companies to develop respiratory device, autoinjector and prefilled syringe training solutions designed to provide positive patient onboarding experiences, reduce errors and improve patient outcomes. Cross-disciplinary designers and engineers provide fully customised solutions from the first concept sketch through to production, in both regulated and non-regulated environments.

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## ABOUT THE AUTHOR


**Craig Baker** is Executive Vice-President at Noble, a product development company with a focus in designing and manufacturing drug delivery training and patient onboarding solutions. Joining the company just a few years after its creation, Craig holds an undergraduate degree from the University of Iowa and a Masters degree from the University of South Carolina. In addition, he has 10 years of management experience in the marketing industry and the pharmaceutical & healthcare field. This insight into both industries is an important advantage for the future growth of Noble.

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