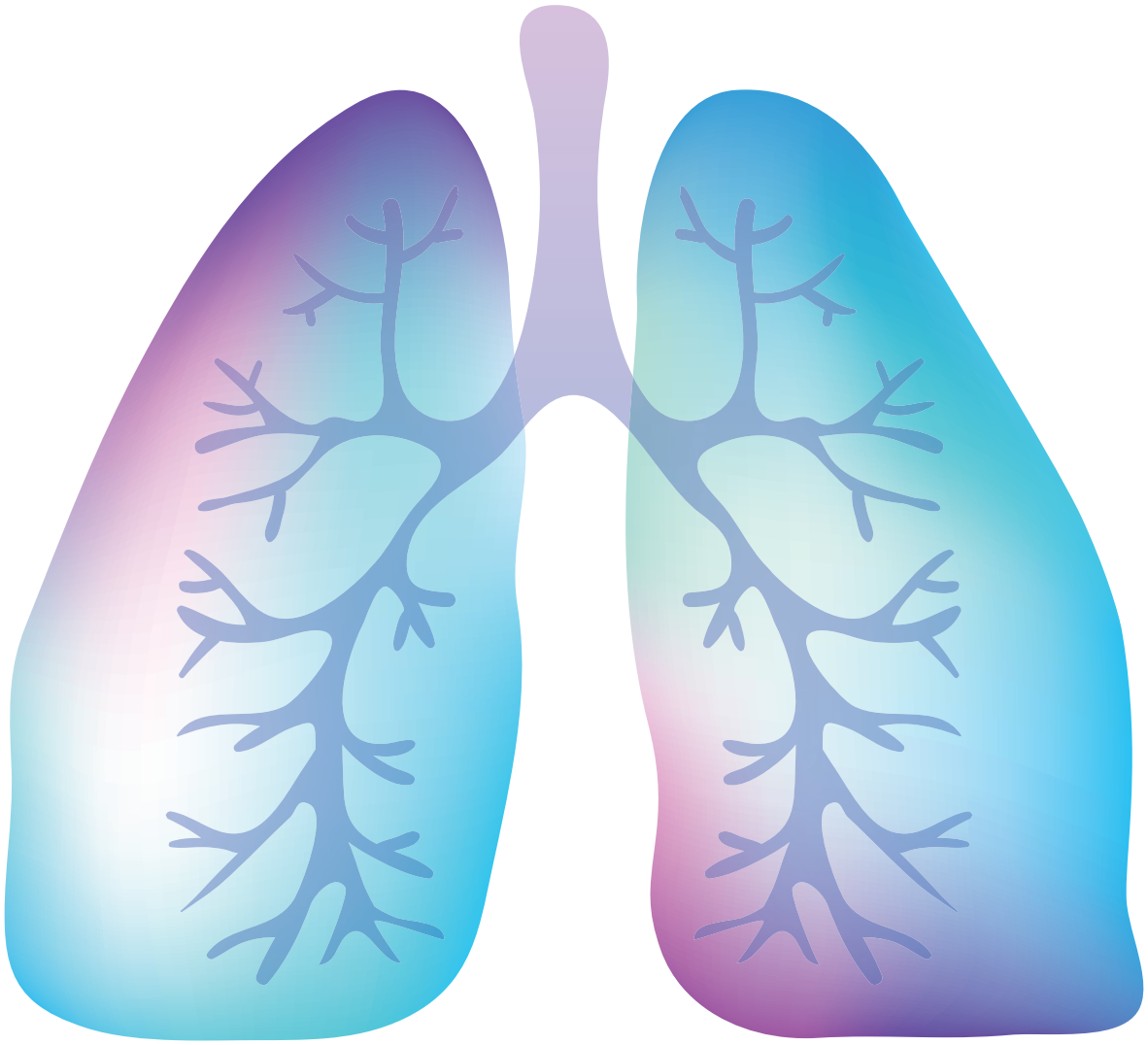
PULMONARY & NASAL DRUG DELIVERY

ON drugDELIVERY



OUTSTANDING ISSUE SPONSOR

Aptar pharma

APRIL 20TH 2020 • ISSUE NO 106

YOUR PARTNER...

FROM DEVELOPMENT TO COMMERCIALIZATION

Scientific expertise and testing strategies for innovator and generic OINDPs

- Human Usage Studies
- Device Selection
- Formulation Screening

Alternative BE Studies

- Regional Drug Deposition
- Plume Velocity
- Evaporation Fraction

- In Vitro Testing
- Drug Product Characterization Studies
- Priming/Repriming
- Temperature Cycling
- Device Robustness
- Stability Studies

- Batch Release Testing
- Long-term Stability Testing
- Root Cause Analysis
- OOS/OOT Investigation

NOW FEATURING cGMP COMPLIANT LABORATORY

LEARN MORE:

www.proveris.com
contactus@proveris.com
+1 508 460-8822

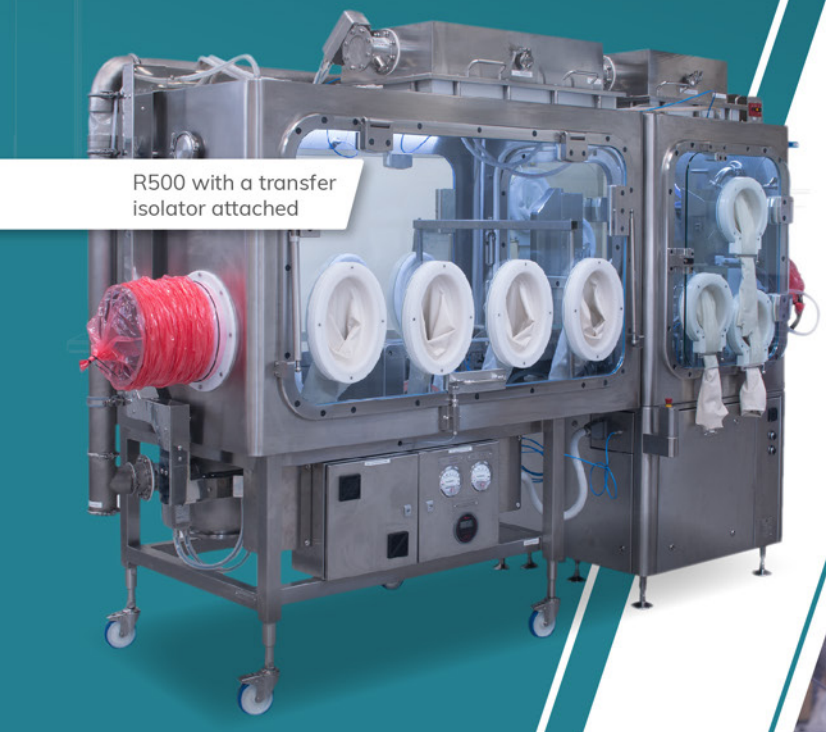
proveris SCIENTIFIC

FUTURE-PROOF POWDER FILLING

R500/R1000
Robotic Powder Filler

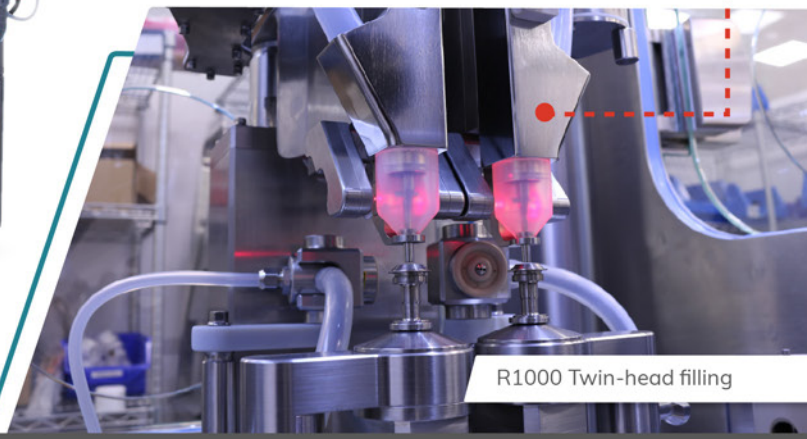
INCORPORATING ***FILL2WEIGHT.***
THE WORLD'S FASTEST GRAVIMETRIC POWDER MICRO-DOSER

- Ultra-low dose weight option (1mg +)
- Fills 1000 capsules per hour
- Fills challenging powders
- Negative pressure, full containment option
- Scalable, high-speed filling
- 100% weight check
- Infinitely variable dose weight
- Rapid changeover
- Compact, GMP design



R500 with a transfer isolator attached

Fill capsules and inhalation devices on the same machine



R1000 Twin-head filling

CONTACT US

+44 (0) 1926 408 933 enquiries@3pinnovation.com www.3pinnovation.com

Contents

ONdrugDelivery Issue N° 106, April 20th, 2020

PULMONARY & NASAL DRUG DELIVERY

This edition is one in the ONdrugDelivery series of publications from Frederick Furness Publishing. Each issue focuses on a specific topic within the field of drug delivery, and is supported by industry leaders in that field.

EDITORIAL CALENDAR

May 2020	Injectable Drug Delivery
Jun	Connecting Drug Delivery
Jul	Novel Oral Delivery Systems
Aug	Industrialising Drug Delivery
Sep	Wearable Injectors
Sep/Oct	Drug Delivery & Environmental Sustainability
Oct	Prefilled Syringes & Injection Devices
Nov	Pulmonary & Nasal Drug Delivery
Dec	Connecting Drug Delivery
Jan 2021	Skin Drug Delivery: Dermal, Transdermal & Microneedles
Feb	Prefilled Syringes & Injection Devices
Mar	Ophthalmic Drug Delivery
Apr	Pulmonary & Nasal Drug Delivery

EDITORIAL:

Guy Furness, Proprietor & Publisher
T: +44 1273 47 28 28
E: guy.furness@ondrugdelivery.com

SUBSCRIPTIONS:

Audrey Furness, Marketing Executive
E: subscriptions@ondrugdelivery.com
10-12 issues of ONdrugDelivery published per year, in print and digitally.
Print + Digital subscription: **£99/year + postage**.
Digital Only subscription: **free**.

ADVERTISING:

Guy Furness, Proprietor & Publisher
T: +44 1273 47 28 28
E: guy.furness@ondrugdelivery.com

MAILING ADDRESS:

Frederick Furness Publishing Ltd
The Candlemakers, West Street, Lewes
East Sussex, BN7 2NZ, United Kingdom

ONdrugDelivery is published by Frederick Furness Publishing Ltd

Registered in England: No 8348388
VAT Registration No: GB 153 0432 49
ISSN 2049-145X print / ISSN 2049-1468 pdf

Transforming bright ideas into brilliant opportunities for decades

Aptar Pharma – the go-to drug delivery expert

When pharmaceutical companies around the world want to develop safe, efficient and compliant medicines, they turn to Aptar Pharma for proven drug delivery solutions.

Leveraging our therapeutic insights, over 25+ years of regulatory expertise and the widest portfolio of solutions and services in the industry, we accelerate and derisk our customers' drug development process, helping them transform bright ideas into new market opportunities to improve and save patients' lives.

Let's partner together on your next bright idea. Visit **www.aptar.com/pharma** to get started.

Delivering solutions, shaping the future.

Aptar pharma

RESPIRATORY DRUG DELIVERY: THEN, NOW AND SOON

Brennan Miles, a Senior Consultant at Team Consulting, takes a look back at respiratory drug delivery over the last few decades to see what we can learn from the past – and looks ahead to what the future might look like, covering sustainability, device regulation, and formulation milestones.

Respiratory drug delivery has come a long way in the last few decades, with a raft of changes in legislation, standards and industry trends. Whilst it's impossible to predict the future, it's interesting to take a look back, explore how our industry has progressed over the last 30-plus years and consider what areas we are likely focus on in the coming decades.

> "Should we potentially sacrifice patients' disease management by withdrawing or changing devices that are environmentally damaging? Or should patient health take priority over environmental protection?"

ENVIRONMENTAL CONCERNS AND SUSTAINABILITY

Environmental and sustainability concerns are hot topics for the respiratory drug delivery sector – and have been, in one form or another, for some time. Environmental factors such as air quality can have a huge impact on respiratory conditions, and improvements in the treatment of existing diseases, so it's a hugely important area for the industry in general. A drive towards protecting the environment in the late 1980s triggered one of the biggest recent changes in the respiratory industry and – whilst the conversation around the environmental impact of the industry has since moved to encompass other areas – it remains a huge driver for change.

In 1987, the Montreal Protocol was agreed and signed by 167 countries, due to growing global concerns over the depleting ozone layer. The agreement was designed to protect the environment by phasing out the use of harmful substances, including chlorofluorocarbon (CFC) propellants which were widely used in pressurised inhalers at the time. This change had two important effects: it triggered development of alternative hydrofluorocarbon (HFA) based propellants and prompted more research effort into other device-reliant drug-delivery methods such as dry powder inhalers – which work without propellants, instead using patients' respiratory effort to aerosolise the drug.

The effect of the shift away from CFCs is clearly visible in contemporary devices, and there has recently been much discussion in the industry around HFA alternatives to further address sustainability and wider environmental concerns. Some types of HFAs, whilst not as damaging to the ozone layer as CFCs, still represent a potent greenhouse gas, and calls for discontinuing or at least limiting their use are growing. The problem with this, however, is that whilst current propellant-based inhalers may be detrimental to the environment, they are also an important part of the lives of hundreds of thousands of patients worldwide.

This raises a big question – should we potentially sacrifice patients' disease management by withdrawing or changing devices that are environmentally damaging? Or should patient health take priority over environmental protection? There is no easy answer but significant effort is being spent to find a reasonable solution, including the development and approval of more environmentally friendly HFA propellants and other inhalation technologies.

Consumer product companies have been making serious moves for several years to improve the environmental impact of products and packaging. These include switching to recycled or sustainable materials and reducing the use of single-use plastics. The medical industry necessarily tends to move slower than our consumer counterparts – generally about 10 years behind consumer sector

Brennan Miles
Senior Consultant
T: +44 1799 532749
E: brennan.miles@team-consulting.com

Team Consulting
Abbey Barns
Duxford Road
Ickleton
CB10 1SX
United Kingdom

www.team-consulting.com

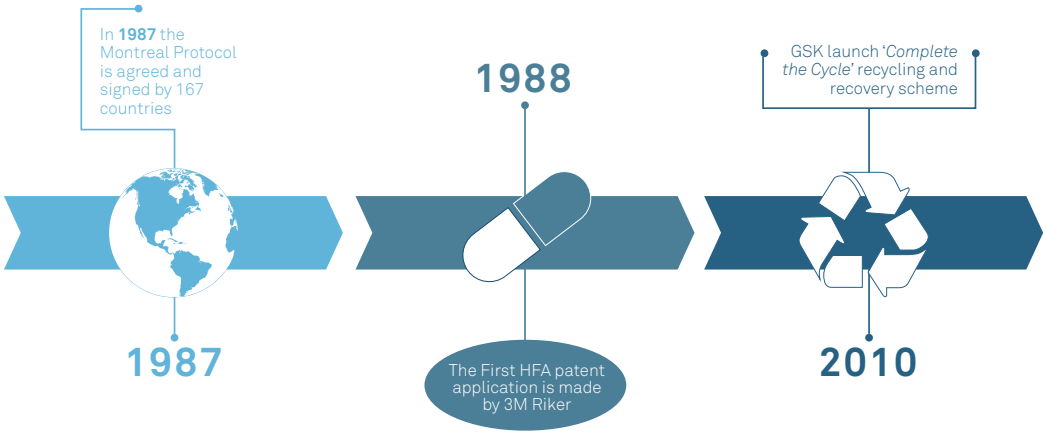


Figure 1: Environmental milestones in respiratory drug delivery.

trends – but sustainability has been firmly on the respiratory agenda for a few years now (Figure 1). It is clearly a growing driver, with companies and countries alike making big commitments to sustainability initiatives.

In 1987, our main concern was the damaged ozone layer. But today there are many other concerns that affect the environment, such as the prevalence of plastics, particularly in single-use devices. In medical device development it's easy to overlook the positive environmental impact that small changes can make, as patient safety comes above all other issues. However, devices like inhalers that are produced in very high volume provide great opportunities for reducing environmental impact in low-risk areas. Some examples include developing smarter packaging concepts to reduce bulk and weight as well as making use of the wide range of sustainable materials that are already available. We can expect to see more focused effort in the early design phases to identify low-risk areas where alternative – or perhaps recycled – materials can be used without presenting a risk to the patient.

More thought is also being given to how devices are managed at the end of their lives, recovering devices to recycle the materials used (rather than incinerating them as usually happens). Inhaler recycling schemes are being introduced in many areas – Teva recently launched one such scheme in Ireland, and GSK has recycled 1.2 million inhalers as part of its Complete the Cycle recycling and recovery scheme since 2010.

Typically, major shifts in the medical devices industry only come about when pushed by regulation, and we should expect some developments in this area soon. There remains the complex underlying issue of finding a balance between patient health and environmental health, especially when each affects the other.

REGULATION, REGULATION, REGULATION

Many of the standards and regulations that we take for granted in the medical devices industry today have existed in their current form for less than 30 years. The Medical Devices Directive (MDD 93/42/EEC) was first adopted in 1993 to harmonise laws relating to medical devices within the EU. Prior to the MDD, every European country had its own laws, regulations and different ways of approving medical devices, although mutual recognition agreements were an effective way to allow devices approved in one territory to be approved across many. Operating under the same regulations across multiple European countries is beneficial to pan-European corporations because it streamlines the regulations device developers need to adhere to.

The MDD has undergone several amendments over the years (see Figure 2) but the largest change will happen shortly when it transitions into the Medical Devices Regulation (MDR). There are some significant changes in the new regulation, such as a shift to a more complete lifecycle approach, and an increased number of safety requirements: the word "safety" appears 290 times in the MDR compared with only 40 in the MDD.

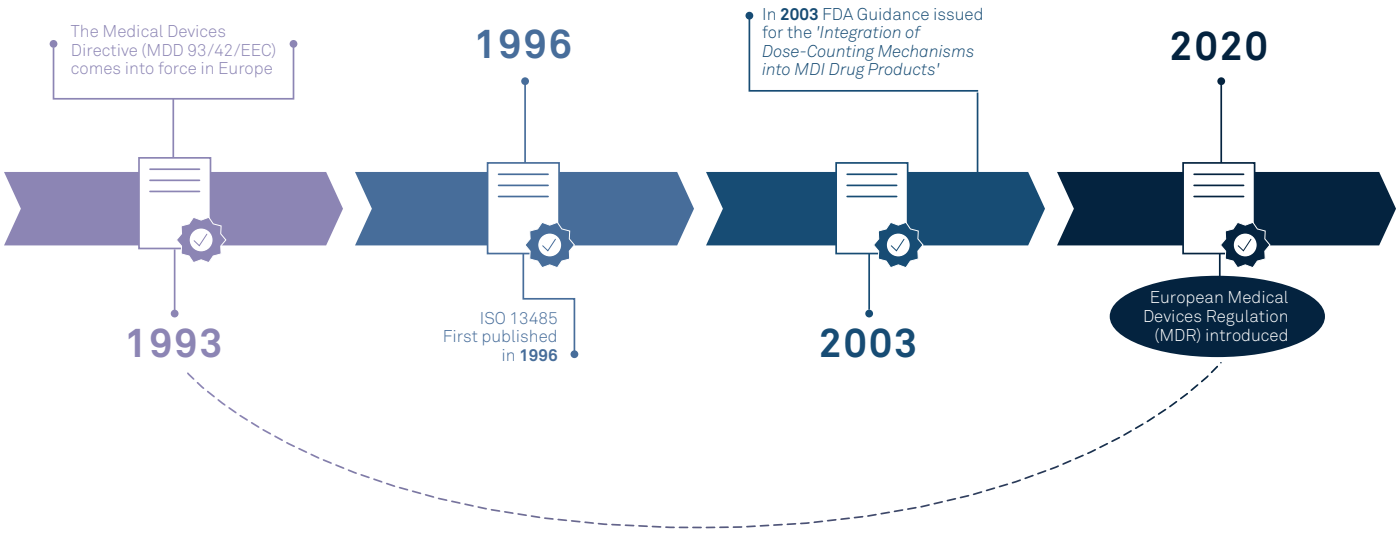


Figure 2: Key medical device regulations introduced since 1993.

Another key regulatory milestone in the industry came in 1996 when ISO13485 was published – a standard that forms the basis of quality management systems for European medical device developers and manufacturers. The MDD talked about the need to have a quality management system in place but ISO 13485 describes what that means in practice and plays a hugely important role for medical device design, development and manufacturing. Before this, manufacturers typically deferred to the principles of ISO 9001, which established the basic requirements for a supplier to assure product quality but was not specific to the medical devices industry.

The year 1998 saw the introduction of ISO 14971, covering the requirements for risk management during medical device development and post-production. It has been an immensely important standard for defining risk for medical devices – the combination of probability of occurrence of harm and the severity of that harm – so that risks can be identified and mitigated in a systematic way. Patients do and should take for granted that medical devices are safe for them to use and this is exactly why good risk management is so important for medical device developers.

Specifically, for inhaler devices it was only in 2003 that the US FDA issued its guidance for "integration of dose counting mechanisms into MDI products", which prompted an abundance of new dose counter innovations for inhalers. In 2009, ISO 20072 was published which describes device design verification requirements and test methods. The standard requires some specific and challenging environmental conditions to be maintained for the testing procedures. It will be interesting to see what innovations new and future standards prompt in our industry.

> "Whilst there's a lot to be learned from landmark successes in respiratory drug delivery such as TOBI, there's perhaps even more to be learned from failures."

FORMULATION MILESTONES

There is no typical length of time that it takes for a new drug to be tested and approved. The best rule of thumb is that it can take anywhere from 10 to 15 years for an experimental drug to move from preclinical testing in the laboratory to gaining regulatory approval and use. It has been estimated that only one in every 5,000 new drugs makes it to market. With odds this bad, it is remarkable that so many of the most valuable respiratory formulations (Figure 3) were discovered in recent years.

In 1990, Glaxo (now GSK) launched Serevent (salmeterol) – the first long-acting beta-agonist (LABA) for the maintenance of asthma and COPD. This was followed in 1998 by Seritide (salmeterol + fluticasone propionate), which is marketed as Advair in the US. Seretide/Advair remains the best-selling asthma treatment of all time, generating revenues of over £5.7 billion.

You can't discuss inhalation formulation advances without mentioning Sir David Jack (1924–2011). He was the exceptional research scientist behind many of the blockbuster respiratory medicines that came out of Glaxo over the years, including Ventolin (salbutamol), Serevent, and Becotide (beclomethasone dipropionate). These drugs are still widely prescribed to treat asthma and, even decades later, no better equivalent exists. Sir David even continued to carry out research work after his retirement from Glaxo. As recently as 2011 the drug development company Verona Pharma announced that it was seeking commercial licensing agreements for Ensifentrine, an anti-asthma and hay fever treatment developed by Sir David as an alternative to conventional steroids and beta-agonists.

Another milestone in respiratory drugs that deserves a mention is tobramycin solution for inhalation (TOBI) which was approved in 1997 for the treatment of cystic fibrosis (CF), which severely affects the function of the lungs. TOBI was the first inhaled antibiotic for the treatment of CF and has been credited with significantly extending the life expectancy of CF patients. TOBI represents one of the few success stories in systemic inhaled therapies, outside of asthma and COPD treatment.

Whilst there's a lot to be learned from landmark successes in respiratory drug delivery such as TOBI, there's perhaps even more to be learned from failures. Exubera – the first inhaled insulin to be approved by the FDA – is in the latter category of respiratory milestones. It represents one of the most interesting examples in recent

> "Medical device companies and pharmaceutical firms have come to understand that the trade-off between sustainability and profit is an outdated concept."

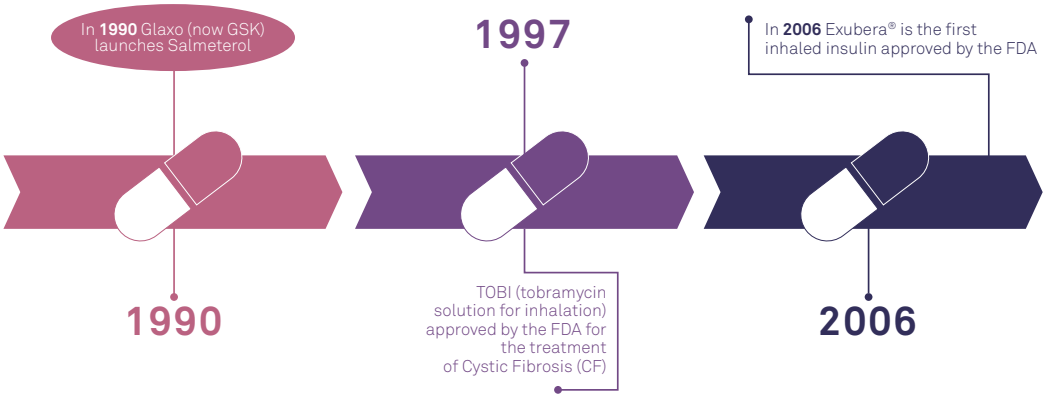


Figure 3: Respiratory drug formulation milestones.

history of how a poor understanding of patients' needs and a difficult-to-use device ultimately led to a major failure to gain market acceptance. Following a 2006 launch by Pfizer, it was eventually withdrawn at an estimated loss to Pfizer of $2.8 billion (£2.3 billion). It's difficult to pinpoint the reasons Exubera wasn't successful but a combination of fundamental issues meant that it didn't follow in the footsteps of TOBI as a successful inhaled systemic therapy.

PREDICTING THE FUTURE

There has been so much innovation with respiratory medicines and inhaler devices over the last 30 years that it is impossible to guess where the industry is headed in the next 30 years. We can, at least, think about what is likely to happen in the foreseeable future and how some of the current hot topics such as sustainability, regulation and formulation innovation may evolve.

In the past, many businesses have viewed their commitment to improving the environment as something that should be addressed when they are instructed to, rather than seeing it as core to their values and strategy. This is now changing. Medical device companies and pharmaceutical firms have come to understand that the trade-off between sustainability and profit is an outdated concept. They are now reacting to the world around them and recognise that environmental concerns are also their (and their shareholders') concerns.

Good opportunities exist for making medical devices greener: focusing on the manufacturing process to reduce production waste and reduce the need to ship materials, components and sub-assemblies to different manufacturing sites; specifying recycled (or recyclable) materials during the development of new devices; and reducing the device packaging that is delivered to the patient (for example, by combining packaging and instructions for use and by using simple cardboard support trays to replace plastics).

> "These new device technologies may well be the key that opens the door to new inhaled therapies beyond asthma and COPD."

Another approach is to reduce the complexity and physical mass of the devices. A few years ago, Team Consulting put together a concept for a novel inhaler that was essentially a cardboard tube with a simple piercing mechanism to release the drug from an innovative single-dose blister. Pioneering solutions like this should be seriously considered in the next few years to supplement current respiratory device offerings. We need to encourage more focus on sustainable thinking in the early phases of a new product design in combination with programmes that deal with the collection and recycling of used devices. Expect to see some real changes in this area soon.

Improving patient adherence is clearly a major theme for the delivery of inhaled medicines. Worldwide, non-compliance is a major challenge to the delivery of healthcare. Adherence is also closely linked to sustainability because the better patients follow their medical instructions, the less wastage and overuse of medicines and devices there are. The industry is attempting to tackle this through new technologies, such as companion apps that give patients reminders to take their drugs, and device training instructions. These can also work alongside the emergence of smart devices that actively assist the patient to inhale correctly to improve the drug delivery effectiveness. New technology also has a downside because it increases device complexity, so the benefits need to be carefully weighed and balanced to decide how and where the technology is used to be most effective.

It's incredibly difficult to predict where the new inhaled therapies are going to come from and what they are going to be. We do know that inhalation of drugs into the lungs is one of the least invasive routes and works well for topical therapies to treat respiratory disorders. It is perhaps somewhat astonishing that more systemic therapies have not been developed for the inhaled route, possibly in part because of the failure of Pfizer's Exubera programme. Reassuringly, there have been some recent developments in this field – in 2014, for example, the FDA approved a new inhaled insulin (Afrezza) to treat diabetes.

We also know that good clinical outcomes in respiratory medicine rely on a combination of drug formulation and delivery device that is simple to use and produces good deposition of the drug inside the lung. Recent new device technology development activities have seen an emergence of improved nebulisation devices and a renewed interest in liquid mist inhalers. Technologies such as this have the capability to deliver more complex formulations which would have otherwise been impossible in a dry powder form. These new device technologies may well be the key that opens the door to new inhaled therapies beyond asthma and COPD.

ABOUT THE AUTHOR

Brennan Miles is an experienced respiratory drug delivery consultant and designer. Prior to joining Team, he spent several years as a Senior Design Engineer with Pfizer. Mr Miles has worked on a range of surgical and drug delivery products including dry powder inhalers, injectors and ophthalmic devices for a wide variety of therapies. He is the named inventor on a number of patents and has also had several papers published.

ABOUT THE COMPANY

Team is an award-winning medical device design and development consultancy. For more than 30 years, it has worked closely with clients at the world's leading pharmaceutical and device companies to develop better medical devices.

IS NOW THE TIME TO SHAKE UP THE pMDI ENVIRONMENT?

In this article, Chris Baron, Director of Business Development, Aptar Pharma, explores how the use of propellants in pressurised metered dose inhalers has evolved – and how alternative propellants could be a catalyst for greater patient adherence.

Given that humans are largely creatures of habit, it's no surprise that most of us find it uncomfortable to truly embrace change. When the 1987 Montreal Protocol initiated the phasing-out of ozone-depleting substances, including chlorofluorocarbon (CFC) propellants, those who work with pressurised metered dose inhalers (pMDIs) were naturally nervous. As it happened, the switch was beneficial not just to the ozone layer but also to the pMDI carbon footprint.

Today, the industry is faced with a similar challenge – how to move away from propellants such as hydrofluoroalkanes HFA P227 and HFA 134a and towards newer, more environmentally friendly approaches aimed at further reducing the sector's carbon footprint.

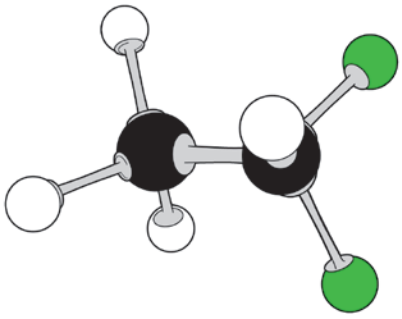
Just six months ago, experts could not say with any certainty that one such alternative – HFA 152a (1,1-difluoroethane, Figure 1) – would work. We knew it was more environmentally friendly but would it pass the technical trilogy of excellent toxicology, limited flammability and reduced environmental impact while maintaining formulation stability (Figure 2)? All without losing sight of the greatest challenge of all – ensuring patient safety and supporting regimen adherence. These are, after all, life-enhancing, life-saving treatments for many patients.

In this article we will explore how the industry's use of propellants has evolved and consider where we could end up in the drive for greater sustainability, providing some context on the impact pMDIs have on the environment today, while at the same time suggesting some areas for improvement.

We will also discuss how HFA 152a and other alternative propellants could be a catalyst for greater patient adherence, and how greater adherence could in itself be an effective route to improved sustainability.

KEEPING UP WITH CLIMATE SCIENCE

While sustainability dominates today's agenda, environmental science has not always enjoyed such prominence. Indeed, when the first pMDI was introduced in 1956,



A colorless, odorless, non-toxic low boiling liquid
In large scale industrial use (~150Ktpa), as:

- Polymer precursor
- Aerosol propellant (e.g. hairsprays, deodorants)
- Foam blowing agent
- Air conditioning and refrigeration

Figure 1: HFA 152a – a low global warming potential (GWP) medical propellant.

Chris Baron
Director of Business Development
M: +33 6 30 95 53 31
E: chris.baron@aptar.com

Aptar Pharma
Route de Falaises
27100 Le Vaudreuil
France

pharma.aptar.com

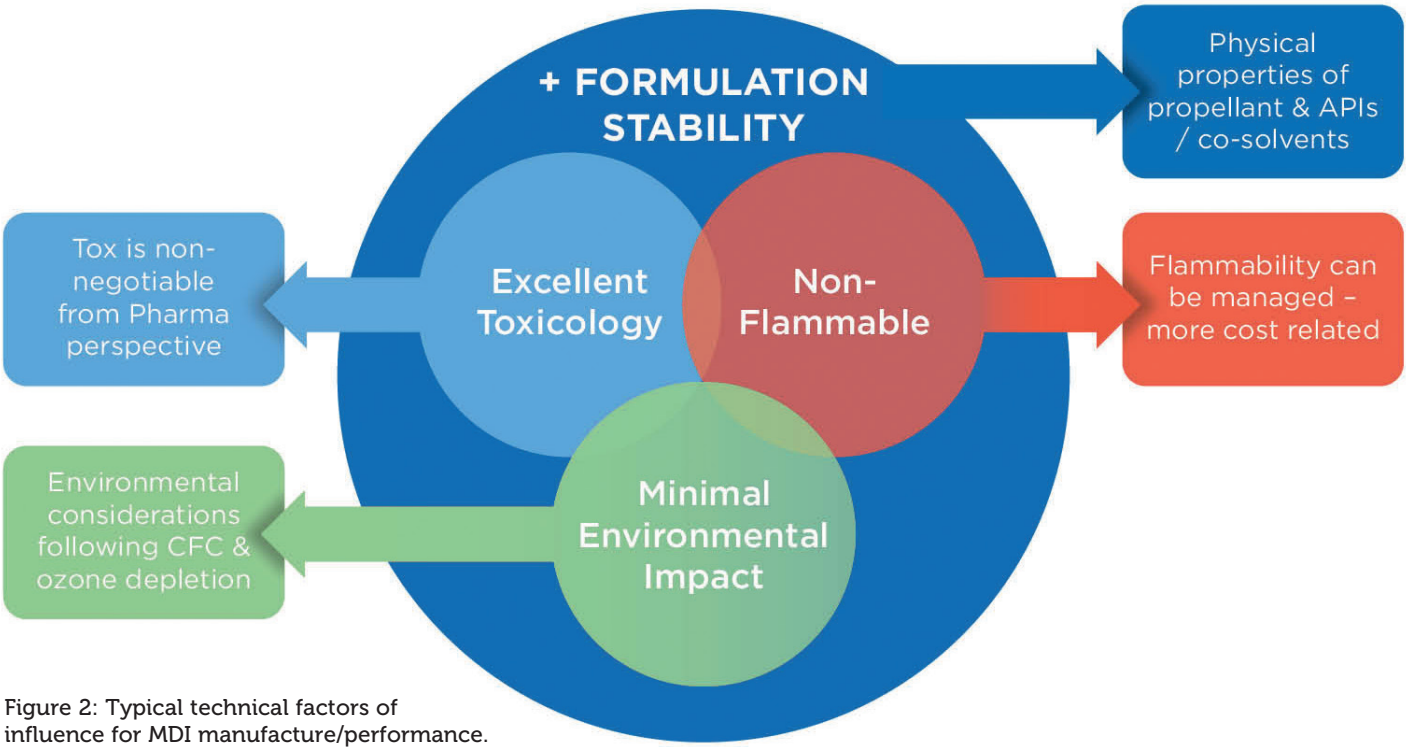


Figure 2: Typical technical factors of influence for MDI manufacture/performance.

it was almost another two decades before the term "global warming" became popularised through the publishing of a paper by US geochemist Wally Broecker in 1975.[1]

The following decade saw growth in the evidence base for the damaging impact that so-called "greenhouse gases" were having on the environment, including their contribution to the depletion of the ozone layer. This culminated in 1987 with the establishment of the Montreal Protocol, which regulated the consumption and production of compounds harmful to the ozone layer. Within the decade, CFCs – the family of gases most commonly used as a pMDI propellant – were to be phased out, although in the case of pMDIs an exemption was granted until alternative products using HFA propellants could be safely brought to market.

It was in 1995, some eight years after the signing of the Montreal Protocol, that the first HFA-based salbutamol product was launched in the UK. By 2012, the US FDA banned the manufacture and sale of CFC-based products entirely.

Given that 400 million pMDIs were sold in 2014, the result of the move from CFC to HFA has been a net reduction of around 2,600 tons of CFCs being released into the atmosphere every year.[2]

While not as significant as other CFC-heavy sectors, this reduction has helped contribute to a reversal of the depletion of the ozone layer while also ushering in a decline in the sector's carbon footprint. In October 2019, satellite measurements from NASA and NOAA registered the ozone hole at 3.9 million square miles – the smallest level since records began. While unusual weather patterns were a factor in this figure, experts suggest the ozone will be fully repaired by the 2060s.

"The move to restrict HFAs presents an ongoing challenge for those involved in the manufacture and development of pMDIs."

NOW HFAS ARE UNDER SCRUTINY

But the environmental story of pMDIs does not end there. In recent years, as the issue of sustainability has escalated to a climate emergency, the focus on limiting the use of products with the potential to impact the environment has become more acute. As a result, there is an emphasis on reducing the use of other fluorocarbons that have a global warming impact, beyond just CFCs.

Collectively known as F-gases, this family accounts for around 2% of total greenhouse gas emissions, and their use is dominated by the air-conditioning and refrigeration industry. However, F-gases also include the HFCs used as propellants in pMDIs – predominantly in the form of HFA 134a and HFA P227, albeit only accounting for a very small proportion (see Figure 3).

The restriction on F-gases has been made official through the Kigali Amendment (2016) to the Montreal Protocol, which came into effect in 2019 and seeks to phase down the use of HFCs by 85% by 2047. The situation regarding compliance is not necessarily consistent across the globe, however. In the US, despite the introduction of the Significant New Alternatives Policy (SNAP) programme and its intention to identify and evaluate substitutes for ozone-depleting substances, pMDIs remain fully exempt.

In Europe, legislation to phase down the use of F-gases restricts their use through a quota system and specific bans. Medical use exemptions are applied to pMDIs but the products are impacted by regulation linked to the phasing out of industrial HFC grades, which are used as the basis for the purified HFAs used as propellants. As these products are phased out, taxation

"The challenges of repurposing are well known, both from a manufacturing and regulatory perspective as well as in terms of efficacy and patient compliance."

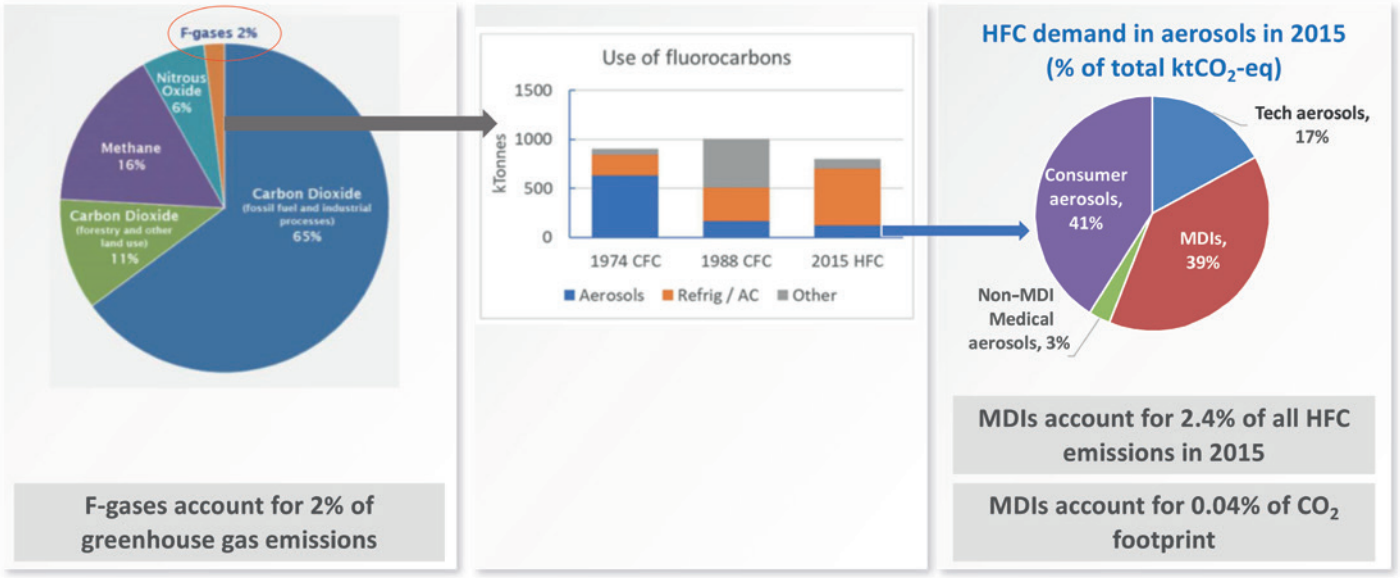


Figure 3: Use of fluorocarbons (F-gases).
Sources: US Environmental Protection Agency Web Page (https://www.epa.gov/ghgemissions/global-greenhouse-gas-emissions-data); Hauck HR, "Do Medical CFCs Threaten the Environment?" J Aerosol Med, 1991, Vol 4(3), pp 169-174; Technology & Economic Assessment Panel, Meeting of Parties, Kigali, 2016.

and inflated quota pricing are leading to significant cost increases that will no doubt be passed through to the price of medical-grade gases. With the pMDI exemptions only applied on a temporary basis, there is also a chance they will be subject to withdrawal when next reviewed in 2021 if the European Commission decides to enforce measures to accelerate the adoption of lower-carbon alternatives.

Amid the inconsistencies, it is clear that the move to restrict HFAs presents an ongoing challenge for those involved in the manufacture and development of pMDIs, who find themselves in a position similar to that experienced in 1987, when the Montreal Protocol outlined a new CFC-free future and presented a clear challenge to find a commercially viable way forward.

FINDING NEW ALTERNATIVES

In the short term, the manufacture of pMDIs will continue as normal as the supply chain recalibrates its approach. Any immediate impact is likely to be felt in a shifting dynamic between product pricing and margin, with HFA costs set to continue their rise.

In the longer term, there will have to be consideration of alternatives. In terms of drug delivery methods, options are available that have comparatively lower carbon footprints, including dry powder inhalers (DPIs), soft mist inhalers (SMIs) and portable nebulisers. However, the challenges of repurposing are well known, both from a manufacturing and regulatory perspective as well as in terms of efficacy and patient compliance.

Here at Aptar Pharma, we are already committed to defining the next phase of the pMDI market. As stocks of current propellants deplete, inevitably leading to a sustained increase in pricing, we believe now is the time for pharmaceutical companies to align themselves with more environmentally friendly propellants. HFA 152a and HFO 1234ze, for example, present significantly lower global warming potential (GWP) compared with existing HFA propellants.

With these lower-carbon alternatives, the key question that must be answered is whether they can successfully balance the required levels of toxicology and flammability, ensuring formulations remain

> "With lower-carbon alternatives, the key question that must be answered is whether they can successfully balance the required levels of toxicology and flammability, ensuring formulations remain stable and efficacy is not impaired."

stable and efficacy is not impaired. In the case of HFO 1234ze, the environmental case is incredibly strong and flammability is limited – but toxicology concerns have been raised in the context of its use as a medical propellant.[3]

In the case of HFA 152a, the environmental case is also compelling. Furthermore, an exhaustive full-inhalation propellant toxicology study is entering the final year of a two-year study, with no adverse findings raised to date. Properties such as a lower flammability limit (LFL) of 3.8% mean there are still important safety hurdles, primarily from a manufacturing perspective, that need to be overcome before HFA 152a can be introduced within a marketable product but, overall, the indications are promising. Indeed, calculations based on research presented by the University of Manchester[4] have shown that a month's worth of medication taken using a salbutamol + EtOH product – but propelled by HFA 152a – has a similar carbon footprint to a single healthy bite of a beefburger, with around 1kg of CO_2 per 100 doses.

LIMITING CARBON IMPACT THROUGH INNOVATION AND PATIENT COMPLIANCE

At Aptar Pharma, we are focused on finding more sustainable, lower-carbon propellant alternatives, and have already undertaken significant work to evaluate the compatibility of our metering valves with more environmentally friendly options, including formulations based on HFA 152a. As a company, we have committed resources to these programmes, with the support of our research and development laboratories, and filling capabilities in Le Vaudreuil (France).

Collaboration with fluoroproducts specialist Koura and a range of pharmaceutical companies is enabling Aptar Pharma to screen metering valves across multiple model formulations and optimise new valve configurations for the use of HFA 152a. This has allowed us to show that the distinct properties of this gas, such as its low liquid density, do not pose a problem in working with suspensions.

Important developments such as this, when coupled with other technical innovations targeted at optimising patient behaviour and compliance, will in time become part of the wider range of factors to support a reduction in the carbon impact associated with pMDIs. Connected devices have the potential to bring real benefit here, providing the basis to increase patient awareness around adherence and promote the sustained, correct use of inhalers. For a global population increasingly aware of their environmental impact, the benefit of reducing their carbon impact just provides an additional incentive to improved compliance.

A STEP-CHANGE IN pMDI SUSTAINABILITY

As this new generation of lower-carbon products emerges, it's important to put some of the more dramatic headlines associated with current HFA-based pMDIs into context. It must be remembered that pMDIs represent a small proportion of the overall use of HFAs, and that HFAs themselves are part of a collective family that represents 2% of greenhouse gases. In fact, MDIs account for just 0.04% of the total carbon footprint. Over the course of a year, it would take 275 million pMDIs used for maintenance therapy to create the equivalent level of CO_2 output by a single 1,000 MW coal power station.

The fact remains that pMDIs offer unique benefits as a mechanism for delivering essential medicines. Experts are unanimous in their view that asthma patients must have access to the most suitable treatments when they need them. Also, with an estimated 95% of portable rescue medications administered using pMDIs, the importance of familiarity and ease of use should not be underestimated.

Change, rightly, is coming. Having successfully risen to the challenge of eradicating CFCs from the supply chain, pharmaceutical companies and their partners are now responsible for establishing greener alternatives to HFA-based inhalers. The potential of HFA 152a, in tandem with innovation to drive greater patient compliance, presents an evolutionary pathway for the pMDI sector to continue to meet its dual commitments to patients and the planet.

ABOUT THE COMPANY

For pharma customers worldwide, Aptar Pharma is the go-to drug delivery expert, providing innovative drug delivery systems, components and active packaging solutions across a wide range of delivery routes including nasal, pulmonary, ophthalmic, dermal and injectables. Aptar Pharma Services provides early stage to commercialisation support to accelerate and derisk the development journey. With a strong focus on innovation, Aptar Pharma is leading the way in developing connected devices to deliver digital medicines. With a global manufacturing footprint of 14 manufacturing sites, Aptar Pharma provides security-of-supply and local support to customers. Aptar Pharma is part of AptarGroup, Inc (NYSE:ATR).

REFERENCES

1. *Broecker W, "Climatic change: Are we on the brink of a pronounced global warming?". Science, 1975, Vol 189 (4201), pp 460–463.*
2. *Stein S, Thiel C, "The History of Therapeutic Aerosols: A Chronological Review". J Aerosol Med Pulm Drug Deliv, 2017, Vol 30(1), pp 20–41.*
3. *Lindley A, Noakes T, "Consideration of hydrofluoroolefins (HFOs) as potential candidate medical propellants". White Paper, Mexichem Flour (now Koura), April 2010.*
4. *Jeswani H, Azapagic A, "Life cycle environmental impacts of inhalers". J Clean Prod, 2019, Vol 237.*

ABOUT THE AUTHOR

Chris Baron is Director of Business Development in asthma and COPD at Aptar Pharma. For the last 10 years he has been located at Aptar Pharma's manufacturing facility in Le Vaudreuil, France, where he oversees global business development activities for Aptar's inhalation drug delivery devices (MDIs and DPIs) and their respective services pertaining to the application fields of asthma and COPD. Mr Baron has 29 years' experience working in the field of inhalation drug delivery, with significant expertise in metering valve technologies for pressurised metered dose inhalers and their accessory/peripheral device technologies, including dose indicators and breath-activated inhalers.

AN ENVIRONMENTALLY SUSTAINABLE, PATIENT-CENTRED SOLUTION FOR ASTHMA AND COPD

In this article, Sara Panigone, PhD, Sustainable Device Transition Leader; Federica Sandri, PhD, Sustainable Device Transition Project Officer; and Gabriele Nicolini, PhD, Head of Global Medical Affairs, all of Chiesi Farmaceutici, provide a considered and well-referenced analysis of carbon-minimal pMDIs for asthma and COPD, stressing the importance of balancing environmental sustainability with therapeutic efficacy to provide a sustainable and patient-centred solution.

Globally, chronic pulmonary conditions cause a significant burden, and are among the leading causes of morbidity and mortality.[1] Asthma and chronic obstructive pulmonary disease (COPD) are the most common chronic pulmonary diseases; it is estimated that there are at least 300 million patients with asthma and 250 million patients with COPD worldwide.[2-4] Approximately 3.2 million and 400,000 deaths are attributable to COPD and asthma each year, respectively.[1] COPD is currently the third leading cause of death worldwide, with the burden expected to increase further within the next 10 years.[3,5]

Despite this, chronic respiratory diseases are often overlooked compared with other major causes of morbidity and mortality.[6] No cure exists for either COPD or asthma; both conditions are primarily managed with chronic use of inhaled therapies delivered via an inhaler. Three main types of handheld inhaler are available – pressurised metered dose inhalers (pMDIs), dry powder inhalers (DPIs) and soft mist inhalers (SMIs).[7] Choosing the most suitable inhaler for each patient is as important as choosing the most appropriate drug, as patient preference and ability to use a device may influence adherence to treatment.[7] The most commonly used inhaler in Europe is the pMDI (Figure 1)[8], which relies on the driving force of propellants to atomise droplets containing drugs for deposition in the lungs.[9]

> "The most commonly used inhaler in Europe is the pMDI[7], which relies on the driving force of propellants."

ENVIRONMENTAL IMPACT OF INHALERS

Annually, an estimated 800 million pMDIs are manufactured globally, using more than 11,500 tonnes of propellants.[10]

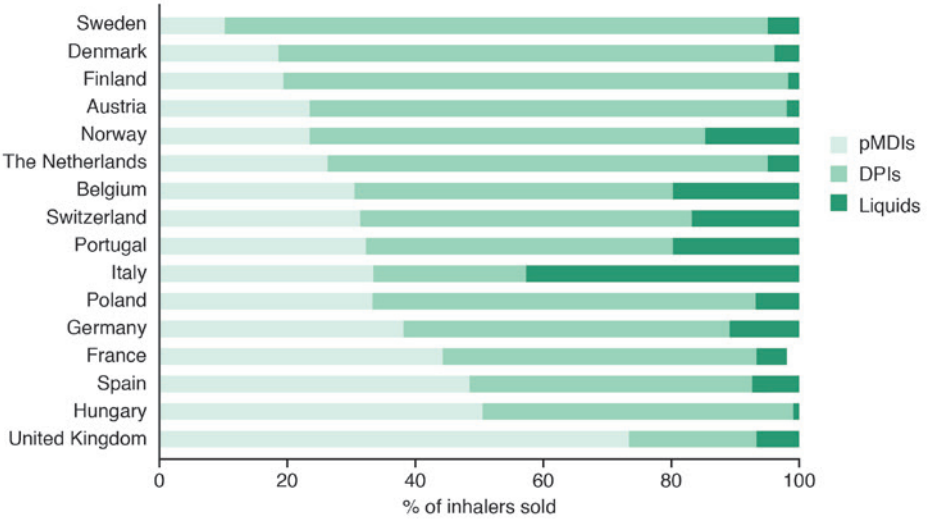


Figure 1: Proportion of inhalers sold by device type in 16 European countries from 2002–2008.[8] ("Liquids" refers to nebulised formulations.)

Dr Sara Panigone
Sustainable Device Transition Leader
T: +39 0521 279628
E: S.panigone@chiesi.com

Dr Federica Sandri
Sustainable Device Transition Project Officer
T: +39 0521 1689374
E: f.sandri@chiesi.com

Dr Gabriele Nicolini
Head of Global Medical Affairs
E: g.nicolini@chiesi.com

Chiesi Farmaceutici
26/A Via Palermo
43122 Parma
Italy

www.chiesi.com

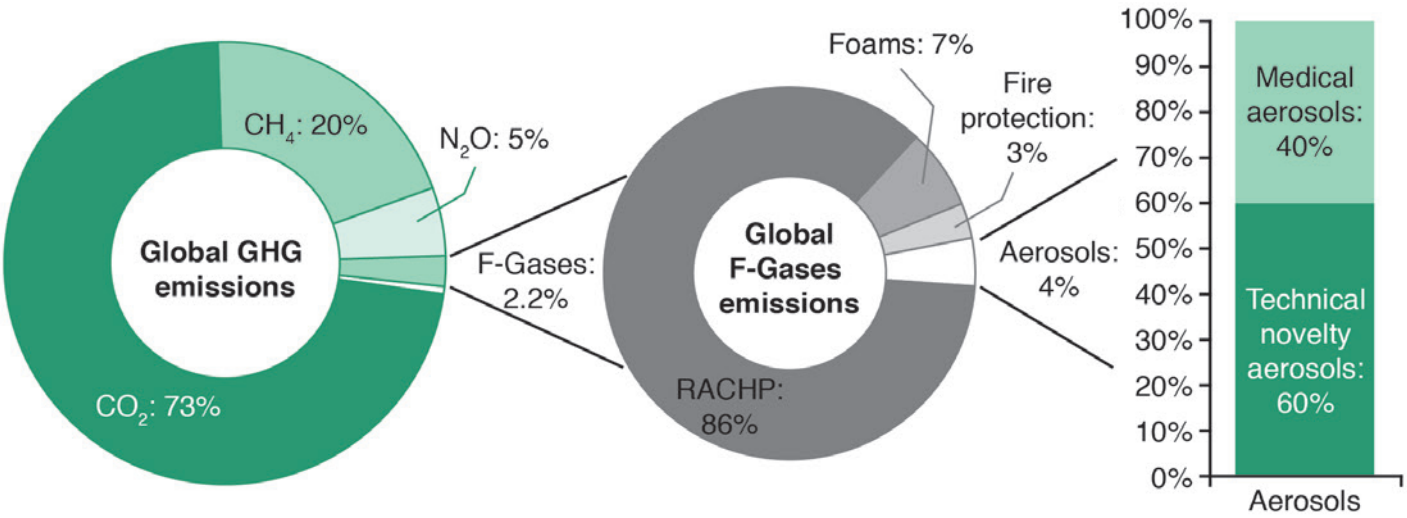


Figure 2: Global annual anthropogenic greenhouse gas (GHG) emissions by gas type and distribution of market use of fluorinated gases (F-Gases).[20,23] (RACHP = refrigeration, air conditioning and heat pump.)

Chlorofluorocarbons (CFCs) were also used as propellants for pMDIs until 1989, when the Montreal Protocol banned the use of CFCs as ozone-depleting substances in order to prevent further damage to the ozone layer.[11] This prompted a global, industry-wide transition from CFC propellants; in the case of pharmaceutical products, this translated into a progressive switch towards non-ozone-depleting hydrofluorocarbon (HFC) propellants (also known as hydrofluoroalkane (HFA) propellants), specifically HFA 134a and HFA 227ea.

Since CFC production for manufacturing pMDIs peaked in 1997 at approximately 10,000 tonnes, the transition from CFCs to HFCs led to a 97% reduction to approximately 300 tonnes in 2013, significantly reducing the carbon emissions associated with propellant use in pMDIs.[12] A number of companies, including Chiesi, executed the move from CFC to HFC pMDIs, including to HFC 134a, which has the lowest global warming potential (GWP) of all propellants approved for pharmaceutical use.[13]

PATIENT BENEFITS ASSOCIATED WITH HFCs

In addition to the reduced environmental impact of HFC pMDIs compared with CFC pMDIs, other technical advancements with HFC pMDIs led to improved patient outcomes. CFC pMDIs were suspension based and required shaking before use; this heterogeneity often caused dose variability.[14] Moreover, CFC suspension formulations needed to be delivered with a relatively large device aperture diameter to avoid blockage. This led to higher velocity and lower duration of the aerosol plume, resulting in increased drug deposition in the oropharynx.[14] Additionally, the relatively large particles – 3.5 µm mass median aerodynamic diameter (MMAD) – aerosolised by suspension-based CFC pMDIs did not reach the small airways (≤2 mm in diameter).[15] However, it is well known that dysfunction of the small airways is linked to symptoms in patients with COPD or asthma.[16,17]

Technical advancements have enabled some drugs to be dissolved within the HFC propellant. Alongside the advent of HFC suspension-based pMDIs, this also led to the introduction of solution-based pMDIs, a homogeneous solution that does not require shaking before use. Such solutions are compatible with devices with smaller aperture diameters, leading to lower velocity and higher duration of the aerosol plume.[14]

Specific formulation technologies, such as Chiesi's Modulite technology, have enabled the related solution-based pMDIs to be tailored for extra-fine drug delivery, reducing the particle size of emitted aerosol (<2 µm MMAD) and thereby allowing deeper penetration in the bronchial tree, effectively reaching both large and small airways.[14] The reduction in particle size, lower velocity and higher duration of aerosol plume in such HFC solution-based pMDIs also facilitates patient co-ordination between actuation of the device and inhalation, which is a common obstacle with the use of pMDIs.[14]

> "pMDI inhalers account for a very small proportion (≤0.1%) of global emissions.[20,23]"

Pharmacokinetic data also showed that with a dose from a solution-based HFC pMDI that uses Modulite technology (which is 2.5 times lower than from a CFC-based pMDI), pulmonary absorption was 86% higher and systemic exposure was 35% lower than a CFC-based pMDI, resulting in less cortisol suppression.[18] In addition, HFC pMDIs do not result in dose loss when stored inverted or in a cold climate and have significantly lower dose variability at the end of each canister's life compared with CFC pMDIs.[15]

CONTROVERSIES SURROUNDING HFCs

As concerns over climate change have grown in recent years, the general industrial use of HFC propellants is now the object of a phasing-down strategy agreed by EU Regulation N° 517/2014 and the Kigali Amendment to the Montreal Protocol.[19,20] The aim of this phasing down, which has already started in Europe, is to encourage use of low GWP alternatives and to reduce consumption and emissions of high GWP HFCs. Currently, the EU regulation recognises an exemption for HFCs for pharmaceutical use, including pMDIs.[19] However, in some countries, governments have started actions to assess the contribution of pMDIs to total CO_2 emissions and to propose short-term solutions.

There is growing interest from some healthcare systems that a reduction in HFC emissions could be primarily achieved by reducing use of pMDIs and increasing use of DPIs, which are propellant free. As an extreme example, the UK has taken a radical approach, stating that the NHS should aim to reduce the impact of respiratory treatments by 50% before

> "Many expert respiratory healthcare providers have expressed concern that implementation of a device switch initiative may lead to detrimental effects on quality of care and patient outcomes."

2022 by increasing prescriptions of low GWP inhalers.[21] This approach was supported by data that showed switching to DPIs from pMDIs would result in large carbon savings.[22] This has proven controversial, since fluorinated-gas (F-gas) usage only accounts for 2.2% of total annual greenhouse gases emissions – and refrigerators and air conditioning units contribute to the majority of F-gas usage (86%) (Figure 2).[20,23] Therefore, pMDI inhalers account for a very small proportion (≤0.1%) of global emissions.[20,23]

Overall, DPIs have a lower carbon footprint (CF) than pMDIs. Usage is the major CF contributor for pMDIs due to the presence of propellants.[24,25] Conversely, for DPIs, raw materials for manufacturing are the greatest contributors.[24,25] However, introducing a propellant with lower GWP could significantly reduce the CF of pMDIs to within the range of DPIs.[24-26]

POTENTIAL PATIENT DRAWBACKS

Many expert respiratory healthcare providers have expressed concern that implementation of a device switch initiative may lead to detrimental effects on quality of care and patient outcomes. Adverse outcomes have been previously demonstrated following an enforced switch of stable respiratory patients to alternative inhalers; switching resulted in reduced disease control and an increased number of healthcare visits in both asthma and COPD patients.[27-29]

The optimal choice for the most suitable inhaler for each patient is a complex decision taken between the treating physician and the patient.[2,30] Patient preference and empowerment, through informed decision making, are vital to achieving the best possible outcomes in patients with COPD or asthma. If access to pMDIs is restricted, the physician's ability to tailor treatment to patients will be limited. Moreover, many respiratory physicians caution that the implementation of a device switch initiative may create a stigma associated with the use of pMDIs, as emotive issues such as climate change may cause patients to feel pressurised into switching from their preferred therapy.

Switching from a patient's preferred therapeutic option may be detrimental to their treatment outcomes; patients should not be stigmatised for taking approved medication that is essential for treating their condition. In asthma, a major challenge is to motivate people to take the correct treatment regularly, while in people with COPD, feelings of self-blame are common. Such stigmas may lead to decreased adherence to therapy, resulting in adverse effects on patient outcomes and their quality of life.[31,32] Evoking feelings of guilt in those who need or choose pMDIs must be avoided; discussions on the issue of climate change need to be framed within the context of the wider political setting if the wider climate change issue is to be addressed meaningfully.

PATIENT-TAILORED INHALER CHOICE

Long-term disease control and patient management in asthma and COPD patients with low adherence remains a challenge. Poor inhaler technique remains a major barrier to achieving disease control in patients with asthma or COPD and is prevalent in 31% of patients.[33] The importance of achieving correct delivery of drugs by efficient inhaler use cannot be underestimated; proper inhaler technique leads to improved symptom relief and quality of life – and reduces morbidity,

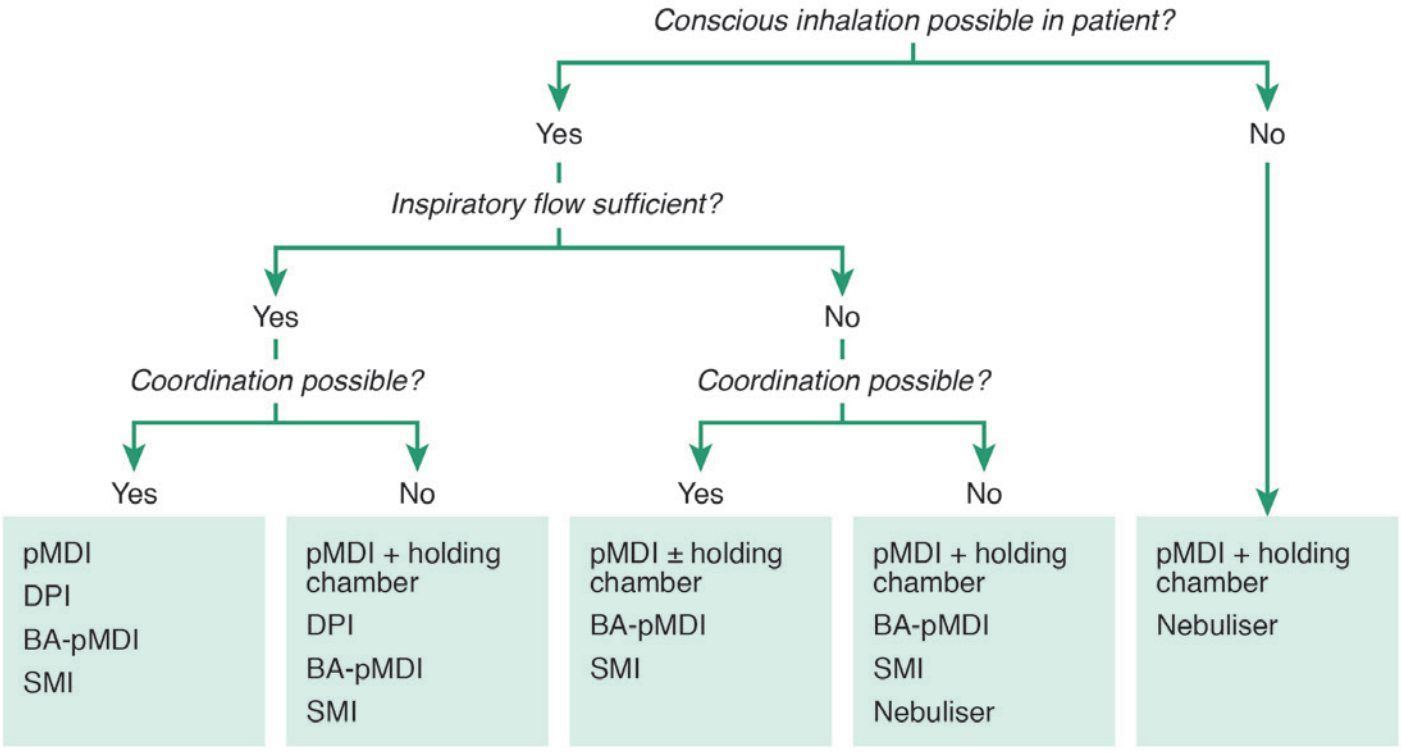
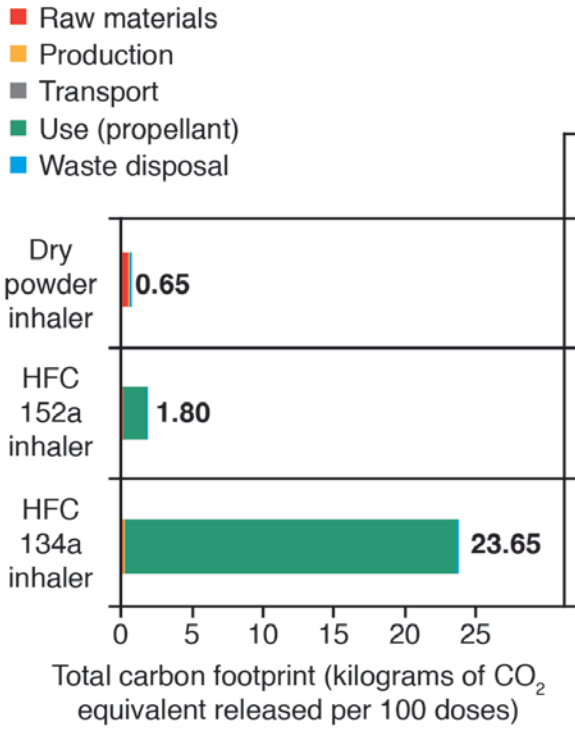


Figure 3: Inhaler type decision tree in patients with asthma or COPD.[42] (BA = breath actuated)



	Raw materials	Production	Transport	Use (propellant)	Waste disposal
Dry powder inhaler	0.46	0.13	0.02	-	0.04
HFC 152a inhaler	0.13	0.03	0.01	1.61	0.01
HFC 134a inhaler	0.17	0.06	0.01	23.4	0.01

Figure 4: Comparison of the carbon footprint of three different types of inhaler.[24]

> "Since pMDIs need to remain an option for patients, a major unmet need exists for low GWP alternative propellants in pMDIs."

mortality and acute hospital care costs.[34-38] However, only 22% of patients have complete confidence in their inhaler technique.[39]

Many developments have been made to improve patient confidence and their inhaler technique, and hence improve patient outcomes. For example, most studies that have implemented inhaler technique educational programmes in patients with asthma or COPD have resulted in significantly improved inhaler technique following intervention.[40] Stable patients with asthma whose treatment is initiated on pMDIs have achieved better disease control than those given the same drug prescribed with a DPI.[41]

Overall, evidence suggests that tailoring inhaler choice to a patient's ability to use specific devices, coupled with ongoing education to support optimal inhaler usage, may improve patient confidence and enhance both adherence and disease control.[42,43] Improved inhaler technique, adherence and disease control, in addition to proper disposal of empty inhalers, will contribute to reducing the total CF of pMDIs.[22] Therefore, asking stable patients using pMDIs to switch to DPIs for non-clinical reasons is concerning, and will likely negatively impact disease control. Inhaler choice should be based on patient characteristics (Figure 3)[42] and patient preference. Since pMDIs need to remain an option for patients, a major unmet need exists for low GWP alternative propellants in pMDIs to achieve a reduced CF in respiratory treatments, without risking adverse effects on patient outcomes.

DEVELOPMENT OF A CARBON MINIMAL pMDI

Development of pMDIs containing a low GWP propellant have the potential to reduce the carbon footprint of pMDIs by 90%,[25] but, critically, will also ensure a continued choice for physicians and patients, and avoid any negative impact on patient health. Recently, companies producing pMDI maintenance therapies have announced plans to introduce carbon minimal pMDIs by 2025.[43,44] Chiesi's planned carbon minimal pMDI uses Koura's HFA 152a (1, 1-difluoroethane) as a candidate propellant.[43]

HFA 152a is classified as a low GWP propellant, as its GWP value is significantly lower (138 GWP for 100-year time horizon) than that of both HFA 134a and HFA 227ea (1,300 and 3,350 GWP for 100-year time horizon, respectively).[23] Due to the lower liquid density of HFA 152a compared with HFA 134a and HFA 227ea, early indications are that a lower weight of propellant is needed per dose, resulting in additional carbon savings.[10]

Initial research into HFA 152a use in pMDIs has been promising, showing similar performance levels to HFA 134a and HFA 227ea.[10] Given HFA 152a is used more commonly in consumer aerosols, the toxicology of HFA 152a is well characterised and is similar to HFA 134a.[10] Studies to address the gaps in industrial toxicity knowledge have been successful; inhalation safety studies are underway and long-term toxicology testing on HFA 152a is expected to be completed in 2021.[10] Moreover, first-in-human clinical trials have now begun.[45]

Development of HFA 152a inhalers will significantly reduce the CF of pMDIs, to a level within the range of DPIs (Figure 4).[24] Short-term approaches to reduce the environmental impact by limiting use of pMDIs are likely to undermine innovation of such carbon-minimal pMDIs. Introducing a carbon-minimal pMDI will allow a seamless transition from pMDIs, providing large carbon savings but also maintaining patient choice and ensuring continuity of care without potential adverse health effects.

CONCLUSIONS

While the impact of harmful gases on our environment needs to be reduced, it is vital that any action taken does not inadvertently jeopardise patient safety and outcomes. Therefore, pMDIs must remain a prescription option for all asthma and COPD patients, particularly for those where pMDIs are the preferred choice. Chiesi's plan – which includes the development of and the transition to pMDIs containing low GWP propellant (HFA 152a) – has the potential to offer environmental benefits whilst maintaining patient choice and wellbeing.

ABOUT THE COMPANY

Chiesi Farmaceutici is an international, privately-owned pharmaceutical company based in Parma, Italy, dedicated to the research, development and sales of innovative medicines in the field of respiratory, neonatology and rare diseases. In December 2018, Chiesi Group adopted the legal status of Public Benefit Corporation and, in June 2019, became the first global pharmaceutical group to obtain B Corp Certification. B Corp represents a new kind of business that balances purpose and profit, legally required to consider the impact of decisions on workers, customers, suppliers, community and the environment. As part of this commitment, Chiesi announced plans to become carbon neutral by 2035.

REFERENCES

1. *GBD 2015 Chronic Respiratory Disease Collaborators, "Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015". Lancet Respir Med, 2017, Vol 5(9), pp 691–706.*
2. *Global Initiative for Asthma (GINA): Global strategy for asthma management and prevention. Update 2014 and Online Appendix. Available at http://www.ginasthma.org. Accessed 23 March 2020.*
3. *World Health Organization (WHO), "Chronic obstructive pulmonary disease (COPD)". 2019.*
4. *Diab N, Gershon AS, Sin DD et al, "Underdiagnosis and Overdiagnosis of Chronic Obstructive Pulmonary Disease". Am J Respir Crit Care Med, 2018, Vol 198(9), pp 1130–1139.*
5. *Lozano R, Naghavi M, Foreman K et al, "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010". Lancet, 2012, Vol 380(9859), pp 2095–128.*
6. *Quaderi SA, Hurst JR, "The unmet global burden of COPD". Glob Health Epidemiol Genom, 2018, Vol 3, e4.*
7. *Usmani OS, "Choosing the right inhaler for your asthma or COPD patient". Ther Clin Risk Manag, 2019, Vol 15, pp 461–72.*
8. *Lavorini F, Corrigan CJ, Barnes PJ et al, "Retail sales of inhalation devices in European countries: so much for a global policy". Respir Med, 2011, Vol 105(7), pp 1099–1103.*
9. *Ferguson GT, Hickey AJ, Dwivedi S, "Co-suspension delivery technology in pressurized metered-dose inhalers for multi-drug dosing in the treatment of respiratory diseases". Respir Med, 2018, Vol 134, pp 16–23.*
10. *United Nations Environment Programme. Report of the Medical Technical Options Committee (MTOC) 2018 Assessment Report. 2018. Available at http://ozone.unep.org/Assessment_Panels/TEAP/Reports/MTOC/MTOC-Assessment-Report-2014.pdf. Accessed 23 March 2020.*
11. *The Montreal Protocol on substances that deplete the ozone layer. Final Act (Nairobi: UNEP1987). Federal Register 1994, 59FR56276–56298.*
12. *United Nations Environment Programme. Report of the Medical Technical Options Committee (MTOC) 2014 Assessment Report. 2014. Available at http://ozone.unep.org/Assessment_Panels/TEAP/Reports/MTOC/MTOC-Assessment-Report-2014.pdf. Accessed 23 March 2020.*
13. *Carbon Footprint Italy 2019. Available: http://www.carbonfootprintitaly.it/p-2019-0008/ Accessed 23 March 2020.*
14. *Nicolini G, Scichilone N, Bizzi A, "Beclomethasone/formoterol fixed combination for the management of asthma: patient considerations". Ther Clin Risk Manag, 2008, Vol 4(5), pp 855–64.*
15. *Leach CL, "The CFC to HFA transition and its impact on pulmonary drug development". Respir*

ABOUT THE AUTHORS

Sara Panigone is the Sustainable Device Transition Leader, managing a cross-functional team working on carbon minimal pMDI, in Chiesi Farmaceutici. She joined Chiesi headquarters in 2007 as a Scientific Advisor. In January 2011, she assumed the role of Competitive Intelligence Manager and, in June 2016, the role of Head of Global Competitive Intelligence Department. She graduated in Medical Biotechnology in 2004 at the University of Milan (Italy); between 2004 and 2007 she obtained a PhD in Biotechnology Applied to Medical Sciences in collaboration with Stanford University (CA, USA), where she worked as a visiting researcher for 18 months.

Federica Sandri is the Sustainable Device Transition Project Officer in Corporate Marketing of Chiesi Farmaceutici, having joined Chiesi in October 2018 as part of the Competitive Intelligence team. Graduating in 2014 in Industrial and Molecular Biotechnology, she completed a PhD in Molecular Biology, with a thesis focused on Environmental Microbiology, in 2018 at the University of Bologna (Italy), in collaboration with the University of Pennsylvania (PA, USA).

Gabriele Nicolini is Head of Global Medical Affairs at Chiesi Farmaceutici. He joined Chiesi in 1999, after graduating in Pharmacy and obtaining a PhD in Experimental Respiratory Pathophysiology. He has 20 years of experience in medical roles, with a focus on respiratory diseases, and 15 years of experience in clinical research including design, management and publication of approximately 20 clinical studies. A reviewer and member of the editorial board for international journals, Dr Nicolini is author and co-author of more than 40 articles and reviews in peer reviewed journals including the New England Journal of Medicine, Lancet Respiratory Medicine, Thorax and ERJ.

Care, 2005, Vol 50(9), pp 1201–6.
16. *Crisafulli E, Pisi R, Ajello M et al, "Prevalence of Small-Airway Dysfunction among COPD Patients with Different GOLD Stages and Its Role in the Impact of Disease". Respiration, 2017, Vol 93(1), pp 32–41.*
17. *Postma DS, Brightling C, Baldi S et al, "Exploring the relevance and extent of small airways dysfunction in asthma (ATLANTIS): baseline data from a prospective cohort study". Lancet Respir Med, 2019, Vol 7(5), pp 402–416.*
18. *Bousquet J, Poli G, Acerbi D, "Systemic exposure and implications for lung deposition with an extra-fine hydrofluoroalkane beclometasone dipropionate/formoterol fixed combination". Clin Pharmacokinet, 2009, Vol 48(6), pp 347–58.*
19. *European Commission. Regulation (EU) No 517/2014 of the European Parliament and of the Council of 16 April 2014 on Fluorinated Greenhouse Gases and Repealing Regulation (EC) No 842/2006 Text with EEA Relevance. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2014.150.01.0195.01.ENG Accessed: 23 March 2020.*
20. *OzonAction Kigali Fact Sheet 2. 2017. Available at: https://wedocs.unep.org/bitstream/handle/20.500.11822/26867/7877FS02_C_Uses_EN.pdf?sequence=1&isAllowed=y Accessed 23 March 2020.*
21. *House of Commons Environmental Audit Committee. UK Progress on Reducing F-gas Emissions. 18 April, 2018. Available at: https://publications.parliament.uk/pa/cm201719/cmselect/cmenvaud/469/469.pdf. Date last accessed: 23 March 2020.*
22. *Wilkinson AJK, Braggins R, Steinbach I, Smith J, "Costs of switching to low global warming potential inhalers. An economic and carbon footprint analysis of NHS prescription data in England". BMJ Open, 2019, Vol 9, e028763.*
23. *IPCC Fifth Assessment Report (AR5), 2014. Available at: https://www.ipcc.ch/report/ar5/syr/ Accessed 23 March 2020.*
24. *Jeswani HK, Corr S and Azapagic A, "Reducing carbon footprint of metered dose inhalers". Inhalation, 2017.*
25. *Jeswani HK, Azapagic A, "Life cycle environmental impacts of inhalers". Journal of Cleaner Production, 2019, Vol 237, 117733.*
26. *Janson C, Henderson R, Löfdahl M et al, "Carbon footprint impact of the choice of inhalers for asthma and COPD". Thorax, 2020, Vol 75(1), pp 82–84.*
27. *Björnsdóttir US, Gizurarson S, Sabale U, "Potential negative consequences of non-consented switch of inhaled medications and devices in asthma patietns". Int J Clin Pract, 2013, Vol 67 (9), pp904–10.*
28. *Björnsdóttir US, Sigurðardóttir ST, Jonsson JS et al, "Impact of changes to reimbursement of fixed combinations of inhaled corticosteroids and long-acting β_2-agonists in obstructive lung diseases: a population-based, observational study". Int J Clin Pract, 2014, Vol 68(7), pp 812–819.*
29. *Doyle S, Lloyd A, Williams A, "What happens to patients who have their asthma device switched without their consent?" Prim Care Respir J, 2010, Vol 19(2), pp 131–9.*
30. *Dolovich MB, Ahrens RC, Hess DR et al, "Device selection and outcomes of aerosol therapy: Evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology". Chest, 2005, Vol 127(1), pp 335–71.*
31. *Lycett H, Wildman E, Raebel EM et al, "Treatment perceptions in patients with asthma: Synthesis of factors influencing adherence". Respir Med, 2018, Vol 141, pp 180–9.*
32. *Mäkelä MJ, Backer V, Hedegaard M, Larsson K, "Adherence to inhaled therapies, health outcomes and costs in patients with asthma and COPD". Respir Med, 2013, Vol 107(10), pp 1481–90.*
33. *Sanchis J, Gich I, Pedersen S, "Systematic review of errors in inhaler use: has patient technique improved over time?" Chest, 2016, Vol 150(2), pp 394–406.*
34. *Usmani OS, Scullion J, Keeley D, "Our Planet or our patients – is the sky the limit for inhaler choice?" Lancet Respir Med, 2018, Vol 7(1), pp 11–13.*
35. *Giraud V, Allaert FA. "Improved asthma control with breath-actuated pressurized metered dose inhaler (pMDI): The SYSTER survey." Eur Rev Medand Pharmaco, 2009, Vol 13(5), pp 323–30.*
36. *Giraud V, Roche N, "Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability". Eur Respir J, 2002, Vol 19(2), pp 246-51.*
37. *Melani AS, Bonavia M, Cilenti V et al, "Inhaler mishandling remains common in real life and is associated with reduced disease control". Respir Med, 2011, Vol 105(6), pp 930-8.*
38. *Melani AS, Paleari D, "Maintaining Control of Chronic Obstructive Airway Disease: Adherence to Inhaled Therapy and Risks and Benefits of Switching Devices". COPD: J Chron Obst Pulmon Dis, 2016, Vol 13(2), pp 241–50.*
39. *Amin AN, Vaidyanathan G, Roughley A, Small M, "Confidence in correct inhaler technique and its association with treatment adherence and health status among US patients with chronic obstructive pulmonary disease". Patient Prefer Adherence, 2017, Vol 11, pp 1205–12.*
40. *Klijn SL, Hilgsmann M, Evers SM et al, "Effectiveness and success factors of educational inhaler technique interventions in asthma & COPD patients: a systematic review". NPJ Prim Care Respir Med, 2017, Vol 27(1), pp 24.*
41. *Price D, Roche N, Christian Virchow J et al, "Device type and real-world effectiveness of asthma combination therapy: an observational study". Respir Med, 2011, Vol 105(10), pp 1457–66.*
42. *Dekhuijzen PNR, Vincken W, Virchow JC et al, "Prescription of inhalers in asthma and COPD: Towards a rational, rapid and effective approach". Respir Med, 2013, Vol 107(12), pp 1817–21.*
43. *"Chiesi outlines €350 million investment and announces first carbon minimal pressurised Metered Dose Inhaler (pMDI) for Asthma and COPD". Press Release, Chiesi, December 4, 2019.*
44. *"Investing in a sustainable future for patients with respiratory disease". Press Release, AstraZeneca, January 22, 2020.*
45. *"'Green' Medical Propellant Receives FDA Approval to Proceed to Clinical Trials". Press Release, Koura, February 4, 2020.*

ON drugDELIVERY

2020/21 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
May 2020	Injectable Drug Delivery: Formulations & Devices	PASSED
June 2020	Connecting Drug Delivery	May 14, 2020
July 2020	Novel Oral Delivery Systems	Jun 4, 2020
August 2020	Industrialising Drug Delivery	Jul 2, 2020
September 2020	Wearable Injectors	Aug 6, 2020
September/ October 2020	**NEW TOPIC - INAUGURAL ISSUE! Drug Delivery & Environmental Sustainability**	**Aug 20, 2020**
October 2020	Prefilled Syringes & Injection Devices	Sep 3, 2020
November 2020	Pulmonary & Nasal Drug Delivery	Oct 1, 2020
December 2020	Connecting Drug Delivery	Nov 5, 2020
January 2021	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Dec 3, 2020
February 2021	Prefilled Syringes & Injection Devices	Jan 7, 2021
March 2021	Ophthalmic Drug Delivery	Feb 4, 2021
April 2021	Pulmonary & Nasal Drug Delivery	Mar 4, 2021

ONE CUSTOMER, ONE CAPSULE

Capsules are the very essence of Qualicaps®

As a company dedicated to capsules we have a unique perspective on how to contribute to health.

Qualicaps® delivers pharmaceutical-grade capsules together with a comprehensive service along the drug product life cycle through our global team of commercial, scientific and technical services.

Quali-V®-I capsules for inhaled drug delivery.

Strict Microbiological Control

Better Aerosolization

Inner Surface Control

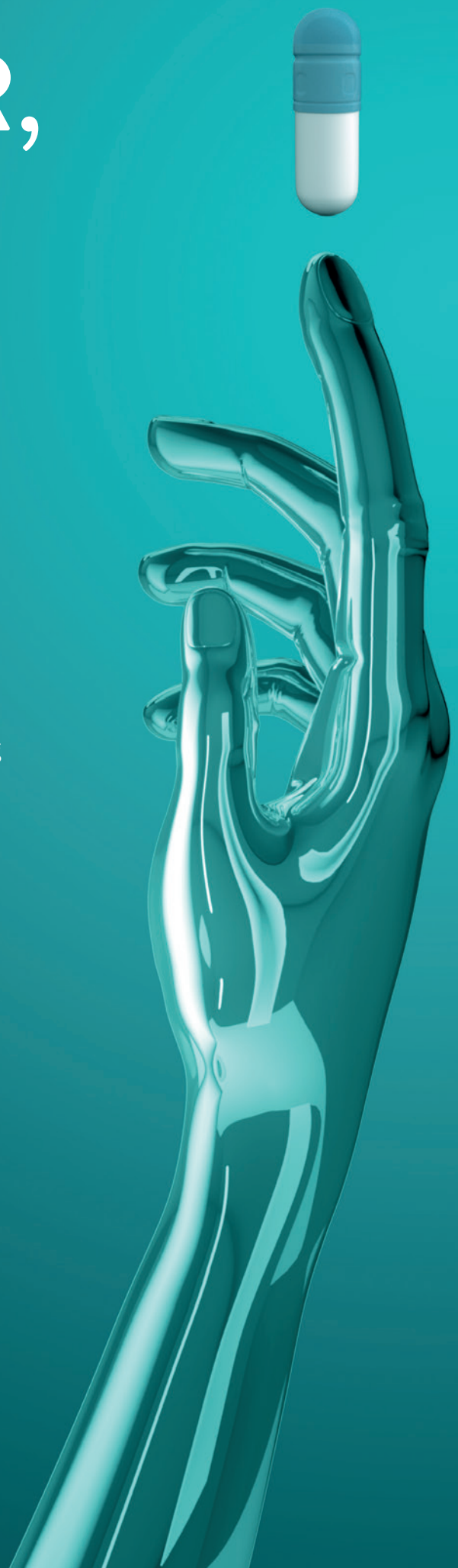
Reduced Powder Adhesion

Superior Puncturing Properties

Quali-V®-I Extra Dry, when a minimum moisture content level is required

Lower moisture content (2.0 - 3.5%)

Qualicaps



THE OPTIONS FOR CREATING A MORE SUSTAINABLE INHALER

With growing pressure to tackle climate change, Phil Seeney, a Drug Delivery Specialist at PA Consulting, looks at the arguments in favour of creating more sustainable inhalers, and examines potential strategies to accomplish it.

Despite the current coronavirus pandemic, climate change remains a serious global problem, and addressing it is an urgent priority. There is general agreement that everyone has a role to play in reducing the carbon footprint (CF) and global warming potential (GWP) of the products we use every day.

Recently, the hydrofluoroalkanes (HFAs) used in pressurised metered dose inhalers (pMDIs) have come under attack.[1,2,3] There is much debate as to the overall impact and GWP of pMDIs but for the UK NHS (and others), they form a significant percentage of the organisation's CF and GWP. GSK calculated that 32% of its carbon footprint was from patient use of its pMDI inhalers, with its dry-powder inhalers (DPIs) having a carbon footprint approximately one twenty-fifth of a propellant-based inhaler.[4]

Thus, alternative approaches to pMDIs have to be found, even though their contribution to global emissions is less than 0.05% of all greenhouse gas emissions.[5] Encouraging patients and their medical practitioners to switch from pMDIs to DPIs to reduce their CF may be acceptable and appropriate for some patients. The UK National Institute for Health and Care Excellence (NICE) even provides guidance on the inhaler selection decision process and considers CF.[6] However, DPIs are not suitable for all patients – e.g. hospitalised chronic obstructive pulmonary disease (COPD) patients, those with inadequate inspiratory flow, etc.

Furthermore, there are practitioner concerns that patients' health could be at risk if, in changing to a DPI, patients who may have taken years to stabilise risk losing the established control of their asthma and experience exacerbations, resulting in hospitalisation or death. In the interim, companies are actively investigating replacing the current HFAs with HFA 152a which has a claimed CF approximately the same as a DPI[7] – but it will take time and effort to prove equivalence.

> "We are potentially at a cusp where the holistic cost of an inhaler – including its environmental cost – must be considered from a fresh viewpoint at the start of any project."

Many of the pMDI products in use are well-proven, long-standing drugs that provide effective treatment for millions of patients globally.[8] However, despite this, we can expect increased regulatory and market pressure on pharmaceutical companies, suppliers and bulk users (hospitals, etc) to reduce their use. It would therefore be prudent for developers of inhalers to address these needs now, given the time it takes to achieve regulatory approval for new products, even using existing drugs.

So, what are the options for pharma and device developers/suppliers given the likelihood that future legislation imposes limits on GWP/CF for inhalers? (Assuming the target is to reduce the GWP and CF of respiratory devices, without compromising patients' health).

It is unlikely that there will be a single, universal solution to the problem and the answer is going to be delivered by a multi-pronged approach to inhaler design and drug delivery, together with a progressive adoption of more sustainable options. However, we are potentially at a cusp where the holistic cost of an inhaler – including its environmental cost – must be considered from a fresh viewpoint at the start of any project.

The approach to sustainable design, and particularly redesign, is to adopt the principles of the five Rs:

- **Replace** – replace unsustainable materials with ones from sustainable sources or with much lower GWP/CF.

Phil Seeney
Drug Delivery Specialist
T: +44 7767 400 279
E: phil.seeney@paconsulting.com

PA Consulting
Global Innovation and Technology Centre
Back Lane
Melbourn
Hertfordshire
United Kingdom

www.paconsulting.com

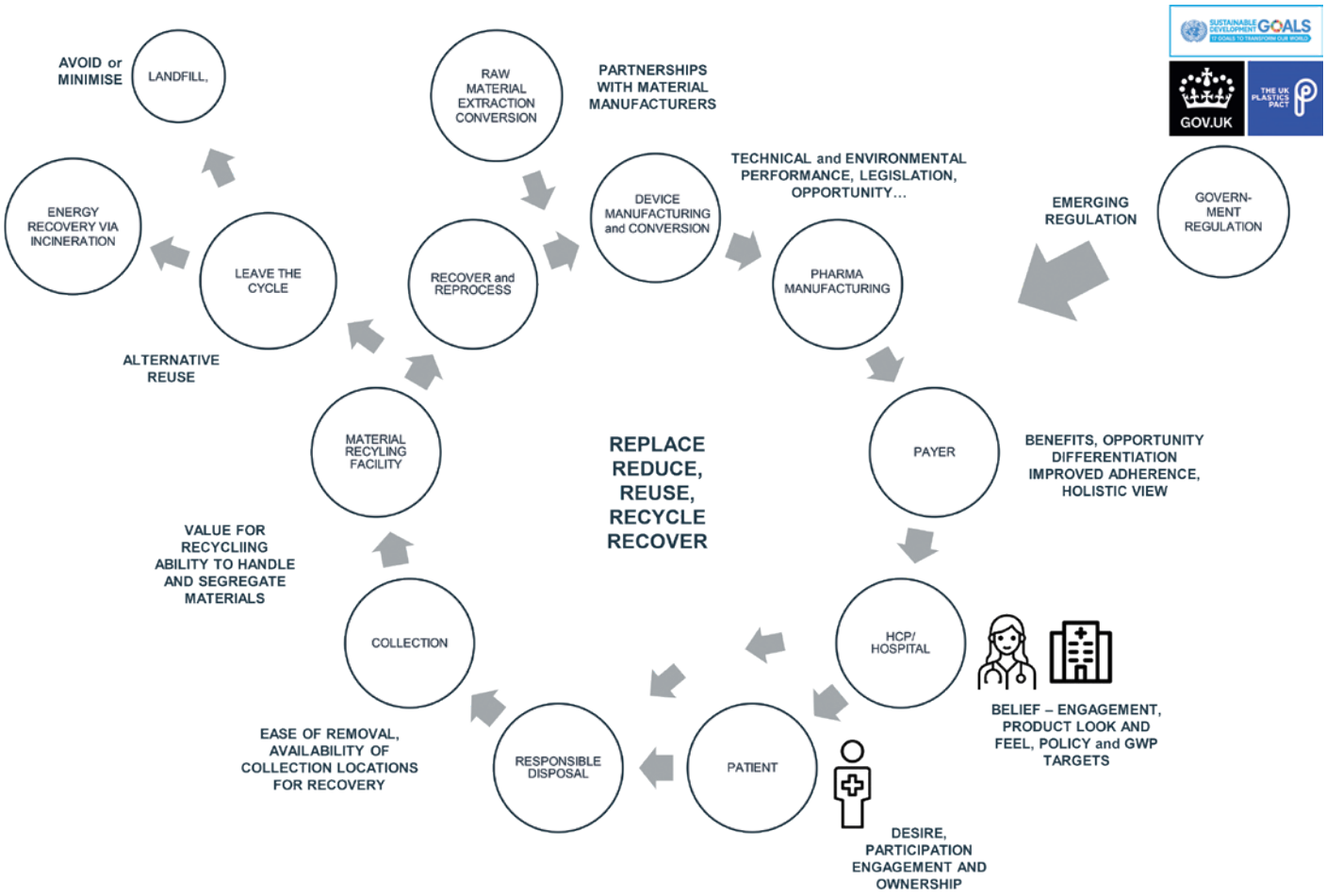


Figure 1: The holistic vision – a virtuous cycle of sustainable design.

- **Reduce** – reduce unsustainable high GWP/CF materials which cannot be replaced with better alternatives.
- **Reuse** – create reusable/refillable systems that have a longer market life and, as a consequence, a reduced environmental impact/dose (the "planetary cost" of ownership is reduced). This also has the potential to reduce the financial cost/dose for some products.
- **Recycle** – design the product to enable the separation and recovery of recyclable materials for reuse in the same product supply chain (where possible) or in other supply chains with sufficient demand.
- **Recover** – as a final measure, recover the energy from the materials by incinerating in an energy recovery plant, avoiding disposal via incineration/landfill.

It is important to note that these are not individual solutions – a preferred solution may be a combination of multiple approaches comprising all elements (Figure 1). Even if we can create an inhaler that uses sustainable materials and/or reduces the content of less sustainable materials, it will still be preferable to design an inhaler format that is reusable and reduces whatever environmental impact the device has through multiple use cycles and ultimately disposal.

It is not the intention of this article to describe how to perform a full lifecycle analysis (LCA) of the inhaler journey, cradle to grave. There are tools and databases available now that can support design teams in assessing the GWP and CF of materials and processes, and these should be used to evaluate alternative concepts and model environmental impacts. However, we already know that the use of current HFAs is a main contributor to the GWP of pMDIs and that, once this is resolved, the pressure will then be placed on multiple material, disposable systems (e.g DPIs) that will then lose the currently perceived advantage over pMDIs.

The following sections examine potential options using the "replace to recover" approach identified above.

REPLACE AND REDUCE

Although replacing HFAs in pMDIs with other variants is a valid, short-term approach with potentially little change to other components, a more radical longer-term approach should investigate all the potential ways a drug solution could be delivered to the lung. A first investigation therefore could consider the alternative technologies that can produce an aerosol suitable for inhalation, to avoid the use of HFAs or reformulating as a dry powder.

Figure 2 shows some of the principal technologies that might yield suitable new products (including a DPI). We then need to devise selection criteria to initially perform a coarse assessment of these technologies against targets of performance, cost per dose, environmental impact, development risk, etc. For example, a refillable, reusable, mechanically pressurised device, using a novel aerosolisation element, may tick all the boxes and also deliver the benefits of reusability.

However, if we home in on a solution too early, there is a danger that the development may not deliver the concept's full potential. It is important that, in the next step, the concept is evaluated against a broader range of requirements. To do this, we have to map out the lifecycle of the product and understand the process it goes

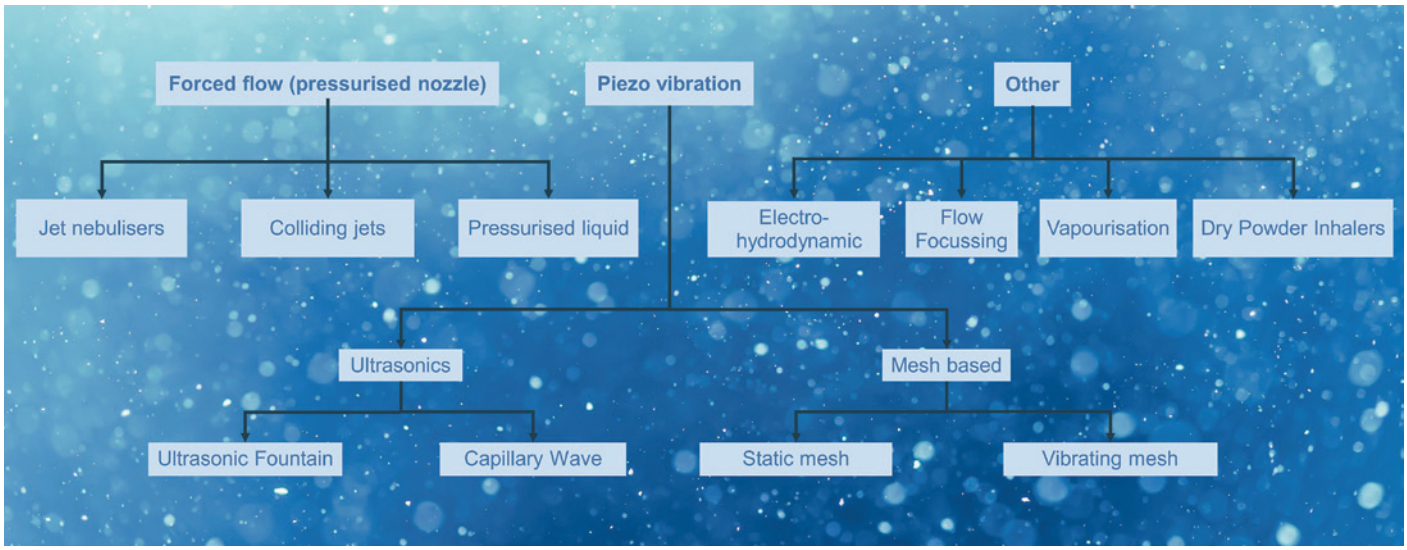


Figure 2: A selection of aerosalisation technologies.

through at each stage of its life, including raw material sourcing, conversion, recycling and recovery/disposal. This is where, for a drug delivery device, the challenge becomes more demanding.

Even if the strategic plan is to gradually phase out pMDIs and develop DPIs that are even more sustainable than current products (anticipating pMDI manufacturers will develop more sustainable products and current DPIs will not retain the sustainability high ground without further development), the broad outline approach above still applies – it is product and solution agnostic.

For example, we consider here the challenge of developing a DPI that is aiming at an idealised solution but the approach could equally apply to an autoinjector or other drug delivery system that uses a range of engineering polymers and metals and, due to this complexity, is difficult to recycle and is typically disposed of after one month's use.

We all know we can sort household waste and segregate different materials to different recycling and recovery streams. However, it is not so straightforward for a drug delivery device where we have to consider:

- Is the product (or part of it) clinical waste – e.g. sharps or potentially biologically contaminated?
- Is there any drug remaining in the product? Can the drug contact components be separated, cleaned and recovered with a net environmental benefit?
- How can we (by design) use existing recovery infrastructures rather than having to create dedicated plant and infrastructure – e.g. as is needed for the recovery of unused HFAs from pMDIs?
- Can we create inhalers where significant parts of the device can be reused – i.e. in a refillable concept, extending the life of the main "engine" such that even if more exotic, robust engineering polymers are needed, the GWP/CF is reduced by 90% through extending product life from one month to one year or longer?
- The collection and handling of inhaler waste products (e.g. from hospitals, pharmacies, central locations, etc).

> "For inhalers in general use, 58% of patients own up to disposing of their inhalers in household waste, much of which ends up in landfill, so we must help patients change their habits."

However, for inhalers in general use, 58% of patients own up to disposing of their inhalers in household waste,[9] much of which ends up in landfill, so we must also help patients change their habits.

In the short term, we may need to accept that some critical components in a DPI still have to be made from special engineering polymers and that it will take time for the emerging plant-based and more sustainable polymers – such as polylactic acid (PLA) as a replacement for acrylonitrile butadiene styrene (ABS) – to evolve sufficiently to meet demanding requirements and standards of life-critical drug delivery systems.

It is important to recognise that sustainability is not the primary aim of the development – it is one of the requirements. Keeping patient and performance needs at the forefront, the redesign provides an opportunity to improve the usability and patient experience (clinical outcome) and reduce environmental impact. This can be achieved by rethinking how we transition from current inhalers to solutions which provide inhalers that are better for the patient and better for the planet.

REUSE

Making DPIs reusable has the potential to reduce the GWP/CF by 90% or more if we make them a little more robust, such that the primary engine can reliably provide a 12-month duty cycle with monthly replacement drug cartridges. However, there are other considerations and decisions of usability that surface for refillable versus disposable devices:

- How do we address the need to provide a dose counter?
- Can the dose counter be automatically reset when a new refill is inserted or does the dose counter have to stay with the drug cartridge (increasing the disposable element)?

"Providing new inhalers that gain patient confidence can take us down a virtuous cycle where all parties benefit from this opportunity to overhaul inhaler design, use and recovery."

- How do we prevent a part-used drug cartridge being removed and then reinserted and resetting the counter incorrectly?

The development team has to rise to these challenges and create truly innovative solutions for the next generation of reusable, refillable DPIs.

RECYCLE AND RECOVER

Even if we have a concept that can use more sustainable materials, minimises the use of fossil fuel derived polymers and is reusable, how do we recycle and ultimately recover the disposable and reusable elements? Can the disposable elements be recycled or recovered, given they are contaminated with drug and also potentially a biohazard? Can trying to clean and recover these elements provide a net environmental benefit or are we now in the tail of diminishing returns? Of course, the reusable element of our new DPI (almost by definition) will comprise potentially valuable materials and should be designed to optimise recycling.

The development team should try to minimise the number of materials used, especially if they are fossil-fuel based, and – where differences in performance are needed – try to select materials that can use the same recycling pathway. For example, if sustainable PLAs have been used, these might be chemically recovered in dedicated recycling plants rather than being lumped in with other general polymer recycling streams. Whatever the options, it is clear a redesign of the DPI requires a modular concept where the individual modules are designed to be reusable, recyclable and/or in some other way recoverable – the intention being to avoid any element ending up as landfill.

Some 235 million people worldwide[8] who suffer from asthma use currently effective and life-changing inhaled medications. They will need to be transitioned to more sustainable alternatives once it is demonstrated these are as effective and usable, in a similar or even better way, than current products. Providing new inhalers (DPIs or liquid systems) that gain patient confidence can take us down a virtuous cycle where all parties benefit from this opportunity to overhaul inhaler design, use and recovery.

But what will it cost? Improved, reusable inhalers need not be significantly more expensive if we factor in improved adherence, improved outcomes and reduced patient hospitalisation costs, delivered by better next-generation products. We need to move to a more holistic "cost" model, both in monetary and environmental terms. The cost to the planet and patients in defending the current position and maintaining the status quo is no longer acceptable – change is on the horizon; and it's happening now.

ABOUT THE COMPANY

PA Consulting is a global innovation and transformation consultancy with more than 3,200 specialists working in a number of key industries. It has over 40 years' experience in the design, development, characterisation and evaluation of drug delivery devices. PA has dedicated inhaled and parenteral drug delivery teams, covering both conventional and smart connected devices using low-cost printed electronics and electronic-free acoustic connectivity. Services include complete device development, device identification, selection and customisation, device strategy, product characterisation, development of custom test equipment, human factors studies, design verification programmes and transfer to manufacturing.

REFERENCES

1. *"Use a 'greener' inhaler if you can, patients told". BBC News Website, April 8, 2019.*
2. *"Asthma carbon footprint 'as big as eating meat'". BBC News Website, October 30, 2019.*
3. *Wilkinson AJK, Braggins R, Steinbach I et al, "Costs of switching to low global warming potential inhalers. An economic and carbon footprint analysis of NHS prescription data in England". BMJ Open, 2019, Vol 9 (10).*
4. *"We are committed to reducing carbon emissions across our entire value chain". Company Web Page, GSK. (www.gsk.com/en-gb/responsibility/environment/carbon, Accessed April 2020)*
5. *Pritchard JN, "The environmental impact of MDI propellants – what now". J Aerosol Med, Vol 33(2) (Abstracts of Drug Delivery to the Lungs, Edinburgh, UK, December 11-13, 2019), p A-2.*
6. *"Inhalers for asthma". Patient Decision Aid, NICE, May 23, 2019.*
7. *"Mexichem discusses potential for using HFA 152a as pMDI propellant". OINDP News, December 2016.*
8. *Kluger J, "How One Commonly Used Asthma Inhaler is Damaging the Planet". Time Magazine, November 2019.*
9. *"Complete the Cycle: Breathe new life into your old inhalers". GSK Leaflet, March 2018.*

ABOUT THE AUTHOR

Phil Seeney is a Drug Delivery Specialist and a member of the applied science team at PA Consulting in Cambridge, UK. He is a mechanical engineer and industrial designer with more than 45 years' product development experience covering the healthcare, consumer durable and fast-moving goods sectors. For the past 30 years, he has specialised in drug delivery and medical devices, particularly inhaled drug delivery, its associated technologies and manufacturing. Mr Seeney supports companies in the development of novel inhalation devices and in the identification and acquisition of new/emerging technologies.

MERXIN®

OFF-THE-SHELF OR CUSTOM-MADE? CHOOSING A DRY POWDER INHALER

In this article, Philippe Rogueda, PhD, Chief Business Officer, Quality Director, Merxin, discusses the manifold factors that need to be taken into account when choosing a dry powder inhaler – beyond just the target disease, formulation and patient population.

Due to the vast number of variables that come into play, development of dry powder inhalers (DPIs) presents a complex challenge. As a result, developers of DPIs face many high-stakes, difficult decisions. One of the most consequential decisions involves the basic approach to selection of the delivery device – will you develop a novel inhaler tailored precisely to your specific formulation and patient population or will you select an off-the-shelf device that you can adapt for your product?

> "Will you develop a novel inhaler tailored precisely to your specific formulation and patient population or will you select an off-the-shelf device that you can adapt for your product?"

Developing a new device from scratch is costly and time consuming – and comes with all the risks associated with any new technology. In addition to the time necessary for the basic design of the inhaler, a proprietary device will likely require proprietary manufacturing equipment as well as substantial resources invested in regulatory approval. And no matter how much you invest in testing, you will take the product to market with no guarantee that the device will be accepted by clinicians and patients.

On the other hand, for a novel product, customising a device offers certainty that the formulation will have its optimum shot at succeeding in clinical trials and will equally ensure that competitors will have a difficult time producing a generic. For generic products, designing a new non-AB rated device means you don't need to wait for the existing reference product intellectual property (IP) to expire – allowing you to launch the generic product earlier. However, marketing non-substitutable generics is more costly than substitutable products, partly due to the need for a sales force. In addition, the non-substitutable inhaler may have trouble competing with AB-rated generics.

Using an off-the-shelf DPI has the potential to get you to market cheaper and faster than developing a new device whilst minimising the risk associated with the delivery technology. However, you lose out on the possible value of the IP, and many developers fear that an off-the-shelf inhaler cannot be fully optimised for their formulation, leading to sub-standard delivery and possible clinical or commercial failure. Is that fear justified? Not necessarily.

A HIGH RESISTANCE DEVICE IS JUST AS GOOD AS A LOW RESISTANCE ONE

Many developers believe that DPI device selection consists entirely of identifying

Dr Philippe Rogueda
Chief Business Officer,
Quality Director
T: +44 1553 403 070
E: philippe@merxin.com

Merxin Ltd
1 Innovation Drive
King's Lynn
Norfolk
PE30 5BY
United Kingdom

www.merxin.com

"The market shows no evidence of a correlation between the delivery parameters of various DPI devices and how well they sell."

the target diseases and patient population followed by developing a device to do the best possible job of delivering the formulation once the dose and dosing regimen have been established. The 2018 US FDA draft guidance on metered dose inhaler (MDI) and DPI quality considerations specifies that: "Development of an MDI or DPI product should involve consideration of aspects such as aerosol delivery characteristics, portability, ease of use, device constituent part robustness, inclusion of a dose counter, appropriateness of a lockout, cleaning needs and suitability to the patient population."[1]

If it were true that the optimal dry powder delivery device for the formulation is necessarily the best device for the product, then developing a new inhaler for each formulation would be the only way to get the best device. And what do developers believe makes the best device? Much of the industry believes that high-resistance inhalers are better than low resistance; active devices are better than passive; bigger payloads are better than smaller; and simpler design is better than intricate.

Recent research, however, suggests that none of that is true. A 2014 article in *Advanced Drug Delivery Reviews* observes that: "Several misconceptions about optimal inhaler performance manage to survive in modern literature. It is, for example, still widely believed that a flow-rate-independent fine particle fraction (FPF) contributes to an inhalation performance-independent therapy, that dry powder inhalers perform best at 4 kPa (or 60 L/min) and that a high resistance device cannot be operated correctly by patients with reduced lung function."[2]

The authors add: "In practice, excellent results can be obtained with high and medium–high resistance DPIs." And they note that: "A major advantage of high resistance DPIs is that they reduce the flow rate and this favours central and peripheral lung deposition."[2] In fact, studies have shown that, even in the midst of exacerbations, patients with reduced lung function can produce sufficient pressure drop to use high resistance inhalers properly.[3] A deep breath might be uncomfortable but it is effective.

The market shows no evidence of a correlation between the delivery parameters of various DPI devices and how well they sell. HandiHaler (Boehringer Ingelheim (BI)), one of the highest resistance inhalers, has demonstrated its ability to deliver medication effectively even for COPD patients with moderately to severely limited airflow[4] and is also one of the top-selling COPD therapies worldwide. In addition, HandiHaler generates an FPF that is actually higher than the FPF produced by the low resistance Diskus device (GSK), and both of those DPIs sell better than the Spiromax (Teva), which can generate a much higher FPF.

When it comes to active versus passive delivery, Jeff Weers and Andy Clark (both of Respira Therapeutics) have studied that issue carefully and assert that: "Contrary to current industry perceptions, passive DPIs provide the greatest opportunity to achieve drug delivery to the lungs that is independent of how a patient inhales through a portable inhaler."[5]

SIMPLE DESIGN IS DIFFERENT FROM SIMPLE USE

As to the idea that simpler devices are better than more complicated ones, it's true that fewer operational steps leave less room for patient error in using the device – but that is unrelated to the complexity of the device design. Whilst patients may say they feel more comfortable with a simpler device, a simple design will not fix common patient errors such as forgetting to exhale or exhaling into the device. And while it's true that a simpler design means fewer parts and therefore less cost, a simple design is also simple for competitors to copy.

It is important to avoid confusing complexity of design with complexity of handling. HandiHaler, which is made of 16 parts, requires 11 steps to operate; Diskus is made of 15 parts and requires three steps to operate; Respimat (BI) has 34 parts and requires five steps to operate; and Ellipta (GSK) is composed of 30 parts and requires three steps to operate. Which of those is simple?

What is important is to consider all the factors that may contribute to the success or failure of the product when deciding whether to make a novel device or to adapt an existing device. Those factors go well beyond delivery parameters. In practice, whilst delivery effectiveness is important,

"Whilst delivery effectiveness is important, companies usually end up selecting a DPI based on equally important factors such as availability, marketing, company culture, IP, financial or manufacturing requirements."

BOX 1: PERFORMANCE WILL BE JUST ONE OF NUMEROUS FACTORS INFLUENCING YOUR CHOICE OF DPI DEVICE.

- Device performance
- Therapeutic target
- API Dose
- Patient population
- Device aesthetics
- Technology availability
- IP protection
- Investment required and device price
- Marketing preferences
- Financial position of the company
- Regulatory strategy
- Clinical needs
- Technology available at the company already
- Company bias: e.g. Who has the final say? What has been done before?
- Project timelines
- Final aim of the project: e.g. proof of concept for an API, generic product; fully proprietary finished dosage form.

companies usually end up selecting a DPI based on equally important factors such as availability, marketing, company culture, IP, financial or manufacturing requirements (see Box 1). Even for generic products, the choice between fully substitutable or not, hybrid solution or improved device, is more of a strategic and commercial decision than a scientific one.

A GENERIC EXAMPLE: ELLIPTA DPI

Take GSK's Trelegy Ellipta, for example. It's unlikely that anyone optimising a DPI design for a triple combination therapy would come up with the Ellipta device. But the Ellipta inhaler delivers the formulation well enough, reinforces brand continuity, is activated in three steps, offers GSK substantial IP protection, and requires a sizeable investment to copy – making it difficult for generics manufacturers to produce. As a result, potential competitors must choose between waiting years for patents to expire in order to make a fully substitutable AB-rated generic device or adapting a non-substitutable delivery device to the fluticasone/umeclidinium/vilanterol formulation to get to market earlier.

Developers faced the same dilemma with Advair Diskus. Early on – at a time when no off-the-shelf AB-substitutable devices for Diskus, such as Merxin's MRX001, were available – some companies attempted to develop their own substitutable devices but few of those programmes went smoothly. In Europe, Celon's Salmex DPI, which is currently marketed in Poland, was for a while the only fully substitutable approved version of Diskus, after Sandoz's Forspiro.

In the US, where the last Diskus device patent expired in 2016, Sandoz abandoned its generic Advair Diskus programme in January 2020 and, as of March 2020, Hikma was still trying for approval of its version (based on Vectura technology), having resubmitted its abbreviated new drug application (ANDA) in November 2019.

The only US approvals resulted from approaches that at first glance seem riskier. Mylan's Wixela Inhub, approved by the FDA in January 2019, is actually a hybrid in which the user handling experience is the same as the reference device but the dispensing and aerosolisation mechanisms differ. In effect, the development of a hybrid like Wixela resulted in costs and risks comparable to a new device but with the benefits of a generic device. Note that Wixela was approved as substitutable even though its shape and user steps are significantly different from Diskus.

Taking an even more creative approach, Teva submitted a new drug application (NDA) for a fluticasone propionate/salmeterol DPI using its own Respiclick device and then developed a substitutable generic of its own product – AirDuo Respiclick – instead of Advair. Teva's approach, using a completely novel device, eliminated the need to design around the existing IP and allowed for an earlier launch of the generic product.

Does this mean that developers who want to make generic Ellipta products have to take huge risks?

By far the safest and least expensive path is to wait for the GSK patents to expire and make a DPI using the Ellipta mechanism, with a different case if necessary. GSK's Arnuity formulation is protected until 2021, Breo/Relvar until 2025 and Incruse until 2027. The last patents for the Ellipta device expire in 2030 – the same year as the protection for Trelegy and Anoro.

> "Whatever route you choose, it's important to finalise device selection as early in the development process as possible."

GENERIC OR CUSTOMISED?

The Ellipta device is even more challenging for generic device developers to copy than Diskus, in part because the dual-cavity Ellipta – which is essentially two mini-Diskus mechanisms in a single housing – contains 28 parts, and manufacturing the Ellipta device is known to involve more than 100 suppliers. In addition, the use of dual blister strips in a DPI is protected by a patent until 2028, and other aspects of the design related to the open-inhale-close (OIC) dosing process are protected until 2030. Other companies already at work on substitutable devices for Ellipta have protected their own IP. Designing around existing patents is possible but challenging.

Designing a new device, substitutable or not, to avoid existing Ellipta IP could result in an early filing and would offer

Generic	Customised
Pros	
Substitutable	Own identity
Established technology	High IP protection
Faster to bring to market	Deterrent to generics
Less risk with developing technology	Performance tailoring
Able to use established supply chain	Adaptable to API/formulation needs
Familiar with patients and doctors/nurses	Improved patient handling
Known performance	Opportunities to simplify manufacturing
No need for extensive sales force (generics case)	Opportunities to benefits from latest device technology
Cons	
No control of identity	Will require extensive demonstration of usability
Limited IP protection	New tools will be needed
Others will copy your device	New technology might bring up unexpected development challenges
Device performance is fixed, only formulation can change	Unknown risks associated with new technology

Table 1: Summary pros and cons of generic and customised devices.

IP protection and the potential for added benefits such as improved functionality. A new device with better aerosolisation might allow for a lower dose to achieve a similar clinical effect – or the new inhaler might provide a better user experience with fewer handling errors and could possibly help a generic product to command a higher price than a 505(j) option. This route, however, involves more risk and cost (Table 1).

The hybrid option of keeping the user handling experience while modifying the dispensing and aerosolisation mechanisms, although somewhat more expensive and riskier than copying the originator device after patent expiry, ensures an AB-rated device and can open the door to an early filing before expiry of the originator patents. Merxin's MRX006 dual cavity DPI, for example, is designed specifically to enable a generic 505j dual or triple combination therapy product to be filed before existing patents expire.

WHERE TO TURN FOR HELP

Whatever route you choose, it's important to finalise device selection as early in the development process as possible because using a placeholder device early on has the potential to result in catastrophic delays if regulatory agencies require you to repeat clinical trials with the device that will be marketed.

That's why it is critical to consult companies like Merxin that have expertise in regulatory and market issues, as well as proven success in the engineering and design of DPIs. We will help you to define realistic boundaries for your decision, taking all important factors into account, to reduce risk and cost no matter what you decide.

Our track record with generic HandiHaler and Respimat is a testimony to our expertise and ability to deliver inhalers. Our expertise supports your projects.

ABOUT THE COMPANY

Merxin designs and supplies generic and customised inhaler device platforms, including multidose dry powder inhalers, capsule dry powder inhalers, soft mist inhalers, no heat no PG vaping devices and devices tailored to cannabinoid delivery to the lungs and nasal cavities. Customers combine Merxin device platforms with their drug formulation to make final dosage forms that are supplied to users and patients. Merxin has been assessed and certified as meeting the requirements of ISO 13485:2016 for the Design, Development and Supply of inhalers. Established in the UK in 2015, with manufacturing capacity across the globe and an international client base, the company is adding more products to its portfolio and expanding rapidly.

REFERENCES

1. *"Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products – Quality Considerations". US FDA, 2018.*
2. *Hoppentocht M, Hagedoorn P, Frijlink HW, de Boer AH, "Technological and practical challenges of dry powder inhalers and formulations". Adv Drug Deliv Rev, 2014, Vol 75, pp 18–31.*
3. *Demoly P, Hagedoorn P, de Boer AH, Frijlink HW, "The clinical relevance of dry powder inhaler performance for drug delivery". Respir Med, 2014, Vol 108(8), pp 1195–203.*
4. *Chodosh S, Flanders JS, Kesten S, Serby CW, Hochrainer D, Witek Jr TJ, "Effective Delivery of Particles with the HandiHaler® Dry Powder Inhalation System over a Range of Chronic Obstructive Pulmonary Disease Severity". JAerosol Med, 2001, Vol 14(3), pp 281–87.*
5. *Weers, J, Clark, A, "The Impact of Inspiratory Flow Rate on Drug Delivery to the Lungs with Dry Powder Inhalers". Pharm Res, 2017, Vol 34, pp 507.*

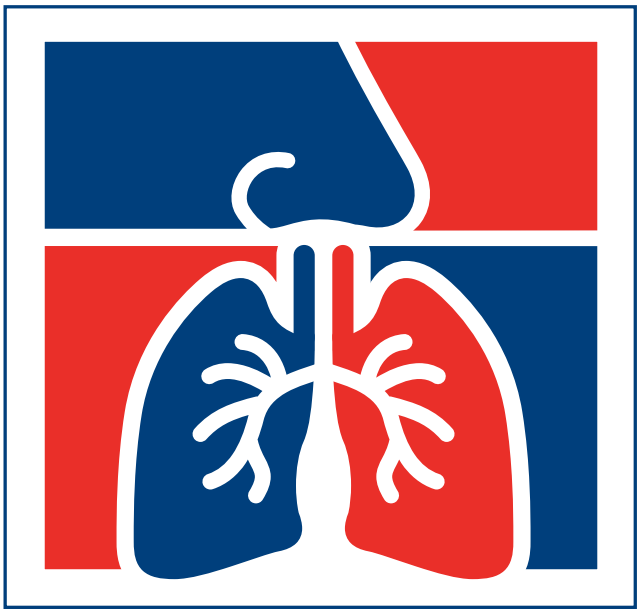
ABOUT THE AUTHOR

Philippe Rogueda, PhD, FRSC, CChem, CSci, CIng, EURIng, Co-founder and Chief Business Officer of Merxin, is a Fellow of the Royal Society of Chemistry and OINDP expert with an accomplished track record delivering technology and global projects across R&D and commercial industrialisation. Dr Rogueda has held a number of positions in the inhaled drug delivery space, starting as a formulation scientist in the pMDI formulation labs of AstraZeneca; as a principal scientist at Novartis designing DPI, nasal and nebulised inhaled therapies; as an Executive Director of Inhaled Products R&D at Actavis/TEVA; before setting up Merxin to make inhaler technology accessible to a wider audience. Rogueda is principal consultant at Aedestra (Hong Kong), founder of Inhalation Asia (Hong Kong), and of Anthocan (UK) a company dedicated to the formulating of inhaled cannabis therapies.

RDDONLINE.COM

RDD 2020 DIGITAL

Respiratory Drug Delivery



Starts April 26 & runs 24/7 on your screen

Digital Presentations, Posters & Exhibition

VCU School of Pharmacy

IPAC-RS

The Global Regulatory Landscape and Advances in Digital Technology

Transforming the OINDP-Patient Experience

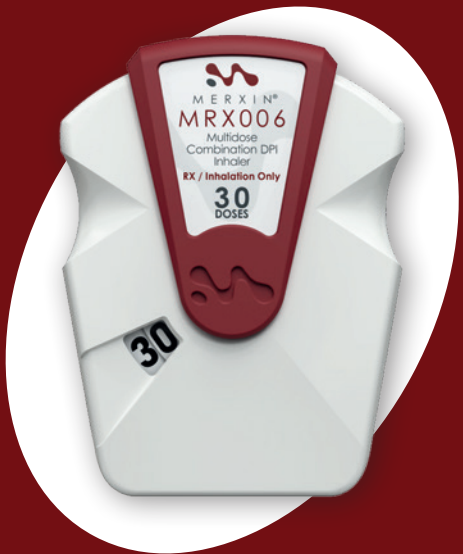
Digital presentations & more

MERXIN®

WE MAKE THE WORLD HEALTHIER
ONE BREATH AT A TIME

GENERIC & CUSTOMISED

MRX006 is a multicavity multidose dry powder inhaler (DPI). MRX006 is based on the open-inhale-close principle. It is suitable as an AB-rated substitutable device for triple therapy combinations: vilanterol, umeclidinium, fluticasone.



www.merxin.com **info@merxin.com**

NEW DRUG-NEBULISER COMBINATION PRODUCTS: CONSIDERATIONS BEYOND PERFORMANCE

In this article, `Nicolas Schwenck, Portfolio Manager eFlow Partnering, and Michael Hahn, Director eFlow Partnering & Strategy, both of PARI Pharma, summarise the critical success factors for bringing a new vibrating membrane nebuliser for a drug-device combination product to the market. They highlight opportunities and pitfalls – starting from the evaluation phase, through the development phase and finally during commercialisation.

In the business of developing new drug products for inhalation, one obvious fact is the necessity of a device which aerosolises the drug formulation such that it can be transported and deposited into the lung. This implies a decision on the device type and technology.

Nebulisers are currently the preferred device type for aerosol generation and delivery when it comes to new liquid drug introductions,[1,2,3] and vibrating membrane nebulisers (examples shown in Figures 1 & 2) seem to have recently taken a lead over jet and ultrasonic nebulisers.[4]

With the idea for a new treatment and drug formulation in mind, the pharma company starts looking for a suitable device capable of supporting early first-in-human studies (safety), followed by efficacy studies through to commercialisation and capable of fulfilling all the requirements arising from the different development stages. During a first screening phase, off-the-shelf available devices are tested *in vitro* and, preferably, a device manufacturer is contacted to prepare first steps for the development of an optimised drug-specific device configuration.

> "All membrane or mesh nebulisers are portable devices suitable for today's mobile lifestyle."

Figure 1: The eFlow Technology nebuliser – a vibrating membrane nebuliser.

Dr Nicolas Schwenck
Portfolio Manager eFlow Partnering
T: +49 89 742 846 915
E: nicolas.schwenck@pari.com

Michael Hahn
Director eFlow Partnering & Strategy
T: +49 89 742 846 831
E: michael.hahn@pari.com

PARI Pharma
Moosstraße 3
82319 Starnberg
Germany

www.pari.com

Figure 2: An eFlow aerosol head with the piezo-actuated membrane.

In the past, five established manufacturing companies provided high-quality membrane nebulisers to the market. Recently, the number of available membrane nebulisers for drug aerosolisation – i.e. with a relevant product and aerosol quality – has grown and more manufacturers have started entering the market.[3]

Their products differ in price, quality and technical features. Device concepts vary widely, even when leaving aside digital support features such as apps or smartphone-enabled expanded software capabilities or the potential to improve adherence with digital solutions,[5] which will inevitably become an integral part of future devices.

All membrane or mesh nebulisers are portable devices suitable for today's mobile lifestyle. Some devices have minimised size and weight, others use aerosol chambers with a valve system or breath-trigger modes to increase delivery efficiency. While all of these aspects are important for the device selection stage, long-term success of the newly developed drug product strongly depends on device reliability, ease of use and short treatment time.

That means, starting from a technical and performance aspect, there are several devices available and selection is complex. Not only do the available nebuliser products differ from a conceptual and technical point of view but also the business concepts of the manufacturing companies. Some offer general purpose systems, others drug-specific nebulisers with optimised performance and design, and a unique brand available for exclusive use with only one drug product.

"Long-term success of the newly developed drug product strongly depends on device reliability, ease of use and short treatment time."

"The decisive factors for aerosol performance parameters are how much drug deposits in the targeted regions of the lungs and how much time is required to administer an efficacious dose."

In the end, the clinical and commercial success of a new inhalation product does, of course, rely on the efficacy and safety of the drug – but it also depends considerably on the device adding the aspect of usability and, thus, on the combination of drug and device. This requires a strong collaboration between the pharma company and the device company.

EVALUATION AND SELECTION OF THE NEBULISER

The decisive factors for aerosol performance parameters are how much drug deposits in the targeted regions of the lungs and how much time is required to administer an efficacious dose. Another important aspect is the amount of drug which deposits in other regions – e.g. the upper airways or the environment – since this can have potential side effects. Special attention is required in the case of complex or fragile active pharma ingredients such as proteins, peptides or phages which may be negatively affected by the nebulisation process. Those target characteristics which are specified for the target patient population are tested during the various clinical phases.

As a first step, the pharma company chooses a device which is able to nebulise the new drug formulation properly with respect to nebulisation time, particle size distribution and a stable nebulisation process. This phase is often called the feasibility phase. During this phase, the drug formulation is nebulised for the first time. Standardised *in vitro* performance tests are conducted to determine the aerosol characteristics, and possible challenges with the nebulisation of the drug formulation can be identified early on.

The aerosol characteristics strongly depend on the formulation's physicochemical properties in combination with the nebuliser. There can be huge variations in the aerosol characteristics between various combinations of formulations and nebulisers. Every individual combination should therefore be characterised.[6] In order to optimise the aerosol characteristics, it may be useful, even at this stage, to adapt the nebuliser and/or the formulation.

Ideally, the drug formulation and the nebuliser are optimised together. However, in many cases the formulation is already developed and lengthy stability assessments and testing for potential toxicology, for example, are already underway. In such cases it is advantageous if the nebuliser technology is flexible and allows for multiple optimisation options solely on the device side – e.g. the aerosol droplet size distribution can be tailored by adjusting the pore size of the membrane rather than changing the formulation.[7] Three important steps during feasibility testing are shown in Figure 3.

It is thus recommended that the combination of drug and device be tested using the experience of a specialist laboratory. Some device manufacturers offer this testing as a service. The laboratory conducting the tests should have specific experience in testing drug-device combinations for inhalation products because, even during this early feasibility phase, relevant results for later Phase II and Phase III (take home) trials can be obtained to mitigate risks for those phases.

Furthermore, input from engineers as part of the feasibility team, with deep understanding of the device characteristics, can prove valuable in terms of device optimisation. Additionally, the combined expertise in testing methodology and execution, device development, and mechanical and electrical engineering can be complemented with knowledge of regulatory requirements and local registration procedures in major markets to make all the difference for a focused and accelerated start into a successful joint development project. In the end, all of this directly helps to minimise the development costs and timeline as well as raising the overall likelihood of success for the combination product.

Once the feasibility phase is concluded and an appropriate nebuliser meeting the technical requirements has been selected, the first preclinical testing – e.g. in disease animal models or toxicology studies –

Figure 3: During the feasibility phase – (top to bottom) NGI, breath simulator, and laser diffraction measurements.

is conducted. At this stage, the selected nebuliser design needs to be adapted to the study set-up and to the small tidal volumes of the animals for reproducible aerosol delivery. To overcome this challenge, some vibrating membrane nebulisers allow for the entrainment of the aerosol from the nebuliser to the animal in a controlled manner by means of a transportation gas flow – e.g. the Aeroneb Lab (Aerogen) or a special eFlow Technology (PARI Pharma) nebuliser.[8, 9]

Based on the toxicity results from animal studies, a Phase I clinical trial can be set up and first data in humans can be obtained to confirm safety including upper dose limits which, once again, demands flexibility in the design of the device to cover a broad dose range – e.g. by adjusting the fill volume or delivering acceptable aerosol for varying concentrations.

The evaluation phase concludes when the pharma company has selected a device company and the respective nebuliser. At this stage, it has been confirmed that the nebuliser meets those aerosol characteristics which are predicted to result in the optimal deposition of the aerosol in the target region of the respiratory tract. Such characteristics are identified based on pathological considerations as well as current expert know-how in aerosol science, based on or described in the literature.[10-13]

The actual proof is obtained later when the drug-device combination enters Phase II clinical trials where appropriate primary end points must be met to demonstrate efficacy. Following the evaluation phase, the actual development of the specific drug-device combination product is conducted.

In the remainder of this article, we highlight and discuss some important aspects of device development as shown, for example, for the investigational drug-device combination products described in the literature[14,15] and the subsequent commercialisation after approval. These aspects go well beyond technical considerations but are similarly critical for the success of an inhaled product.

DESIGN CONTROL

Both the US 21 CFR part 820 and ISO 13485 require medical device developers and manufacturers to implement a comprehensive quality management system (QMS) as a basis for later approval documentation of the device (e.g. the NDA of the combination product or the technical

"Human factors evaluation as part of risk management plays a special role in the development process."

documentation according to the European Regulation (EU) 2017/745 commonly known as the Medical Device Regulation). Part of this QMS is a proper design control and the creation of a design history file to document the development process of the device as part of the combination product.

The starting point for design control is the set of user requirements which is translated into technical means in the design input requirements. The design's validation and verification experiments, respectively, provide evidence that the nebuliser meets both user and design input requirements. Additionally, a clinical evaluation and risk management plan needs to be designed and implemented.

All these steps require close collaboration between the pharma company and the device company. In particular, human factors evaluation as part of risk management plays a special role in the development process emphasised by the US FDA guideline Applying Human Factors and Usability Engineering to Medical Devices issued in 2016 as well as the IEC62366.[16]

The consideration of usability is important early on in the development process in order to implement the respective studies into the overall development plan of the drug-device combination product. If human factors engineering is not carried out properly at the right time, it may result in significant delays.[17] As the human factors evaluation has to be carried out with an appropriate sample of patients from the intended target patient population, this step can only be carried out with the final device for the specifically designated patients.

Human factors is another area for a joint effort by the pharma and device companies. Human factors specialists on the device developer side can provide their experience in designing and conducting efficient human factors studies in compliance with guidelines as well as with current thinking of regulatory bodies. An exemplary human factors evaluation process was the use and optimisation of the eFlow Closed System specifically for elderly COPD patients.[18]

"In addition to technical and design control challenges, a deep understanding of the regulatory requirements for both drug products and medical devices is crucial."

DEEP REGULATORY KNOWLEDGE AND TRACK RECORD

In addition to technical and design control challenges, a deep understanding of the regulatory requirements for both drug products and medical devices is crucial. In many cases, pharma developers have such regulatory understanding for drug products but are less knowledgeable with respect to medical device regulations in different territories. Experienced device manufacturers can complement the pharma developers with their regulatory know-how.

Since these device companies are typically active in several projects simultaneously, they frequently interact with regulatory authorities over many years and understand both the guidelines and the interpretation by the relevant authorities. Furthermore, the device manufacturers have a great interest in providing coherent and appropriate information to regulators on the device technology across different projects. If a selected nebuliser manufacturer has such extensive experience with regulatory authorities, pharma companies substantially mitigate the regulatory risk coming from the device.

RELIABLE DEVICE MANUFACTURING CAPABILITIES AND SUPPLY

By far the most expensive part of the development of a drug-device combination product is the clinical trials. Nowadays, during development of an inhaled

Figure 4: Reliable device manufacturing capabilities are crucial for commercial success.

combination product, companies use just one rather than several nebulisers to minimise both costs and the risk inherent in clinical trials. Thus, safety and efficacy are established for a product only with one specific delivery device which becomes part of the label of the combination product. The pharma company therefore depends, for both clinical development and after approval, on the availability of the respective nebuliser in the required quality and quantity.

Figure 4 shows strongly quality controlled and highly automated production facilities. Poor or variable device performance due to quality issues may impair results of clinical trials. In particular, when novel device technologies are used which are not yet produced at a relevant commercial scale, the manufacturer may have a limited knowledge of the production process variability and appropriate quality assurance tools which many pharma companies consider a severe risk for their development. Furthermore, timely availability of high-quality nebulisers is mandatory in order to stick to tight project timelines.

The number of nebulisers required to conduct preclinical and clinical development is quite small. This quickly changes as soon as launch preparations start. Well ahead of the anticipated approval date, pharma companies prepare for launch by ordering drug product and devices to de-risk the actual launch and create a considerable safety stock based on their forecasts. This significantly increases the demand for nebulisers before approval and may require scale-up efforts.

Once the launch is successfully mastered, a stable and reliable production, change control process and supply chain for the device must be in place to guarantee market supply and to recoup development and marketing investments into the drug-device combination. For pharma companies this means their commercial success relies on a single source for the critical device component of the product.

Thus, in a professional device selection process, pharma companies – in addition to technical and clinical requirements – add process variability, manufacturing and quality management capabilities to their checklist when they select a nebuliser partner for the development and commercialisation of the combination product in order to mitigate their risk. A relevant track record of the device manufacturer is a positive indicator for such important additional attributes.

ORGANISATIONAL STRUCTURE AND STRATEGIC ORIENTATION

All previously outlined capabilities come with high complexity involving many disciplines and organisational functions which increase with progressing clinical development and require a tight and open collaboration between the pharma partner and the device partner. A deep and trusting collaboration is crucial for the success of every project. Accordingly, proficient pharma companies evaluate the organisational structure and skill set of the device partner when they select a delivery device for their drug product. The high development risk of an inhaled drug-device combination product and the initial low quantities of nebulisers needed to conduct clinical trials presumes a mutual long-term strategic interest of the device manufacturer and the partnering pharma company.

INTELLECTUAL PROPERTY AND EXCLUSIVE COLLABORATION

The development of inhaled drug products is a process which is long, risky and resource intensive. Hence, once regulatory authorities approve a product, it is important for pharma companies to strengthen the competitive position of a product beyond superior safety and/or efficacy. The most common form of intellectual property protection in this industry are patents which usually expire 20 years after they are filed. However, as patents are filed relatively

> "The device partner must demonstrate the capability as well as the strategic commitment to partner with pharma companies to support and endure the long-lasting drug development process."

early during development, the development time needs to be subtracted from that 20-year period when it comes to economic considerations.

Effective patent protection of a combination product may be based on claims for the drug product, the device or the combination of both. Of course, in order to benefit from device-related patents, the pharma company must have exclusive rights to such patents (e.g. via a licence from the device developer) for use with their drug product. This includes proprietary technological and manufacturing know-how and expertise which are essential to ensure the drug-device combination is a success in the market.

In the US, the marketing authorisation holder of the drug product may choose to list patents which protect the approved product in the FDA's publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations" (commonly known as the Orange Book). Until the expiry of patents validly listed in the Orange Book, the agency will not approve a generic product under an ANDA.

In some circumstances, even patents on the device may be eligible for the Orange Book listing if the marketing authorisation holder has the (exclusive) right to reference such patents.[19] Additional market exclusivity mechanisms may apply, such as under an orphan drug designation or if a product is considered a "qualified infectious disease product" under the Generating Antibiotic Incentives Now Act.

If an optimised nebuliser with highly specific delivery characteristics is used in the pivotal clinical trials, it is also required that such a device be used after approval. The regulations for generic drug products – e.g. in Europe according to article 10.1 of the Directive 2001/83/EC or an abbreviated application according to article 10.3 of the same law – require the same delivery performance of the test and the reference product.[20] If the reference product uses a nebuliser with a unique delivery performance, it may be very difficult to copy such a reference product. This is also recognised by the FDA as the agency stated in relation to the approval of the first generic of Advair: "The FDA recognises challenges companies face when seeking to develop hard-to-copy complex generics, such as drug-device combination products, including when the drugs are incorporated into inhalation devices like this."[21]

Hence, the exclusive collaboration (including an exclusive licence to device patents, technological and manufacturing know-how and expertise, and an exclusive supply relationship) between the device manufacturer and the pharma company can be an important part in the protection strategy for an inhaled product.

CONCLUSION AND OUTLOOK

Compared with other dosage forms, the development of inhaled drug products is particularly risky and many products fail during development.[22] The reasons for the disproportionately high failure rates of respiratory drug development may be multifactorial and can be partly caused by complexity.[23] Not only the drug product needs to be developed but also a suitable device. Thus, in order to reduce the risk of inhaled drug development, experienced pharma companies conduct a proper due diligence not only on the device technology but also on the company which develops and produces the devices.

Risk mitigation for a nebulised drug development project involves close collaboration with a competent device partner offering a high-performing and reliable nebuliser technology which can be flexibly adapted to the formulation, a record of accomplishment. The device partner must demonstrate both the capability – e.g. staff with expert know-how, resources, manufacturing infrastructure and quality management systems – as well as the strategic commitment to partner with pharma companies to support and endure the long-lasting drug development process.

The device patent portfolio and an exclusive collaboration with the nebuliser manufacturer may be part of the protection strategy for an inhaled product and together help pharma companies to recoup the significant investments needed for its development and marketing.

ABOUT THE COMPANY

PARI Pharma develops and manufactures optimised eFlow Technology nebulisers in co-operation with, and for, partners from the pharma industry. Pharma companies developing innovative drugs for inhalation approach PARI because of its experience in drug and device development. The eFlow Technology platform is suitable for a wide range of patient populations and drug formulations. It enables short development times for nebulisers optimised for specific medications. PARI has a committed team with a considerable track record. As of today, five commercial drug-specific eFlow Technology nebulisers administer specific inhaled medications.

REFERENCES

1. *Elphick M et al, "Factors to consider when selecting a nebulizer for a new inhaled drug product development program". Expert Opin Drug Del, 2015, Vol 12(8), pp 1375–1387.*
2. *Martin A, Finlay W, "Nebulizers for drug delivery to the lungs". Expert Opin Drug Del, 2015, Vol 12(6), pp 889–900.*
3. *Pritchard J et al, "Mesh nebulizers have become the first choice for new nebulized pharmaceutical drug developments". Ther Deliv, 2018, Vol 9(2), pp 121–136.*
4. *Pritchard J, "Nebulisers: Time to Reinvent the Wheel". ONdrugDelivery Magazine, Issue 92 (Nov 2018), pp 10-15.*
5. *Koehler Y, Fuchs C, "Monitoring Nebuliser Usage & Lung Function in Clinical Trials". ONdrugDelivery Magazine, Issue 87 (Jun 2018), pp 66-70.*
6. *Denk O et al, "Meeting Formulation Challenges for Reproducible Delivery Using eFlow® Technology". Proc RDD Europe, 2013, Vol 1, pp 163–174.*
7. *Knoch M, Keller M, "The customised electronic nebuliser: a new category of liquid aerosol drug delivery systems". Expert Opin Drug Del, 2005, Vol 2(2), pp 377–390.*
8. *Mitchell J, "Abstracts from The Aerosol Society Drug Delivery to the Lungs 20 Edinburgh International Conference Centre Scotland, UK December 9–11, 2009". J Aerosol Med Pulm D, 2010, Vol 23(6), pp 415–440.*

9. *Tservistas M et al, "A Novel Nebulizer Based on eFlow® Technology can Simultaneously and Efficiently Administer Aerosolized siRNA Formulations and Supplemental Oxygen for the Treatment of RSV in Infants". 20th Drug Delivery to the Lungs Conference, December 2009.*
10. *Lizal F et al, "Development of a realistic human airway model". Proc Inst Mech Eng, Part H: J Eng Med, 2012, Vol 226(3), pp 197–207.*
11. *Finlay W, "The mechanics of inhaled pharmaceutical aerosols: an introduction", 2nd Edition. Academic Press (Publ), June 1, 2001.*
12. *James A et al, "The respiratory tract deposition model proposed by the ICRP task group". Radiat Prot Dosim, Vol 38(1–3), 1991, pp 159–165.*
13. *Schwenck N, "Aerosol characterization for the development of novel inhalation devices: in vitro experiments". SimInhale COST Action: Int Conf on Current Challenges and Future Opportunities for Inhalation Therapies, 2019.*
14. *Gessler T et al, "The safety and pharmacokinetics of rapid iloprost aerosol delivery via the BREELIB nebulizer in pulmonary arterial hypertension". Pulm Circ, 2017, Vol 7(2), pp 505–513.*
15. *Li Z et al, "Development and inhalation properties of Amikacin Liposome Inhalation Suspension (ALIS) for treatment of Mycobacterium avium complex (MAC) lung infections". Drug Delivery to the Lungs Conference, Dec 2019.*
16. *"Applying Human Factors and Usability Engineering to Medical Devices. Guidance for Industry and Food and Drug Administration Staff". US FDA, 2016.*
17. *"scPharmaceuticals Receives Complete Response Letter". Press Release, scPharmaceuticals, June 13, 2018.*
18. *Gallem T, "The eFlow 'Closed System' (CS) – A Novel Device Platform For Liquid Aerosol Drug-Device Combinations". ONdrugDelivery Magazine, Issue 50 (Jun 2014), pp 13-16.*
19. *"Approved Drug Products with Therapeutic Equivalence Evaluations". US FDA Orange Book, 2020.*
20. *"Guideline on the requirements for clinical documentation for orally inhaled products (oip) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents". Adopted Guideline, EU EMA, January 22, 2009.*
21. *"FDA approves first generic Advair Diskus". Press Release, US FDA, Jan 30, 2019*
22. *Mestre-Ferrandiz J, Sussex J, Towse A, "The R&D cost of a new medicine". Research Report, Office of Health Economics, Dec 2012.*
23. *Barnes P et al, "Barriers to new drug development in respiratory disease." Eur Respir J, 2015, Vol 45(5), pp 1197-1207.*

ABOUT THE AUTHORS

Nicolas Schwenck is responsible for the strategic management of the nebuliser portfolio based on eFlow Technology, in co-operation with pharma companies. After a diploma in aerospace engineering and research visits to KTH (Stockholm, Sweden) and the University of Bergen (Norway), he acquired his PhD in 2015 from the University of Stuttgart (UoS, Germany). After guest lecturer positions at UoS and the German University in Cairo (Berlin campus, Germany), he led PARI's Technology Platform Aerosol Physics, where his main research interest was *in vitro* experiments of flow and aerosol deposition in the human lungs to improve respiratory therapies. Dr Schwenck's current position is Portfolio Manager eFlow Partnering.

Michael Hahn heads up a team of business development, contract and portfolio managers. It is key for these functions to build and maintain long-lasting relationships with PARI's pharma partners. Mr Hahn joined PARI in 2006 and held different positions in research and development, and business development, with increasing responsibility. He earned a master's degree in Electrical Engineering and an MBA, both from Technical University of Munich (Germany).

Aerosol technology for pharmaceutical excellence.

Expert in manufacturing metering valves, bag on valves, and actuators for a wide range of pharma applications.

Pulmonary, nasal, topical & rectal delivery, pain relief, skin treatments, hand sanitizing, nutraceutical & food supplements

The Lindal KHFA metering valve:

- **Open chamber or capillary retention design**
- **Suitable for suspension, solution and hybrid formulations**
- **Offers performance meeting international specifications**

More info:
Visit: www.lindalgroup.com
Email: info@lindalgroup.com

LINDAL GROUP

Your Innovation Partner.

Nanopharm
an Aptar pharma company

DEVELOPING AN *IN VITRO* DISSOLUTION AND RELEASE SYSTEM FOR ORALLY INHALED DRUG PRODUCTS

In this article, Robert Price, PhD, Chief Scientific Officer, Nanopharm, critiques regulatory routes for the development of generic OINDPs, runs through recent announcements and developments of note from regulators, and describes how Nanopharm has pioneered the concept of structural Q3 equivalence.

Why do so many switchable generic pulmonary therapies fail at the final hurdle, causing immeasurable frustration and incurring very measurable, non-recoverable costs of several millions of dollars? That's one of the questions we aim to answer in this article.

We will explore an alternative bioequivalence pathway to the current US FDA weight-of-evidence approach – and the need to develop *in vitro* studies that measure the local rate and extent of absorption of a representative lung dose. These scientifically valid measurements are critical in supporting the FDA's concept of microstructural Q3 equivalence testing for locally acting products, essentially increasing the evaluation of pharmaceutical equivalence through physicochemical and functional product characteristics.

Finally, we will present a next-generation, patented, aerosol dose collection apparatus that can harmonise both *in vitro* dissolution and *in vitro* release testing of orally inhaled drug products (OIDPs) – removing the guesswork and providing pharma partners with an unprecedented level of confidence to submit, safe in the knowledge that the data is robust.

THE CURRENT STATE OF PLAY

The current Q1, Q2 weight-of-evidence approach requires a comparative clinical endpoint bioequivalence (BE) study for an abbreviated new drug application (ANDA) of all orally inhaled and nasal drug products (OINDPs). Datamonitor's 2015 *Catalyst Report: A regulatory and economic analysis in Europe and the US*, suggests that the weight-of-evidence approach costs more than US$100 million (£81 million) to bring any AB-rated (i.e. that meet BE standards as demonstrated by *in vivo* and/or *in vitro* testing compared with an approved reference standard) inhaled drug to the US market. The cost of a single, 900+ person clinical endpoint BE study is circa $45 million. These studies typically have high variability and low sensitivity, and cannot detect any formulation differences between test and reference products. They really only confirm local equivalence.

For this reason (and in their words) "even though there is a current, clear regulatory pathway utilising the weight-of-evidence approach for BE assessment of OINDPs",

> "RLD batch selection for BE testing is a lottery. The critical quality attributes are a moving target and, unless we can characterise and understand the source of RLD variability, we will continue to witness expensive failures."

Prof Robert Price
Chief Scientific Officer
T: +44 1633 748 880

Nanopharm
Cavendish House
Hazell Drive
Coedkernew
Newport
NP10 8FY
United Kingdom

www.nanopharm.co.uk

the FDA's Office of Generic Drugs (OGD) has recognised the need to find more sensitive and surrogate Q1, Q2 and Q3 based approaches (see Figure 1 for definitions) to demonstrate BE assessment of OINDPs. The need is to find approaches that are more cost and time sensitive. Historically, there have been very limited alternatives to clinical endpoint BE studies for OINDPs. Today, regulators and companies like Nanopharm are actively engaged in the development of both existing and novel *in vitro* techniques to aid the deformulation of the reference listed drug (RLD) and establish Q3 bioequivalence for these complex generic development programmes.

Inhaled biopharmaceutics and the development of new alternate BE approaches using a collective weight-of-evidence from *in vitro* studies will become critical in the development of bioequivalent, locally acting OINDPs.

STOP GAMBLING AND START INVESTING SMARTLY

Sandoz has tried and failed to launch a generic alternative to GlaxoSmithKline's respiratory blockbuster Advair, incurring a $442 million development cost in the process. In October 2016, Sandoz filed a citizen petition with the FDA asking that the agency delay approval of any abbreviated new drug applications (ANDAs) for a generic version of Advair Diskus until pharmacokinetic (PK) BE testing could be shown to account for batch-to-batch variability in the reference drug. In March 2017, the FDA denied the citizen petition on technical grounds.

Although the PK plasma concentration is disconnected from a clinical response, it does appear to be directly related to the physicochemical and release characteristics of the active drug. PK studies suggest that successful *in vitro* based equivalence of the aerodynamic particle size distribution (APSD), as per the product specific guidance, may not directly ensure *in vivo* equivalence in pulmonary absorption, safety profiles and therapeutic efficacy of the test with the RLD.

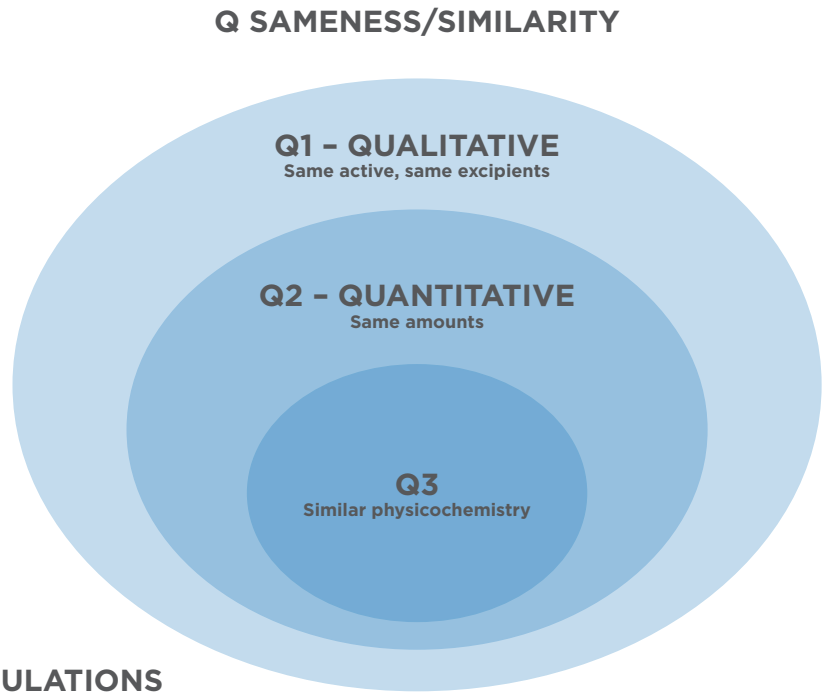


Figure 1: Q1, Q2 and Q3 definitions for sameness and similarity.

The bottom line is that RLD batch selection for BE testing is a lottery. The critical quality attributes are a moving target and, unless we can characterise and understand the source of RLD variability, we will continue to witness expensive failures. We require a combination of advanced *in vitro* aerosol performance testing and access to appropriate and validated physicochemical characterisation methods to enable rapid reformulation of RLD batches, as well as assessing Q3 equivalence as part of an *in vitro* BE weight-of-evidence approach.

THE CONCEPT OF MICROSTRUCTURAL EQUIVALENCE

The 2003 Federal Drug and Cosmetic Act, section 505(j)(8)(A)(ii)[1] states: "For a drug that is not intended to be absorbed into the bloodstream, the Secretary may assess bioavailability by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at the site of action."

> "*In vitro* dissolution and/or *in vitro* release testing has successfully provided a means of evaluating the release properties through the integrated effects of several physical and chemical properties of a formulated product."

The FDA has now introduced the concept of microstructural (Q3) equivalence to address these measurements for locally acting products. Q3 increases the evaluation of pharmaceutical equivalence to physicochemical and functional product characteristics, and provides a real step change in approach. Q1 only evaluates the same components while Q2 only evaluates the same components in the same concentration. But finding a comparable RLD has been a lottery based on luck rather than science.

Q3 provides for the same components in the same concentration with the same arrangement of matter. ANDAs have been successfully approved based on Q1/Q2 with Q3 approaches for locally acting gastrointestinal (GI) oral products, and transdermal and nasal products. We have also seen recent and significant progress in Q3 evaluations for topical semi-solid dosage forms, led by the FDA. These product-specific guidances provide specific physicochemical characterisation requirements (e.g. rheology, particle sizing, polymorph identification) for comparing the physical and structural similarity for each batch of test and RLD product

In vitro dissolution and/or *in vitro* release testing has successfully provided a means of evaluating the release properties through the integrated effects of several physical and chemical properties of a formulated product. As stated by the FDA's non-sterile semisolid dosage forms for scale-

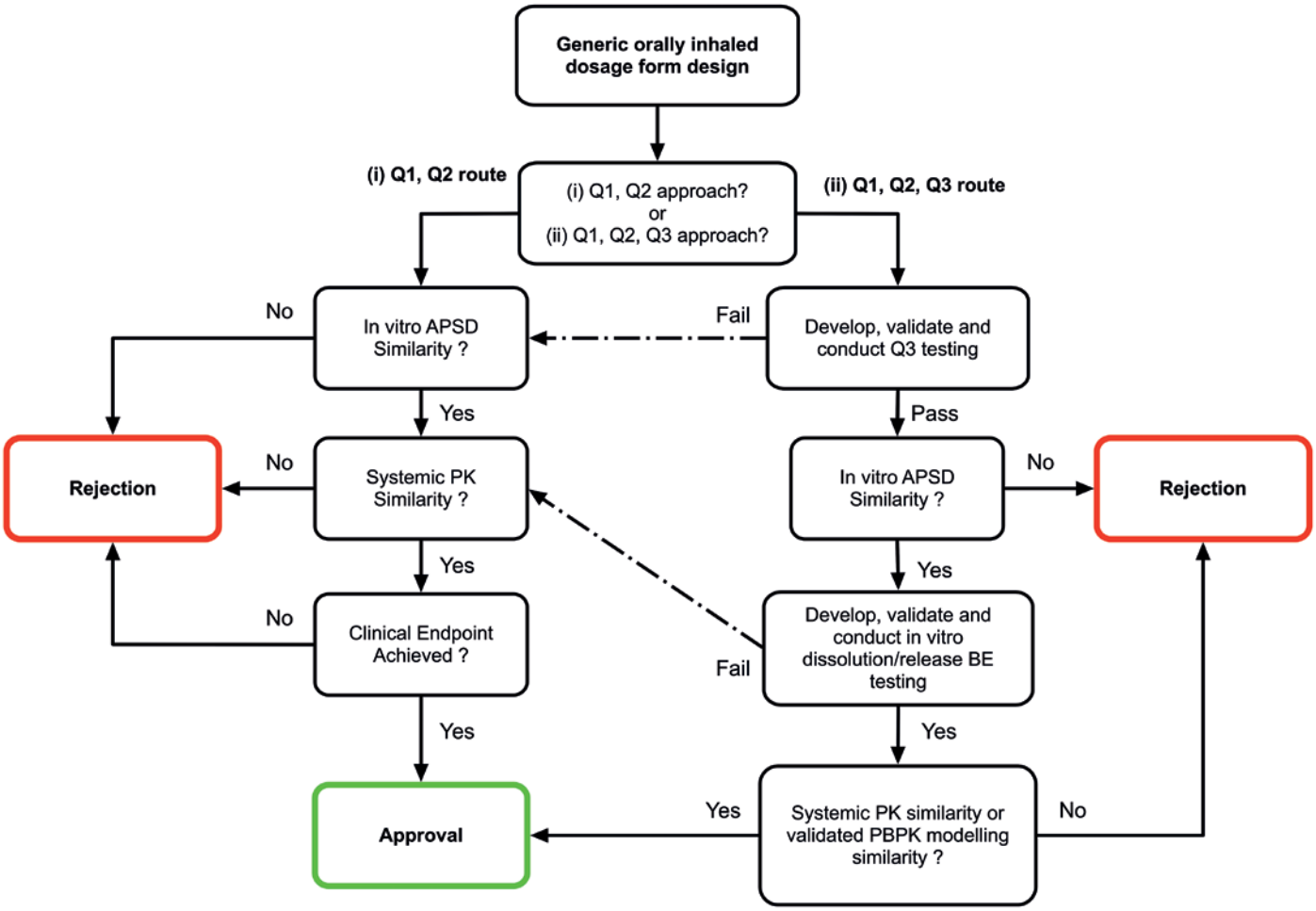


Figure 2: A new approach to bioequivalence.

up and post-approval changes (SUPAC-SS) guidelines: "*In vitro* release testing has shown promise as a means to comprehensively assure consistent delivery of the active component(s)."

In a recent move, the FDA has provided, for the first time, a possible alternative non-clinical BE pathway for an ANDA submission of a solution MDI (Teva's Qvar Redihaler).[2]

Nanopharm has pioneered the concept of structural Q3 equivalence for OINDPs. SmartTrack uses methodologies to bridge *in vitro* measurements and *in vivo* performance of OINDPs through clinically relevant mouth-throat models, dissolution testing, advanced *in silico* modelling and simulation tools (Figure 2). Using its proprietary aerosol collection apparatus, Nanopharm investigates the *in vitro* dissolution, formulation microstructure and realistic aerodynamic particle size distribution performance of generic and reference products with representative mouth-throat models (Figure 3).

These data, with realistic breathing profiles, are employed in an *in silico* regional deposition model with physiologically based pharmacokinetic simulation of both local and systemic exposure. SmartTrack has proved indispensable in guiding product development programmes, and local bioavailability and BE assessment of OINDPs, as well as supporting regulatory decision making.

> "The big hurdle to date in the development of Q3 tools has been that the mode of aerosol collection has lacked uniformity."

IN VITRO RELEASE TESTING

A new addition to the SmartTrack portfolio service offering is *in vitro* release testing (IVRT). With the exception of a range of lipophilic inhaled corticosteroids (ICSs), the aqueous solubility and dose number of the majority of respiratory based products are not dissolution-rate limited in the airway surface liquid (ASL) of the lung (Figure 4). Each aerosolised product will require specific, product-by-product based physical and structural Q3 testing. This is in addition to the development of validated *in vitro* release testing for the demonstration of comparative *in vitro* drug release rates of the active drug from the representative lung dose between test and reference aerosolised products.

While an *in vitro* release test is not expected to directly correlate with, or be predictive of, *in vivo* BE, the measurement of the *in vitro* release rate (IVRR) can provide a comparative test of the local rate of release of the active drug between test and RLD batches. *In vitro* release testing can also be useful as a characterisation tool of finished product performance in controlling both device and formulation variables as well as assessing stability issues over time.

The bespoke IVRT system has been developed specifically to measure the release rate of the impactor stage mass (ISM) of an aerosolised product, using Nanopharm's validated dose-independent Q3 aerosol dose-collection apparatus. In the weight-of-evidence approach, population BE

Figure 3: The smart method for aerosol collection.

> "The current weight-of-evidence approach is a $442 million gamble. RLD batch selection is a lottery based on luck rather than science."

testing of the *in vitro* is undertaken on the ISM, which is defined as the sum of the drug mass on all stages of the impactor, excluding the top impactor stage because of its lack of a specified upper cut off size limit.

The big hurdle to-date in the development of Q3 tools has been that the mode of aerosol collection has lacked uniformity. The critical element is to develop a methodology that can be validated and measures the key quality attributes of drug release – in a uniform way. In response, Nanopharm has developed a proprietary aerosol dose collection system for both Q3 physicochemical characterisation and *in vitro* dissolution and release testing of OIDPs.

The IVRT system has been engineered as an immersion cell system, initially developed as an *in vitro* performance test of drug release from topical semisolid dosage forms.

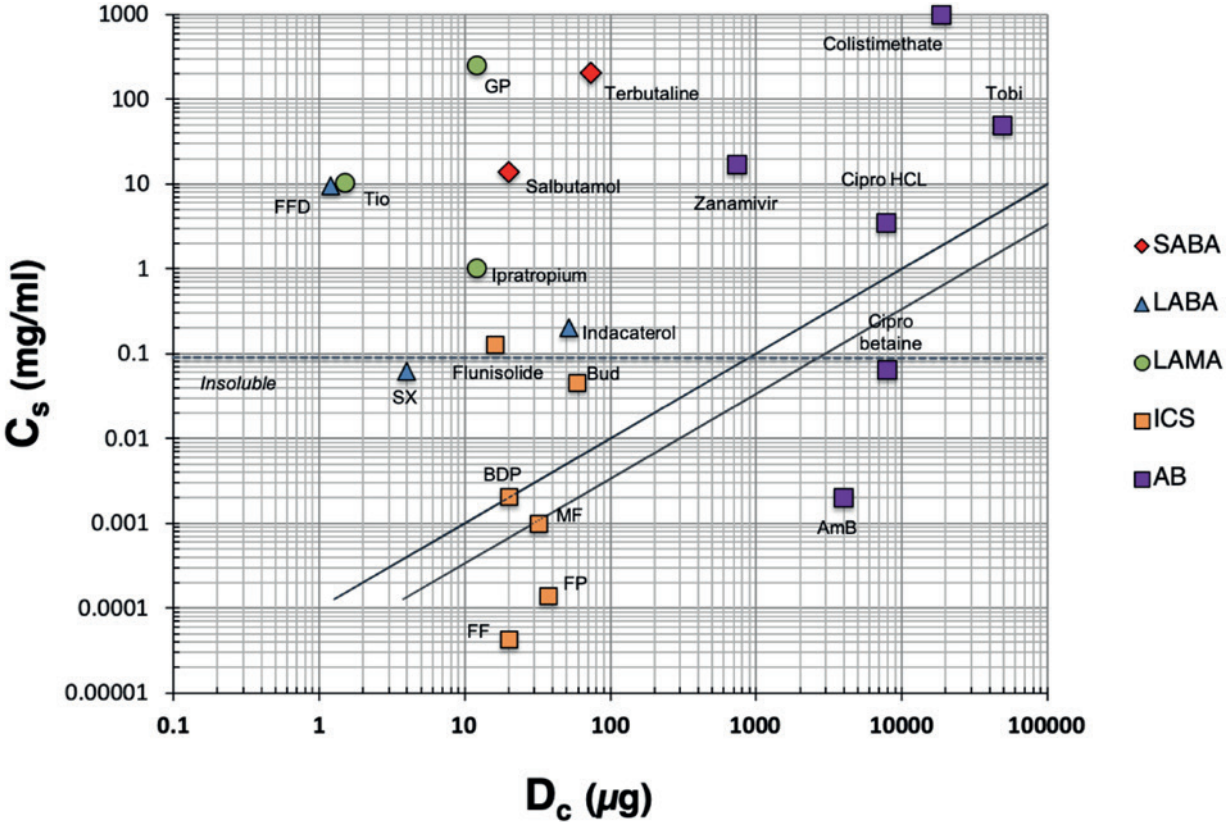


Figure 4: Comparative dissolution rates of various inhaled APIs.[3]

The IVRT system is illustrated in the Higuchi plot of the differences in the *in vitro* release rate of beclomethasone dipropionate from a Fostair 100/6 solution metered dose inhaler (MDI) and a Fostair 100/6 NEXThaler dry powder inhaler (DPI) (Figure 5).

For equivalent ISM doses, the *in vitro* release rate reflects the difference in the physical state of the dispersed active drug. This difference in the physical state between these dispersed aerosolised products can be described by microstructural differences and are characterised by physicochemical properties such as polymorphic form, aerodynamic particle size and shape.

CONCLUSION

It is clear that inhaled biopharmaceutics and the necessary *in vitro* tools required for predicting clinically relevant endpoints of safety and efficacy have become significant in the development of bioequivalent OINDPs.

The current weight-of-evidence approach is a $442 million gamble. RLD batch selection is a lottery based on luck rather than science. We have established, through robust simulations, that the dissolution rate is the key to drug retention in the lung, and that this is the catalyst for more successful developments of reliably bioequivalent formulations and products.

The FDA has introduced, and is championing, the concept of microstructural (Q3) equivalence, with ANDAs approved based on Q1/Q2 with Q3 approaches for locally acting GI oral products, and transdermal and nasal suspensions.

At Nanopharm, we have pioneered the concept of structural Q3 equivalence for OINDPs, providing valid and reproducible approaches for topical generic product equivalence – in turn, reducing the time and cost barrier associated with new generic drug development.

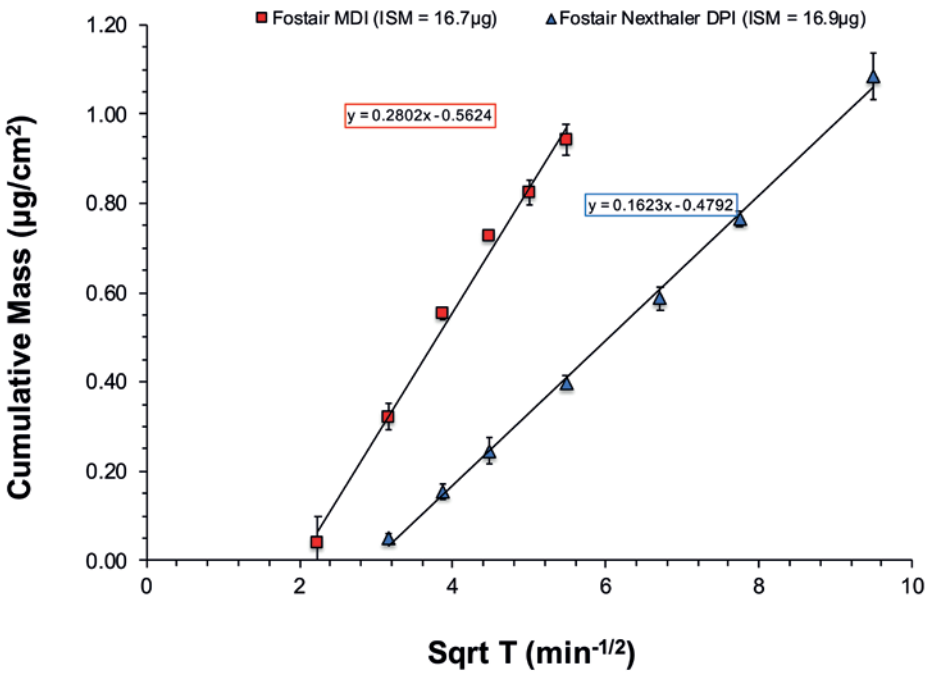


Figure 5: Higuchi plot of the differences in the in vitro release rate of beclomethasone dipropionate from a Fostair 100/6 solution MDI and a Fostair 100/6 NEXThaler DPI.

ABOUT THE COMPANY

Nanopharm, an Aptar Pharma company, is a specialist contract research organisation (CRO) offering product design and development services for orally inhaled and nasal drug products (OINDPs). Nanopharm operates a fee-for-service model, helping its clients navigate the scientific, technical and regulatory challenges in developing nasal and respiratory drug products from discovery through to clinical investigations. It provides an integrated drug development service covering advanced materials characterisation, device and formulation development, and inhaled biopharmaceutics.

REFERENCES

1. *"Title 21 - Food and Drugs Chapter 9 - Federal Food, Drug and Cosmetic Act Subchapter V - Drugs And Devices Part A - Drugs and Devices Sec 355 - New drugs". US Code, 2010 Edition. (http://www.govinfo.gov/content/pkg/USCODE-2010-title21/html/USCODE-2010-title21-chap9-subchapV-partA-sec355.htm – Accessed April 2020)*
2. *"Administrative and Correspondence Documents Relating to NDA Application Number 207921 for QVAR Redihaler (beclomethasone dipropionate)". US FDA CDER. (www.accessdata.fda.gov/drugsatfda_docs/nda/2017/207921Orig1s000AdminCorres.pdf – Accessed April 2020)*
3. *Hastedt J et al, "Scope and Relevance of a Pulmonary Biopharmaceutical Classification System, AAPS/FDA/USP Workshop March 16-17th, 2015 in Baltimore, MD". AAPS Open, 2016, 2:1.*

ABOUT THE AUTHOR

Robert Price is the Chief Scientific Officer and Founder of Nanopharm (now an Aptar Pharma company), and Professor of Pharmaceutics at the University of Bath (UK). His research addresses the relationship between the physical, chemical and interfacial properties of materials and their influence on the microstructural properties of complex formulations.

Dr Price graduated with a BSc in Physics and a PhD in Physical Chemistry from University of Wales College of Cardiff. After several years as a post-doctoral research fellow, he joined the Department of Pharmacy and Pharmacology at Bath in 2000, and was awarded a personal chair in 2008. During this time, he also co-founded and successfully grew Nanopharm to become a leading provider of orally inhaled and nasal drug product design and development services. He has authored more than 120 research articles and has been granted a number of patents. He has received the Royal Pharmaceutical Society Science Medal and the Royal Society of Chemistry Innovation Award for his research.

DDL2020

DRUG DELIVERY TO THE LUNGS

Europe's premier pulmonary and nasal drug delivery conference

9/10/11 December 2020

EDINBURGH INTERNATIONAL CONFERENCE CENTRE

Call for Papers Now Open

Deadline for Submission **Friday 17th July**

Deadline to apply for Emerging Scientist Presentation June 30th

Session Themes for conference paper submissions are:

Sustainability:
looking at current initiatives and beyond to early ideas/concepts that could potentially have an impact for our industry

Artificial Intelligence in drug development

Biological barriers to pulmonary delivery

Challenges of treating respiratory diseases across the globe

Nasal drug delivery

Pat Burnell Young Investigator Award:
Finalists give a poster and oral presentation

Submit your Conference Paper and apply for awards online:

www.ddl-conference.com

PUBLIC INTEREST & INCENTIVES FOR INNOVATORS OF INHALED PRODUCTS

In this article, Igor Gonda, PhD, Chief Executive Officer & Founder of Respidex; David Cipolla, PhD, Vice-President, Research, Insmed; and Philippe Rogueda, PhD, Chief Business Officer & Co-Founder, Merxin, discuss the changes needed to increase the number of approved generic orally inhaled drug products (OIDPs) whilst providing additional incentives to innovators to meet the needs of the general public.

The debate about how to reduce healthcare costs is on everyone's mind but one key question remains unanswered – how can we accommodate the needs of the general public for accessible and affordable healthcare whilst preserving the motivation for innovators to make large, long-term and risky investments to discover and develop new therapies?

We will start with the opportunity to decrease healthcare costs through the approval of generic OIDPs. One of the key factors is naturally the effort required to obtain approval of a generic version of an OIDP, especially in the US as this is potentially the biggest market with the highest drug prices. Remarkably, the push to bring these prices down is one of the very few areas upon which the US president and his political opponents seem to agree!

The impact of generic product introduction in the US is indisputable: according to a US Association for Affordable Medicines (AAM) report, generic medicines saved US$253 billion (£206 billion) in 2016.[1] Considering that the total US retail cost of prescription drugs that year was about $389 billion, this is certainly no small change – representing a 40% reduction. Whilst prescription drugs represented less than 12% of the total annual US healthcare costs in 2016 of $3.3 trillion, increasing the availability of generics is clearly one of the ways to contain the seemingly unsustainable growth of healthcare costs.

The challenge for society and its leadership is to maintain a responsible balance between lowering the cost of drugs whilst supporting the existence of an innovative industry[2] with its impressive achievements in recent history.[3,4] Let us not forget that it is this industry that has enabled us to deal successfully with diseases, notably many types of cancer and HIV, whose diagnosis not so long ago was the equivalent to a death sentence and can now be cured or treated with dignity as a chronic disease – if the patient can afford the treatment. Inhalation products contributed significantly to the increased life expectancy of cystic fibrosis patients and made living with chronic diseases – asthma and COPD – much more bearable.

"The challenge for society and its leadership is to maintain a responsible balance between lowering the cost of drugs whilst supporting the existence of an innovative industry with its impressive achievements in recent history."

WHAT IS THE CURRENT STATUS FOR OIDPS?

Respiratory diseases already constitute one of the highest global health burdens and are on the rise.[5] The existence of an innovative industry that can successfully deal with existing problems as well as swiftly respond to new and often sudden crises, such as the COVID-19 pandemic, is crucial for the wellbeing of all. Although the immediate focus is on oral therapy for the management of the current crisis, the transmission of the virus can occur by inhalation and the key aspects of its morbidity and mortality are respiratory complications. It is possible that locally acting agents administered by inhalation may ultimately be most suitable both for prophylaxis and treatment of this and other viral infections affecting the respiratory tract.

Let us take a more focused look at the competition from generics among

Dr Igor Gonda
Chief Executive Officer & Founder
T: +1 510 731 8820
E: igonda@respidex.com

Respidex, LLC
PO Box 218
Dennis, MA 02638
United States

Dr David Cipolla
Vice-President, Research
T: +1 732 487 7252
E: david.cipolla@insmed.com

Insmed, Inc
700 US Highway 202/206
Bridgewater, NJ 08807-1704
United States

www.insmed.com

Dr Philippe Rogueda
Chief Business Officer & Co-Founder
T: +44 1553 403070
E: philippe@merxin.com

Merxin Ltd
1 Innovation Drive
King's Lynn
Norfolk, PE30 5BY
United Kingdom

www.merxin.com

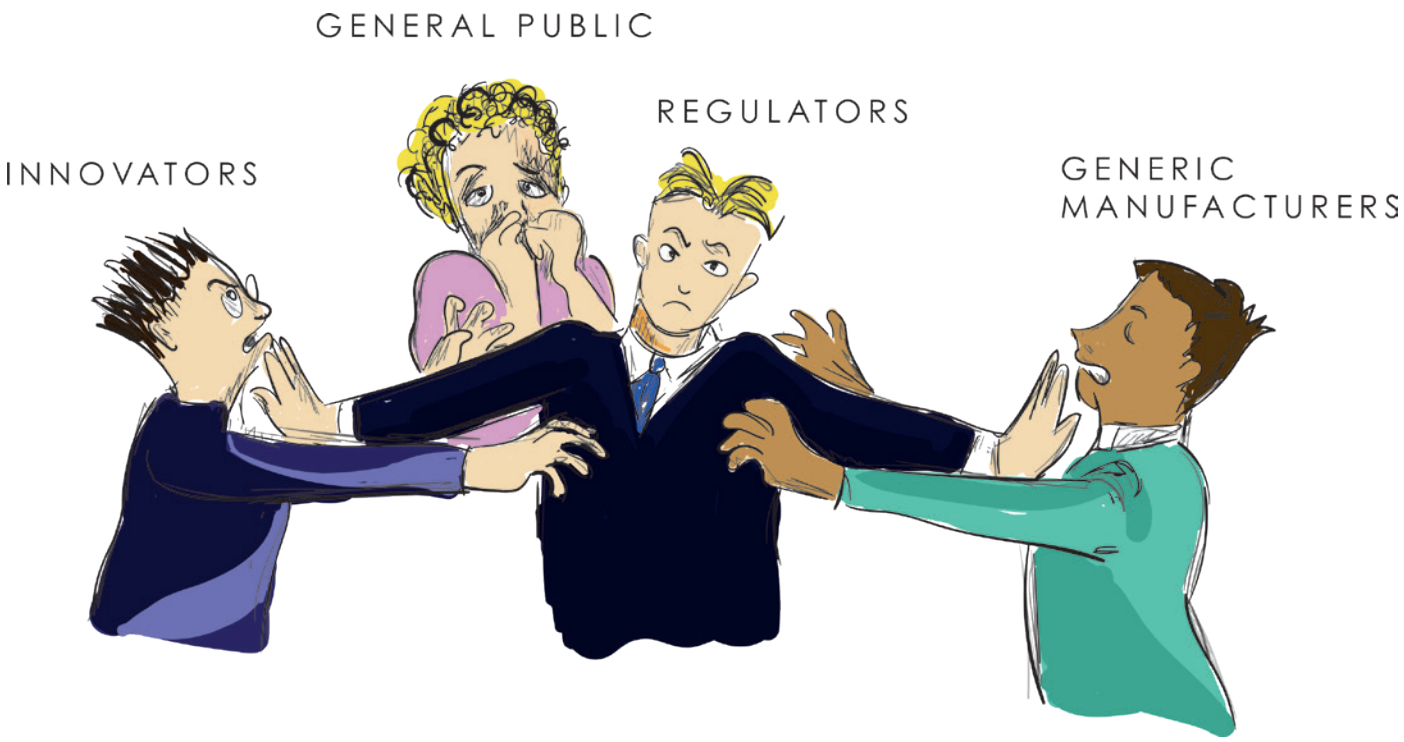


Figure 1: Regulatory hurdles, formalised in the requirements of the amount of evidence deemed adequate for approval, represent an obstacle to generic OIDP approvals, affecting various stakeholders.

respiratory products: the availability of generics in this category contributed $7.4 billion savings in the US in 2016.[1] Although this is significant, it represents less than 3% of the overall annual impact of the introduction of generics. Interestingly, the biggest contributor to this number was the genericised version of Merck & Co's Singulair (montelukast), which ranked as the eighth highest generic cost saver at $4.7 billion. Whilst Singulair is indicated for asthma, it is given orally and ingested, not inhaled. Yet the asthma inhaler market in the US is much bigger than oral asthma drugs. Based on the above figures for the total impact on savings from all other generic respiratory products, the savings from generic inhalers in 2016 represented only about 1% of the total savings.

POTENTIAL CAUSES OF LOW NUMBER OF GENERIC OIDPS

There is no doubt that the size of the market for an innovator's product is a major attraction for generic manufacturers to develop substitutes. The generic industry weighs that against the cost, risk and time to obtain approval of such generics. Whilst patent protection and the potential impact of litigation play an important role, other key factors include the regulatory hurdles formalised in the requirements of the amount of evidence deemed adequate for approval (Figure 1).

These challenges are recognised by the US FDA. Upon the approval of the first generic version of Teva's ProAir HFA (albuterol solution metered dose inhaler (MDI)), the FDA commissioner said: "MDIs like these are known as complex generics, which are traditionally harder to copy because of their complex formulation or mode of delivery. As a result, too many complex drugs lack generic competition even after patents and exclusivities no longer block generic approval. Supporting development and approval of generic copies of these complex medicines so that these products can get to patients has been a major focus of our efforts to improve competition and access and to lower drug prices. Getting more generic copies of complex drugs to the market is a key priority for how we'll help bring new savings to consumers."[6]

The multiple facets of the importance of generic OIDPs for the general public *vis a vis* the difficulties with the regulations of their entry were expressed by the FDA in conjunction with the approval of Mylan's Wixela – the generic version of Advair – in 2019, 19 years after the US approval of GSK's NDA:[7] "Advair was the only dry powder inhaler combination product available for many years, and its manufacturer earned about $5 billion a year in revenue for this one treatment. Because it is a combination of two drugs administered by an inhaler (the device component), it is a very complex product to copy." The public interest could not have been better exemplified than by the quote from a patient, published in the FDA's Office of Generic Drugs Annual Report: "Thank you so very, very much for this — you have no idea how this generic brand will change the lives of untold numbers of people who were struggling to pay for their asthma medicine. I paid $398.96 for my inhaler back in January and today, when the cashier at the pharmacy told me that my total was only $188.65, I almost broke down in tears! Again, thank you from the bottom of my heart!"[7]

Although these two approvals of generic versions of important inhalation products in the US may signal that more are probably coming, the barriers to entry are currently still very high as per current product specific guidances (PSGs) issued by the FDA. As of March 2020, these guidances for MDIs and dry powder inhalers (DPIs) mandate successful conduct of PK and PD clinical trials in addition to extensive *in vitro* studies, often requiring "dauntingly large numbers of patients to demonstrate bioequivalence (BE)" – the quoted expressions are from an FDA presenter at a recent workshop on harmonisation of approval of generic products:[8] These BE studies must be carried out with variable reference products and against statistical criteria that fail to acknowledge the variability of the reference products.

To illustrate the associated hurdles at present for generic manufacturers of OIDPs in concrete numbers, development of Wixela took more than a decade and $700 million.[9,10] This represents a big effort even for a large pharmaceutical company – Novartis gave up on its programme towards a generic Advair inhaler after many years and a write-off of about $442 million.[11] The financial details of the Perrigo-Catalent programme that resulted in the approval of their generic version of the ProAir HFA are not publicly known but they received three complete response letters from the FDA during their long ANDA process, confirming long time lines and likely high development costs.[12]

The FDA has invested a substantial effort in its internal research as well as funding extramural activities to provide a scientific basis for approval of OIDPs, and more specifically MDIs and DPIs. When summarising the achievements to 2017 and the path forward, the FDA Generic Drug Products report stated with reference to OIDPs: "In the next five years of generic drug product user fee amendments (GDUFAs), there are a few overarching goals for OIDPs. The first goal will be to build on the research of the first five years of GDUFA to create clear pathways to establish BE, without the need for comparative clinical endpoint studies."[13]

The concerns about the inability to ascertain equivalence solely on the basis of *in vitro* testing seems to be driven primarily by the lack of consensus on the impact of the rate of dissolution for poorly soluble locally acting inhaled drugs. To quote from the above cited report: "There is no standardised, validated method to measure drug dissolution. Additionally, there is no clear understanding of how *in vitro* parameters might correlate with *in vivo* dissolution for these products; i.e. lack of an *in vitro* to *in vivo* correlation. Understanding the dissolution process could eventually predict therapeutic behaviour based on these *in vitro* characteristics."[13]

We certainly think that the equivalence of *in vitro* test results between the generic and reference products for other critical aspects of the performance of OIDPs – notably those related to the regional deposition in the respiratory tract and systemic exposure – should be sufficient for approval without the need for human studies.

Unfortunately, the sentiments about the lack of scientific consensus for poorly soluble inhaled drugs do not seem to be relevant in the context of drugs that are highly water soluble and/or delivered in a solution formulation, such as the ProAir HFA, and yet it would appear that both human PK and efficacy studies are still required for ANDAs for this product.[14] Let us hope that the FDA will achieve its goal to remove the requirements for ANDAs to contain human studies for the majority of OIDPs by 2022 and subsequently for all of them. Perhaps the new beclomethasone MDI PSG which provides some wiggle room for a waiver of human studies if the *in vitro* package is convincing enough, is a sign of more enlightened times to come.[15]

Faster and more cost-effective generic product development, however, will require more than just changes in the US regulatory hurdles. To show equivalence, even *in vitro*, it is necessary to have access to the reference materials (API and drug products) as well as the methods and specifications. In an ideal world – which we believe can be achieved in this respect – there would be internationally accepted reference standards as well as API, and critical excipient and drug product monographs containing all the information required to show adequate quality of the generic product through compliance with the same standards as the innovator product.[8]

After all, the innovators do not have to conduct a clinical trial every time they release a new batch of drug product. Neither do they need to run clinical trials in many other circumstances – e.g. changes of sources of the API or manufacturing facility,[16] that would be subject to a supplemental NDA. In those situations, *in vitro* tests used for the product release and in-process checks are usually adequate for such supplemental approvals to mitigate many of the risks similar to those posed by the introduction of generic substitutes. Of course, both the innovator and the generic companies are and should continue to comply with the high standards of good manufacturing practice (GMP).

COMPENDIAL MONOGRAPHS AND REFERENCE STANDARDS

There is a strong correlation between the existence of USP monographs and the availability of generic products; not surprisingly, inhalation products have the smallest proportion of monographs relative to the total that are eligible for generic substitution of OIDPs based on the Orange Book (19.4% monographs for inhalation versus the highest category – oral dosage forms – with 79.4% of eligible orals).[17]

> "We do not believe that the relationship between the number of generic products and availability of monographs is just a spurious correlation."

We do not believe that the relationship between the number of generic products and availability of monographs is just a spurious correlation. We think it is reflected in the lack of approvals for MDIs and DPIs and caused in part by the very onerous ANDA approval hurdles and the absence of relevant monographs. It should be a major risk mitigation for the general public and the FDA to waive the requirement for human studies for bioequivalence if the generic products are made to comply to the battery of tests used in quality control systems of the innovators. Such monographs also have the advantage of resulting from a consensus process subjected to continuous public scrutiny by all key stakeholders.

POTENTIAL WIN-WIN-WIN PATH FORWARD

Today, there is neither a stick nor a carrot available to the FDA or the USP to facilitate the availability of product-specific monographs and reference standards. The history of FDA regulations suggests that meaningful regulatory incentives are a powerful motivation for innovator companies.[2,18] The US Hatch-Waxman Act that was introduced in 1984 to accelerate the introduction of generic products recognised the discrepancy between the patent protection duration and the length of new product development – and to reflect that, it afforded increased regulatory exclusivity periods.[1] Extension of regulatory exclusivity and acceleration of product approval provided a variety of attractive stimuli for industry – e.g. priority review vouchers for the development of orphan indications, breakthrough drugs, paediatric indications and novel antibiotics.

We suggest that similar incentives from the FDA could be used to motivate innovators to provide timely assistance to publish the relevant monographs and enable provision of critical reference standards for regulators and generic manufacturers (Figure 2).

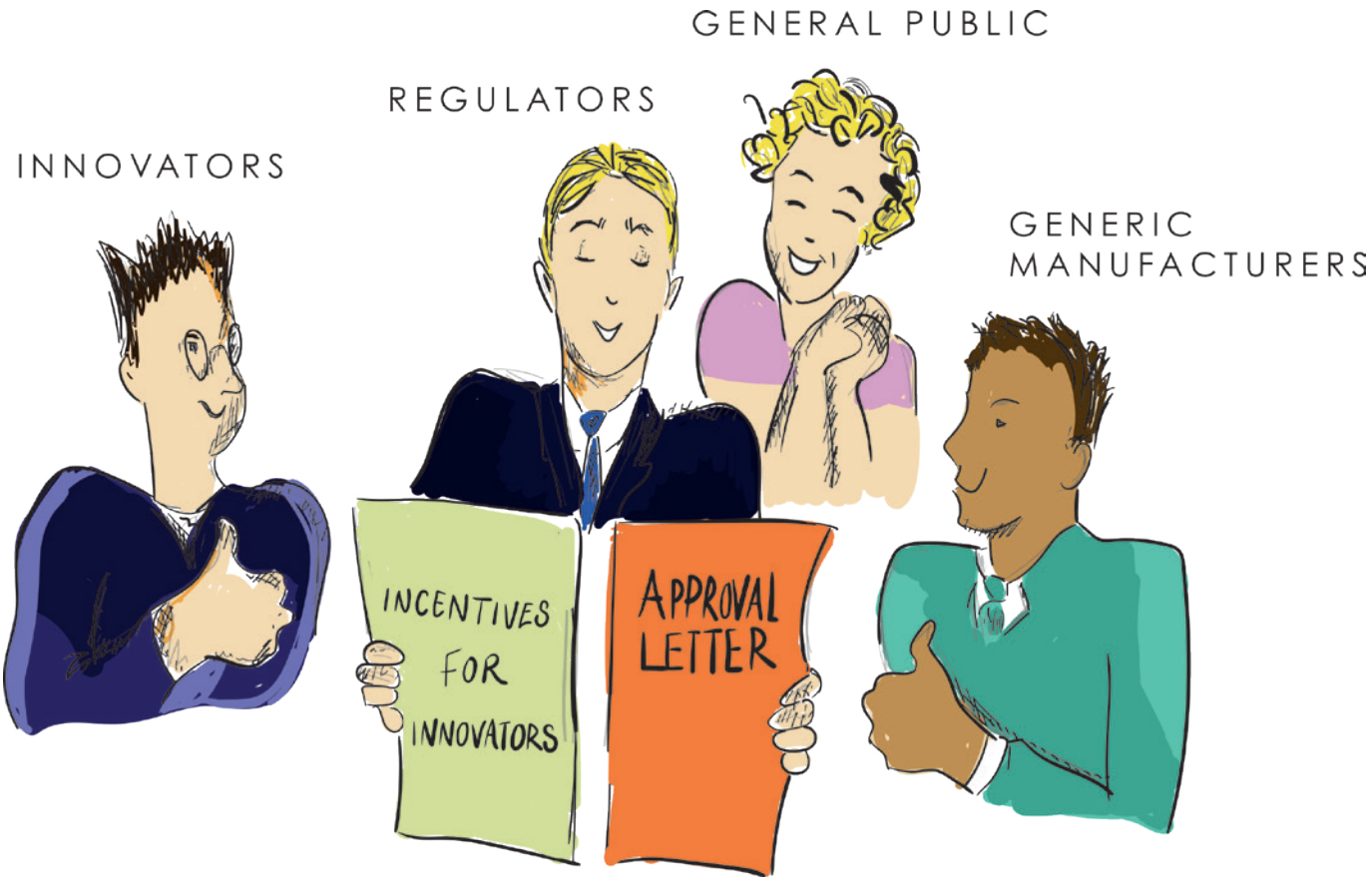


Figure 2: Regulatory incentives would prompt more generic OIDP developments and there could be benefits for innovators too, representing a win for all stakeholders.

> "The absence of monographs for many important OIDPs is the likely reason why even companies with significant resources are reluctant to attempt to develop the first and then a second and subsequent generic products."

The USP already has the right to develop monographs with third parties if the innovator is unwilling to do so.[19] However, there appear to be no incentives at present for generic or innovator companies to work with the USP to develop such monographs. The absence of monographs for many important OIDPs is the likely reason why even companies with significant resources are reluctant to attempt to develop the first and then a second and subsequent generic products.

The economic impact of the presence of monographs as a causal factor for a greater availability of generics was estimated to be more than $6 billion in cost savings to US healthcare in 2016;[17] the cost savings to the generic manufacturers would likely be highly significant. Given the size of the inhalation market in the US and the sparsity of inhaled generics for the major inhalation products that are off patent, the opportunity seems very significant.

We believe that some additional exclusivity (e.g. similar to what was implemented for biologics) or attractive regulatory incentives, such as priority review vouchers, could be used to compensate the innovators for the mandatory publication of their quality control methods and specifications, and provision of reference standards to enable the compendial product monographs. This would require urgent implementation of the current compendial[19] and regulatory[20,21] efforts to have such monographs ready for the generic industry no later than five years prior to the anticipated first legal entry of a generic version of the product.

Similar incentives for publication of monographs could be provided to the first-to-approval generic manufacturers if the innovator did not participate in a timely collaboration with USP. Marketing of such generic products would still only be possible under the existing patent laws applicable in the territory.

For the innovators, the regulatory incentives may outweigh the losses due to the earlier entry of generic competitors. But perhaps they will also save them substantial costs incurred to protect their markets through litigation against generic manufacturers. And they will be able to refocus those efforts on what they are best appreciated for – innovative research leading to approval of superior therapies.

REGULATORY HURDLES FOR INHALER DEVICES

An important development in the context of generic OIDPs that is also likely to have a positive impact on innovators is the FDA's greater flexibility in approaching the question of equivalence of devices. The recently issued draft guidance[22] appears to allow more flexibility and a much more relevant decision-making process than the strictly legalistic definition of the device sameness: it allows human factors studies to provide evidence that the device for the generic product is equivalent to the innovator's product from a perspective that is highly relevant to the patient.

The approval of Wixela as a generic substitute of Advair is an example of the flexibility afforded by the FDA for a device which not only looks different from the innovator's product but is also operationally different, in at least one respect – the device resistance – that is generally viewed as a critical attribute of an OIDP, especially a DPI.[23]

Exercising such meaningful, carefully considered flexibility would also assist innovators in bridging between devices during development as well as post approval, thus reducing the length, cost and risk of development of new inhalation therapies.

ABOUT THE COMPANIES

Respidex is a consultancy helping pharmaceutical companies in their R&D activities, regulatory strategy, financing and commercialisation of products for prevention, diagnosis and treatment of diseases. Respidex clients include small early preclinical companies as well as enterprises in late-stage clinical development.

Insmed is a global biopharma company developing treatments for patients with serious and rare diseases. Its first commercial product, ARIKAYCE® (amikacin liposome inhalation suspension), is the first therapy approved in the US for the treatment of refractory *Mycobacterium avium* complex (MAC) lung disease as part of a combination antibacterial drug regimen for adult patients with limited or no alternative treatment options. Insmed's earlier-stage clinical pipeline includes INS1007, a novel oral reversible inhibitor of dipeptidyl peptidase 1 with therapeutic potential in non-cystic fibrosis bronchiectasis and other inflammatory diseases, and INS1009, an inhaled formulation of a treprostinil prodrug that may offer a differentiated product profile for rare pulmonary disorders, including pulmonary arterial hypertension.

Merxin designs and supplies generic and customised inhaler device platforms, including multidose dry powder inhalers, capsule dry powder inhalers, soft mist inhalers, no heat no PG vaping devices and devices tailored to cannabinoid delivery to the lungs and nasal cavities. Customers combine Merxin device platforms with their drug formulation to make final dosage forms that are supplied to users and patients. Merxin has been assessed and certified as meeting the requirements of ISO 13485:2016 for the Design, Development and Supply of inhalers. Established in the UK in 2015, with manufacturing capacity across the globe and an international client base, the company is adding more products to its portfolio and expanding rapidly.

REFERENCES

1. *"Generic Drug Access & Savings Report 2017". Research Report, AAM, June 2017.*
2. *Khullar D, Ohn JA, Trusheim MS, Bach PR, "Understanding the Rewards of Successful Drug Development – Thinking Inside the Box". NEJM, 2020, Vol 382, pp 473-480.*
3. *Lichtenberg FR, "How many life-years have new drugs saved? A three-way fixed-effects analysis of 66 diseases in 27 countries, 2000-2013". Int Health, 2019, Vol 11, pp 403-416.*
4. *Lichtenberg FR, "Pharmaceutical Innovation, Mortality Reduction, and Economic Growth". US National Bureau of Economic Research Working Paper No 6569, May 1998.*
5. *"The Global Impact of Respiratory Disease" – Second Edition. Forum of International*

ABOUT THE AUTHORS

Igor Gonda, PhD, is the Founder of Respidex, a San Francisco-based consulting company. Dr Gonda has held a variety of executive positions in US and Australian private and public pharmaceutical and biotech companies. His research focus was primarily in the area of drugs and biologics administered to the lung and nose conducted in industry and, prior to that, in universities in England, Australia and the US. Dr Gonda's current interests additionally include the prevention and cure of the COVID-19 respiratory infection, the involvement of patient advocacy groups in pharmaceutical R&D, venture philanthropy and the regulatory process to accelerate availability of cures for their diseases, and in opportunities for making individualised precision medicines faster and cheaper.

David Cipolla, PhD, has >25 years of experience with a focus on the development of formulation and drug delivery technologies to support pharma product development. Dr Cipolla is Vice-President, Research at Insmed, where he is part of a team developing novel, targeted therapies to help serve the critical unmet needs of patients battling serious rare diseases. Prior to joining Insmed in 2018, he was Vice-President, Preclinical Research at Aradigm covering all phases of product development and before that he worked at Genentech developing and characterising the delivery of protein aerosols to the airways, culminating with the approval of Pulmozyme® rhDNase for the management of cystic fibrosis in 1993. Dr Cipolla holds a chemical engineering degree from MIT (SB) and UC Davis (MS) and a pharmacy degree from the University of Sydney (PhD). He served as chair of IPAC-RS, chair of the ISAM Regulatory Affairs Working Group and ISAM Board Member.

Philippe Rogueda, PhD, FRSC, CChem, CSci, CIng, EURIng, Co-founder and Chief Business Officer of Merxin, is a Fellow of the Royal Society of Chemistry and OINDP expert with an accomplished track record delivering technology and global projects across R&D and commercial industrialisation. Dr Rogueda has held a number of positions in the inhaled drug delivery space, starting as a formulation scientist in the pMDI formulation labs of AstraZeneca; as a principal scientist at Novartis designing DPI, nasal and nebulised inhaled therapies; as an Executive Director of Inhaled Products R&D at Actavis/TEVA; before setting up Merxin to make inhaler technology accessible to a wider audience. Rogueda is principal consultant at Aedestra (Hong Kong), founder of Inhalation Asia (Hong Kong), and of Anthocan (UK) a company dedicated to the formulating of inhaled cannabis therapies.

Respiratory Societies, 2017.

6. *"FDA approves first generic of ProAir HFA". Press Release, US FDA, February 24, 2020.*
7. *"Ensuring Access to Safe, Affordable, and Effective Generic Drugs". Annual Report, Office of Generic Drugs, 2019.*
8. *4th International Workshop of the Global Bioequivalence Harmonization Initiative, Bethesda, MD, US, December 12-13, 2019.*
9. *Product Website, Mylan's Wixela. (www.wixela.com, Accessed April 2020)*
10. *"Mylan Announces FDA Approval of Wixela™ Inhub™ (fluticasone propionate and salmeterol inhalation powder, USP), First Generic of ADVAIR DISKUS® (fluticasone propionate and salmeterol inhalation powder)". Press Release, Mylan, January 31, 2019.*
11. *"A $442M failure: After years of work and an FDA rejection, Novartis calls it quits on Advair copy". Fierce Pharma, January 29, 2020.*
12. *"Perrigo, Catalent get generic of Teva inhaler approved on 4th go-round". Fierce Pharma, February 20, 2020.*
13. *"FYs 2013-2017 Regulatory Science Report: Locally-Acting Orally Inhaled and Nasal Drug Products", Report, US FDA, Feb 20, 2018.*
14. *"Draft Guidance for Industry: Albuterol Sulphate". US FDA, April 2013, Revised June 2013, December 2016, March 2020.*
15. *"Draft Guidance for Industry: Beclomethasone Dipropionate". US FDA, Recommended January 2016, Revised March 2020.*
16. *"Guidance for Industry: Changes to an Approved NDA or ANDA". US FDA, 2004.*
17. *Murimi-Worstell IB, Ballreich JM, Seamans MJ, Alexander GC, "Association between US Pharmacopeia (USP) monograph standards, generic entry and prescription drug cost". PLoS One, 2019, Vol 14(11), e0225109.*
18. *Darrow JJ, Avorn J, Kesselheim AS, "FDA Approval and Regulation of Pharmaceuticals, 1983-2018". JAMA, 2020, Vol 323, pp 164-176.*
19. *"USP Guideline for Submitting Requests for Revision to USP-NF. General Information for All Submissions". US Pharmacopeia, April 29, 2016.*
20. *Finished Product Monographs in the European Pharmacopoeia. PharmTech, June 2, 2014.*
21. *"Guidance for Industry: Harmonizing Compendial Standards With Drug Application Approval Using the USP Pending Monograph Process". US FDA, July 2019*
22. *"Draft Guidance for Industry: Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA". US FDA, January 2017.*
23. *Cooper A et al, "Wixela Inhub® Dry Powder Inhaler – In Vitro Performance Compared with Advair Diskus and Inhalation Profiles in Patients with Asthma or Chronic Obstructive Pulmonary Disease". Am J Respir Crit Care Med", 2019, Vol 199, A2207.*

HOSOKAWA EXTENDS BLENDER RANGE FOR DPI FORMULATIONS

Here, Bert Dekens, Application Manager, Pharma, Hosokawa Micron, announces the extension of the the company's established Cyclomix modular blending technology range, to include small (R&D) scale, mid-range and large-scale systems.

Hosokawa Micron's Cyclomix blending technology (Figure 1) has become well-accepted for high-shear blending of dry powder inhaler (DPI) formulations. Cyclomix has proven to be very effective for tuning mixing energy to the delicate adhesion/cohesion balance. Multiple systems have been sold and delivered for this challenging application.

> "Cyclomix has proven to be very effective for tuning mixing energy to the delicate adhesion/cohesion balance."

Blending formulations for DPIs is a delicate matter. In order to disperse active ingredients in their lactose carriers one needs to break up the cohesive forces between the fine particles, which requires a certain mechanical energy. However, if the energy applied to the formulation is too high, the adhesive forces between the carrier and the actives will also be too high, which limits separation during inhalation.

Finding the right balance for the required mixing energy is the critical issue and calls for a very efficient mixer. Delivering a fully homogeneous blend, without deterioration of the particles, is a prerequisite. The Cyclomix high-shear blender has proven to be perfectly suitable for this application.

Figure 1: The Cyclomix blending technology for high-shear blending of DPI formulations.

Bert Dekens
Application Manager, Pharma
T: +31 314 373 376
E: b.dekens@hmbv.hosokawa.com

Hosokawa Micron BV
Gildenstraat 26
7005 BL Doetinchem
Netherlands

www.hosokawa-micron-bv.com

"If the energy applied to the formulation is too high, the adhesive forces between the carrier and the actives will also be too high, which limits separation during inhalation. Finding the right balance for the required mixing energy is the critical issue."

In order to optimise support to our customers, the range of Cyclomix systems has been streamlined into three platforms:

- Systems suitable for R&D with product bowls of 100 mL, 1 L and 2 L
- Mid-range systems for 5 and 15 L batches
- Large-scale systems for batches up to 100 L.

Cyclomix systems are modular and – besides offering exchangeable product bowls – can be tailored to local requirements by combining options. Systems ranging from straightforward but functional to highly sophisticated are possible.

Features are available for:

- Charging and discharging of toxic materials
- Stand-alone or "through the wall" design
- Cooling by tap water or water chiller
- Lift to support bowl changing
- Clean in place (CIP).

Besides the standard options available, Hosokawa Micron can also offer bespoke solutions to meet specific requirements. All systems comply with EU CE and ATEX regulations.

ABOUT THE COMPANY

Hosokawa Micron is a global supplier of process equipment and systems for the mechanical and thermal processing of dry and wet powders. The company specialises in the design and manufacture of mixing, drying and agglomeration technologies.

Hosokawa Micron maintains extensive facilities for R&D, testing, manufacturing, toll processing and after sales services. It has a total of around 170 employees. The company turnover outside Europe is around 30% and the export quota totals around 85%. Hosokawa Micron BV is a wholly owned subsidiary of the Japanese Hosokawa Micron Corporation.

ABOUT THE AUTHOR

Bert Dekens is Application Manager, Pharma, for the Hosokawa Group, focusing on DPI blending markets. Mr Dekens holds a key position in the DPI network within the International Hosokawa Group and is well established in the DPI market.

OTI TOPIC

ADVANCING ASPRIHALE® TO PIVOTAL PK/PD STUDY

Mark Stansfield, Senior Project Manager, and Kambiz Yadidi, Founder and Chief Executive Officer, both of Optitopic, discuss results of their pilot Phase I clinical study of dry-powder inhalation of aspirin.

Dry-powder aspirin inhalation company Otitopic recently completed a pilot clinical study – *"A Phase I, Single-dose, Open-label, Pilot Study to Compare the Pharmacodynamics and Pharmacokinetics of Acetylsalicylic Acid Inhalation Powder with Non-Enteric-Coated Chewable Aspirin in Healthy Adults"*.

The effects of Asprihale® are a distinctly more rapid, potent and consistent pharmacodynamic (PD) response than the current standard of care (reference listed drug). The immediate antiplatelet and inhibitory effects of Asprihale® would be expected to translate to meaningful clinical benefits in the early evolution of arterial thrombosis.

The very high levels of serum thromboxane B2 (TxB2) suppression and complete arachidonic acid (AA)-induced platelet aggregation response – both within two minutes – are unprecedented for a non-parenterally administered antiplatelet therapy. The individual data for both AA-induced platelet aggregation and TxB2 inhibition show more rapid and predictable response in two minutes than chewable aspirin.

> "Asprihale® reaches maximum plasma concentration in two minutes versus 20 minutes for 162 mg non-enteric coated chewable aspirin."

> "The very high levels of TxB2 suppression and complete AA-induced platelet aggregation response – both within two minutes – are unprecedented for a non-parenterally administered antiplatelet therapy."

Asprihale® is a novel, proprietary aspirin formulation delivered via a dry powder inhaler (DPI), entering the bloodstream faster than oral tablets. Once the US FDA grants approval, the rapid onset of action indicates a promising role for Asprihale® in the treatment of acutemyocardial infarction.

In the clinical trial, subjects were administered a single dose of acetylsalicylic acid (ASA) as either a chewable tablet (162 mg) or by inhalation. Regarding Asprihale® pharmacokinetics (PK), there is a 1.6-fold greater C_{max} of aspirin when inhaled, which is similar to intravenous

Mark Stansfield
Senior Project Manager
T: +1 800 299 9047
E: marks@gppirx.com

Kambiz Yadidi
President and Chief Executive Officer
T: +1 310 616 6111
E: kamy@gppirx.com

Otitopic
10390 Santa Monica Blvd #200
Los Angeles
CA 90025
United States

www.otitopic.com

"This rapid exposure is unprecedented and has enormous implications for early disruption of an emerging thrombus, where differences in time of restoration of blood flow within minutes with different therapies can be life changing."

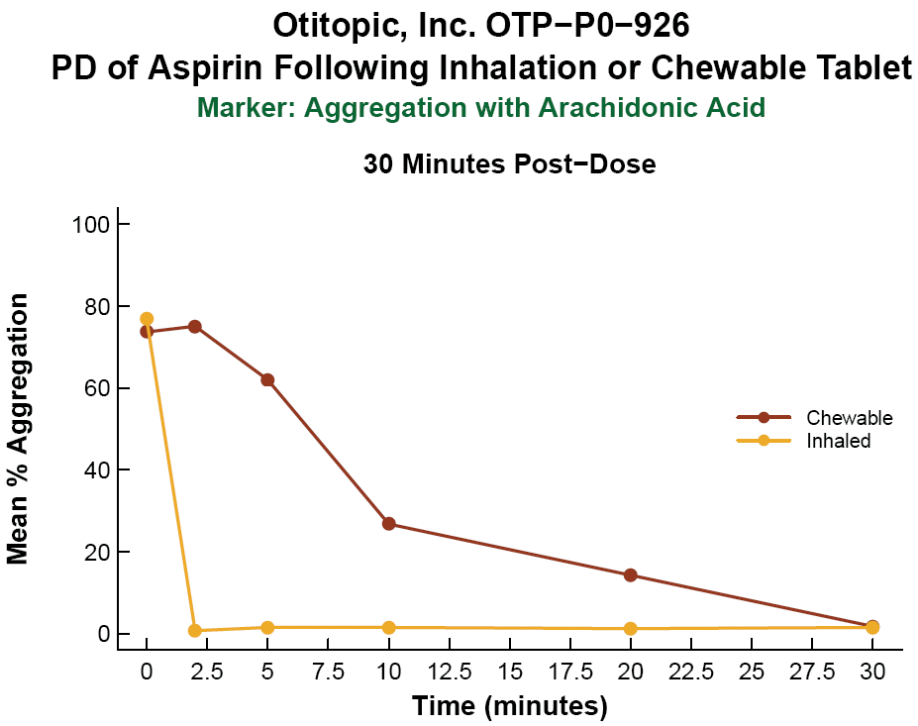


Figure 1: Asprihale® completely inhibits AA-induced platelet aggregation within two minutes versus 30 minutes for chewable aspirin.

administration. Asprihale® aspirin exposure occurred more rapidly compared with chewed aspirin. Asprihale® reaches maximum plasma concentration in two minutes versus 20 minutes for 162 mg non-enteric coated chewable aspirin. This rapid exposure is unprecedented and has enormous implications for early disruption of an emerging thrombus, where differences in time of restoration of blood flow within minutes with different therapies can be life changing.

TxB2 and platelet aggregation were measured and evaluated at baseline and at each PK timepoint post dose – two, five, 10, 20, 30 and 40 minutes, and one, four and 24 hours. Following administration of the inhaled formulation, TxB2 levels fell rapidly over the first two minutes. Asprihale's early and consistent reduction in TxB2 led to early and consistent suppression of platelet aggregation by AA in two minutes.

Figure 1 displays percentage aggregation versus time when aggregation was induced with AA. For the inhaled formulation, AA-induced aggregation was completely suppressed at two minutes post-dose; for the chewable tablet, at 30 minutes post-dose. The effect was maintained for 24 hours for both treatments.

A PK/PD analysis was performed to evaluate the effect of T_{max} on the time to reach 5% platelet aggregation when induced by AA. A strong linear relationship was found between ASA T_{max} and time to onset of its antiplatelet effect. Earlier attainment of C_{max} (i.e. shorter T_{max}) leads to earlier onset of action with Asprihale®.

Otitopic is advancing towards its pivotal PK/PD study following discussions with the FDA. The randomised pivotal study, which is expected to initiate in the fourth quarter of this year, will compare the pharmacodynamics, pharmacokinetics, safety and tolerability of acetylsalicylic acid inhalation powder with non-enteric coated chewable aspirin. The team is looking forward to starting its pivotal study.

Otitopic® is a registered trademark of Otitopic LLC

ABOUT THE COMPANY

Otitopic is a late-stage dry powder inhalation of aspirin company with a track record of success in pharmaceutical product drug delivery and drug device development. Asprihale® is a novel, proprietary aspirin formulation administered via a DPI, entering the bloodstream faster than oral tablets. Otitopic is on track with Asprihale® to file a US NDA in 2021/2022 for a novel drug device combination product to reduce the risk of vascular mortality in patients with suspected acute MI. Otitopic is pioneering a new class of dry-powder inhalation in the cardiovascular medicine field, based on the company's proprietary drug delivery platform. This patented technology leverages inhalation as the route of administration, enabling rapid inhibition of platelet aggregation, aimed at providing powerful new therapeutic capabilities.

ABOUT THE AUTHORS

Mark Stansfield is Senior Project Manager at Otitopic, with more than 11 years' experience in the development of inhaled medications and oral drug formulations. He has extensive product development program management and clinical development and operations experience, including products for the treatment of cancer, chronic obstructive pulmonary disease, asthma, viral infections and acute thrombotic conditions such as heart attack and stroke.

Kambiz Yadidi, Chief Executive Offiver at Otitopic, has over 28 years of management experience across the pharma space. He has been involved in biopharmaceutical businesses in dry powder inhalation drug development, inhalation devices, nasal delivery drug development and nasal drug delivery devices. These companies include Sinus Dynamics and MedQuip. He has also been involved in industry organisations as a board member of Cedars-Sinai Hospital (LA, CA, US) Board of Governors.

intertek
Total Quality. Assured.

OPTIMISING NASAL DRUG PRODUCTS FOR SYSTEMIC DELIVERY

In this article, David Ward, Formulation and Manufacturing Lead at Intertek Melbourn, discusses the benefits of systemic nasal delivery, describes a number of formulation strategies, and explains how to optimise absorption through properly informed formulation and device selection.

Nasal sprays are non-invasive and generally well tolerated by most patients, which drives a relatively high patient compliance rate compared with other more invasive and painful delivery routes.

Historically, nasal sprays have been used primarily for the treatment of topical conditions such as seasonal rhinitis (hayfever), cold symptoms and sinusitis, where the systemic absorption of these drugs is undesirable due to effects that could occur to the hypothalamic–pituitary–adrenal axis, bones, eyes or other parts of the anatomy.

More recently, there has been increased interest in delivering drugs to the nose for systemic conditions, with products already successfully marketed for the treatment of migraine, osteoporosis, the reversal of opioid overdose, hormone replacement, epileptic seizures, depression and flu vaccinations. There is also interest in nasal delivery for the treatment of Parkinson's, Alzheimer's, anxiety, antipsychotic-induced weight gain and vertigo (Table 1). A range of therapeutic agents such as proteins, peptides and nucleic acid-based agents are being considered for

INN (Proprietary names)	Therapeutic Target	Stage
Sumatriptan (Imigran,Tosymra)	Migraine	Marketed
Calcitonin (Miacalcin, Fortical)	Osteoporosis	Marketed
Naloxone (Narcan, Evzio, Nyxoid)	Opioid overdose	Marketed
Oestradiol (Aerodiol)	Hormone replacement	Marketed
Midazolam (Nayzilam)	Epileptic seizures	Marketed
Diazepam (Valtoco)	Epileptic seizures	Marketed
Esketamine (Spravato)	Resistant depression	Marketed
Live attenuated influenza vaccine (Fluenz Tetra/FluMist)	Influenza	Marketed
Levodopa, Glutathione, Nicotine, Insulin	Parkinson's disease	Clinical
Insulin	Alzheimer's disease	Clinical
Testosterone	Anxiety	Clinical
Betahistine (AM-125, AM-201 Auris Medical)	Vertigo, antipsychotic-induced symptoms	Clinical
Lorazepam (NRL-2, NRL-3, NRL-4 Neurelis)	Acute anxiety, status epilepticus, psychomotor agitation	Clinical

Table 1: Examples of nasal delivery products on the market and in development.

David Ward
Formulation and Manufacturing Lead
T: +44 1763 261648
E: david.ward@intertek.com

Intertek Melbourn
Saxon Way
Melbourn
Hertfordshire
SG8 6DN
United Kingdom

www.intertek.com

delivery by non-invasive routes such as nasal, however, a major concern for some of these new therapeutic agents is their poor absorption characteristics.

WHY CHOOSE SYSTEMIC NASAL DELIVERY?

There are several advantages of the nasal route. The different tissue types in the nasal cavity allow for systemic delivery, possible nose-to-brain delivery and access to the lymphatic system for vaccines and biologics. This means that nasal delivery can be used to avoid parenteral administration of some compounds, with relatively rapid absorption that also has the benefit of avoiding the hepatic first-pass effect, where the therapeutic agent is rapidly metabolised by the liver into inactive components, therefore, reducing efficacy. The method of delivery is also a simple process so leads to good patient compliance as actuating a device into the nose is preferable to most people than having to inject themselves.

As with other routes of administration, there are some disadvantages to nasal delivery. The nasal anatomy, by design, is quick to clear material from entry to the airways via mucociliary clearance. This is where the cilia covering the nasal mucosa drag mucus and deposited material from the front of the nose to the throat where it is swallowed. This means there is typically a short window for absorption to occur. The natural nasal cycling of the nose can also affect absorption rates – this is an approximate two-and-a-half-hour cycle where one side of the nose is more congested than the other, with the process alternating between sides. So, if your dose consists of only one shot into the nose, then absorption could vary depending on which nostril is used.

Similarly, many people have deviated septa which can change the deposition properties on each side, and we must also consider that everyone's nasal geometry is slightly different and inconsistent absorptions of the drug product – for example, caused by infections blocking the nasal passages – will occur.

"There are three routes to help optimise systemic absorption, two of which are formulation based and the third involves device selection."

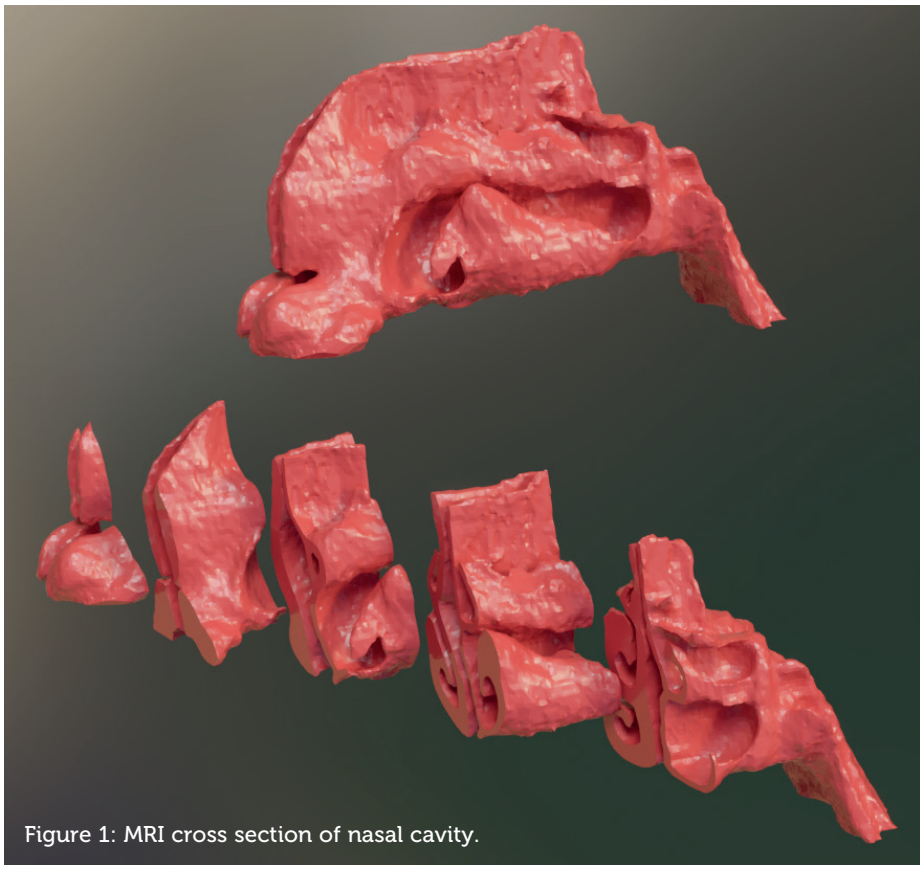


Figure 1: MRI cross section of nasal cavity.

Simplifying the nasal anatomy, there are broadly three main areas of interest. First, the turbinates, which have a large surface area and can therefore be used for systemic delivery. Second is the olfactory region at the top of the nasal cavity, which is responsible for our sense of smell, but could also be useful for direct nose-to-brain delivery of particular treatments, such as those for migraine, Parkinson's or Alzheimer's, or any molecule that cannot pass the blood/brain barrier. Thirdly, towards the very back of the nasal cavity there is nasal associated lymphoid tissue, which is connected to the lymphatic network and can induce a mucosal and systemic immune response, so is therefore a good target for delivery of vaccines and biologics.

A sectioned solid representation of the nasal cavity is shown in Figure 1 – generated from MRI scans of the head. It shows, from the left, the nostrils leading to the nasopharynx and throat to the right of the image, which illustrates how complex the structure of the nasal cavity is. It comprises a network of very narrow passageways, including two narrow slits at the front of the nose, called the nasal valve, where much of a nasal spray is deposited, particularly in the case of traditional aqueous nasal sprays, although some other types of device can have higher deposition in the more posterior areas.

"Strategic formulation development can be used to increase residency time of the active in the nasal cavity."

Other limitations of nasal delivery include low permeability of the nasal tissues for high molecular weight therapeutics, solubility of the API, pH and lipophilicity of the drug and also the presence of proteolytic enzymes that may give rise to degradation of the drug substance in the nasal cavity. Lipophilicity is specifically relevant for biologics, where engineering to improve lipophilic properties of the biomolecule can lead to loss of structural integrity whilst susceptibility to enzyme activity can lead to degradation.

To help overcome these challenges, there are three routes to help optimise systemic absorption, two of which are formulation based and the third involves device selection.

OPTIMISING SYSTEMIC ABSORPTION THROUGH FORMULATION

Strategic formulation development can be used to increase residency time of the active in the nasal cavity using either bioadhesives or viscosity adjusters to slow down the rapid mucociliary clearance in the nose and increase the amount of drug delivered.

Common excipients include natural polysaccharides which show interesting biological properties, including biocompatibility, biodegradability and bioadhesion. A key example is chitosan which has been used in several trials but is not in any marketed products to date. Another bioadhesion agent is carboxymethyl cellulose. A mixture of carboxymethylcellulose and microcrystalline cellulose is commercially available as Avicel RC591 (DuPont) which forms a non-Newtonian fluid that is free flowing when being mixed or sprayed but then forms a thick gel following actuation. This time-dependent shear thinning behaviour helps uniformity of content when mixed, accurate dosage and ease of sprayability for nasal sprays. There are also common thickening excipients such as polyethylene glycol, polyvinylpyrrolidone and glycerol.

To enhance the absorption of poorly permeable drugs, another strategy is to use permeability enhancers such as Neurelis's Intravail (n-dodecyl beta-D-maltoside) which is included in marketed products of sumatriptan (Tosymra) and diazepam (Valtoco) and has been shown to increase the absorption of nalmefene.[1]

Figure 2 lists some other permeability enhancers investigated during clinical trials. Surfactants can enhance absorption with more than one mechanism – these include perturbing the cell membrane by leaching of membrane proteins, opening of tight junctions or preventing enzymatic degradation of the drugs. These surfactants are mainly used and studied in oral drug administration. However, there have been several studies looking at their application in nasal and pulmonary drug delivery. Surfactants such as polysorbates and lecithin, for example, have been found to increase the solubility of both the active and its permeability.

> "Surfactants such as polysorbates and lecithin have been found to increase the solubility of both the active and its permeability."

SELECTED PERMEABILITY ENHANCERS & SOLUBILISERS

- Intravail
- Polysorbate 20/80
- Cyclodextrins
- Lecithin
- HPMC
- Oleic Acid
- Propylene Glycol

Figure 2: Permeability enhancers.

Modifying the inhaled particle surface with agents that enhance their absorption is a potential route to formulation strategy. For example, spray-dried, polymer-coated liposomes composed of soy phosphatidylcholine and phospholipid dimyristoyl phosphatidylglycerol coated with alginate, chitosan or trimethyl chitosan increased penetration of liposomes through the nasal mucosa over uncoated liposomes when delivered as a dry powder.

OPTIMISING SYSTEMIC ABSORPTION THROUGH DEVICE SELECTION

A key requirement of the delivery device is the compatibility with the formulated product with regard to stability. It is important to establish if there is any observation of degradation of the product that is being influenced by the materials of construction. The design must be user friendly and be reliable in use to give consistent metering across the life of the product for multi-dose devices. All materials of construction should be reviewed and an assessment of potential extractables/leachables and adsorptive properties should be made. Various orifice and actuator combinations are available, so better targeted delivery can be achieved through careful selection.

There are a multitude of devices to select from, including the traditional multidose aqueous spray pumps – which deposit the drug primarily at the front of the nose, not reaching much further – and monodose sprays which have a similar performance. But there are several other types of device to consider that can lead to greater deposition towards the back of the nasal cavity, such as dry-powder devices, which can drive the drug deeper into the nasal cavity (e.g. Optinose's Exhalation Delivery Systems, and Aptar Pharma's UDS). There are also nasal pMDIs, which use a volatile propellant so are less likely to drip out of the nose, and nebulisers that create small droplets that can be inhaled further into the nose. Nemera is currently developing a pMDI device (RetroNose) that is actuated into the mouth and then exhaled through the back of the nasal cavity, giving a greater deposition in the areas of interest.

> "By combining the formulation development with device selection, it is possible to maximise the systemic exposure of the therapeutic."

By combining the formulation development with device selection, it is possible to maximise the systemic exposure of the therapeutic by a combination of targeted delivery to the areas of the nasal cavity giving optimal absorption characteristics, reducing the clearance time from these areas and accelerating the absorption while resident. When making this selection, it is important to consider the therapeutic use and dosing regimen (whether multidose daily treatment or monodose for vaccine or rescue medicines), drug cost, device costs, potential intellectual property, drug/excipient interactions, device interactions (whether small molecule or biologic), patient demographic and ease of use.

INTERTEK SOLUTIONS

The recent expansion at our Centre of Excellence for Inhaled and Nasal Drug Development in Melbourn, UK, has focused on new, powerful *in vitro* analytical strategies, integrated with formulation, stability and clinical trial material

manufacturing to enable our clients' key decision-making activities throughout the product development lifecycle.

The Intertek formulation development team offers design and optimisation of formulations for nasal drug products as well as powders, capsules, liquids and solids, semi-solids, inhaled, nebulised, pressurised and topical drug formulations. We provide focused understanding from an early stage of development tailored to your new chemical entities and generic products, from feasibility through to development support, Phase I and II clinical trials, scale-up and transfer to commercial manufacturing.

Our expertise helps accelerate project timelines and includes preformulation, excipient-API compatibility assessment and optimisation, physicochemical testing, formulation screening, lab-scale formulation and accelerated stability studies to achieve the desired product characteristics.

Prior to preclinical studies, we can offer a range of analytical capabilities including solubility assessment, dissolution, solid state characterisation, particle morphology (Malvern Morphologi 4 ID), forced degradation and stability screening, in order to select the optimal development candidates.

Our experience in powder characterisation can drive insight into understanding powder-formulation characteristics, and our physical and chemical testing methods can determine particle size (light scattering, microscopy), thermal properties (DSC, TGA), powder rheology, morphology (powder X-ray diffraction) and spectroscopic profiles (FTIR, Raman).

The approach taken by the Intertek formulation development team enables small quantities of drug product to be developed using experimental design methodologies supported by testing at every stage. By integrating screening, analysis and stability storage, our specialists can provide a range of formulations in a timely and cost-effective manner in order to identify the most promising candidates to progress through to clinical development. As a result, we can save you time by reducing method and technology transfer time as well as effort.

With a holistic approach to service provision – including raw material quality control, scale-up, pilot-scale batch manufacturing and testing, GMP clinical batch manufacturing, stability storage and impurities testing, as well as release testing with qualified person release – we offer a one-source solution for material supplies for use in Phase I and II clinical trials.

ABOUT THE COMPANY

With more than 25 years of experience in supporting clients' orally inhaled and 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's network of more than 1,000 laboratories and offices and over 44,000 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.

REFERENCES

1. *Philip Krieter P, Gyaw S, Crystal R, Skolnick P, "Fighting fire with fire: development of intranasal nalmefene to treat synthetic opioid overdose". J Pharmacol Exp Ther, 2019, Vol 371(2), pp 409–415.*

ABOUT THE AUTHOR

David Ward is Formulation and Manufacturing Lead for Intertek Melbourn. He has worked in the pharmaceutical and device development sectors for more than 20 years across innovative pharma companies and device design and product development, specialising in formulation, analysis and clinical production approaches for orally inhaled and nasal drug products. He has worked across many device types including pressurised metered-dose inhalers, dry-powder inhalers, nasal products and nebulisers.

RETRONOSE: IMPROVING NASAL DELIVERY THROUGH A NEW AND IMPROVED DEVICE

Here, Laurent Vecellio, PhD, Research Engineer, CEPR, INSERM U1100, University of Tours, and Scientific Director, Nemera; Déborah Le Pennec, Research Technician, CEPR, INSERM U1100, University of Tours; Guillaume Grevin, Senior Design Engineer, Nemera; and Alain Regard, Technology Product Manager, Nemera; evaluate the performance of the RetroNose nasal drug delivery device.

The clinical efficacy of a nasal treatment depends on how it is deposited in the nose. Since the pharmaceutical target (local, systemic, brain) is directly related to a specific nasal anatomical site, it is becoming increasingly important for device manufacturing experts to support new drug development in this therapeutic area.

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. The number of applications using the nasal route for local and systemic treatments is on the rise.

At Nemera, integrating early stages of drug development and translating the work into impactful product designs aligns perfectly with our purpose – we put patients first. Furthermore, our ultimate goal is to produce improved drug administration devices that in turn increase therapeutic efficacy. To achieve this objective, it is critical to get input and feedback across the various stages of development to ensure we avoid eventual deficiencies and use time and resources optimally.

> "The main objective of our study was to evaluate the influence of the mouthpiece design on deposition in the upper airways using a nasal cast."

With this in mind, three years ago we initiated a collaboration with the Research Center for Respiratory Diseases (CEPR) of Inserm and the University of Tours (France) to develop a different and portable delivery technology called RetroNose. CEPR's know-how in respiratory preclinical and clinical research joining forces with Nemera's expertise in the development of drug delivery devices made for a powerful partnership. The resulting technology, RetroNose, enables better drug deposition in the distal region of the nose without lung deposition.

The first outcomes of our collaboration with CEPR were presented in 2018, to demonstrate the advantages of RetroNose – resulting in improved particle deposition in an upper airways model for local, vaccine and systemic drugs delivery.

RETRONOSE AT A GLANCE

The concept of nasal drug delivery via the oral route using a pressurised metered dose inhaler (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.

RetroNose is a completely new drug delivery concept to dispense drug formulation to the nasal cavity. The principle of this concept is to deliver a spray through the oral cavity to deposit the drug in the nasal cavity from rear to front. To avoid aerosol penetration in the lung and to ensure deposition efficacy, the

Dr Laurent Vecellio
Research Engineer
CEPR, INSERM U1100,
University of Tours, France
Scientific Director
Nemera
E: vecellio@med.univ-tours.fr

Déborah Le Pennec
Research Technician
CEPR, INSERM U1100,
University of Tours, France

Guillaume Grevin
Senior Design Engineer
E: guillaume.grevin@nemera.net

Alain Regard
Technology Product Manager
Nemera
E: alain.regard@nemera.net

Nemera
20, Avenue de la Gare - B.P. 30
38292 La Verpillière Cedex
France

www.nemera.net

Figure 1: RetroNose concept.

aerosol drug is automatically delivered during the nasal expiratory phase. The drug particles are driven by the expiratory flow through the oropharynx, then the rhinopharynx finally entering the nasal cavity where they are deposited on all nasal surfaces. Figure 1 summarises the process.

In vitro deposition studies performed in nasal casts have shown a homogeneous deposition of drug in the rhinopharynx and the nasal cavity, where a standard nasal spray would offer a proximal deposition localised in the front of the nasal cavity (Figure 2).[3] The deposition profile can be tweaked through the adjustment of some key design parameters of the drug-device combination product. For example, RetroNose also delivers drug into the sinuses, where a standard nasal pump will not.

The RetroNose concept can be compared to the retro nasal olfaction when you eat or drink. Odour molecules can easily travel from the mouth to the nasal cavities via this connection in the throat to reach the olfactory receptors and evoke a smell perception. This is why patients with chronic rhinosinusitis (CRS) often complain of alterations in the "taste" or "flavour" of food and drink. They have deficits in retro nasal olfaction, with worse scores in patients with nasal polyposis.[1]

CLINICAL EVIDENCE

A recent study on CRS patients has shown how corticosteroid deposition distribution in the nasal cavities can have an impact on clinical outcomes.[2] It demonstrated the importance of homogeneous deposition in the different target regions of the nasal cavity to improve treatment efficacy.

Additionally, in another recent study, five asthmatics with rhinosinusitis were successfully treated with an aerosol therapy exhaled through the nose using a similar concept.[4] Hence the use of a pMDI as an alternative to a nebuliser for delivering drugs to the nose via the buccal cavity is relevant.

INFLUENCE OF SPACER & MOUTHPIECE ON RETRONOSE PERFORMANCE

We have used a nasal cast to study the influence of a spacer and different mouthpiece designs on deposition in the upper airways from RetroNose delivery.

Spacer

A range of materials was used in the design of this study, such as a canister filled with HFA 134a propellant (no surfactant) with a 90 µL valve and a pMDI actuator (NM200, H&T Presspart, Germany). Another canister with three particle sizes (3, 12 and 20 µm in terms of volume mean diameter) has also been tested.

The doses used were 100 µg delivered by three pMDI suspensions. The mouthpieces used for the study were: an actuator used with a standard mouthpiece without spacer; and an actuator used with a mouthpiece including a spacer.

The aerosol deposition in the upper airways was then studied using the VCU anatomical model (Virginia Commonwealth University, Richmond, VA, US). The regions of interest to the model being:

- Nasal cavities
- Mouth
- Oropharynx
- Trachea
- Lungs.

The trachea model connected to an absolute filter, a humidified air source

"RetroNose also delivers drug into the sinuses, where a standard nasal pump will not."

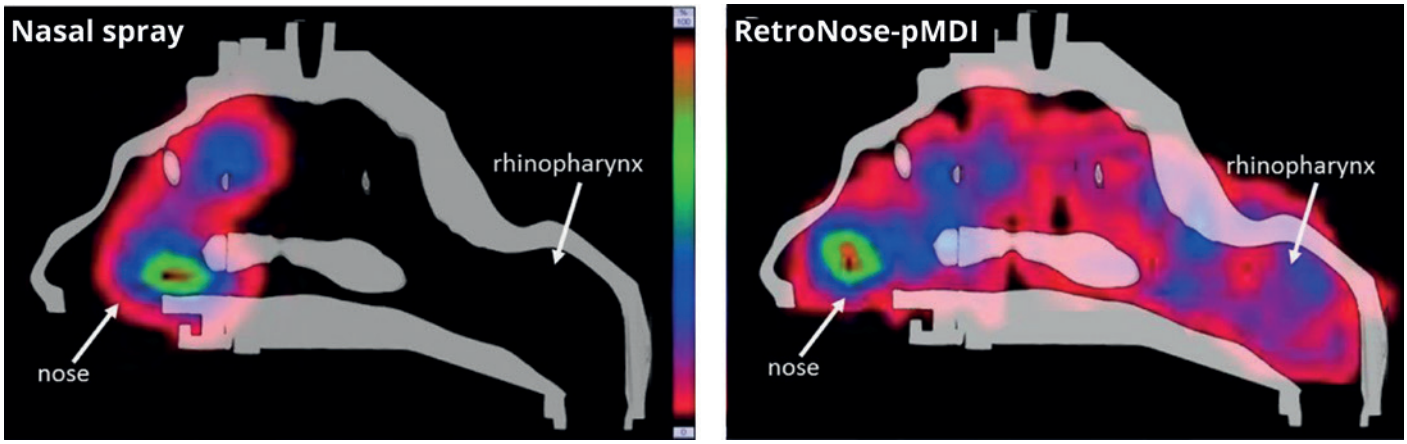


Figure 2: Scintigraphy deposition in nasal cast models using a nasal spray pump and the RetoNose pMDI.

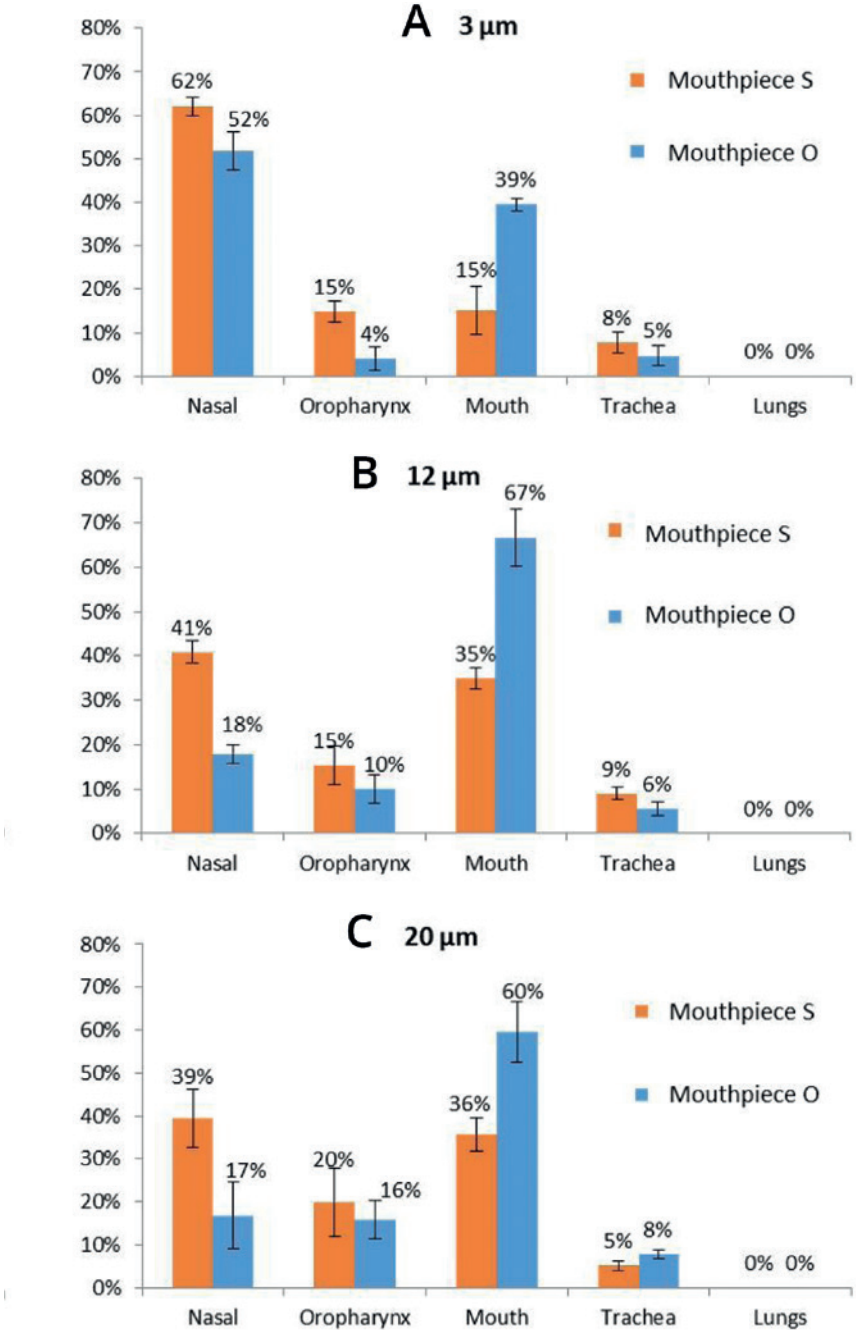


Figure 3: Influence of spacer on deposition in the different regions of an upper airway VCU cast model using RetroNose.

at a flow rate of 60 L/min studied the expiratory flow rate and a vacuum pump connected to an absolute filter located near to the nose model collected the totality of the exhaled aerosol. The active compound was assayed by a spectrophotometric method (Figure 3).

Results of the study showed the following:

- No active compound was detected in the filter (lung model)

The below observations were drawn using mouthpiece-S in comparison with mouthpiece-O:

- A reduced deposition in the mouth was observed
- An enhanced deposition in the nasal cavities
- A decrease of emitted dose (-32% for pMDI-A, -52% for pMDI-B, -15% for pMDI-C).

These results can be explained by the spacer effect for the optimised mouthpiece decreasing the particle velocity, collecting larger particles and consequently reducing the particle impaction in the mouth. Comparison between particle sizes shows an increase of nasal penetration when there is a decrease of particle size.

Mouthpiece Design

The design development also included work around the tongue position to open the oropharynx and make an easier aerosol pathway to the nasal cavities. A specific mouthpiece has been designed and evaluated on six healthy volunteers. As opposed to a standard mouthpiece that doesn't provide easy access to the oropharynx, the RetroNose optimised mouthpiece gives direct access to the oropharynx through the soft palate and the tongue (Figure 4).

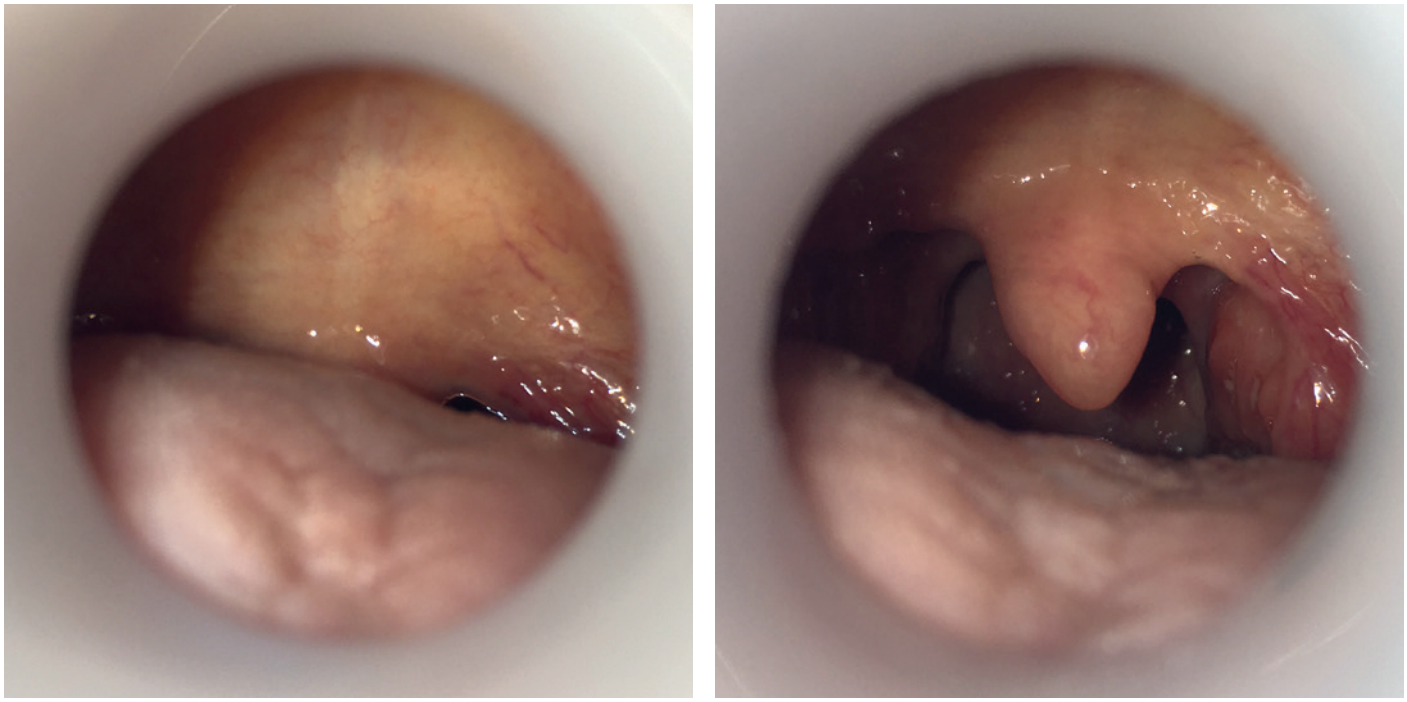


Figure 4: Images of the soft palate with mouthpiece O (left) and mouthpiece S (right) showing the open aerosol pathway through the oral cavity, giving access to the oropharynx. RetroNose mouthpiece to help the aerosol pathway through the oral cavity.

In order to evaluate the influence of the anatomical mouthpiece on drug deposition, we developed two different upper airway cast models. Both have the same nasal cavities but with two different oral cavity models: one corresponding to the anatomy when using a standard mouthpiece and the other corresponding to the anatomy when using the anatomical RetroNose mouthpiece. We measured the deposition distribution with the RetroNose pMDI (12 µm of VMD, 60 L/min) using these models and we observed a fourfold difference in terms of deposition in the mouth when using the anatomical mouthpiece compared with the standard mouthpiece. Mouthpiece design helped to improve the RetroNose pMDI device performances in terms of deposition reduction in the oral cavity.

MAIN BENEFITS OF RETRONOSE

The results of this study reinforce the benefits of the RetroNose technology.

RetroNose improves drug efficacy via a wide and homogeneous deposition:

- applicable to local treatment (e.g. corticosteroids for CRS)
- applicable to systemic treatments
- low deposition distribution variability versus nasal sprays.

RetroNose technology allows a deposition in the back of the nasal cavity and the rhinopharynx, presenting opportunities:

- to treat nose and throat in one go
- for vaccines (lymphatic system)
- to reduce patient-to-patient variability by avoiding the nasal valve passage.

The RetroNose pMDI concept involves device operation steps similar to breath-actuated pMDIs. Triggering upon positive pressure in the mouth from nasal expiration is possible with a mechanical trigger. and also possible with electronics.

CONCLUSION

Nemera understands how vital it is to continue exploring customised solutions for nasal delivery treatments to address unmet medical needs. RetroNose targets nasal disorders through the oral cavity.

An optimised mouthpiece including a spacer reduces the mouth deposition when using the RetroNose technology with a pMDI to target the nasal cavities. This conclusion is aligned with similar studies conducted with pMDIs for lung delivery. Spray triggering upon positive pressure in the mouth seems a good path to ensure drug delivery in the nasal expiratory phase. In the future, a potential next step would be to test the clinical efficacy of RetroNose and its acceptance by patients through the human factors perspective.

ABOUT THE COMPANY

Nemera is a world leader in the design, development and manufacture of drug delivery devices for the pharmaceutical, biotechnology and generics industries. Nemera offers a comprehensive portfolio of products and services across ophthalmology, nasal, inhalation, dermal, transdermal and parenteral delivery. Nemera's vision is to be the most patient-centric drug delivery device company. Nemera always puts patients first, providing high-quality solutions that have a demonstrable impact on patients' health.

REFERENCES

1. *Othieno F et al, "Retronasal olfaction in chronic rhinosinusitis". Laryngoscope, 2018, Vol 128(11), pp 2437–2442.*
2. *Reychler G et al, "Effect of three-drug delivery modalities on olfactory function in chronic sinusitis". Laryngoscope, 2015, Vol 125(3), pp 549–555.*
3. *Vecellio L et al, "Deposition in three nasal cast models with a new concept of nasal administration (RetroNose) vs nasal spray". Drug Delivery Congress, 2018.*
4. *Kobayashi Y et al, "A novel therapeutic use of HFA-BDP metered dose inhaler for asthmatic patients with rhinosinusitis: Case series". Int J Clin Pharmacol Ther, 2014, Vol 52(10), pp 914-9.*

10TH ANNUAL PODD

PARTNERSHIP OPPORTUNITIES IN DRUG DELIVERY

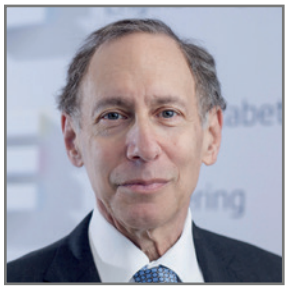
OCTOBER 8-9, 2020 ● RENAISSANCE BOSTON WATERFRONT HOTEL, BOSTON, MA

Strategic Level Partnering Event with the Widest Range of Drug Delivery Technologies

2020 LEADERSHIP

Event Co-Chair
Barbara Lueckel, PhD
Roche

Event Co-Chair
Shawn Davis, PhD
AstraZeneca



Keynote
Robert Langer, PhD
MIT

Keynote
Sangeeta Bhatia, MD, PhD
MIT

DDS Soapbox Chair
Patrick Lim Soo, PhD
Pfizer

Track Chair
Matthew O'Brien, PhD
Pfizer

Track Chair
Ullrich Bruggemann
Takeda

Track Chair
Keith Horspool, PhD
Boehringer Ingelheim

450+ Attendees
Expected

105+ Speakers

525+ Meetings
Confirmed between attendees

15% DISCOUNT WITH CODE ODD15

LEARN MORE AT: THECONFERENCEFORUM.ORG

Nemera

we put patients first

Advancia®

The advanced level of patient adherence

Advancia® user-independent nasal pump guarantees a full dose delivery for every single spray. It is suitable for preserved and preservative-free formulations.

www.nemera.net • information@nemera.net • +33 (0)4 74 94 06 54

• INHALATION • EAR NOSE THROAT • PARENTERAL • OPHTALMIC • DERMAL

Drug Delivery Partnerships

October 12-14, 2020
Hyatt Regency Orlando
Orlando, Florida

VISIONARY IDEAS, DISRUPTIVE TECHNOLOGY & partneringONE® TO MAXIMIZE PRODUCT LIFECYCLE & GENERATE NEW REVENUE STREAMS.

Our stellar keynote lineup will speak on the industry's hottest topics including:

- Innovations and Future Outlook on drug device and formulation technology and patient centric design
- Drug Delivery, Device and Formulations for New and Advanced Therapies
- Drawing the Parallels of Innovation from Design Firms to Pharma
- Regulatory considerations on new FDA and EU-MDR Regulations on Combination Products and the USP 800

Patient-Focused Drug Development and Delivery: The View from a New Player
Dr. Vlad Coric, MD, CEO and Director, biohaven pharmaceuticals

Challenges and Opportunities to Improve the Subcutaneous Delivery of Biologics
Rakesh Dixit, Ph.D., DABT, President & CEO, Bionavigen, Former Vice President, R&D, MedImmune

What Will it Take to Succeed in Drug Delivery – A Look into What's Coming
John Chiminski, CEO, Catalent, Inc.

USP 800 - How it will Effect Drug Delivery and Formulations
Lana Shiu, MD, Executive Director, Medical Device Regulatory Affairs, Global Regulatory Affairs and Safety, Amgen

Brain Delivery of Biologics – VIA Cerebrospinal Fluid
Shraddha Sadekar, Ph.D., Scientist, PKPD, Genentech

Innovations in Drug Delivery that are Shaping the Future of Drug Product Science and Manufacturing
Ronald Smith, Ph.D., Scientific AVP, Merck Research Laboratories

Drug Delivery Partnerships International

@DrugDelivery365
#DDPCONF

Save 10% off current rates with code DDP200N

www.DDPevent.com

Delivering our widest range of nasal actuators for a solution as individual as your customers

Introducing the expanded Pacifica actuator range from Aptar Pharma. A unique Bag-on-Valve solution for your nasal saline product offering.

Everyone is different. But when it comes to nasal dispensing solutions, we all want the same thing – to meet the needs of customers while ensuring an optimized manufacturing process for you.

At Aptar Pharma we are here to make your life easier. Our expanded range of Pacifica actuators for Bag-on-Valve nasal solutions gives you access to a comprehensive choice of continuous dispensing options covering the widest range of applications to help advance your product offering.

Pacifica Soft is made for more gentle applications and designed for delicate noses of every age. **Pacifica Duo** fulfils two needs with one product. By simply twisting the nozzle, one can alternate between spray for gentle applications and jet for rinsing.

Made from medical grade resins, Pacifica takes our extensive range to a new level, providing several design features including a premium look and integrated overcap, customization options, comfortable actuation and handling, and an integrated tamper-evident mechanism.

When it comes to nasal dispensing, more heads are better than one. Follow your nose and contact the experts at Aptar Pharma to find out more about the Pacifica range. Visit **www.aptar.com/pharma**

Delivering solutions, shaping the future.

Aptar
pharma

an Aptar pharma company

THE IMPORTANCE OF TRAINING AND ONBOARDING FOR INTRANASAL RESCUE THERAPIES

With a recent resurgence in nasal drug repurposing, Joe Masci, Executive Director, Business Development at Noble, an Aptar Pharma company, looks at the importance of training and onboarding for intranasal rescue therapies.

Nasal drug repurposing has seen a real resurgence recently, driven by several factors. From an economic perspective, partners benefit from reduced development costs, intellectual property (IP) creation, increased market share and extended lifecycle. The regulatory pathways, such as the US 505(b)2, sometimes complemented by orphan drug designation, are faster and less complex. It may also provide an opportunity to respond to a currently unmet medical need.

Patients benefit too – they feel empowered because medical staff intervention and supervision can be reduced, putting patients back in greater control of their lives. And, of course, nasal drug delivery does provide simplified access, often with an intuitive, user-friendly method of delivery.

That said, repurposing does remain a complex exercise and that complexity is often underestimated. We are now seeing a new generation of industry newcomers and disruptors making their mark, particularly in the rescue therapy space. Narcan® (naloxone), a competitive antagonist to opioids in the central nervous system (CNS) – and more recently a short-term treatment for seizure clusters in patients with epilepsy – are examples of existing therapies repurposed for nasal drug delivery.

So why nasal drug delivery? Primarily because of better patient convenience, greater personal empowerment and improved user compliance but also to overcome particular objections to certain more invasive delivery routes. It also means the patient does not need a healthcare professional (HCP) to administer the drug, which could be life critical in an emergency scenario where, for example, the patient has fainted or is unconscious. Essentially, anyone can be of assistance in administering an intranasal product.

> "As well as confirming that intranasal administration via a Unidose delivery device was the easiest dose to administer, the study also revealed a significant improvement in study participants' ability to administer the dose when trained prior to administering the drug.[5]"

But therein lies a challenge. In principle, anyone can help. But when faced with an emergency scenario, will people have the confidence to come to someone's aid? The levels of anxiety when using a drug delivery device can be high under normal circumstances, let alone under stress and using a product you are unfamiliar with.

Joe Masci
Executive Director,
Business Development
T: +1 603 470 9907
E: jmasci@gonoble.com

Noble
121 South Orange Avenue
Suite 1070
Orlando
FL 32801
United States

www.gonoble.com

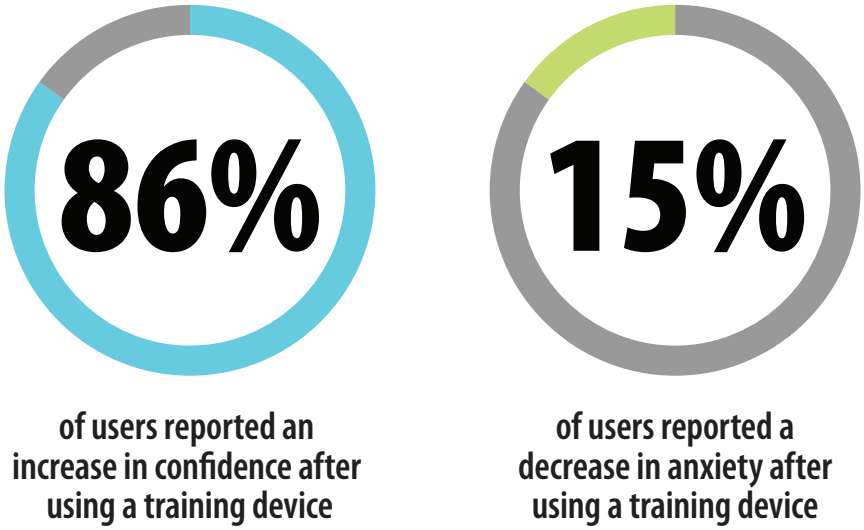


Figure 1: Proper training and onboarding help build user confidence, which in the rescue therapy setting can be a crucial factor.

> "A University of Texas study found that only 16% of adults with an epinephrine autoinjector prescription were able to demonstrate how to properly use that device."

Noble has extensive experience in medical device training solutions, patient onboarding strategies and multisensory product development that can be leveraged to help improve patient outcomes through proper device usage in either a chronic or emergency therapy setting.

PATIENT DEVICE TRAINING

For some, the value of patient training may not be immediately evident, particularly as device developers strive to make devices more intuitive with the goal of improving adherence rates. Nonetheless, data from various studies affirms the need for effective patient training.

In a study of more than 16,000 patients, effective training was an integral element of a patient support programme that was responsible for a 77-85% decrease in treatment abandonment.[1] Training has also been found to not only reduce errors but also aid psychologically. Some 86% of users reported an increase in confidence after using a training device, with 15% of users reporting a decrease in anxiety after using a training device (Figure 1).[2]

A REAL CHALLENGE

In the following section, we explore three recent repurposed nasal therapies where the requirement for effective training is quite evident.

The first repurposed intranasal seizure medication received US FDA approval in 2019. This therapy enables epileptic patients and their care partners to benefit from a simple and intuitive Unidose nasal device to treat seizure clusters. Rescue treatment of seizure clusters is critical because when left untreated, they can increase the risk of physical injury and neurological damage. Despite the potentially serious impact of seizure clusters, many diagnosed patients may go untreated because of the stigma associated with existing emergency remedies.[3]

A second intranasal seizure medication was approved by the FDA in January 2020, further expanding rescue treatment options for epileptic patients and their circle of care partners. These two products now offer patients and caregivers much greater flexibility when developing seizure rescue plans.

Although not yet approved by the FDA, several companies are developing rescue therapies for severe allergic reactions by repurposing epinephrine via Unidose and Bidose nasal delivery devices. If approved by the FDA, intranasal epinephrine products may address commonly cited issues with epinephrine autoinjectors, including ready access, discomfort with needles and a lack of proper training in device use.

The lack of training in the proper use of emergency autoinjectors has been well documented in several studies. A University of Texas study found that only 16% of adults with an epinephrine autoinjector prescription were able to demonstrate how to properly use that device. Another study by Northwestern University found that one-third of parents indicated that their child's doctor did not provide any training on the proper use of an epinephrine autoinjector.[4]

TRAINING FOR AN EMERGENCY

Unidose nasal delivery devices are comparatively simple and intuitive to use; however, there does remain a real need for robust stakeholder training, particularly when it comes to rescue therapy administration. The key considerations include improving user care partner confidence and countering training decay. Within one hour, people will have forgotten an average of 50% of the information presented. Within 24 hours, they have forgotten an average of 70% of new information and, within a week, they have forgotten 90% of new information.

Reducing any anxiety surrounding the administration of the drug product, overcoming the stigma that may exist with legacy FDA-approved therapies for these conditions and addressing negative transfer (the tendency to apply skills from a previous task to a new task) may all result in errors in administration.

As with all products that place the burden of administration in the hands of the user, care partner or even an onlooker, proper training and onboarding helps to build user confidence – which in the rescue therapy setting can be a crucial factor. Offering a well-designed training kit that includes a resettable demonstration device (Figures 2 & 3) can help ensure a high level of user confidence in what will be unscheduled, stressful and potentially life-threatening circumstances. These scenarios will inevitably create a high level of anxiety, with unpredictable effects on the user.

Training not only reduces errors but can help address user anxiety. In 2014, we conducted some research in conjunction with Auburn University (AL, US), testing 55 injection-naïve users. Our data showed that providing access to training prior to using a self-administration combination product results in an 86% increase in confidence after using a training device.

A recent study conducted by the University of Binghamton (NY, US) was undertaken to evaluate the effectiveness of different routes of administration for the

Figure 2: Noble's resettable devices are the core of its training and onboarding kits.

Figure 3: For optimal user training, the Noble Unidose training device closely replicates the look and feel of Aptar Pharma's UDS, the drug delivery device upon which it is based.

"Training is most successful when users are equipped with a mechanical training device that replicates the look, feel and operation of the device as closely as possible."

delivery of naloxone to opioid overdose patients. As well as confirming that intranasal administration via a Unidose delivery device was the easiest dose to administer, the study also revealed a significant improvement in study participants' ability to administer the dose when trained prior to administering the drug.[5] Separate research also suggests that training is most successful when users are equipped with a mechanical training device that replicates the look, feel and operation of the device as closely as possible.[1]

PRACTICE MAKES PERFECT

As we have already discussed, training decay – the tendency to forget what we've been taught – can also play a crucial role. By the very nature of the situation, the circumstances for having to administer rescue therapy medications for severe seizures or anaphylaxis will be unpredictable and unplanned. A variety of steps can be taken to counteract the effects of training decay, including equipping users with a training kit and a resettable demonstration device.

In our own study, we looked to understand how patients interact with training collateral during the first 14 days of their treatment. The study was composed of three cohorts who received different training stimuli for use during the decay period. Some 56% of participants who only had access to the instructions for use (IFU) made critical mistakes during administration. By contrast, one group given just a training device and a second group receiving a training device and instructional video completed all steps perfectly. Those participants with access to the training kit practised at least three times over a two-week period, strongly suggesting that access to a kit can empower users to master the self-administration process. In all, 92% of all study participants indicated that they would prefer to receive a training device to take home and practise with.[6]

IMPACT ON LIMITED HEALTHCARE RESOURCES

Prior to the FDA approval of the first intranasal therapy, the only FDA-approved rescue treatment for epileptic seizure clusters was a rectal gel. Despite its efficacy, there is an inevitable stigma associated with this route of administration, and studies indicate that most care partners would instead prefer to rely on the assistance of emergency personnel in a seizure emergency.[7] Equally, the challenges of using emergency epinephrine autoinjectors to treat severe cases of anaphylaxis are well documented.

> "By collaborating on the integration of a device training strategy, pharmaceutical partners can benefit from a unique market entry strategy."

One study revealed that 52% people who suffered a severe allergic reaction chose to seek in-clinic medical attention rather than use an available autoinjector.[8]

Every study referenced so far demonstrates how training can enable patients and caregivers to take better control of their medication regimen. Training, together with more patient-friendly devices, also benefits the wider healthcare community – removing dependence on HCPs and freeing limited resources for other patients.

BREAK OLD HABITS AND CREATE NEW ONES

Negative transfer – where previous knowledge interferes with new learning – is a real threat to the effective use of devices. For example, users familiar with over-the-counter nasal decongestants may wrongly assume that a Unidose nasal delivery device must be primed before use. Clearly, following that premise with an emergency Unidose device could have a catastrophic outcome as that action would use up the single rescue dose.

WHERE TRAINING ADDS VALUE

We know that 50% of HCPs do not receive training with new delivery devices, and that 49% of HCPs do not train patients. We also know that 86% of patients misuse autoinjectors. This all adds up to a significant opportunity to establish differentiation and competitive advantage through training programmes. By collaborating on the integration of a device training strategy, pharmaceutical partners can benefit from a unique market entry strategy – one that is the epitome of a patient-centric approach: "Not only have we delivered an intuitive, life-saving device, but we will also help you use it."

An effective training strategy can help with future product development, too. Understanding the users' view of what is needed by population type, therapy area and even by dosing, provides real insight that can fuel research and development for future devices. At Noble, we believe our value proposition is as much about enabling the next generation of better devices as it is about enabling users with current technologies.

A CASE STUDY

The first intranasal treatment was developed using the Aptar Pharma Unidose device for intermittent, stereotypic episodes of frequent seizure activity in people living with epilepsy. The treatment is intended be used by non-HCPs – making it imperative that patients and caregivers are trained in the proper administration of the drug.

Noble developed the nasal trainer for this product that replicates the look and function of the real device, whilst being easily resettable by twisting the plunger. The kit includes packaging and training device IFUs, ensuring that end users are properly equipped with the knowledge and confidence to administer the emergency medication quickly and effectively – and empowering patients to engage their care partners with the knowledge that this new rescue therapy is simple to use.

CONCLUSION

We have acknowledged that drug repurposing has seen a real resurgence recently, primarily because of the lower cost of market entry and the more streamlined regulatory pathway. Particularly for the administration of rescue therapies, nasal drug delivery offers real benefit – essentially, anyone can be of assistance in administering the product. However, in the stress-filled emergency scenario, how can we help ensure that onlookers or caregivers are ready to deliver the product timely and error-free?

Delivery device training is becoming more of an accepted practice but there are nuances between a normal self-administration scenario and an emergency one. Significant physiological factors come into play which can be overcome with an effective stakeholder training and onboarding solution – enabling users to understand and, most importantly, remember how to use the device properly and with confidence.

Training should not be viewed as a nice to have. In a world where patient centricity is the primary driver, training should become an integral part of pharmaceutical partners' product launch strategy. The benefits in return are significant – value-add to the product proposition; deeper understanding of user behaviour; and, ultimately, wider acceptance and greater adherence. If training isn't on today's agenda, be prepared because it will certainly be on the priority list very soon.

ABOUT THE COMPANY

Noble is focused on fostering healthy patient outcomes for those who self-administer drug therapies, through the development of robust training devices and onboarding solutions for the world's top pharma brands and biotech companies. Noble manufactures and commercialises training devices that mimic the exact feel, force and function of drug delivery devices such as autoinjectors, prefilled syringes and onbody, nasal and pulmonary devices in order to increase patient adherence and confidence, and decrease usage errors. Noble is an Aptar Pharma company.

REFERENCES

1. *Mease P et al, "Impact of a Patient Support Program on Abandonment of Adalimumab Treatment Initiation in Patients with Rheumatoid Arthritis, Ankylosing Spondylitis, and Psoriatic Arthritis". ACR, Sept 2016.*
2. *"Multisensory training reduces errors". Poster, Noble, PDA Universe of Prefilled Syringes & Injection Devices Conference, Oct 2014.*
3. *Bonds R et al, "Misuse of medical devices: a persistent problem in self-management of asthma and allergic disease". Ann Allergy Asthma Immunol, 2015, Vol 114(1), pp74-76 e2.*
4. *"Parents in Dark About Using Epinephrine for Kids' Food Allergies". Northwestern Now, Jan 2016.*
5. *"Nasal spray found to be quickest, easiest way to deliver antidote naloxone for opioid overdose". News Medical Life Sciences, Jan 2020.*
6. *"Improving Patient Onboarding & Outcomes Through Training". Noble white paper.*
7. *Penovich PE, Buelow J, Steinberg K et al, "Burden of seizure clusters on patients with epilepsy and caregivers survey of patient, caregiver, and clinician perspectives". Neurologist, 2017, Vol 22, pp 207–214.*
8. *Warren C et al, "Epinephrine auto-injector carriage and use practices among US children, adolescents, and adults". Ann Allergy, Asthma and Immunol, 2018, Vol 121(4), pp 479-491.*

ABOUT THE AUTHOR

Joe Masci, Executive Director of Business Development at Noble, an Aptar Pharma company, is responsible for new business development, business strategy and the Noble sales team. He has more than 30 years of experience in the design, development and manufacture of mechanical and electronic devices and 14 years' direct experience in the drug delivery device segment. Prior to joining Noble in January 2019, Mr Masci served as Director of Business Development for the Bespak division of Consort Medical. He earned a Bachelor of Science in Mechanical Engineering from The Massachusetts Institute of Technology and served in the US Navy for five years.

Nasal training devices with a twist

Noble's Unidose training device replicates the form and function of Aptar Pharma's UDS and features a novel ***twist*** reset function, making it easy for users and caregivers to practice how to administer a dose quickly, safely and effectively.

Twist reset mechanism

As the popularity of nasal Unidose and Bidose devices gains momentum, particularly in the rescue therapy segment, so does the need for effective training. Noble's training platform solution accelerates your market entry strategy on several levels - enabling your drug product's training program to get to market quicker, minimizing development, tooling and testing time, while supporting your brand.

Learn more: **GoNoble.com/Unidose**

noble®
an Aptar pharma company

INNOVATIVE DRUG-ELUTING ADHESIVES: APPLICATION IN CHRONIC RHINOSINUSITIS

In this article, Maria Pereira, PhD, Chief Innovation Officer, Elise DeVries, Head of Innovation & Strategy, and Camille Legros, PhD, Head of Formulation, all of TISSIUM, introduce novel applications in the treatment of chronic rhinosinusitis for the company's programmable synthetic polymers and an associated delivery device.

TISSIUM is developing fully synthetic, biomorphic, programmable polymers, which can be used in several ways – to seal or adhere to tissue, as 3D-printed scaffolds, and for localised drug delivery.

The technology at the foundation of TISSIUM's polymer platform was developed at The Massachusetts Institute of Technology (Cambridge, MA, US), Harvard Medical School (Boston, MA, US), and Brigham and Women's Hospital (Boston).[1] The first product based on TISSIUM's polymer platform (SETALIUM) received CE mark approval in 2017 for use as an add-on to sutures during vascular surgery.

The polymer technology is based on the combination of safe, naturally occurring compounds (glycerol and sebacic acid) to form a viscous pre-polymer that can be applied to internal tissues during surgical procedures, both open and minimally invasive. The high viscosity of the pre-polymer allows it to be precisely applied with minimal displacement by body fluids.

Once applied to the target location, the viscous pre-polymer is activated (polymerised) using an external blue light. The resulting bond is both adhesive and elastic, allowing the polymer to comply with the underlying tissue while remaining strongly adhered. Furthermore, this biocompatible polymer biodegrades over time. The properties of the polymer technology, precise delivery and on-demand activation, give the surgeon full control over the procedure.

TISSIUM is currently expanding the range of applications for its core polymer platform. The unique ability of TISSIUM's polymer platform to be leveraged in many different ways is due to the modular platform design: each use case leverages a targeted polymer formulation, distinct delivery device and specific activation technology (Figure 1).

> "The polymer can be loaded with drugs and deployed potentially anywhere in the body, including through minimally invasive procedures, to create a drug depot that delivers drugs locally for extended periods of time."

In addition to being applied as a sealant or adhesive, where the polymer is activated on demand inside the body, the pre-polymer can be used as a 3D-printing resin to build high-resolution 3D printed scaffolds. This is being applied by TISSIUM, for example, in the design of nerve guides to promote the repair of peripheral nerves. Furthermore, the polymer can be loaded with drugs and deployed potentially anywhere in the body, including through minimally invasive procedures, to create a drug depot that delivers drugs locally for extended periods.

> "TISSIUM is leveraging the adhesive and drug delivery properties of its polymer platform for its first drug-device indication to address chronic rhinosinusitis."

Dr Maria Pereira
Chief Innovation Officer

Elise DeVries
Head of Innovation & Strategy

Dr Camille Legros
Head of Formulation

TISSIUM
BIOMORPHIC
PROGRAMMABLE POLYMERS

TISSIUM
74 rue du Faubourg Saint-Antoine
75012 Paris
France

www.tissium.com

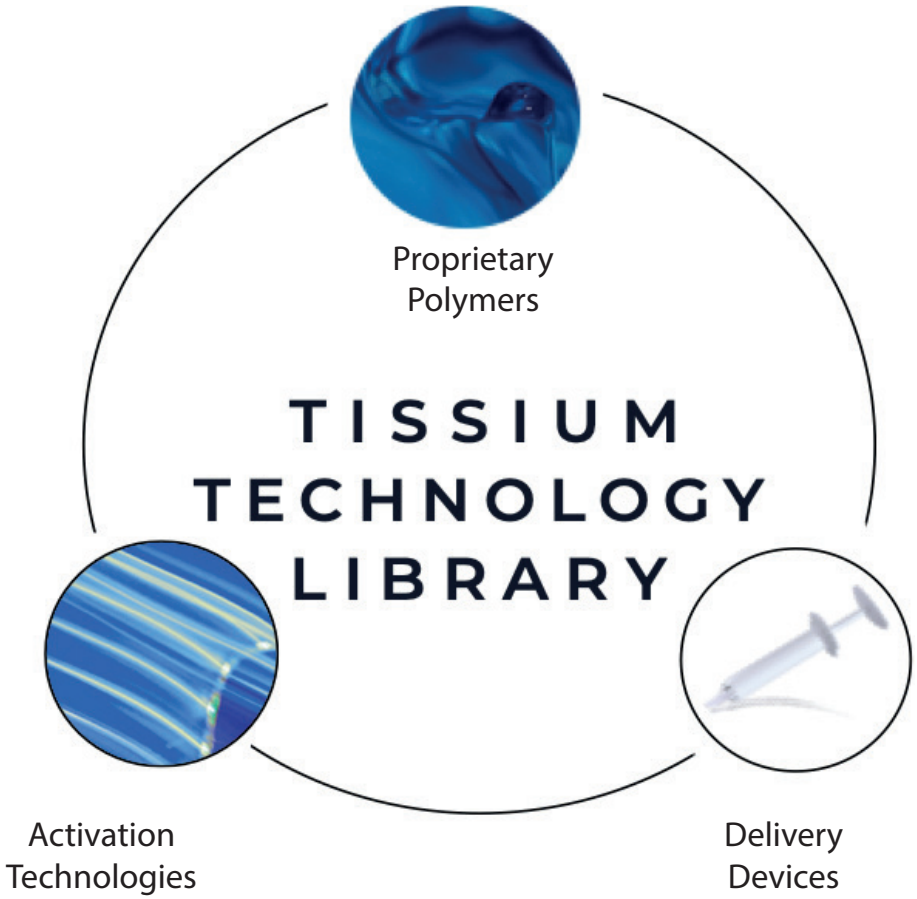


Figure 1: TISSIUM's modular platform design, comprising the polymers, delivery devices and activation technologies, enables products for different clinical indications.

"The intimate contact between the adhesive polymer and the mucosa is expected to result in a high drug concentration for passive diffusion to the inflamed tissue."

MODULAR PLATFORM DESIGN

This modular platform design enables the extension of the technology for applications with different tissue types and therapeutic indications. To support this growth, TISSIUM has scaled up its own manufacturing capabilities, with a 1,300 m^2 manufacturing site in Roncq (France) equipped with clean rooms (totalling 300 m^2) and an analytical laboratory extending over 140 m^2.

TISSIUM is leveraging the adhesive and drug delivery properties of its polymer platform for its first drug-device indication to address chronic rhinosinusitis (CRS). In this scenario, the polymer, loaded with a drug, is delivered through minimally invasive endoscopic techniques to the sinonasal cavity. A later phase of this project will address the use of this solution in other procedures and therapeutic domains where targeted local delivery of bioactive agents is of critical need.

CASE STUDY: ADDRESSING THE BOTTLENECK OF STEROID DELIVERY IN CRS PATIENTS

CRS is defined by the chronic inflammation of the paranasal sinus. Despite the simple definition, this is a complex disease that incorporates many different conditions and endotypes that impact the treatment outcomes.

Regardless of the underlying etiology, all CRS patients endure a long treatment pathway which often does not provide effective treatment or long-term palliation of their disease (Figure 2). The combination of repeat medical management, office visits, sinus surgery and maintenance therapy costs the US a total of US$12 billion (£10 billion) per year in direct costs alone. While functional endoscopic sinus surgery (FESS) provides the most targeted therapy, it does not have long-term efficacy for up to 65% of patients, with 20% of them opting to undergo repeat surgery to "treat" their disease.[3]

A common denominator in the treatment of all CRS conditions is the use of corticosteroids to control the inflammatory processes. Systemic corticosteroids are used in selected patients but widespread

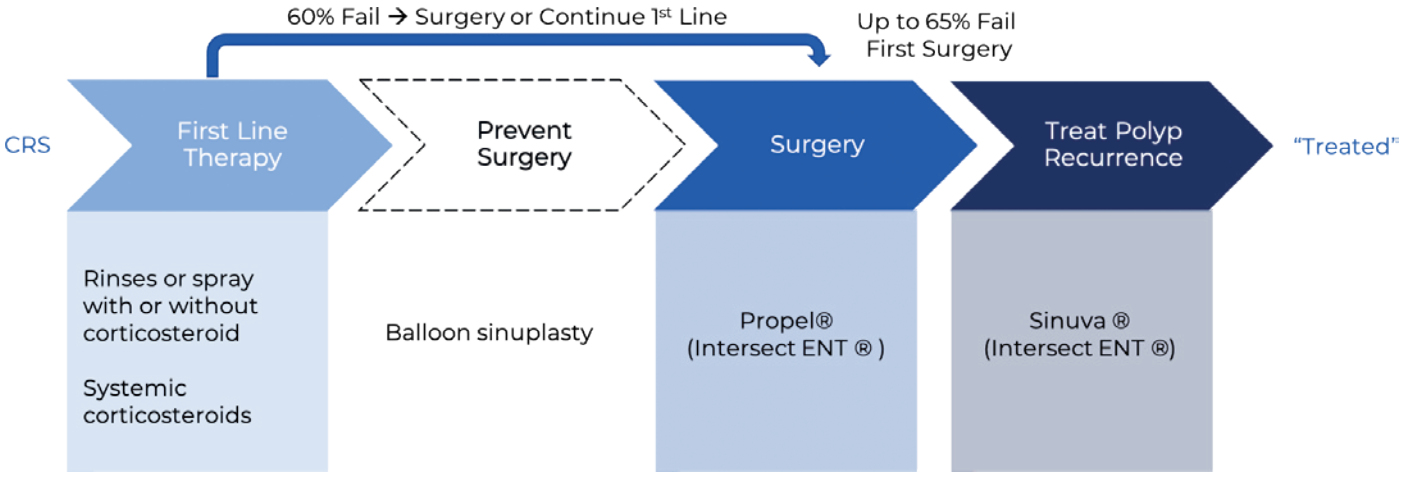


Figure 2: Patient treatment pathway and opportunities for innovation in CRS.

use is limited due to the systemic toxicity of such drugs. Instead, administration of topical corticosteroids is almost universal, and often performed through the use of nasal sprays and rinses. However, the bioavailability in the most critical locations (e.g. sinus) is limited, especially in patients that have not undergone FESS. Up to 60% of the spray or rinse washes away in the first 15 minutes,[4] leaving patients untreated between doses. Furthermore, as with many self-administration products requiring repeated use, patient compliance is a challenge.

To tackle this problem, steroid-eluting stents have been developed with the aim of improving sinus patency. Despite positive clinical studies, more data is still required to determine the cost-effectiveness of such solutions.[5] Furthermore, such stents have been associated with several downsides such as:

1. Low drug loading
2. Limited contact with mucosal tissue
3. Limited duration of release
4. Crusting of the device
5. Dislodgement
6. Delivery limited to locations that are easily accessible (i.e. approved devices are limited to post-surgery scenarios) and where mechanical anchoring is feasible.

Given the challenges in CRS treatment, where targeted steroid delivery is required in distinct anatomies, TISSIUM's polymer is uniquely poised to address this problem. Leveraging the adhesive and drug device properties of its polymer platform, TISSIUM is working on a novel device to enable precise drug deposition with extended steroid release to the sinonasal mucosa, independent of patient anatomy. The intimate contact between the adhesive polymer and the mucosa is expected to result in a high drug concentration for passive diffusion to the inflamed tissue.

Furthermore, by avoiding the need for anatomical anchors, TISSIUM expects to apply this concept not only for the treatment of post-surgery patients but also as a targeted solution between basic medical management and surgery. This approach may offer a solution to patients who have previously exhausted all options – those where medical management is ineffective but who are not eligible for, or elect not to undergo, surgery – thereby minimising the overall cost to the healthcare system and the burden on the patient.

Steroid Delivery for Chronic Rhinosinusitis
Antibiotic Delivery for Acute Sinusitis, Chronic Rhinosinusitis
Post-operative antimicrobial treatment to prevent infection
Pain relief for Septoplasty patients
Long Acting **Medical Therapy** for Rhinitis

Figure 3: Examples of use cases for TISSIUM drug delivery technology in ENT.

BREADTH OF OPPORTUNITIES IN NASAL DRUG DELIVERY AND BEYOND

For TISSIUM, CRS is just the first step in its drug-device platform, as the TISSIUM polymers can benefit treatment paradigms across other disease states as well. Due to the unique properties of the material – such as strong adhesion to both biologic and prosthetic tissues and the capacity to release small molecules in a controlled manner over time – this technology may be of great benefit to other surgical or office procedures where targeted local delivery of bioactive agents is of critical need.

A natural next step from CRS treatment is use of the steroid-loaded polymer for decreasing inflammation in allergic and non-allergic rhinitis patients. Similarly, loading of the polymer with antibiotics in place of steroids could introduce a new paradigm for targeted antibiotic delivery to the sinonasal cavity. Looking to the ENT space more broadly, there are myriad clinical needs that could be addressed by such a technology (Figure 3).

The polymer's versatile properties can be applied in other anatomic areas as well. In particular, local diseases involving inflammation, infection or pain could benefit from a technology that provides local therapy in lieu of traditional systemic dosing. Especially in the case of steroids and pain medication, the advantages of controlled drug delivery include a potential reduction in both the overall systemic dose and the associated side effects versus traditional systemic medications. Additionally, the ability to target the dose to specific anatomy using the adhesive polymer will allow for a localised therapeutic effect that does not depend on the patient – thereby eliminating the pervasive problem of patient compliance.

"For TISSIUM, CRS is just the first step in its drug-device platform, as TISSIUM polymers can benefit treatment paradigms across other disease states."

"The ability to target the dose to specific anatomy using the adhesive polymer will allow for a localised therapeutic effect that does not depend on the patient – thereby eliminating the pervasive problem of patient compliance."

ABOUT THE COMPANY

TISSIUM is a privately owned life sciences company based in Paris, France that is dedicated to the rapid development and commercialisation of a unique synthetic polymer platform to address clinical needs. The company's platform is based on a proprietary polymer family with properties including the ability to conform to, and integrate with, surrounding tissue to enable natural healing. Furthermore, the modular design of the polymers enables customisation to match tissue-specific requirements for different therapeutic areas. The company also develops delivery and activation devices for enhanced performance and usability of its family of polymers.

REFERENCES

1. *Lang N et al, "A Blood-Resistant Surgical Glue for Minimally*

Invasive Repair of Vessels and Heart Defects". Sci Transl Med, 2014, Vol 6(218), 218ra6.

2. *Rudmik L, "Economics of Chronic Rhinosinusitis". Curr Allergy Asthma Rep, 2017, Vol 17(4), p 20.*
3. *DeConde et al, "Prevalence of polyp recurrence after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis". Laryngoscope, 2017, Vol 127(3), pp 550–555.*
4. *Shah SA et al, "Regional deposition of mometasone furoate nasal spray suspension in humans". Allergy Asthma Proc, 2015, Vol 36(1), pp 48–57.*
5. *Hopkins C, "Chronis Rhinosinusitis with Nasal Polyps". N Engl J Med, 2019 Vol 381, pp 55–63.*
6. *Fokkens W, Reitsma S, "New delivery forms of nasal corticosteroids". J Allergy Clin Immunol, 2019, Vol 143, pp 87–88.*

ABOUT THE AUTHORS

Maria Pereira leads the Innovation Hub at TISSIUM. She co-invented TISSIUM's polymer technology while a PhD student at Prof Jeff Karp's Laboratories at Brigham & Women's Hospital (Boston, MA, US). She has been recognised for her research by *MIT Tech Review*'s "35 Innovators Under 35" in 2014, as well as *Forbes* in its "30 under 30" selection in healthcare in 2015. Dr Pereira holds a PhD in bioengineering from the MIT-Portugal programme and an MBA from INSEAD (Fontainebleau, France).

Elise DeVries is the Head of Innovation & Strategy at TISSIUM. Prior to TISSIUM, she attended the Stanford Biodesign Fellowship and worked for three years as an independent consultant in strategic marketing for a variety of medical device companies both large and small. She started her career as a Senior R&D Engineer and Project Manager for CareFusion (now Becton Dickinson). Ms DeVries also teaches classes on the biodesign process to aid companies in idea generation for new product development.

Camille Legros is Head of Formulation at TISSIUM, where she leads the formulation activities related to the company's drug-device programmes. Prior to TISSIUM, she worked at Saint Gobain as a Research Engineer, where she led and co-ordinated research projects for different business units, within a research group specialising in polymers and binders. Dr Legros holds a PhD in polymer chemistry from the University of Bordeaux (France).

DCA

Helping our clients
connect with the future

www.dca-design.com