

Keeping Pace with Increasing Complexity in Pharmaceutical Analytics

Founded in 1995 in response to a growing need for outsourced pharmaceutical stability testing, A&M STABTEST has developed into a broad analytical service provider. In this interview with The International Pharmaceutical Industry Journal, the company looks back at its origins and discusses how increasingly complex drug products, inhalation therapies, new analytical technologies and digitalisation are changing the requirements for pharmaceutical analytics.

Please introduce A&M STABTEST. How was the company founded, and which analytical testing services does the company provide to the pharmaceutical industry today?

The story of A&M STABTEST began with four analytical scientists who studied together at the University of Cologne and later worked in the pharmaceutical industry, gaining first-hand experience of its analytical and regulatory requirements. In the early 1990s, new ICH guidelines and increasing post-authorisation requirements created a growing need for stability testing, while external capacity remained limited. The four scientists recognised this gap and, in 1995, founded A&M STABTEST as one of the first German GMP-certified provider to offer pharmaceutical analytics and stability testing as a strategic outsourcing solution.

GMP has been at the core of the company from the beginning. A&M STABTEST has been GMP-certified since its foundation and is operating in an international regulatory environment since many years, including regular inspections by the EMA, the FDA and other regulatory authorities.

From these beginnings, the company has developed considerably. Today, A&M STABTEST employs nearly 400 people across two sites in Bergheim and Mainz and provides analytical services along the pharmaceutical product lifecycle. Our work ranges from API and excipients testing through process performance qualification (PPQ) to finished pharmaceutical products and combination products. It also includes packaging and drug-device testing, including extractables

and leachables, material characterisation, container closure integrity and functional testing.

Our scientific scope has expanded accordingly. In addition to classical pharmaceutical analytics and stability testing, we provide analytical method development, transfer and validation, quality control and release testing, mass spectrometry, bioassays, biopharmaceutical characterisation and specialised inhalation analytics. We work with classical small molecules as well as biological molecules, complex formulations and new therapeutic approaches.

For us, development is therefore not simply about adding laboratory space or new instruments. It is about continuously building the analytical capabilities and specialist expertise required as pharmaceutical products and regulatory requirements become more complex.

What sets A&M STABTEST apart? How does the company differ from other analytical service providers?

A characteristic of A&M STABTEST is the combination of scientific expertise, flexibility and personal communication. We are large enough to offer a broad analytical portfolio and support complex projects in a regulated pharmaceutical environment. At the same time, we have maintained direct communication structures.

For our customers, this means that they are not simply sending samples to a laboratory and receiving results some weeks later. They communicate directly with the scientists involved in their projects.

This becomes particularly important when something does not work as expected – and in pharmaceutical development, this can always happen. In such situations, you need more than an analytical result. You need people who understand the method and the product and who can discuss possible solutions with you.

Another important aspect is specialist knowledge. Particularly when dealing with unexpected results or working under

time pressure, a good understanding of the customer's regulatory requirements is essential. Many of our employees have been with A&M STABTEST for many years, building extensive knowledge of specific products, analytical methods and their history. This experience allows us to assess unexpected results in the appropriate context and provide the analytical support required.

For us, good service therefore means more than generating GMP-compliant data. We also want to understand why an analysis is needed, which question has to be answered and how the results will be used.

What are the key analytical challenges associated with testing dry powder and metered-dose inhalers, and how do you help customers address them?

Inhalation products are particularly interesting from an analytical point of view because you are not only analysing the formulation, but also the performance of the complete drug-device combination.

For both dry powder inhalers and metered-dose inhalers, parameters such as Aerodynamic Particle Size Distribution (APSD), and Delivered Dose (DD) are essential. It is not sufficient to determine how much active pharmaceutical ingredient is present in the product. You also need to understand how the dose is delivered, which particle sizes are generated and whether this performance is reproducible.

With DPIs, for example, airflow plays an important role because the patient's inspiratory effort contributes to the dispersion of the powder. MDIs have different challenges, particularly regarding consistent aerosol generation and dose delivery. Each inhalation system therefore has to be understood and tested according to its specific characteristics.

The analytical procedures themselves are also demanding. Cascade impaction requires specialised equipment, several analytical steps, controlled environmental conditions and, most importantly, experienced analysts.

For this reason, we have invested in the necessary instrumentation as well as

dedicated inhalation laboratories with controlled temperature and humidity conditions. However, having the right equipment is only one part of it. You also need people who perform these analyses regularly and understand the critical parameters of the method and the product.

You can buy an instrument quite quickly. Building the necessary experience takes years.

What trends are currently shaping the development of inhalation therapies, and how are they influencing analytical testing requirements?

One interesting development is that inhalation is no longer only associated with classical respiratory indications such as asthma or COPD. The lung is increasingly being considered as a route for more complex therapeutic molecules. We see growing interest in nanoparticle-based formulations, biological molecules and nucleic-acid-based approaches, for example LNP-formulated mRNA and DNA.

From an analytical perspective, this makes the situation much more complex. Classical inhaler performance testing remains essential. We still need to understand Delivered Dose and aerodynamic particle behaviour, but these tests increasingly have to

be combined with advanced characterisation of the formulation and the active substance.

As a result, different analytical areas are coming closer together. Aerosol science may need to be combined with mass spectrometry, particle characterisation, biological assays or other specialised technologies.

At the same time, there is greater focus on the device and packaging components that are in contact with the pharmaceutical formulation. This means that extractables and leachables are becoming increasingly relevant, together with other aspects of packaging and device testing such as material identification and characterisation, container closure integrity and functional testing.

This shows that inhalation analytics is becoming increasingly multidisciplinary. It is no longer only about testing aerosol performance, but about understanding the formulation, the device and their interaction as a complete system.

How does A&M STABTEST ensure it consistently meets the quality expectations of customers and the requirements of global regulatory authorities?

For a pharmaceutical analytical service provider, quality as well as trust and confidence are fundamental. Our customers

rely on our data for regulatory submissions, batch release and other important decisions. They therefore need confidence not only in the results, but also in the processes and people behind them.

Our laboratories operate according to current GMP requirements, applicable regulatory guidelines and customer-specific requirements. We also have many years of experience with regulatory inspections and customer audits, including repeated FDA inspections.

However, compliance alone does not create trust. Customers also expect reliable timelines, transparent communication and scientifically sound investigations when unexpected results occur. This requires experienced scientists who understand the method, the product and its regulatory context. Many of our employees have worked with certain methods and customer products for many years, building specialised knowledge that can be particularly valuable when assessing unusual results.

For us, quality therefore combines regulatory compliance, scientific expertise and reliable processes. Together with open communication, these elements create confidence in our work and the long-term trust required between a pharmaceutical company and its analytical service provider.



How is A&M STABTEST continuing to develop its analytical capabilities?

We grow with our customers. We listen closely to their needs and follow how their products and pipelines are developing.

For us, the question is not just, "Which new instrument should we buy?" The more important question is, "Which analytical problems will our customers have to solve in the coming years?" This is what drives the development of our capabilities.

We are currently strengthening areas such as inhalation analytics, extractables and leachables – including new requirements such as USP <665> – and force measurement, while continuing to expand our capabilities for complex pharmaceutical and biopharmaceutical products.

Scientific exchange is also important for us. We organise technical workshops at our sites, bringing together customers, specialists and industry partners for presentations, demonstrations and informal exchange.

This October, our Mainz workshop will focus on OINDP testing and inhalation analytics, co-hosted by Copley, while the Bergheim workshop will cover advanced protein characterisation, co-hosted by Bio-Techne/R&D Systems.

These are not intended as sales events. They provide an opportunity to discuss technologies, practical applications and real analytical challenges. At the same time, the exchange helps us understand which capabilities our customers may need from us in the future.

What does the future of the company look like?

We want to remain a reliable analytical partner for our customers as their products

and analytical requirements become more complex. Quality control and stability testing will remain important parts of our business, while we continue to evolve with the market and develop areas that require specialised infrastructure and scientific expertise.

Inhalation is one example. As more complex therapeutic modalities are developed for pulmonary and nasal delivery, we can combine established OINDP testing with advanced analytical technologies to address the resulting analytical challenges.

Digitalisation is another important topic. We have started a long-term project that will gradually bring our complete operations into one integrated system. It is not simply about replacing paper with electronic documents, but about connecting processes and data across the company. In a GMP-regulated environment, this transformation has to be carefully planned, validated and implemented step by step.

We are therefore developing A&M STABTEST on several levels at the same time – scientifically, technologically and operationally.

Finally, you came to A&M STABTEST from a different professional background. How does this influence your role in Business Development?

That's right. I'm a trained molecular biologist, and before joining A&M STABTEST I spent 15 years in product sales and the management of service projects in life science research. Moving into pharmaceutical analytics meant entering a new and highly regulated field, but my scientific background and commercial experience provide a useful perspective for my responsibilities at A&M STABTEST.

Business Development at A&M STABTEST is mainly strategic. We analyse developments

in the pharmaceutical market, follow new technologies and therapeutic trends, monitor the competitive environment and identify areas where A&M STABTEST should further develop its analytical portfolio. Another important part of our role is positioning the company in the market and representing A&M STABTEST within regional and wider life science and pharmaceutical networks.

For me, this combination makes pharmaceutical analytics an exciting market to work in. I enjoy the exchange and collaboration with our customers and industry partners, and I look forward to the new challenges and opportunities the coming years will bring.

UPCOMING WORKSHOPS

A&M STABTEST Technical Workshops 2026

07+08 October, Mainz: **OINDP Testing & Inhalation Analytics** – co-hosted by Copley

Further information and registration:

<https://events.am-labor.de/mz/workshop/07-08.10.26>

15 October, Bergheim: **Advanced Protein Characterisation** – co-hosted by Bio-Techne/R&D Systems

Further information and registration:

<https://engage.bio-techne.com/amstabtest>



**Dr. Regina
Ohmer**

Dr. Regina Ohmer joined A&M STABTEST's Business Development team in 2025, following 15 years in the life science industry, including positions at Tebubio and Singleron. Her experience covers customer-focused business development, project management and marketing, and she represents A&M STABTEST in regional and international industry networks. A trained Biological Technical Assistant, she holds a PhD in Molecular Genetics from the University of Cologne.



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Why Is the Nasal Route Redefining Systemic and CNS Drug Delivery?

Converging Trends Driving Changes in Nasal Route Medicines

Until about ten years ago nasal drug delivery was primarily associated with the treatment of local conditions such as allergic rhinitis, sinusitis, and nasal congestion. Since then, advances in pharmaceutical sciences, formulation technologies, device engineering, and patient-centric healthcare are redefining therapeutic opportunities in intranasal drug delivery.

A growing number of prescription systemic-acting drugs originally administered in injectable forms have been successfully repurposed and achieved market approval in metered-dose nasal sprays. Innovative clinical stage pharmaceutical companies are focussing on nasal systemic drug delivery as an efficient route of administration for therapies requiring rapid absorption, ease of use, and improved patient experience. By targeting the highly vascularised nasal mucosa, drugs can enter systemic circulation quickly while bypassing gastrointestinal degradation and first-pass hepatic metabolism, offering a compelling alternative to systemic delivery via oral and injectable route. Further advances in nasal delivery are being driven by efforts to target drug delivery to the olfactory zone as the approach underpinning direct nose-to-brain uptake via the olfactory nerve and epithelial pathways. These exploratory drug transportation pathways may enable the development of clinically effective, and more patient-friendly therapies compared with invasive injections.

At Nemera, we see this evolution being driven by several converging trends: the need for non-invasive treatment options, increasing demand for self-administration, and the shift toward healthcare solutions that can be delivered outside traditional clinical settings. This momentum is reflected in market forecasts, with leading intranasal therapies expected to grow at a compound annual growth rate (CAGR) of 14.7% between 2025 and 2030.¹

New Therapeutic Frontiers for Nasal Systemic Drug Delivery

What was once a route dedicated to local

treatments is expanding across multiple therapeutic areas where speed, convenience, and accessibility are critical.

Emergency and Rescue Medicines

Emergency care remains one of the most established applications for nasal systemic drug delivery. Systemic-acting compounds such as naloxone and nalmefene for opioid overdose reversal; epinephrine for acute epileptic seizures and zavegepant and sumatriptan for migraine rescue, have demonstrated the effectiveness of nasal administration in emergency and rescue situations.

The evolution of the nasal naloxone market provides interesting insights into realistic future opportunities in intranasal systemic-acting drug development.

The FDA's approval of Narcan® (naloxone hydrochloride) nasal spray for over-the-counter (OTC) use in March 2023 marked a significant public health milestone. Driven by the urgent need to address the escalating opioid overdose crisis in the United States, where more than 100,000 overdose deaths have been reported annually, largely linked to synthetic opioids such as fentanyl, the decision aimed to expand access to a life-saving treatment capable of rapidly reversing opioid overdoses.² A key factor supporting both the FDA's decision and the subsequent growth of the nasal naloxone market was the inherent usability of the drug-device combination product.

The ready-to-use single dose nasal spray requires no pre-assembly, can be administered quickly without specialised training, and is suitable for use by family members, caregivers, first responders, and bystanders. Based on robust evidence demonstrating the safety of naloxone and the ease with which consumers can correctly use the nasal spray device without healthcare professional supervision, the FDA concluded that OTC availability was appropriate. This combination of clinical effectiveness, accessibility, and user-friendly device design has reinforced the nasal route as a compelling platform for emergency interventions.

Beyond its immediate public health impact, the OTC switch has provided strong

regulatory validation for nasal drug delivery as a route capable of accommodating self-administration in acute critical care situations. The approval has reinforced industry confidence in nasal technologies, encouraging further investment and development across a broader range of therapeutic areas where improved accessibility, emergency intervention, or patient self-management can deliver meaningful healthcare benefits.

Metabolic and Cardiovascular Disorders

For the treatment of severe hypoglycaemia, nasal glucagon was developed primarily to solve a practical problem: injectable glucagon is highly effective pharmacologically, but in a real-life emergency it is often difficult for caregivers to prepare and administer correctly. Clinical studies have shown that nasal glucagon provides comparable glucose recovery while being substantially easier to use.

More recently, the approval of etripamil as an on-demand rescue treatment of Paroxysmal Supraventricular Tachycardia (PSVT) enables patients to self-administer at symptom onset to terminate an episode before requiring emergency intervention and intravenous therapy.

These examples illustrate the potential of the nasal route to create therapeutic value in cardiovascular disease management, enabling patients to manage acute episodes independently and safely, reducing reliance on hospital interventions and supporting the broader trend toward decentralised care.

Neurological and Mental Health Care

The growing burden of mental health disorders, combined with the need for rapid therapeutic intervention, is driving interest in intranasal approaches for central nervous system (CNS)-acting therapies. Among the most notable examples is esketamine nasal spray, approved for treatment-resistant depression and major depressive disorder with acute suicidal ideation or behaviour. Intranasal, esketamine has been shown to provide rapid systemic absorption resulting in clinical benefits and is therefore a viable alternative to traditional oral antidepressant therapies, which may require several weeks to achieve full therapeutic effect.

Beyond depression, pharmaceutical companies are actively exploring intranasal approaches for anxiety disorders, post-traumatic stress disorder (PTSD), schizophrenia, and other neuropsychiatric conditions where rapid symptom control, improved patient adherence, or enhanced CNS exposure may offer clinical benefits. As innovation in formulation science and device technologies continues, mental health care is expected to remain a key area of growth for nasal systemic drug delivery.

Central Nervous System and Brain Diseases

Nose-to-brain delivery continues to attract interest as a non-invasive strategy for transporting therapeutics to the CNS and the brain while potentially circumventing the blood-brain barrier and avoiding undesirable systemic exposure. The therapeutic scope encompasses chronic neurodegenerative conditions, particularly Alzheimer's and Parkinson's diseases and brain tissue damage and primary or metastatic brain cancers.

Therapeutic compounds under investigation range from conventional small molecules to peptides and proteins, including insulin, growth factors and neuropeptides, as well as antibodies, nucleic-acid-based therapeutics and extracellular vesicle-derived biological materials.

However, successful translation will depend not only on the intrinsic properties of the active substance, such as molecular weight, stability, lipophilicity and surface charge, but also on formulation characteristics, nasal anatomy, and delivery-device performance. This is driving research in advanced formulations designed to protect sensitive active ingredients, increase residence time at the nasal mucosa and facilitate transport towards or across the nose-brain interface. Examples include mucoadhesive and thermo-responsive gels, liposomes, polymeric nanoparticles, nanostructured lipid carriers and lipid nanoparticles. Exosomes and other extracellular vesicles are also emerging as biologically derived carriers with potential applications in CNS and brain delivery.

As innovation in pharmaceutical sciences and device design advance in parallel, the N2B route may unlock new therapeutic possibilities for a significant number of high interest compounds that cannot cross the blood-brain barrier.

An Attractive and Fast-Growing Market

Several indicators highlight the growing commercial opportunity for nasal systemic drug delivery:

- Leading intranasal therapies are forecast to grow at a compound annual growth

rate (CAGR) of 14.7% between 2025 and 2030, reflecting sustained investment across both established and emerging therapeutic areas.¹

- The global epinephrine market is projected to exceed \$6 billion by 2033, supported by growing interest in needle-free treatment options and the emergence of novel intranasal alternatives to traditional autoinjectors.³
- The successful commercialisation of products such as Narcan® (naloxone), Baqsimi® (glucagon), Spravato® (esketamine) and Zavzpret® (zavegepant) confirms the ability of nasal delivery technologies to support diverse therapeutic applications, ranging from emergency interventions to chronic disease management.

Together, these trends indicate that nasal delivery is evolving from a niche administration route into a strategically important segment of the drug delivery market.

Device Innovation: Enabling the Next Generation of Nasal Systemic Therapies

As nasal delivery expands into new therapeutic frontiers, successful products increasingly rely on delivery systems that combine performance, ease of use, and development flexibility. Nemer's portfolio of nasal platforms, including UniSpray (Figure 1), DuoSpray (Figure 2) and Guided Stream Technology (Figure 3) have been developed to address the evolving needs of systemic, CNS, and nose-to-brain therapies, providing pharmaceutical companies with scalable, patient-centric solutions that support differentiated products across both established and emerging therapeutic areas.

UniSpray: A Unit-Dose Platform for Emergency and Rescue Therapies

UniSpray is a ready-to-use, primeless nasal device designed to deliver a single metered liquid dose of 100 µL through one-handed actuation and in 360° device orientations. After actuation, the plunger is secured in its final position, providing a visible indication that the device has been used, preventing inadvertent reuse and limiting post-use disassembly (Figure 1). It is compliant with the FDA's strict reliability specifications for rescue and emergency medicines.

UniSpray is strategically positioned as a robust platform for both generic and over-the-counter (OTC) naloxone nasal sprays. It has been evaluated against the reference

Life-saving, emergency & crisis application.



KEY POINTS

- **Single metered dose** of 100 µL
- **One-handed activation** & 360° handling
- Compliant with **reliability** criteria for emergency use applications
- Clear activation **confirmation after use**
- **Proven bioequivalence** versus key reference products

Figure 1: UniSpray IPI2



KEY POINTS

- **Two metered doses of 100 μ L (200 μ L total)**
- **Visual dose indicator**
- **One-handed activation & 360° handling**
- **Compatible with industry-standard filling processes**
- **Supports in vitro bioequivalence strategies**

Figure 2: DuoSpray

product Narcan® through a comprehensive test programme including usability, threshold and interchangeability assessments. These studies demonstrated that users can operate the device safely, reliably and without training, supporting the demands of real-world overdose situations. Importantly, the FDA-reviewed threshold analysis concluded that the identified design differences between UniSpray and the reference product did not affect critical user interactions, dose delivery, activation or overall performance. Furthermore, the subsequent interchangeability assessment confirmed that individuals familiar with Narcan® could transition to UniSpray without additional training. Based on these findings, the FDA determined that no comparative human factors study was necessary, reinforcing UniSpray's suitability as a regulatory-ready platform that can help accelerate the development of affordable generic and OTC naloxone products.

Leveraging Nemera's proven experience in emergency and rescue therapies, this is a regulatory-ready platform supported by bioequivalence data generated in generic development programmes for epinephrine, nalmeferine and zavegepant, helping accelerate development timelines and reduce programme risk.

DuoSpray: Precision for Acute and Rescue Therapies

For therapies requiring accurate bidose administration, DuoSpray provides a ready-to-use solution featuring:

- Two metered sprays of 100 μ L each
- No priming required before use
- User-friendly administration in time-critical situations

These characteristics make DuoSpray particularly well suited for acute and rescue applications, including cardiovascular and neurological indications.

Designed to deliver two sequential doses from a single device, DuoSpray supports treatment regimens that may require dose repetition while maintaining a simple and intuitive administration process. The compact, ready-to-use format eliminates preparation steps and enables rapid treatment initiation when speed and ease of use are essential.

The platform combines patient convenience with dosing flexibility, offering pharmaceutical developers a solution adapted to therapies where a second administration may be required to achieve the desired clinical outcome. Its ergonomic design supports use

by patients and caregivers across a range of care settings, from home-based treatment to healthcare environments.

Compatible with established primary container formats and conventional filling processes, DuoSpray facilitates integration into existing pharmaceutical development and manufacturing pathways. This compatibility can help streamline product development while reducing technical complexity during scale-up and commercialisation.

Guided Stream Technology: Designed for Nose-to-Brain Delivery

Realising the clinical potential of CNS and brain-acting therapeutics requires a non-invasive device capable of depositing a defined liquid volume reproducibly in the olfactory region, a small and anatomically remote area located towards the back of the nasal cavity. Conventional atomised nasal sprays were developed primarily for local or systemic delivery and typically deposit most of the emitted dose in the anterior and inferior nasal passages, with reported olfactory deposition generally below 5%.

Nemera is closing this performance gap with its Guided Stream Technology (GST), which combines an established nasal pump with a proprietary nozzle that generates a narrow, directionally stable liquid stream rather than a dispersed atomised plume. The stream is designed to travel up the septal surface into the olfactory cleft. In an anatomically averaged human nasal cast (Figure 4), GST can deliver over 90% of the administered formulation to the defined olfactory region under controlled *in vitro* conditions.⁶ Formulation deposition performance is maintained across a practical range of device orientations, and the impaction force is comparable with marketed pressurised nasal saline products.^{4,5} Collectively, these findings establish GST as a clinically viable, non-invasive platform ready to progress into R&D and human studies to further knowledge in this field.

Conclusion

Nasal systemic drug delivery is evolving into a major growth segment of the pharmaceutical industry, driven by strong clinical and commercial momentum across emergency and rescue medicines, metabolic and cardiovascular disorders, mental health, and CNS-targeted therapies. As pharmaceutical innovators increasingly seek rapid, non-invasive, and patient-friendly treatment options, device performance and usability are becoming critical determinants of success.



KEY POINTS

- **High olfactory deposition** for targeted CNS delivery
- **Directionally stable liquid stream** technology
- **Robust performance** in simulated clinical settings
- Ready to support **next-generation CNS therapeutics**

Figure 3: Guided Stream Technology

Through platforms such as UniSpray, DuoSpray, and Guided Stream Technology, Nemera is enabling the next generation of nasal therapies by combining robust delivery performance, regulatory readiness, and patient-centric design to support improved treatment access, adherence, and outcomes.

Mentions: BAQSIMI® is a registered trademark of Amphastar Pharmaceuticals Inc. NARCAN® is a registered trademark of Emergent Operations Ltd. SPRAVATO® is a registered trademark of Johnson & Johnson. ZAVZPRET™ is a registered trademark of Pfizer Ireland Pharmaceuticals.



Figure 4 – Nemera CUBO nasal cast showing delivery of a coloured liquid formulation to the representative olfactory zone using the GST device with an automatic actuation, in a controlled experimental setting

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When the Ground Shifts, So Must the Materials

Why converging regulation, sustainability and biologics are rewriting the specification for pharmaceutical materials – and why no company will solve it alone

The pharmaceutical industry is experiencing not one disruption but several at once. PFAS restriction, the propellant transition, expiring device patents and the relentless rise of biologics are colliding – and each is quietly asking the same question of the components that touch our medicines. The answer will not come from a single supplier, but from an ecosystem willing to innovate together.

Walk the halls of CPHI or the Drug Delivery to the Lungs (DDL) conference this autumn and one theme follows you from stand to stand: change. For two decades the materials in our inhalers, injectors, vials and filling lines were treated as settled science. That stability is ending. A cluster of regulatory, environmental and clinical pressures is arriving at once, and beneath every one lies the same question: is the material of construction still fit for what we now ask of it?

The honest answer is rarely “exotic materials everywhere.” For most components, metals, elastomers and commodity plastics remain perfectly adequate, and high-performance polymers have historically been reserved for a device’s few genuinely demanding corners – the high-pressure dosing chamber of a soft mist inhaler being the classic example. What is changing is that those corners are multiplying. A useful rule of thumb: when three demanding requirements must be met at once – strength, say, with chemical inertness and a tight, stable tolerance – a specialist polymer such as PEEK (polyetheretherketone) begins to earn its place. It is worth holding that test in mind through what follows – asking not only what each pressure breaks, but what might quietly fix it.

PFAS: From the Seal to the Coated Stopper

Fluoropolymers such as PTFE and PVDF are everywhere in pharmaceutical operations – in valve seats, seals, gaskets and O-rings on filling lines, in non-stick coatings, and, critically, in



Figure 1: Inhalers, injectors and line components – the materials of construction now under simultaneous regulatory, clinical and environmental pressure.

the spray-coated stoppers and plungers that protect injectable biologics. As PFAS restriction tightens across Europe, forward-looking teams are mapping where those chemistries sit in their bill of materials. Substitution is not uniform: where PTFE is chosen for its lubricity and non-stick behaviour, it is hard to match without real development work. But where a fluoropolymer is doing a sealing or chemical-resistance job, credible non-fluorinated options exist. PEEK, for example, is used for seals, valves and connectors across temperature extremes – from cryogenic handling to high-temperature aseptic processing – and its very low leachables suit it wherever purity in contact with the drug matters most. The lesson: a bill of materials can be unpicked function by function, not all at once.

The Propellant Transition

Greenhouse gas emissions from the pressurised metered-dose inhalers (pMDIs) segment account for a significant proportion of the carbon emissions from the inhalers devices (ref – Asthma and Lung UK. How inhalers affect the environment. Available at: <https://www.asthmaandlung.org.uk/conditions/asthma/how-inhalers-affect-environment>); however, for 30% of patients, it is not possible to replace them with other inhalers (source – IPI Issue 3 of Volume 17 from Autumn 2025). With the Kigali Amendment entered in force in 2019, the segment is undergoing its second most significant transition towards

sustainability since the Montreal Protocol in the 1980s, moving to low-global-warming-potential propellants such as HFO-1234ze(E) and HFA-152a.¹ Each differs from the incumbents in density, vapour pressure and solvating power, altering spray force, valve behaviour and – crucially – the extractables and leachables profile of every polymer and elastomer it touches.² In short, changing the propellant can silently change the requirements of the valve, the seal and the canister lining. Here the material, not the propellant, becomes the variable worth changing: a component that stays inert against a more aggressive chemistry, and sheds few leachables of its own, absorbs uncertainty that would otherwise land on the valve and seal. It is one reason PEEK is increasingly discussed for canister linings, valve components and coatings that must hold up against an unfamiliar propellant.

Patent Cliffs and the Pull Toward Precision

As originator patents lapse, the differentiated engineering migrates from the molecule to the device – and to the materials that make it work. Soft mist inhalers are a case in point: by using a mechanical spring rather than a propellant, they sidestep the propellant debate while improving lung deposition, but that benefit is bought with engineering. The dosing components must withstand pressures of the order of hundreds of bar, hold micron-level tolerances, and remain inert in direct contact with the formulation.



This is a corner where high-performance polymers already have a quiet track record: the dosing components of a class-defining soft mist inhaler were among the first places PEEK was adopted, because it could hold those tolerances under pressure, resist wear across thousands of actuations, and replace an assembly of small machined metal parts with one consolidated moulded component – taking out cost, weight and machining steps. As precision devices proliferate, that experience becomes more relevant, not less.

The Biologics Effect on Injectors

Nowhere is the pressure more visceral than in injectable delivery. The biologics boom – monoclonal antibodies, bispecifics and GLP-1 therapies – is pushing self-injection well beyond its comfort zone. Where autoinjectors once delivered up to 1 mL of a low-viscosity solution, developers now target 2.0–2.25 mL of formulations reaching 50 centipoise or more.³ Higher volume and viscosity mean one thing mechanically: more force, applied for longer, through finer needles. Device engineers describe conventional drive springs as reaching their practical limits, prompting ultra-thin-wall cannulae and alternative energy sources.⁴ Two things follow, and both play to a polymer's strengths. First, thin-walled, load-bearing parts need a high strength-to-weight ratio, and properties can be tuned to the task: carbon-fibre-reinforced PEEK adds stiffness and strength without adding bulk, where every millimetre of device real estate is contested. Second, as these devices migrate from clinic to kitchen table, they must stay robust and dimensionally stable through drops, temperature swings and repeated use. Connectivity compounds

it: as devices gain onboard electronics for adherence telemetry and charging, designers want to cut metal content, free up space and manage the electrical interface – another set of simultaneous demands a strong, dimensionally and dielectrically stable polymer can reconcile.

Five Pressures, One Question

Step back and the pattern is unmistakable. The surface questions differ – can our seals and packaging be re-specified? our valves tolerate new chemistries and forces? our components survive higher forces and viscosities? – but underneath lies the same one: are the materials of construction still fit for purpose, and if not, what can safely take their place? The recurring answer: a material chosen to satisfy several demands at once, not to optimise just one.

From Material Supplier to Innovation Partner

By this stage PEEK has surfaced in almost every story, which is rather the point: it is not a universal answer but an unusually versatile tool in the kit, combining strength, chemical resistance, low moisture absorption, dielectric stability and high-temperature performance with injection-moulding to micron tolerances – and, as a non-fluorinated thermoplastic, standing in for certain fluoropolymers in specific sealing and thin-film roles.⁵ What turns those properties into advantage is evidence: a pharmaceutical-contact grade tested against USP Class VI, USP <87> and USP <661> reassures manufacturers that the part will meet end-part compliance testing, reducing risk and, potentially, time to market. The clearest proof is already in patients' hands. In one class-defining soft mist inhaler, a metal dosing chamber that had to withstand roughly 340 bar was re-imagined in PEEK, preserving the performance of metal while remaining safe in direct contact with the formulation⁶ – and, on a life-cycle basis, consolidated moulded parts can carry a markedly lower carbon footprint than the machined metal they replace. The more important shift, though, is one of posture. The old model – specify a material, buy it by the kilogram, move on – sits poorly with an era in which changing one component can trigger extractables and leachables re-testing, stability restarts and regulatory resubmissions across a whole product. What is needed is not simply a supplier but a development partner: one that brings decades of evidence from other regulated sectors and engages early enough to de-risk the choice rather than merely fulfil it.

It Takes an Ecosystem

None of these pressures can be solved by any single link in the chain: the drug owner controls





Figure 4. Controlled innovation: change coordinated across drug owner, device developer, CDMO, packaging and material partners – so the whole ecosystem is enabled to adapt.

the formulation and dossier, the device developer the mechanism, the CDMO scale-up and fill-finish, the suppliers the parts that touch the drug, and the material scientist what a given polymer can, and cannot, be asked to do. Re-specifying a material ripples through all of them at once – attempt it in isolation and you invite delay, failed qualification or supply risk; approach it together and disruption becomes orderly progress. That is the essence of controlled innovation: change introduced deliberately, evidenced thoroughly and coordinated across the value chain, so uncertainty is reduced at every step rather than transferred downstream.

weather system, whose common denominator is the component that touches the medicine. Teams that treat material selection as a strategic, early and collaborative decision – not a late procurement line item – will convert that turbulence into differentiated, compliant and more sustainable products. The industry does not have to face this alone: the materials, the evidence and the manufacturing routes largely exist. Handled deliberately and early, this upheaval becomes the moment the ecosystem chooses to innovate in a controlled way – moving from disruption to genuine confidence about the medicines, and the patients, that depend on getting the materials right.

From Disruption to Confidence

The market is telling us, from several directions, that materials of construction can no longer be an afterthought: PFAS, propellants, patents and biologics are not separate storms but one

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Alternative Drug Delivery Routes: Opportunities, Challenges, and How to Overcome Them

Topical formulations are often preferable compared to oral and injectable options because they reduce systemic side effects, can efficiently target local delivery, eliminate the need for needles, and can improve patient adherence. These formulations, such as creams, gels, lotions, solutions, sprays, dissolvable patches, and foams, present a more complex medicine as the 'vehicle' is an integral part of the drug product. Topical therapies must be optimised to deliver the required clinical efficacy while providing the desired mix of physical properties that will make the product appealing to the patient, otherwise adherence will be hindered. At MedPharm, we define topical drug delivery as the application of a product directly to an epithelial surface – including the skin (intact or wounded), eye (corneal, intravitreal, and transscleral), respiratory tract (pharyngeal, pulmonary, and nasal), as well as oral, rectal, bladder, nail, and vaginal (including cervical) routes. Each of these delivery pathways presents unique biological and formulation challenges, requiring specialised expertise to navigate successfully and bring products to market with confidence.

Opportunities and Unmet Needs of Alternative Delivery Routes

The topical drug delivery market was estimated to be between \$125 billion and \$150 billion in 2024, depending on how 'topicals' are defined by route of administration. The dermal/skin route of delivery represents most of the market (approximately 40%–50%), primarily driven by the increasing prevalence of skin diseases such as acne, psoriasis, rosacea, atopic dermatitis, and fungal concerns. The ophthalmic route represents about 15% of the market, driven by the rising global prevalence of eye diseases such as macular degeneration, diabetic retinopathy, presbyopia, glaucoma, and eye infections. The nasal route of delivery is a growing area representing about 12% of the market driven by new therapies targeting allergic rhinitis, central nervous system (CNS) disorders, migraines, and vaccines. The oral topical market or delivery to the cheeks and gums



represents about 8% of the market which provides opportunities for oral mucositis, ulcers, and gum diseases. Women's health is another growing area, where about 10% of the market accounts for vaginal drug delivery, focusing on applications such as infections, hormonal therapies, and contraception. The remaining 'other' topical delivery represents about 15% of the market such as rectal, urethral and bladder.

This series examines the advancements and emerging opportunities within the topical drug delivery market. The first article will focus on nasal delivery, examining how to design a robust formulation strategy that addresses the unique barriers and clearance mechanisms of this route. We will also discuss how MedPharm's preclinical models can be used strategically to de-risk your development program, accelerate timelines, and boost confidence in your product's success.

Understanding the Route of Delivery and its Unique Barrier

The nose has evolved to prevent foreign material in inhaled air from gaining access to the body. To this end, the nose has a multilayered system of defences. The innermost layer of this defence is comprised of specialised epithelial cells. These cells are tightly connected to each other to form a continuous, living, and responsive barrier between the air and the inside of the body. These cells are coated in a thin layer of constantly replenishing mucus, which serves

to trap foreign particles such as dust, pollen, and microbes. Between the mucus and the cells are microscopic hairlike structures called cilia, which project from the surface of the cell layer. These cilia wave back and forth in a coordinated fashion to move mucus (along with trapped particulates) up and out of the nose for removal from the body, typically either by swallowing or coughing.

Together, this barrier poses some unique formulation challenges. As with any topical formulation, optimising the movement of the active pharmaceutical ingredient (API) from the formulation to the tissue is important. In the nose, however, the epithelium is expected to react to the presence of formulation and attempt to remove it. Unless checked or accounted for, the physical interaction with the epithelium will accelerate mucociliary transport through increased cilia beat frequency and the efflux of water into the nose through the epithelial layer, diluting the mucus and further increasing the speed of clearance.

From a drug delivery perspective, the overall structure of the nose can be divided into five regions of interest. Going from the outside in, the first of these regions is the nasal vestibule or nostrils. This region has a different epithelium, transitioning from the mucosal layer of the interior of the nose to the dry, tough skin of the exterior. Behind that is the nasal cavity, which is characterised by three rigid, shell-shaped structures called turbinates. These serve to filter, warm,

and humidify inhaled air. The convoluted surface of the turbinates serves to slow the air and induce a turbulent flow, depositing any suspended particles or droplets to the mucus layer for removal before they can reach the lungs. Above the nasal cavity is the olfactory cleft. This small structure is densely packed with olfactory receptors and is connected to the olfactory nerve. The fourth region of interest is the nasopharynx, the region at the back of the nose where the respiratory tract temporarily merges with the oesophagus. Finally, the sinuses form a series of interconnected chambers throughout the nose. Although these are not directly air-conducting, they can serve as targets for certain formulation types.

Each of these regions acts as a unique target for delivery. Formulations intended for rapid absorption into the bloodstream should be delivered to the highly vascularised surface area of the turbinates. Formulations delivered to the olfactory bulb can be directly absorbed into the central nervous system, bypassing the blood-brain barrier. Vaccines are most commonly delivered to the nasopharynx. The combination of API, formulation, and delivery device determines where in the nose a formulation will be delivered. Understanding these interactions is a critically important component of any nasal drug delivery technology.

Formulation Strategies

MedPharm's formulation strategy is consistent across the different epithelium, where the formulation and excipients or ingredients are specifically designed around the drug, the site of action and the target product profile to optimise for drug stability and delivery to the site of action. The site of action may be local to the different epithelium (i.e. skin, nasal, eye, etc.) or systemic delivery to the bloodstream (i.e. transdermal/transepithelial). The excipients or ingredients included in the formulation are specific to the unique barrier properties for the different types of epithelia. For example, formulations interfacing with the skin's protective barrier, which has evolved to

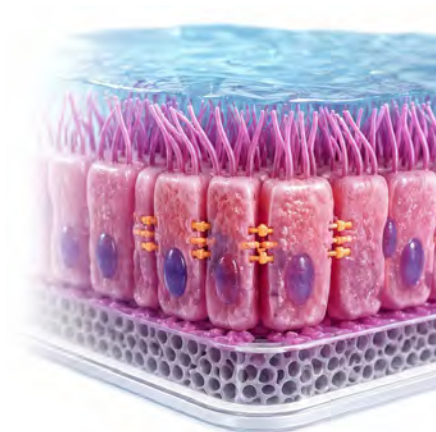
prevent harmful compounds from entering the body, require additional ingredients to aid in delivery.

Topical skin formulations tend to be the most complex (e.g. creams) and often require the most development time. Other routes of delivery, such as nasal, may involve less ingredients but will require a device/drug combination adding a different set of complexities. In all dosage forms, it is preferable to select ingredients already approved for the intended delivery route (e.g. those on the FDA inactive ingredient list) to minimise safety concerns, reduce regulatory hurdles and avoid the need for extensive and costly toxicological work.

Nasal formulation development at MedPharm initially involves preformulation work to determine drug solubility, stability (in excipients suitable for nasal use) and characterisation of the drug substance (e.g., particle size for drugs in suspension). This preformulation work provides vital information to understand degradation pathways/stabilisation strategies, drug loading and the most suitable excipients for use during development of prototype formulations.

Prototype formulations are then developed with close consideration of the target site. The drug solubility data versus required drug loading is used to determine whether a drug in solution or drug in suspension is required. Drug-in-solution systems are simpler, but drug loading may be limited. In contrast, drug-in-suspension formulations are more complex and require control of the drug particle size, both as a drug substance but also in the final product, to ensure effective delivery and to mitigate the risk of irritation in the nose/delivery to the lung, which may afford a higher drug loading. The higher drug loading can enhance drug delivery provided the formulation is designed to improve residence time on the cilia and/or mucous. For both drug-in-solution and suspension formulations it is vital that the device is considered at an early stage and throughout the development to ensure the formulations developed are suitable for use with the device.

The drug, formulation, and device can impact particle size and droplet size. For more targeted delivery to the back of the nose, with the intent to bypass the blood-brain barrier through the olfactory bulb, requires a device that orients the spray and may include carefully designed particles to enable

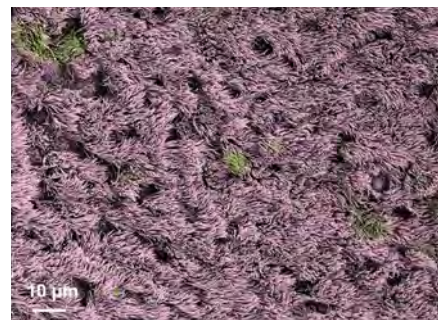
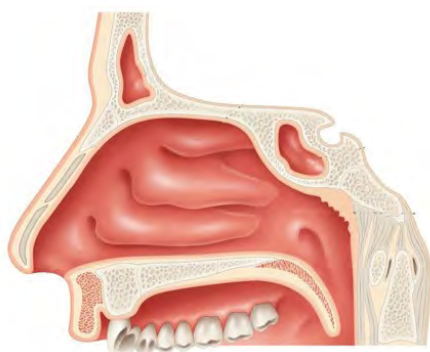


optimal site-specific delivery. Formulation characterisation throughout the development such as particle/droplet size distribution, physical stability, rheology, mucoadhesion assessment, osmolality, cascade impaction, suspension redispersibility and sedimentation, is important to enable selection of the most suitable formulations for short-term stability prior to assessment in preclinical models to enhance the chance of success later in the development pathway.

Use of Preclinical Models for Alternative Delivery Routes

Historically, nasal formulation performance has been assessed using frozen excised tissue from animal cadavers, byproducts of the agricultural industry. Formulation was applied to the apical side (facing the air) of the tissue, and samples were collected from the basolateral side (facing inward) at different timepoints to assess the performance of a given formulation. This model has proven quite successful in the development of nasal drug formulations for decades, and MedPharm has used it with many clients in the development of several drug products.

It has been said that all models are wrong, but some are useful. At MedPharm, we believe that all models are wrong, but some are more useful than others. And there's always room for improvement. This philosophy gave birth to our reconstructed nasal epithelial model (RNE). This model system uses primary human nasal epithelial cells regrown on permeable





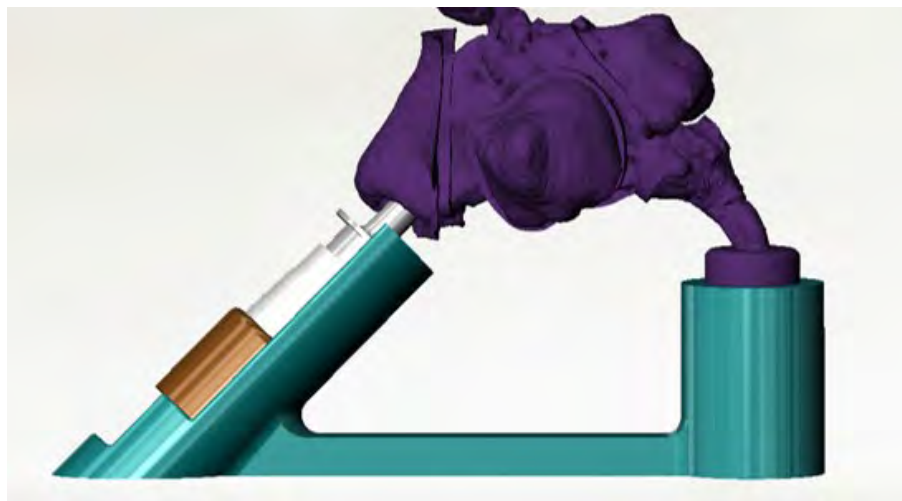
inserts and stimulated to develop into a well-differentiated nasal epithelium. A big part of this stimulation is the culture at an air-liquid interface (ALI). The top side of the tissue is exposed to air, with the bottom side exposed to media. This causes the reconstructed tissue to polarise, forming cilia, producing mucus, and forming tight junctions that make the respiratory barrier unique.

In the past few years, multiple methods of assessing formulation distribution into the nose have been developed in the form of nasal casts that simulate the internal structures of the nose, broken down into the more common regions of interest (e.g., nares, turbinates, olfactory region, and pharynx). Formulations are loaded into devices and sprayed into physical models of the interior of the nose. These models are then disassembled, and drug is extracted from each piece. This can help determine where the drug is being delivered by the device.

Again, these models have proven useful and have shown room for improvement. First, these are made from a single material (e.g., aluminium). Different formulations and APIs

would be expected to adhere, and be extracted from, aluminium at different efficiencies. A low adherence efficiency could allow formulation to transfer from one region to another during disassembly. A low extraction efficiency could affect detection limits, missing places where drug had been delivered. Also, these models are limited to the regions that can be investigated. The pre-ordained regions are useful for development, but there is always room for improvement.

To address these limitations, MedPharm has developed the MedCast™ nasal cast model based on head CT scans. Because the MedCast™ is 3D printed, casts can be quickly made with regions of interest specific to a given delivery strategy. 3D printing also allows for the construction of the MedCast™ from a variety of materials. Part of our method development strategy is to test each of these materials with the formulation to evaluate how well the API adheres to the material, and how efficiently it can be extracted. We can then select the most compatible material for the construction of the MedCast™. This model allows quantitation of the drug from specific regions within the nasal cavity



dependent on your formulation and device combination, therefore giving a closer to 'real world' analysis of the drug product.

How We Can Help You Develop a Product for Alternative Routes of Delivery

MedPharm is an end-to-end CDMO that specialises in topical, transdermal and transepithelial drug product development and commercialisation.



**Charles
Evans**

Charles Evans is Senior Vice President of Pharmaceutical Development at MedPharm, with more than 20 years of experience advancing complex drug products across topical, inhalation, transepithelial, and injectable delivery platforms. He leads global formulation development strategy and has played a key role in the development of MedPharm's proprietary MedSpray® technology.



**Jon
Lenn**

Jon Lenn is Chief Scientific Officer at MedPharm, where he leads global research and development for complex topical and transepithelial drug products. With more than 20 years of pharmaceutical experience, Jon has helped advance innovative biological models, novel test systems, and formulation strategies supporting challenging routes of delivery and product development.



**Jon
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Jon Volmer is Senior Director of Research Biology at MedPharm, with more than 15 years of experience in biotechnology and preclinical drug development. He leads MedPharm's cross-functional Research Biology team, supporting the development of biological models, analytical approaches, and instrumentation for complex topical and transepithelial drug delivery applications.

The Upcoming Inhaled Biologics Therapies: A Data-Driven Analysis of the Inhaled Biologics Clinical Pipeline

In Short

The pipeline is filling up fast. 346 trials registered in 2025 and more than 100 already in 2026, with 127 InhBioX candidates now in Phase II and III.

Infectious disease leads, and vaccines dominate. Infectious disease and COPD are the main indications, and 60% of Covid-19 trials are vaccines.

Synthetic peptides top the molecule list, followed by recombinant proteins and recombinant vector vaccines.

The device gap is the opportunity. Nasal accounts for 57% of the delivery choice because of late phase COVID vaccines, and there is not a single portable inhaler candidate in Phase III: this is a huge opportunity.

Terminations of clinical trial are rarely about the science. Of 68 discontinued trials, 33% stopped for recruitment challenges and 19% for business or strategic reasons. Adverse events, lack of efficacy and regulatory issues accounted for just 10% each.

Biotechs are the creation engines, while Big Pharma has specialised in filing and commercialisation.

The inhaled biologics field is no longer emerging; it has emerged. A structured interrogation of commercial and clinical trial databases identified 346 inhaled biologic trials commencing in 2025 and over 100 already registered in 2026, with 117 candidates in Phase II and III. Biologics now represent 58% of the inhaled clinical pipeline: biologics lead inhaled pipelines. Three molecule classes lead, commanding 40% of the pipeline between them: i. synthetic peptides (16%), ii. recombinant proteins (14%), and iii. recombinant vector vaccines (10%). The pipeline concentrates on two mechanistic strategies: a. receptor agonism and, b. ion-channel activation.

Infectious diseases dominate the indications, with cystic fibrosis, RSV and

idiopathic pulmonary fibrosis, the principal unmet needs. Innovation is, above all, a small-biotech story: 57% of Phase I trials are led by private companies. Analysis of discontinued programmes (N=68) shows that inhaled biologics do not fail on science: recruitment (38%) and regulatory issues (14%) dominate terminations, while adverse events and lack of efficacy together account for only 19%.

Biologic drugs have transformed the treatment of chronic and infectious disease, but their delivery has remained dominated by injection because large molecules do not survive the gastrointestinal tract¹. Two upstream forces are now reshaping this position. First, the science of inhaled biologics, mechanisms, targets and the behaviour of macromolecules in the airway, has been studied intensively. Second, the pace and expertise of biologics manufacturing have accelerated, allowing candidates to be produced at scale. Inhalation and nasal delivery offer a credible alternative route for local delivery to the respiratory epithelium, and for systemic exposure where it is required.

The objective of this work was to quantify the public and searchable inhaled biologics clinical landscape from clinical and commercial databases to establish, on the evidence, what therapies might be coming and when. We looked at volume, molecule classes, targets, indications, sponsors, delivery routes and the specific therapies being advanced.

Methods

For brevity, inhaled biologics are referred to throughout as “InhBioX”. Commercial and clinical trial datasets were extracted from GlobalData’s market and clinical intelligence platforms.² Records were verified against public sources (regulatory registers, company disclosures and the peer-reviewed literature) and checked against drug names and sponsoring organisations.

Candidates were classified by molecule type, biological target, therapy area, development phase, sponsor type and geography, and delivery route. Phase II candidates were mapped against published Phase Transition Success Rates to weigh their probability of advancing, as defined by the

GlobalData database. All figures are drawn from published or publicly verifiable sources, and no proprietary or non-public data are relied upon.

Scale and Shape of the Pipeline

Inhalation at large is highly active: 346 new inhaled trials commenced in 2025, 162 completed, and 88 approvals were recorded. Of these approvals, 80 were Chinese generics and 99% were low-molecular-weight molecular entities. Against this backdrop the key finding is unambiguous: the present is low-molecular-weight entities, and the future is biologics (58% of the inhaled clinical pipeline). The field spans more than 680 therapies across over 350 active organisations.

Development is young and front-loaded. Approximately 100 InhBioX trials were registered in 2026. Across all InhBioX trials registered in 2025 and 2026, 34% are in Phase I and 32% in Phase II.

Above all, innovation is a small-biotech story. Sponsorship reveals a consistent hand-off: 57% of Phase I trials are led by private



#	Molecule type	Programmes	Share
1	Synthetic peptides	19	16%
2	Recombinant proteins	17	14%
3	Recombinant vector vaccines	12	10%
4 =	Live-attenuated vaccines	9	7%
4 =	Monoclonal antibodies	9	7%
6	Gene therapies (mRNA + viral vector)	8	7%
7	Exosomes / extracellular vesicles	6	5%
–	Unclassified / undisclosed	18	15%

Table 1. InhBioX candidates by molecular class (Phase II/III). A further 24 programmes (20%) could not be assigned to a class and are not listed.

companies, whereas 74% of Phase II and III trials are led by institutions. Many of these trials are part of a COVID tail-off, hence the dominance of institutions. Small biotechnology companies and academic groups originate and create these programmes; large pharmaceutical companies buy assets late and act principally as the regulatory and commercial or marketing vehicle that carries them to market.

The United States leads by trial count, but growth is concentrated in Asia-Pacific, and innovation is now genuinely global, exemplified by the outlier NeuroEPO, Cuba's intranasal therapy for Parkinson's disease.

The Therapies Now Advancing

A cohort of named InhBioX candidates is progressing towards the clinic and market (Table 2). They are a heterogeneous group: Rein Therapeutics' LTI-03, a first-in-class Caveolin-1 peptide for idiopathic pulmonary fibrosis; Nano24's EXO-CD24 exosome for ARDS; and two nasal candidates, Blue Lake's PIV5-vectored BLB-101 for COVID-19 and Ethris's IFN- λ mRNA ETH47 for asthma and COPD.



A distinct cystic fibrosis gene-therapy race is under way – ReCode's CFTR mRNA RCT2100, and the AAV programmes SP-101 (Spirovant) and 4D-710 (4DMT). Not all survive: Boehringer Ingelheim's lentiviral BI 3720931 for cystic fibrosis was discontinued in 2026, a reminder that this is a real pipeline with real casualties.

Delivery Routes

57% of Phase II/III candidates use the nasal delivery route, with strong regional variation (Europe 71% nasal; Asia-Pacific leaning pulmonary).

This is highly skewed by COVID vaccines: when all clinical trials are considered, and only trials specifying a route are counted, the nasal route drops to 22.8% and the inhaled route to 24% (unspecified inhaled 17.2%, nebulisers 5%, DPIs 1.8%).

Among Phase III candidates, the identified routes are nebuliser, nasal spray and a single sublingual product; no portable inhaler candidate was identified among the novel biologics.

This is a legacy pattern from COVID trials rather than an optimal or future one. Nebulisers are chosen by default not by design: they are the entry point for Phase I, not

the destination, and are routinely dismissed from Phase II onwards, forcing programmes to repeat and bridge earlier studies at avoidable cost and delay. This is a costly and poor strategy that does great disservice.

As a delivery technology for chronic therapy they belong to the last century, providing neither the formulation stability across manufacturing and storage nor the portability and adherence that these medicines will require at scale. The history of inhaled delivery is one of maturation, with pressurised metered-dose inhalers and nebulisers giving way to dry powder and portable devices as each molecule class stabilised, and there is little reason to expect inhaled biologics to be an exception.

The absence of a portable inhaler in Phase III is therefore best read as a lag that will close, not a permanent feature: once a biologic can be stabilised in a portable format, as synthetic peptides and spray-dried proteins increasingly show, the route follows the molecule – a spray-dried, room-stable oxytocin powder for postpartum haemorrhage being one such example among several.

Inhaled biologics do not, for the most part, fail on the science. Of 68 discontinued programmes only 21 record a specific reason. Among those, recruitment challenges are the single largest cause at 38%, followed by regulatory issues at 14%. Adverse events and lack of efficacy together account for 19%, half the recruitment figure.

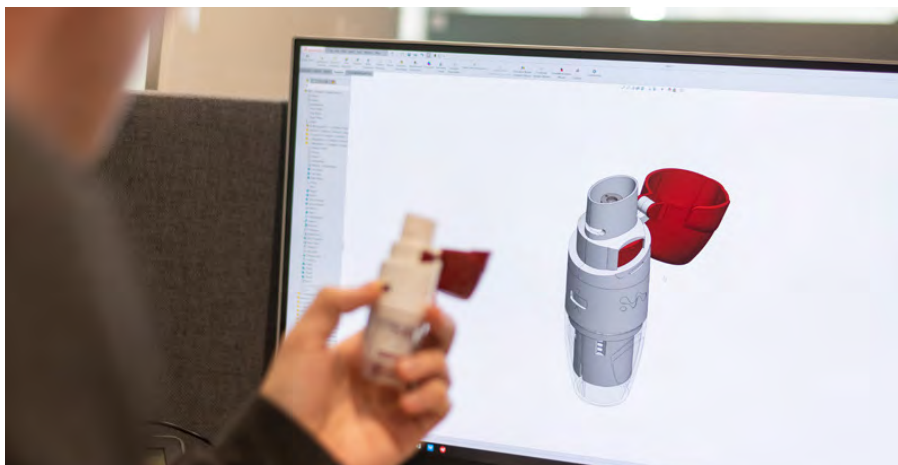
This pattern is consistent with the sponsorship hand-off above: programmes originated by small companies and carried by larger pharmas are exposed to recruitment difficulty and shifting strategic priorities far more than to any failure of the molecule.

Summary & Conclusions

Analysis of clinical and commercial databases shows that the inhaled biologics pipeline

Company / Programme	Molecule	Indication	Route	Phase
Nano24 / EXO-CD24	CD24 exosome	ARDS	Nebuliser	IIb
Blue Lake / BLB-101	PIV5 vector	COVID-19	Intranasal	IIb
Ethris / ETH47	IFN- λ mRNA	Asthma/COPD	Intranasal	IIa
Rein Ther. / LTI-03	Caveolin- 1 peptide	IPF	DPI	II
4DMT / 4D-710	AAV (A101 capsid)	Cystic fibrosis	Nebuliser	II
Spirovant / SP-101	AAV, CFTR transgene	Cystic fibrosis	Nebuliser	I/II
ReCode / RCT2100	CFTR mRNA	Cystic fibrosis	Nebuliser	Ib

Table 2. Selected advanced and upcoming InhBioX candidates



is real, substantial and moving on defined timelines: 346 trials in 2025, over 100 in 2026, and 117 in Phase II/III.

Biologics now represent 58% of the inhaled clinical pipeline: biologics lead inhaled pipelines. The field is led by three molecule classes (synthetic peptides, recombinant proteins and vector vaccines, 40% between them) and concentrates on two target strategies, receptor agonism and ion-channel activation.

Innovation is a small-biotech story: private companies and institutions originate these programmes, while large pharmaceutical companies buy late-stage assets and act as the regulatory and commercial vehicle.

Critically, inhaled biologics do not fail on the science; recruitment and regulatory issues, not efficacy or safety, are the dominant reasons programmes are stopped. A cohort of named therapies is advancing towards patients.

Those late-stage candidates are today tethered to nebulisers, a last-century technology chosen by default rather than by design and, on the evidence of how every previous inhaled class has matured, an interim step rather than the endpoint.

The inhaled biologics therapies are coming: named, dated, and largely on schedule.

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Philippe Rogueda

Philippe co-founded Merxin Ltd in 2015. His expertise spans across multiple facets of the inhalation field, particularly with dry powder and soft mist inhalers. Philippe's passion lies in the development of soft mist inhaler technology, particularly for biologics, which he believes holds immense potential to revolutionise the delivery of inhaled therapies. With over a decade of experience in the inhalation sector, Philippe's deep knowledge and innovative approach to inhalation technologies make him a key figure in advancing medical device development for improved drug delivery systems.

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From Molecule to Market, Faster: Solving Nasal Drug Delivery's Biggest Development Bottlenecks

Formulation, device and manufacturing decisions need to work together, yet they are often made separately, with expertise spread across multiple suppliers. As a result, problems may only become clear once development is well underway: the chosen device may not suit the final formulation, late changes can lead to costly rework, or scale-up risks may not have been addressed early enough. For developers of complex nose-to-brain and systemic therapies delivered nasally, this can mean delays, added cost and regulatory uncertainty.

To address these challenges, Bepak®, along with Upperton, and Resyca®, have brought together their expertise in a new collaboration to provide a more connected approach from early feasibility and formulation development through to device engineering, clinical supply and commercial manufacture for liquid spray, soft mist and dry powder.

We sat down with Bepak CEO Chris Hirst, Upperton CEO Nikki Whitfield, and Resyca CEO Deborah Jones to discuss why this approach is needed and how it could help customers make better decisions earlier, reduce development risk and move promising CNS therapies towards the clinic faster.

What market need led you to form this strategic partnership, and what makes your combined offer different?

Chris Hirst: Interest in nose-to-brain and systemic delivery via the nasal route is growing because of the possibilities it could open up for patients. But these are complex products to develop, and molecule developers need the right support from early formulation work and device selection through to clinical supply and commercial manufacture.

Too often, those decisions are made in silos, with different suppliers responsible for different parts of the programme and no one looking across the whole pathway. That is when mismatches arise, rework causes

delays and scale-up risks are identified too late.

We formed this partnership to address that gap. By bringing formulation development, device selection and optimisation, fill-finish and product supply into one network, we can give customers a clearer, more connected route from molecule to market.

Deborah Jones: The nasal delivery landscape has changed significantly over the past decade. The focus has expanded beyond local conditions such as allergies and sinusitis towards systemic and CNS therapies. Nose-to-brain delivery could create new ways to treat serious conditions, including those where potentially effective medicines struggle to reach the target area.

At the same time, these therapies place much greater demands on the delivery system. For example, reaching specific regions of the nasal cavity requires precise control of deposition, while sensitive molecules such as biologics need to remain stable during delivery. At Resyca, our Ultra Soft Nasal™ platform was developed with these challenges in mind, but the device is only one part of the product.

That's why we formed this partnership which pools our respective expertise in soft

mist technology with formulation expertise, and advanced tools such as deposition modelling to help customers make informed decisions earlier in development and reduce risk in later program delivery. The partnership allows customers to work with a unified team that truly understands the complexity in the entire nasal development customer journey.

Nikki Whitfield: To echo Chris and Deborah, we are also seeing interest extend well beyond traditional local nasal products – into systemic delivery, peptides, biologics and CNS therapies, including those with potential for nose-to-brain delivery. That creates a real formulation challenge, because each molecule brings its own stability, solubility, dose, particle engineering and manufacturability considerations.

For nasal products, early formulation decisions have a major influence on device compatibility, deposition, scalability and ultimately clinical performance, so it is essential that formulation development is not treated in isolation.

By combining Upperton's formulation development and GMP clinical manufacturing expertise with Bepak's liquid and powder device capabilities and Resyca's soft mist technology, we can help customers make

Complex challenges from molecule to market

Turning breakthroughs into next-generation nasal drug-device products means navigating a complex interplay of factors including:

Formulation

- Managing stability, solubility and dose
- Optimising particle engineering and deposition
- Addressing manufacturability from the outset



Device

- Selecting a device compatible with the formulation
- Achieving consistent dose and delivery performance
- Designing for patient usability and real-world use



Anatomy

- Variable nasal anatomy and physiology
- Rapid mucociliary clearance limits nasal residence time
- Targeting the olfactory region or trigeminal nerve for nose-to-brain delivery



Regulation

- Generating the data needed to support regulatory submissions
- Navigating complex and evolving regulatory landscapes
- Managing drug-device combination product requirements



Manufacturing

- Handling complex molecules and sensitive formulations
- Identifying manufacturing complexities before commercialisation
- Maintaining product quality and stability through scale-up



the right decisions earlier and move more efficiently from feasibility through to clinical supply and commercialisation. For developers evaluating nasal delivery for complex and innovative molecules, that joined-up expertise can make a significant difference.

What expertise does each partner bring, and how does it come together as one offer?

Chris Hirst: Bepak has decades of experience manufacturing nasal drug-device combination products, from multi dose aqueous sprays to powder systems. That expertise spans our sites too, combining established nasal spray and powder fill-finish capabilities at Holmes Chapel with novel device development at King's Lynn.

We apply this experience to help partners move through development more efficiently. For example, our modelling and virtual simulation capabilities help us identify potential design issues early, while rapid prototyping allows us to test and refine solutions quickly.

The partnership adds Resyca's soft-mist technology to Bepak's liquid and dry powder portfolio, encompassing both unit dose and multi dose formats. This means we can recommend a platform based on the needs of the molecule, formulation and patient, rather than asking customers to commit to a device before the science is settled.

The real value lies in connecting these choices to the wider development pathway. Customers can access connected support from pre-formulation through to clinical and commercial manufacture, wherever they are in their programme.

Deborah Jones: As Chris says, bringing these capabilities together gives customers a much broader choice of nasal delivery platforms. Resyca adds specialist expertise in soft-mist delivery, aerosol science, device development and regulatory support.

At the heart of our Ultra Soft Nasal™ technology is a proprietary spray nozzle that generates a slow-moving, low-shear aerosol. This can help protect sensitive molecules, including biologics, while supporting targeted deposition within the nasal cavity. The platform is also designed to reduce sensitivity to differences in insertion angle and depth. Combined with its slower, more controlled actuation, this can support more consistent delivery in real-world use.

Our role is to help determine when soft mist is the right approach and tailor its performance to the needs of the product. By bringing deposition science and device performance into the conversation early, we can help customers make better-informed development decisions.

Nikki Whitfield: At Upperton, we support customers by bringing deep expertise in the formulation development of nasal products across the full development pathway, from early pre-clinical feasibility through to late-stage GMP manufacture.

One of the ways we help overcome early obstacles is through our UpperNose™ platform, which enables rapid formulation screening and assessment of nasal product performance at an early stage. This helps customers make better-informed decisions around formulation strategy, device compatibility and manufacturability before significant time and cost have been committed.

A major benefit of this collaboration is that customers do not have to manage multiple disconnected vendors or navigate time-consuming and costly transfers between organisations. Instead, they work with a closely aligned, integrated team from start to finish. That continuity improves decision-making, reduces development risk and ultimately helps accelerate innovative nasal medicines towards the market and into the hands of patients.

From start to finish, what does the process look like for a customer, and what's actually different about it?

Nikki Whitfield: The vision for the collaboration is to offer customers a breadth and depth of knowledge that would be difficult to access through a fragmented development model. By bringing together Upperton's formulation development, analytical, stability and GMP manufacturing expertise with Bepak's device capabilities and Resyca's soft mist technology, we can help ensure each product is developed using scientifically robust approaches and with a clear pathway to the clinic and beyond.

Deborah Jones: Successful CNS nasal therapies need an integrated approach from day one, because the physiology of the nose creates challenges at every stage:

- Spray droplets need to sit within a specific size range to reach the trigeminal

nerve or olfactory region rather than being inhaled

- Rapid mucociliary clearance limits how long a drug stays in contact with nasal surfaces
- Large biological molecules are often unstable once delivered

We start by evaluating the molecule, therapeutic objective and patient population to define a clear target product profile, including which regions of the nasal cavity need to be targeted, so formulation, device performance and usability requirements are aligned from the outset rather than reconciled later.

As programmes move through pre-clinical and clinical development, we generate the performance data needed for regulatory submissions while refining the product for patient use, then shift focus to manufacturability, scale-up and commercial readiness once clinical proof of concept is established.

The benefit for customers is a single team that understands the entire journey from early-stage development through to commercial supply, fewer handovers, fewer gaps for things to fall through, and a faster route to a clinic-ready product.

Chris Hirst: Our goal is to reveal that complexity early, rather than let it surface once a programme is already underway, allowing life-changing CNS-targeted products to have a clearer run to market. With that in mind, we have set out to make our partnership as simple for our customers as possible.

In practice, every customer is assigned a single commercial lead as their touchpoint from early pre-formulation through to scale-up and manufacture. Whichever partner they approach first, they get access to the full network. As such, decisions about target device, scalability, and regulatory and manufacturing requirements are made together and early, not bolted on after the fact. By aligning the formulation and device thinking from day one, we can avoid potential hurdles six months down the line.

What does this actually mean for customers and the wider industry, what's the tangible benefit?

Chris Hirst: In practice, this means that when formulating a nasal therapy, a framework is in place to make sure this is being done with a view toward the target nasal device,



scalability, regulatory and manufacturing requirements, and so on. By engineering our recommendations and process specifically around our customer's specific drug molecule, we are able to improve efficiency and the speed a programme progresses towards the market.

For customers, this translates into faster decisions, because there's no back-and-forth between disconnected suppliers, and reduced risk because the same team that helped shape the formulation is still there at scale-up. It means fewer surprises late in development, less rework, and a faster, more predictable route to a clinic-ready product.

But underneath that, what we're really offering is a partner committed to getting a molecule to patients, not just a supplier for one part of the journey.

Nikki Whitfield: For customers, the ultimate goal of the collaboration is to provide expertise and programme delivery across all of the individual aspects of nasal product development within one integrated project team. A CNS or nose-to-brain therapy does not move through development in a simple linear sequence; formulation, device selection, analytical methods, stability testing, manufacturability, regulatory strategy and clinical

supply all influence one another. Our role is to ensure those workstreams are connected from the outset.

The value of working through this helps customers avoid the silos that can slow programmes down or introduce unnecessary risk. In a fragmented model, a product can move from one vendor to another several times, creating complex technical transfers, potential gaps in product knowledge and, in some cases, the need to repeat work at a new site. That can add time, cost and uncertainty.

By contrast, our collaboration provides a closely aligned team that manages the programme from start to finish. Product knowledge is retained, decisions are made with the full development pathway in mind, and each stage builds on the work that came before it. That integrated approach helps customers move more efficiently from early formulation thinking through to clinical development and ultimately commercialisation.

Deborah Jones: As Nikki says, customers increasingly want integrated solutions that reduce complexity and development risk, rather than having to coordinate multiple suppliers themselves. Through this partnership, customers get access to the Ultra Soft Nasal™ technology, specialist soft mist

device expertise, formulation capability and established regulatory support, alongside manufacturing and commercialisation pathways, with the flexibility to choose whichever delivery technology actually fits their molecule. The aim is a seamless journey that gets therapies to patients faster.



Nikki Whitfield

Nikki, CEO of Upperton, brings 30 years of pharmaceutical and CDMO leadership experience across small molecules and biologics. She has led drug development programmes from early formulation through to late-stage development and pre-launch, overseeing technical strategy, manufacturing, scale-up, regulatory submissions and clinical supply. Her senior leadership roles span biotech, pharma and CDMO organisations.



Chris Hirst

Chris, CEO of Bepak, brings 25 years of experience in the pharmaceutical sector. Previously a member of Recipharm's Executive Committee and Head of its Advanced Delivery Systems business unit, he has led the development and commercialisation of pMDI, DPI and nasal drug delivery technologies, with a strong focus on innovation and sustainability.



Deborah Jones

Deborah Jones, Ph.D., CEO of Resyca, brings more than 20 years of executive leadership experience in life sciences technology. She specialises in commercial growth, international expansion and strategic partnerships, with particular expertise in inhalation and nasal drug development. She has a strong track record of advancing innovative aerosol and spray technologies to enable more patient-focused drug delivery.

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Specialist delivery technologies provided by device partners, including Resyca's innovative soft mist technology

One integrated pathway, from early feasibility to commercial supply

Formulation development

Device screening and optimisation

Device development

Modelling and rapid prototyping

Clinical supply

Commercialisation

Regulatory support

A complex, three-dimensional molecular structure rendered in a light blue color, set against a dark blue background. The structure consists of numerous spheres connected by thin rods, creating a dense, interconnected network.

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LIQUID, POWDER OR SOFT MIST - WE'VE GOT EVERY STEP COVERED

Complex nasal drug development shouldn't have to mean juggling multiple suppliers. Through our collaboration with Upperton, Bespak brings one connected pathway from early feasibility to clinical and commercial supply for your next-generation breakthrough.



Scan to start your
journey from molecule
to market.

Beyond Propellant Replacement: A More Intelligent Development Pathway for Low-GWP pMDIs

The transition to low-global-warming-potential (low-GWP) propellants is one of the most significant changes to pressurised metered dose inhaler (pMDI) development in decades. The environmental driver is clear. The pharmaceutical challenge is considerably more complex.

A pMDI is not simply a drug formulation packaged with a propellant. It is a coupled formulation – container closure – device system in which the propellant contributes directly to metering, atomisation, plume formation, evaporation, and aerodynamic behaviour. Changing one of the fundamental physical components of that system can therefore affect formulation behaviour, device interactions, aerosol generation, dose delivery, regional deposition, and ultimately the evidence required to demonstrate acceptable product performance. The EMA's current low-GWP pMDI guidance reflects that breadth, covering quality, non-clinical, and clinical considerations rather than treating propellant replacement as a narrow formulation change.¹

The development objective is therefore not simply to demonstrate that a reformulated product produces acceptable analytical results. It is to understand whether the aerosol journey remains appropriate from device to patient. That requires a broader set of questions: How does it fly? Where does it land? What arrives? These are connected questions, but they are not answered by the same measurement. That three-part framework sits at the centre of the current Proveris low-GWP scientific strategy.

The low-GWP transition creates an opportunity to reconsider when those questions are asked. Rather than relying heavily on a full, expensive, compendial test package early in development when formulations, valves, actuators, and instructions for use may still be changing, a more efficient strategy is to generate a greater density of rapid, mechanistic, and comparative information first. More resource-intensive testing can then be concentrated on candidates that have already been characterised and understood. This is the principle behind Proveris by Design™ (PbD): generate actionable evidence early, follow the

mechanism, add realism where its required, and confirm the selected product rigorously.

Low-GWP Reformulation Changes a Connected System

The scientific challenge begins with aerosol generation. Following actuation, a metered volume of pressurised formulation passes through the valve and actuator and undergoes rapid pressure reduction, flash evaporation, and atomisation. The aerosol then continues to evolve after leaving the device as droplets or particles interact with surrounding air and volatile components evaporate.

Low-GWP propellants do not have identical thermophysical properties to the currently used HFA-134a. Reviews of HFA-152a and HFO-1234ze(E) have highlighted these differences and their potential consequences for formulation and atomisation.²

Recent experimental studies reinforce the point. Duke and colleagues compared solution pMDIs formulated with HFA-134a, HFA-152a, and HFO-1234ze(E) using APSD, laser diffraction, and high-speed imaging. In the systems studied, HFA-152a produced greater actuator and throat deposition and different plume behaviour, while HFO-1234ze(E) was more similar to HFA-134a in APSD but still showed differences in plume development.³ A subsequent suspension study demonstrated that the presence of suspended drug further modifies the relationship between propellant properties and spray structure, including flash-evaporation behaviour and plume width.⁴

Proveris and collaborators have examined related variables experimentally, including spray characteristics of P-134a and P-152a systems with and without ethanol, and

methods for quantifying evaporation fraction and evaporation rate in HFA-134a and HFA-152a formulations.^{5,6} These studies support the broader development premise that the propellant change can alter the physical processes that generate the aerosol. The Proveris framework treats formulation, device, aerosol, and patient-facing variables as an interconnected system.

The Cost of Understanding Too Late

This problem has a long history in spray and aerosol development. In 2013, Proveris described the “Merry-Go-Round”: repeated cycles of testing, unexpected results, modification, and re-testing when data had not been converted into sufficient product knowledge to direct the next action.⁷

The concept remains relevant because low-GWP pMDI development creates exactly the conditions in which trial-and-error can become expensive. A single propellant change can cascade into uncertainties about formulation, valve, actuator, canister and closure materials, labelled shaking and firing instructions, analytical strategy, deposition behaviour, and the evidence needed for progression.

If a candidate differs from the reference in a compendial result, several explanations may be plausible. The formulation may not redisperse in the same way. Valve delivery may differ. The candidate may be more sensitive to shaking or shake-to-fire delay. There may also be other formulation, device, method, or handling related factors contributing to the observed difference. The result alone does not identify the cause.

This is also where timing becomes economically important. Early development



offers flexibility. Formulation composition, actuator geometry, valve choice, and preparation parameters can still be changed. Later, the same changes can affect stability, scale-up, analytical validation, PK, clinical work, or submission strategy, at greater consequence and cost.

Proveris by Design: More Learning Before More Commitment

Proveris by Design provides a framework for putting that principle into practice. The approach is consistent with Quality by Design thinking: understand the variables; build evidence around the development question with constant analysis; and use the results to guide the next experiment rather than executing a fixed battery of tests regardless of what the data show. Proveris formally describes PbD as a stepwise roadmap for in vitro characterisation of orally inhaled and nasal drug products.^{8,9}

The first step is to understand the product that is being changed or reproduced. For a reference product, that means more than establishing nominal DDU and APSD values. The baseline should include normal batch, device, and shot variability; sensitivity to shaking, delay, and orientation; dose delivery through canister life; aerosol formation and temporal behaviour; and, where relevant, upper-airway or regional deposition. The target is product performance, not meeting a single specification.

The second step is to generate rapid controlled evidence with enough statistical

power to distinguish real differences from noise. This is where more data earlier can be more cost-effective. Rapid screens can investigate multiple formulation and device variables before the programme commits large quantities of product, analyst time, and instrumentation to a full suite of expensive resource-intensive confirmatory methods.

This does not mean “do every possible test early.” It means selecting measurements according to the uncertainty. If the question is whether the device meters consistently, investigate valve delivery and DDU; if the question is whether the aerosol event has changed, interrogate spray pattern, plume geometry, velocity, duration, or evaporation; or if the question is whether the difference remains relevant when the product interacts with a patient, then add breathing, anatomy, or deposition.

Early mechanistic evidence also creates a defensible record of why development decisions were made and can support later root-cause investigation if stability, scale-up or manufacturing introduces a change.

How It Flies

The first scientific layer is how the aerosol is generated and evolves. For low-GWP pMDIs, this is especially important because changing the propellant changes the physical conditions under which atomisation and evaporation occur. “How it flies” includes plume formation, velocity, particle or droplet size, trajectory, duration, and evaporation. These variables are dynamic and interdependent.

Plume-Front Velocity, for example, provides information about how rapidly the aerosol moves away from the actuator. Evaporation measurements depicted help determine how the aerosol changes after emission. Spray Pattern and Plume Geometry provide spatial information about the developing aerosol. There are published methodologies addressing both emitted aerosol velocity and evaporation as additional characterisation variables.^{6,10}

The value is mechanistic. If two products have different deposition behaviour later, understanding how each aerosol was generated can help explain why. Conversely, if mechanistic differences are detected early, the development team can determine whether those differences persist or disappear as the evidence chain progresses.

Where It Lands

After leaving the device, the aerosol interacts with airflow, the mouth and throat, and the branching respiratory tract. At the same time, droplets may continue to evaporate and change size. The combination of velocity, particle or droplet size, trajectory, breathing profile, and anatomy influences where drug is likely to deposit. The Proveris framework makes this relationship explicit: an evolving aerosol is being inhaled into a complex airway, and the two processes together determine deposition.

Regional deposition therefore asks a different question from dose delivery or particle-size characterisation. A product may

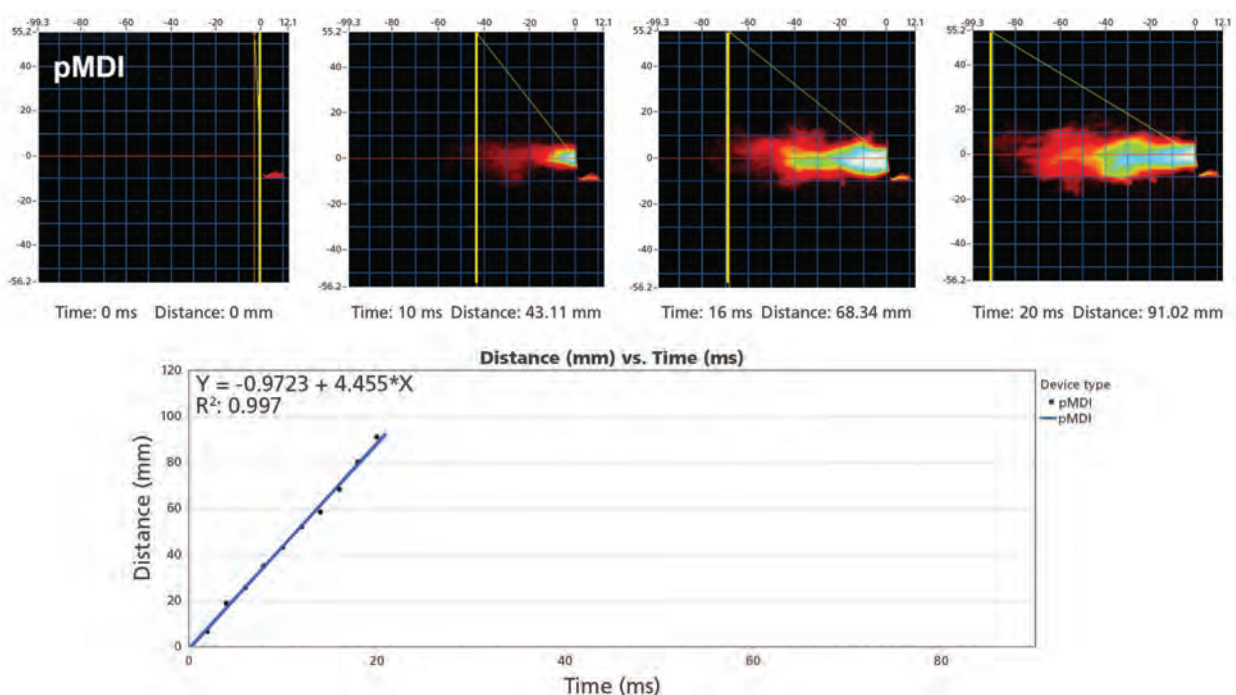


Figure 1: Plume Front Velocity (PFV) images and corresponding distance-versus-time plots.

deliver the expected amount of drug while distributing that dose differently through the respiratory tract under more representative conditions.

Human-relevant deposition models can provide additional context. For example, INVIDA® combines human-relevant oropharyngeal geometry with programmable breathing profiles and regional HPLC quantification to assess deposition across the mouth/throat, tracheal and lung regions. Olsson and colleagues used anatomically correct inlet throats with actual inhalation flow profiles and measured the fraction of drug passing beyond the throat. That ex-throat fraction was shown to predict typical total lung deposition across a range of inhaled products in healthy adults.¹¹

During development, the priority is to understand which formulation, device, administration, and physiological variables influence product performance, and to investigate those relationships while the product can still be changed.

Once those relationships are understood, standardised methods provide the controlled and reproducible framework needed for activities such as release, stability, and routine product control. Human-relevant experiments are therefore most useful during development when they help explain an observed difference or determine whether it is likely to matter under representative use conditions.

The principle is simple: add realism when it can affect the decision.

What Arrives

Once drug has reached a region of the respiratory tract, a further question remains: what has actually arrived, and in what state is it available to continue toward its intended local or systemic action? How is it absorbed?

For conventional small-molecule pMDIs, dissolution may be one important part of this question. For more complex products,

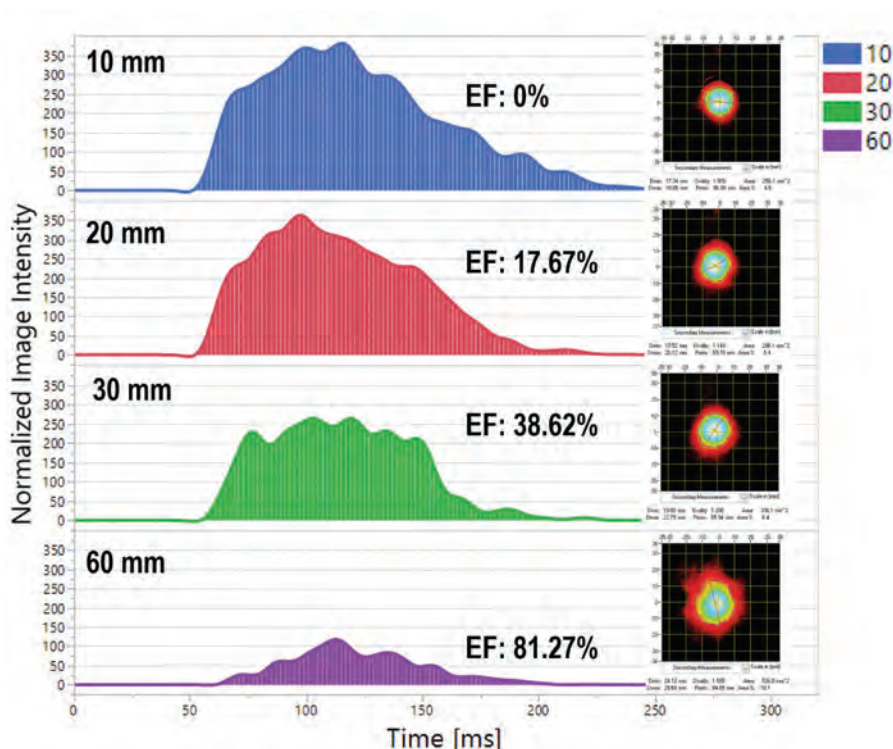
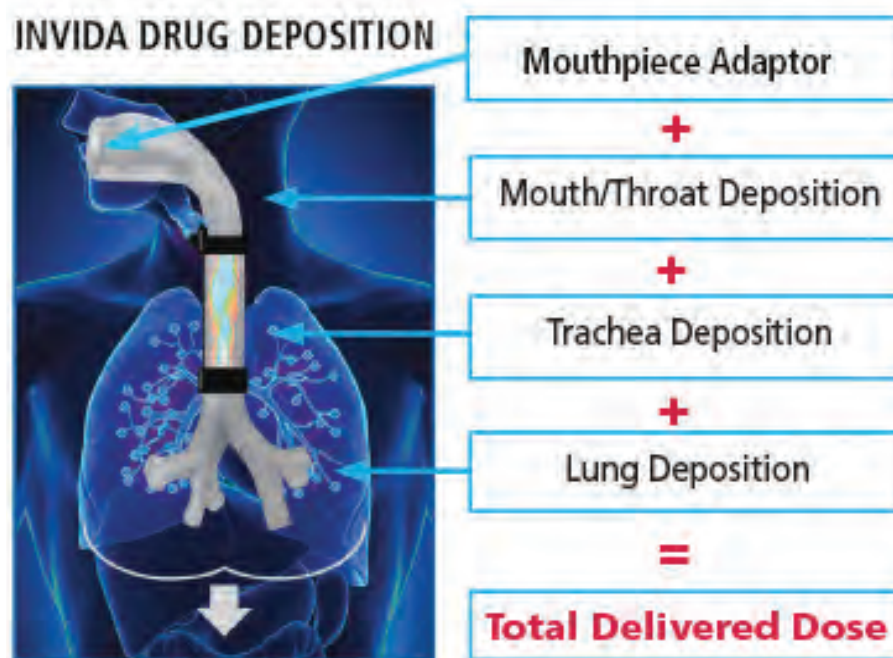
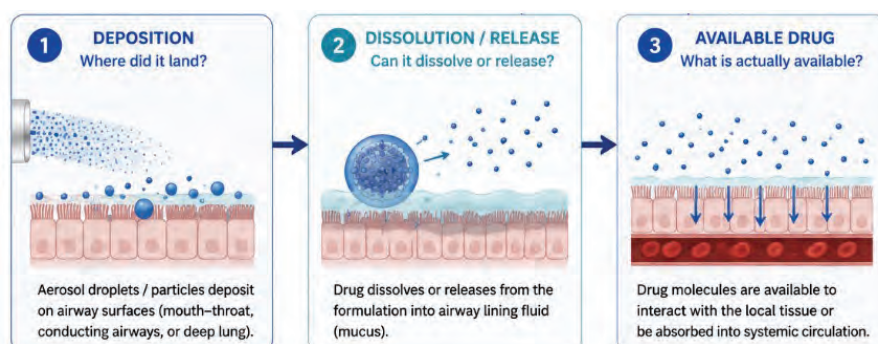


Figure 2: Evaporation measurements determined from Spray Pattern images taken at specified distances from a pMDI mouthpiece.



Schematic of Proveris Scientific's INVADA platform.



the relevant evidence may eventually include molecular integrity, aggregation state, payload association, or other measures of functional integrity. The framework therefore extends “where it lands” into “what arrives”: post-deposition behaviour, dissolution, integrity, and availability.

For low-GWP pMDIs, this does not mean every programme requires an extensive post-deposition package. It means that

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the evidence strategy should be capable of following the drug further when deposition alone does not resolve the uncertainty.

Compendial Testing as Confirmation, Not Discovery

Established compendial and regulatory tests remain essential. DDU, APSD, and other required measurements provide controlled, standardised, and widely accepted evidence of product quality and performance. A full compendial package can be time, material, and analytically intensive. During early screening, when multiple formulations and device configurations remain in play, running the entire package repeatedly may be less efficient, and more costly, than first using faster measurements to establish which candidates are robust and which mechanisms need investigation.

PbD therefore places the larger compendial and confirmatory package later in the learning sequence, after formulation, device, and aerosol behaviour have been characterised and after human-relevant questions have been addressed. The proposed development strategy is therefore formulation screening, device-function screening, aerosol-formation screening, human-relevant evaluation, and finally compendial/confirmatory evidence. The objective is to avoid discovering fundamental product behaviour for the first time when the programme has already reached its most resource-intensive and expensive tests.

From the Laboratory Question to the Development Decision

The same philosophy explains the evolution of Proveris Laboratories. The laboratory was built because customers repeatedly asked for help beyond operating an instrument: method development, troubleshooting, reference-product characterisation, workflow automation, and interpretation of unexpected results.



Those questions often cross analytical boundaries. A problem first observed in a compendial result may originate in formulation, device function, actuation, aerosol formation, or deposition. A laboratory designed around the question rather than the test is therefore able to move through the evidence chain until the uncertainty is resolved. The output is not simply more data. It is a better development decision.

Low-GWP pMDIs as a Model for Better Development Science

The low-GWP transition is an environmental necessity, but it also exposes a broader weakness in conventional development thinking. Endpoint results can provide erroneous reassurance before the system that produced them is fully understood. The transition challenges the industry to preserve patient-facing performance while changing a fundamental component of the aerosol-generation process. That cannot be addressed efficiently by asking one test to answer every question.

A more rational pathway is to understand the reference product, generate high-information evidence early, manage formulation and device variables as a system, follow the aerosol as it is generated and evolves, determine where it lands, investigate what arrives, and then enter compendial and confirmatory testing with a product that is already substantially better understood.

This is the core proposition of Proveris by Design. More data earlier does not mean more indiscriminate testing. It means generating mechanistically useful evidence while change is still possible, escalating complexity when the evidence justifies it, and using confirmatory methods when they provide greatest value. The environmental objective and the patient objective must succeed together. The new propellant must reduce climate impact, but the product must still deliver the medicine appropriately.

The most effective way to de-risk that transition is to understand earlier, connect the evidence across the whole aerosol journey, and make each experiment earn its place in the next development decision.

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Joanne Mather

Joanne Mather is Senior Director of Marketing at Proveris Scientific, she focuses on translating complex scientific and regulatory challenges into practical solutions that help companies in the OINDP space accelerate development and ensure product quality. With a strong background in analytical science and a customer-centric approach, she is dedicated to supporting the industry in bringing effective and reliable aerosolised drug products to market.



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A Pioneer's Path to Transition: How HFO-1234ze(E) Is Shaping the Future of Sustainable Pressurised Metered Dose Inhalers

The pharmaceutical respiratory inhalation sector is entering its second major propellant transition. In response to the Montreal Protocol requirements, the first transition moved pressurised metered-dose inhalers (pMDIs) away from ozone-depleting chlorofluorocarbons (CFCs such as CFC-11) to hydrofluoroalkanes (HFAs), principally HFA-134a and HFA-227ea. These HFAs eliminated the ozone-depletion concern but unfortunately retained high global warming potential (GWP).

Climate change regulation is now driving a further transition. Following the Montreal Protocol, the Kyoto Protocol and the related Kigali Amendment established a global hydrofluorocarbon phasedown trajectory, implemented regionally in the EU through Regulation (EU) 2024/573, which removed the previous quota exemption for HFA-based pMDIs, and in the United States through the American Innovation and Manufacturing (AIM) Act and its implementing allowance programme at 40 CFR Part 84.^{1,2,3} For pMDIs, the challenge is to decarbonise without compromising patient access, inhaler performance, or therapeutic continuity.

This review summarises HFO-1234ze(E) as a successfully approved next-generation propellant, assessing its physical properties, formulation compatibility, toxicological profile, clinical evidence, and regulatory readiness.

Technical and Formulation Considerations

Medical Propellant HFO-1234ze(E), GMP is a hydrofluoroolefin propellant for pMDIs, reducing propellant greenhouse gas emissions by up to 99.9% relative to the incumbent HFAs.^{4,5} Its liquid density of 1.17 g/mL is comparable to HFA-134a at 1.22 g/mL so that suspension sedimentation and creaming behaviour carry across the transition without wholesale reformulation, in contrast to the substantially less dense HFA-152a.^{4,5} HFO-1234ze(E) exhibits no vapor flame limits under standard test conditions and is classified non-flammable under EC Testing Method A11, ISO 10156 and the US DOT standard (ASTM E681), and in the ASTM flame projection, ignition distance and enclosed-space ignition tests.⁴ A narrow flammable range can be observed

Physical Property Comparison of Common pMDI Propellants

Property	HFO-1234ze(E)	HFA-134a	HFA-152a
Chemical formula	CF ₃ -CH=CHF	CF ₃ -CFH ₂	CHF ₂ -CH ₃
Molecular weight (g/mol)	114.0	102.0	66.1
Boiling point (°C)	-19.0	-26.1	-24.0
Density at 21.1 °C (g/mL)	1.17	1.22	0.91
Vapour pressure at 21 °C (psia / bar)	64.2 / 4.42	85.8 / 5.92	77.0 / 5.31
Vapour pressure at 54 °C (psia / bar)	161.7 / 11.15	213.4 / 14.71	190.6 / 13.14
Water solubility (ppm)	225	2200	1700
Flame limits in air at 20 °C (vol%)	None	None	3.7-16.9
GWP (100-year ITH, AR6)	1.37	1530	164
Atmospheric lifetime	19 days	14 years	1.6 years
Manufacturing requirements	No ATEX required	No ATEX required	ATEX required

Table 1. Physicochemical, environmental, and manufacturing properties of common pMDI propellants. The data presented in Table 1 are drawn from the supplier's technical data sheet and product literature and the propellant property comparison presented at Respiratory Drug Delivery 2022.^{5,6}

only where temperature is at or above 30 °C, relative humidity at or above 50%, and a high-energy ignition source is present.⁷ The propellant is thermally and hydrolytically stable, showing no breakdown and no effect on metals after two weeks at 200 °C in the presence of water and metals, and remaining within specification after several years of storage in steel cylinders. Compatibility has been demonstrated with aluminium, tin plate and PET-lined canisters and with common valve gasket materials including grades of butyl rubber, Buna and neoprene, with pMDI valve compatibility testing conducted by Aptar Pharma.⁴ Nonetheless, the best approach is to conduct confirmatory testing with the specific container closure system used.

Formulation studies further demonstrate the suitability of HFO-1234ze(E) across both suspension and solution pMDI formulations. Using static multiple light scattering, salbutamol sulphate suspensions in HFO-1234ze(E) were more physically stable than the equivalent HFA-134a suspensions, with lower migration rates (52 versus 64 mm/hour propellant-only, and 40 versus 53 mm/hour at 5% ethanol); ethanol addition reduced both flocculation and sedimentation, with the benefit plateauing above approximately 5% w/w.⁸ In higher drug-load suspension work, ethanol at 2–5% w/w brought mean delivered

dose onto a 180-microgram target with acceptable uniformity and fine particle doses of 89–114 micrograms per actuation, exceeding marketed comparators, while 15% ethanol reduced fine particle dose to 49 micrograms through increased throat deposition.⁹ Solution formulations of beclomethasone dipropionate, formoterol fumarate and glycopyrronium bromide delivered doses at or above their reference listed drugs with dose uniformity meeting USP 601, and reducing actuator orifice diameter to 0.22 mm raised beclomethasone fine particle dose from 44.1 to 80.2 micrograms and fine particle fraction from 48.0 to 83.7% while lowering MMAD and geometric standard deviation; storage at 40 degrees C/75% RH for 12 weeks produced no statistically significant change in delivered dose and little change in aerodynamic particle size distribution.¹⁰

Compatibility extends beyond simple substitution. Budesonide, marketed only as a suspension because of solubility limits in HFA propellants, formed clear solutions in HFO-1234ze(E) at 14–16% w/w ethanol, meeting USP 601 dose uniformity criteria with higher fine particle dose (51.1 versus 40.6 micrograms), higher fine particle fraction (46.5 versus 36.3%) and markedly finer mass median aerodynamic diameter (MMAD) 1.48–1.56 versus 3.75 micrometres than the suspension

reference product.¹¹ Fluticasone propionate, previously the least characterised active in this propellant because of its hydrophobicity and aggregation tendency, was successfully formulated as a suspension at 2% ethanol with either oleic acid or magnesium stearate, delivering 94.9–105.9% of label claim against the reference at 85.4% with acceptable uniformity and comparable aerodynamic performance.¹² Standard excipients including ethanol, oleic acid, magnesium stearate, citric acid and propylene glycol perform as expected in these systems.⁶

Taken together, the combination of near-zero GWP, non-flammability, HFA-134a-like density and demonstrated container closure compatibility, alongside formulation profiles closely comparable to existing HFA-based products supports HFO-1234ze(E) as a technically viable near drop-in replacement for HFA-134a that can often be implemented using similar materials, excipients, device platforms, and manufacturing approaches. Modest cosolvent adjustment and actuator orifice selection are the principal levers for aligning *in vitro* performance, and in the case of poorly HFA-soluble actives, HFO-1234ze(E) offers formulation opportunities that were previously difficult to achieve with conventional HFAs.

Toxicology and Safety Assessment

A comprehensive toxicological programme has been conducted for HFO-1234ze(E), covering repeated-dose toxicity, safety pharmacology, genetic toxicology, carcinogenicity, reproductive and developmental toxicity, and local tolerance.^{13, 14, 15, 16}

Pharmacokinetic investigations showed very limited metabolism (below 1% of the administered dose) and rapid systemic clearance following inhalation exposure, with peak blood concentrations occurring immediately after dosing and declining rapidly thereafter.¹³ Safety pharmacology evaluations demonstrated no adverse effects on cardiovascular, respiratory or central nervous system function in rats or dogs, and a cardiac sensitisation study in dogs was negative.¹⁴

HFO-1234ze(E) was generally well tolerated in repeat-dose inhalation studies of up to 3 months in mice, 6 months in rats, and 9 months in dogs.¹⁴ In repeat-dose rat studies, the propellant exacerbated progressive cardiomyopathy, a known spontaneous background lesion in this species.¹⁵ These effects were observed principally at exposures of approximately 15,000 ppm, did not increase in severity with longer treatment duration, and

were not seen in mice or dogs. The 6-month rat study established a NOAEL of 5,180 ppm (4,280 mg/kg/day).¹⁴

A multigeneration reproductive toxicity study identified deaths and neurological findings in lactating female rats exposed to 19,400 ppm (approximately 23,000 mg/kg/day). These events were confined to the late lactation period and were not observed in males, non-lactating females, or in any other repeat-dose study.¹⁴ The parental toxicity NOEL was 4,820 ppm, while reproductive performance and offspring development were unaffected at all tested exposure levels. Embryo-foetal development studies in rats and rabbits demonstrated no maternal, reproductive, developmental or teratogenic effects.¹⁴

The propellant showed no genotoxic potential across a complete battery of *in vitro* and *in vivo* studies, including bacterial reverse mutation assays, chromosomal aberration assays, micronucleus tests, and unscheduled DNA synthesis assessments.¹⁵ Two-year inhalation carcinogenicity studies in mice and rats showed no treatment-related neoplastic or non-neoplastic findings, indicating that HFO-1234ze(E) is not carcinogenic under the OECD test conditions of those studies.¹⁶

The non-clinical data support a favourable safety profile.^{14,16} The compound exhibits low systemic toxicity, rapid clearance, negative genotoxicity and carcinogenicity findings, and no adverse effects on fertility or development. The effects observed were limited to high-dose rat studies at exposure levels substantially exceeding those anticipated in clinical use. Key NOAELs were 29,000 mg/kg/day in mice (3 months), 4,280 mg/kg/day in rats (6 months), 5,760 mg/kg/day in the rat reproductive study, and 3,620 mg/kg/day in dogs (3 months).¹⁴

Clinical Experience

Clinical characterisation of HFO-1234ze(E) advanced during 2025 with two randomised, double-blind studies.^{17, 18} Both were designed around the same premise: because non-clinical work showed the propellant appears in blood only transiently and produced no risk at pMDI exposure levels, its effects were expected to be primarily airway-based, making the potential for bronchospasm the key tolerability consideration for a new inhaled excipient.^{14, 17, 18}

Pleasant *et al.* addressed airway sensitivity directly in a Phase IIb, randomised, double-blind, single-dose crossover study in adults with well-controlled or partially controlled

asthma (NCT05850494), using propellant-only inhalers containing no active drug at four inhalations per dose, twice the exposure anticipated for a combination product. HFO-1234ze(E) met non-inferiority to HFA-134a for change from baseline in FEV1 AUC0-15 min against a margin set at the minimum FEV1 change classifiable as reversible and consistent with asthma, and no bronchospasm event occurred in either arm in a study powered to detect such events at a rate of 5% or greater. Both propellants were well tolerated, with no serious adverse events, no adverse events of special interest, and no discontinuations.¹⁷

Usmani *et al.* then evaluated the propellant in its intended commercial configuration in a Phase 3, randomised, double-blind, parallel-group, active-comparator study at 92 sites across nine countries (NCT05573464), comparing budesonide/glycopyrronium/formoterol fumarate dihydrate delivered by HFO-1234ze(E) or HFA-134a in moderate-to-very-severe COPD over 12 weeks, with a prespecified cohort continuing to 52 weeks. Adverse event incidence was balanced at both timepoints, and respiratory adverse events of special interest, selected as most relevant to an inhaled propellant with very limited systemic exposure, showed no difference between groups. Continuous Holter monitoring covering the first inhaled dose, serial ECGs, clinical laboratory tests and vital signs showed no clinically meaningful differences; exploratory lung function and health status indicated comparable therapeutic effect; and no new or unexpected safety signals emerged.¹⁸

The two studies are complementary. The crossover isolates the propellant in a susceptible airway population at supra-therapeutic dosing and finds no effect on lung function and no bronchospasm.¹⁷ The Phase 3 study confirms that this neutrality holds in the finished product across chronic dosing to 52 weeks in an older, comorbid population, consistent with earlier Phase 1 findings of systemic and lung bioequivalence for the active ingredients formulated with either propellant.¹⁹ Taken together, the evidence indicates a similar benefit-risk profile for both propellants and supports substitution of HFO-1234ze(E) for HFA-134a, with real-world evaluation identified as the next step.¹⁸

Regulatory Approval Journey and Timeline

The regulatory pathway for HFO-1234ze(E) in pMDIs reflects a progression of international environmental agreements, agency-level scientific engagement, and initial product approvals spanning nearly four decades.

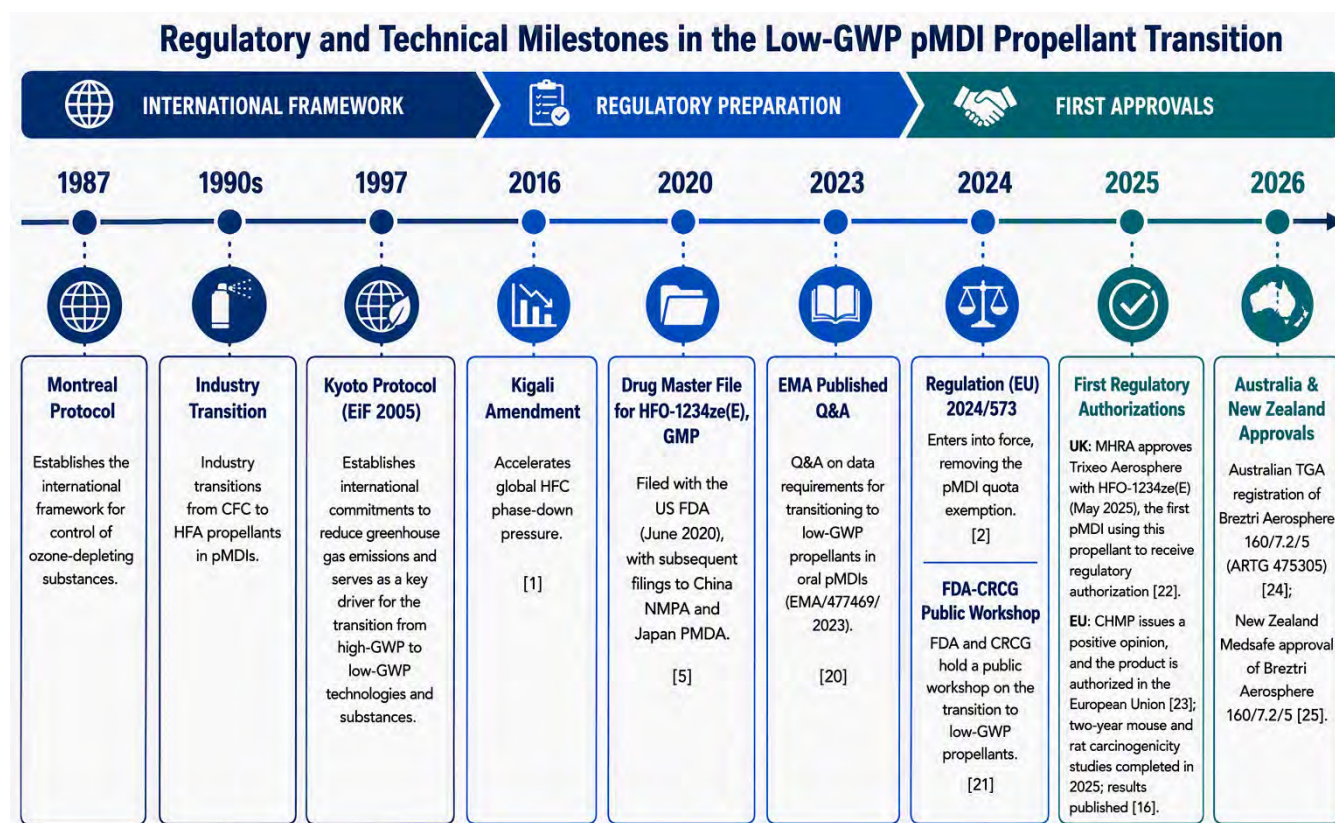


Figure 1. Transition and regulatory approval journey for HFO-1234ze(E): environmental agreements, agency engagement and first pMDI product approvals, 1987 to 2026.

Figure 1 above traces this journey, mapping the key environmental, scientific and regulatory milestones from the 1987 Montreal Protocol through to the first pMDI approvals containing HFO-1234ze(E) in 2025 and 2026.

The 2025 MHRA approval of Trixeo Aerosphere with HFO-1234ze(E) in the United Kingdom represents the first regulatory authorisation of a pMDI product using this next-generation ultra-low-GWP propellant, establishing a precedent for subsequent EU and global submissions.²² As of mid-2026 the propellant is approved for patient use in the United Kingdom, the European Union, Australia and New Zealand.^{23,24,25}

Evolving Regulatory Landscape

In the United States, the FDA 2018 draft quality guidance for MDIs and DPIs remains the primary reference for CMC expectations, covering delivered dose uniformity, aerodynamic particle size distribution, spray pattern, leachables and related critical quality attributes.²⁶ The Agency has not yet issued dedicated final guidance for the low-GWP propellant transition. The 2024 FDA and CRCG public workshop addressed scientific understanding of low-GWP propellants, product performance considerations, and data requirements for both innovator and generic transition programmes, but binding regulatory pathways remain product-specific.²¹ FDA supports the transition to low-GWP

propellants while expecting a science-based demonstration of safety, quality and performance, and has signalled interest in reducing unnecessary testing where confidence in reformulated product safety and effectiveness can be maintained.

The EU and UK framework is more developed. The EMA Q&A on data requirements for transitioning to low-GWP propellants sets expectations for a novel propellant, comprising full novel excipient quality, toxicology and pharmacokinetic data, local tolerance assessment covering ciliary function and airway sensitivity, clinical safety evaluation, and pharmacokinetic bioequivalence demonstrating therapeutic equivalence. Once a propellant has been used in an approved product, the package for subsequent applicants narrows to product quality and demonstration of therapeutic equivalence.²⁰ The EMA draft guideline on the pharmaceutical quality of inhalation and nasal medicinal products (EMA/CHMP/20607/2024) consolidates inhalation product quality expectations and incorporates the Medical Device Regulation, requiring risk-based demonstration of quality, safety and performance comparability, including consideration of therapeutic equivalence and device changes.²⁷ International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS) has published proposed pathways for US FDA approval of low-GWP propellant transitions, providing an industry

reference in the absence of dedicated FDA guidance.²⁸

HFO-1234ze(E) is now supported by a coherent scientific and regulatory evidence base: an AR6 GWP of 1.37, an atmospheric lifetime of approximately 19 days, non-flammable classification under recognised international test methods, a comprehensive non-clinical safety package including two-year carcinogenicity studies in mice and rats, demonstrated formulation compatibility across suspension and solution systems, clinical tolerability data in asthma and COPD populations, and regulatory approval of the first pMDI products incorporating this propellant in four jurisdictions.

Adoption should nonetheless proceed through disciplined product-specific comparability, quality-by-design development, and early regulatory engagement. Sponsors must generate evidence across formulation performance, container closure compatibility, extractables and leachables, stability, delivered dose uniformity, aerodynamic particle size distribution, and clinical bridging where required.

The strongest case for HFO-1234ze(E) rests on its combined ability to reduce inhaler climate impact while preserving the clinical utility, usability, and patient access advantages that define the pMDI platform.

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Soft Mist Inhalers: Enabling the Next Generation of Complex Inhaled Therapies

The inhaled medicines pipeline is changing, expanding from conventional small molecules towards proteins, peptides, nucleic acids and other complex therapeutics.

Pulmonary delivery could broaden the opportunities for complex therapeutics, supporting both local treatment in the lung and systemic delivery.

New therapeutics require new approaches to delivery. Preserving drug integrity through storage, aerosolisation and administration is becoming as important as generating the right aerosol and achieving efficient lung delivery.

Delivery technology is therefore becoming an early strategic development choice. Soft mist inhalers are particularly well positioned to address these emerging requirements and potentially enable the next generation of complex inhaled therapies.

Emerging Opportunity for Pulmonary Delivery of Biologics

Pulmonary delivery of biologics is moving beyond recombinant proteins towards a broader range of therapeutic modalities with five biologics currently approved for direct airway delivery.¹ Specifically, inhaled genetic medicines is emerging with multiple programmes exploring mRNA and viral-vector approaches for cystic fibrosis (CF) and primary ciliary dyskinesia (PCD).²

While growth in biologic therapies remains dominated by injectable products, pulmonary delivery offers an attractive alternative for selected biologics, enabling both direct treatment of the respiratory tract and systemic delivery. The lung's large surface area, thin epithelial barrier and extensive vascular network can support rapid absorption while bypassing gastrointestinal degradation and first-pass hepatic metabolism. As the broader biologics pipeline is predominantly formulated as liquids, liquid inhalation appears to be a natural route, also reflected by in 79% of current inhaled biologic programmes using nebulised delivery.^{2,3}

Yet pulmonary administration brings its own challenges. Formulation stability, aerosol generation, device compatibility, dose delivery and regional deposition are closely interconnected, and a biologic stable in its primary container may not retain its integrity during aerosolisation. For advanced biologics, the delivery system should therefore be considered an integral part of therapeutic development rather than a downstream device or packaging decision.

New Therapeutics Demand New Delivery Technologies

Biologics place specific demands on delivery: proteins are susceptible to aggregation, denaturation and degradation, while mRNA-LNP formulations require preservation of both the nucleic acid payload and nanoparticle structure.^{3,4} The choice of formulation and delivery technology is therefore closely linked. Dry-powder approaches may improve stability but introduce mechanical and thermal stresses during processing, while liquid delivery avoids some of these steps but requires careful control of stability, sterility and aerosolisation compatibility.

Device selection consequently becomes part of the formulation strategy. The challenge is not simply to generate a respirable aerosol, but to do so while preserving integrity and biological function. For complex biologics, delivery technology is an early development choice with consequences for formulation, CMC and programme progression.

Low-Shear Aerosolisation Becomes a Critical Quality Attribute

For sensitive mRNA-LNP and other nano-

particle formulations, aerosolisation must generate a respirable aerosol while minimising mechanical and interfacial stresses that can disrupt the carrier and compromise the encapsulated payload.⁵ Soft mist inhalers offer an attractive alternative to conventional nebulisation, with the aerosol-generation mechanism playing an important role in preserving formulation integrity. Colliding-jet systems such as Respimat® form droplets through impinging liquid jets, whereas Rayleigh-based systems such as the Resyca PFSI® exploit the natural instability of micron-scale liquid jets to generate the aerosol.^{5,6}

These fundamentally different aerosol-generation mechanisms also differ in the energy and mechanical stress imparted to the formulation. High aerosolisation energy has been associated with increased lipid-carrier disruption, loss of encapsulated material and mRNA degradation, while low aerosolisation energy such as for Rayleigh breakup has shown improved preservation of nanoparticle size, encapsulation, mRNA integrity and biological functionality compared with the other nebuliser and SMI technologies (Figure 1).⁷⁻⁹

Current evidence remains predominantly *in vitro* and formulation-specific, but as payloads become more complex and sensitive, aerosolisation stress should be considered. Device performance must therefore extend beyond aerosol characteristics: the relevant question is not only whether a device produces the required aerosol, but whether it preserves and delivers the functional therapeutic. Low-energy Rayleigh breakup offers a promising approach where biologic and nanoparticle integrity is critical.

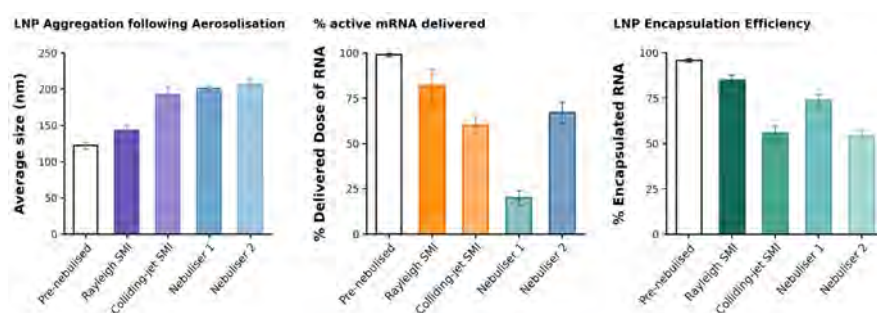


Figure 1: Impact of aerosol-generation mechanism on the integrity and biological functionality of sensitive mRNA-LNP formulations. Comparison of LNP aggregation, mRNA delivery and encapsulation efficiency following aerosolisation using Rayleigh- and colliding-jet SMIs and nebuliser technologies. Adapted from.⁷

Sterile Primary Packaging and Drug Product Compatibility

Preserving biologic integrity extends beyond aerosolisation to storage and administration, making primary packaging an integral part of the delivery-system strategy. Biologics typically require sterile, well-characterised container-closure systems and are often preservative-free, with established formats such as vials and prefilled syringes (PFS) supported by extensive development experience and supply chains. Transferring these products into a dedicated inhalation reservoir can introduce additional compatibility, stability and fill-finish requirements.

One approach is to integrate an established sterile primary container directly into the inhaler, serving as both primary container and drug reservoir. In a PFS-based SMI, a sterilised prefilled syringe can connect directly to the aerosol-generation system through a closed fluid path designed to maintain container-closure integrity (CCI). This minimises product transfer between fill-finish, storage and administration, while supporting refrigerated and frozen supply chains commonly used for biologics.

While this approach can simplify the drug-product pathway, product-specific stability, container-closure compatibility and extractables and leachables assessments remain essential. Building the SMI around established biologics packaging can avoid a bespoke inhalation reservoir and potentially reduce packaging-related development risk and complexity.

Manufacturing Scalability

Beyond simplifying drug-product architecture, primary packaging has important implications for manufacturing scalability.

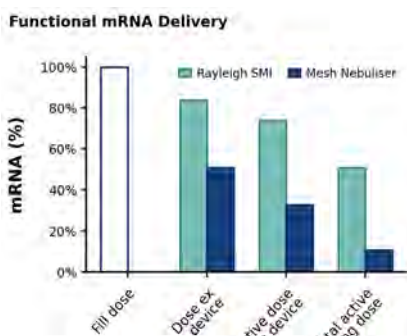


Figure 2: From fill dose to functional mRNA lung delivery. Illustration of how device output, mRNA integrity following aerosolisation and pulmonary deposition collectively determine the predicted functional mRNA dose delivered to the lung for Rayleigh SMI and mesh nebuliser technologies. Adapted from.¹¹

Emerging inhaled biologics often progress through early development with uncertain future demand, making investment in dedicated filling infrastructure, proprietary cartridges and inhalation-specific manufacturing processes a significant development and commercial risk.

A PFS-based SMI offers a different pathway by leveraging existing infrastructure. Prefilled syringes are widely established across the biologics industry, supported by global fill-finish networks, mature processes and scalable supply chains. Using the PFS as both primary container and inhaler reservoir allows drug-product manufacture and aseptic filling to remain within this infrastructure.

This allows the same primary packaging and manufacturing strategy to be maintained from early clinical development through commercial supply, preserving flexibility while avoiding unnecessary technology transfer or premature investment in inhalation-specific filling infrastructure. By leveraging proven biologics manufacturing infrastructure, developers can limit upfront investment, reduce scale-up risk and potentially shorten the path to commercial supply.

Platform Strategy: Balancing Standardisation and Adaptability

A successful device platform strategy balances standardisation with product-specific adaptation. While a common delivery platform can simplify development and manufacturing, different biologics require the delivery system to match the formulation, therapeutic target and deposition profile.

A configurable inhaler platform needs control beyond aerosol generation. Nozzle geometry and pore size should be tailored to droplet formation, while metered volume and spray duration should be adaptable to the required dose. Equally important is the interaction between aerosol and patient. Built-in airflow resistance can passively guide patients towards a more consistent, slow and deep inhalation, reducing patient-to-patient variability and supporting high lung deposition, as demonstrated in studies with different SMI flow resistances.¹⁰

When these parameters are optimally configured, delivery efficiency becomes more than the fraction of drug leaving the device. For complex biologics, the relevant measure is the functional drug reaching the intended lung region. mRNA modelling illustrates this principle, showing how device output, post-aerosolisation integrity and lung

deposition together determine the predicted functional lung dose (Figure 2).¹¹ Optimising this functional lung dose, rather than aerosol performance in isolation, should therefore be a central consideration in developing delivery systems for complex inhaled biologics.

Patient-Centricity and Real-World Use

Optimising functional lung delivery is only valuable if patients can reproduce it in everyday use. Poor inhaler technique, including insufficient inspiratory effort, actuation-inhalation coordination and inconsistent handling, remains an important source of dosing variability, particularly among elderly and paediatric patients and those with respiratory impairment. This is especially relevant for complex biologics, which are often high-value products and may require relatively high delivered doses, making it important to minimise losses and reliably deliver functional drug to the lung.

SMIs are well suited to these challenges. They are compact, portable devices that generate aerosol mechanically rather than relying on inspiratory energy or external power. Their slow-moving, long-lasting aerosol cloud reduces the need for precise actuation-inhalation coordination. Combined with passive flow guidance, these characteristics can reduce dependence on patient technique to support more reproducible lung delivery. These characteristics can also support broader patient-centric design, combining convenient handling and efficient drug use with options such as reusable devices and replaceable drug cartridges to reduce material consumption. For next-generation inhaled therapies, patient-centricity should therefore encompass not only consistent administration, but also portability, efficient use of valuable drug product, affordability and environmental impact.

Regulatory Perspective

Taken together, these interactions between drug product, delivery technology and patient use make the delivery platform an important development and regulatory decision for complex inhaled biologics. Developers may need to demonstrate not only consistent aerosol performance and dose delivery, but also that formulation, primary packaging and aerosolisation preserve critical quality attributes and biological functionality throughout storage and administration, without changes that could affect safety or immunogenicity.

This makes early integration of the biologic and delivery system important. Formulation,

primary packaging and device performance need to be developed together, with attention to stability, sterility, compatibility and preservation during aerosolisation. Identifying these requirements early can reduce the risk of later changes that trigger additional development, manufacturing or regulatory work.

A platform-based SMI approach can help manage this complexity. Established sterile primary packaging, low-energy aerosol generation and a configurable device architecture can provide a common technical foundation across biologic products. Using the same platform from clinical development through commercial supply can reduce the need for changes in primary packaging or delivery technology as a programme progresses. While product-specific regulatory evidence remains necessary, established platform knowledge and manufacturing processes may be leveraged across programmes, reducing technical risk and unnecessary redevelopment.

Looking Ahead

The next generation of inhaled therapies will place different demands on delivery technology. As pulmonary development expands from small molecules towards biologic therapeutics, success will increasingly depend on preserving the drug product while providing efficient, reproducible and patient-friendly administration.

This changes the role of the inhaler. the delivery platform becomes an integral part of the therapeutic product and should be considered from the outset. Soft mist inhalers are well positioned in this landscape. Their compatibility with liquid formulations, mechanically generated aerosols and compact handheld delivery provides a strong foundation for complex therapeutics. Platforms combining these characteristics with low-energy aerosolisation, established sterile primary packaging and adaptable delivery parameters can extend the range of biologics suitable for pulmonary administration (Figure 3).

Ultimately, the opportunity is not simply to develop a better inhaler, but to enable therapies that would otherwise be difficult to deliver effectively through the lung.

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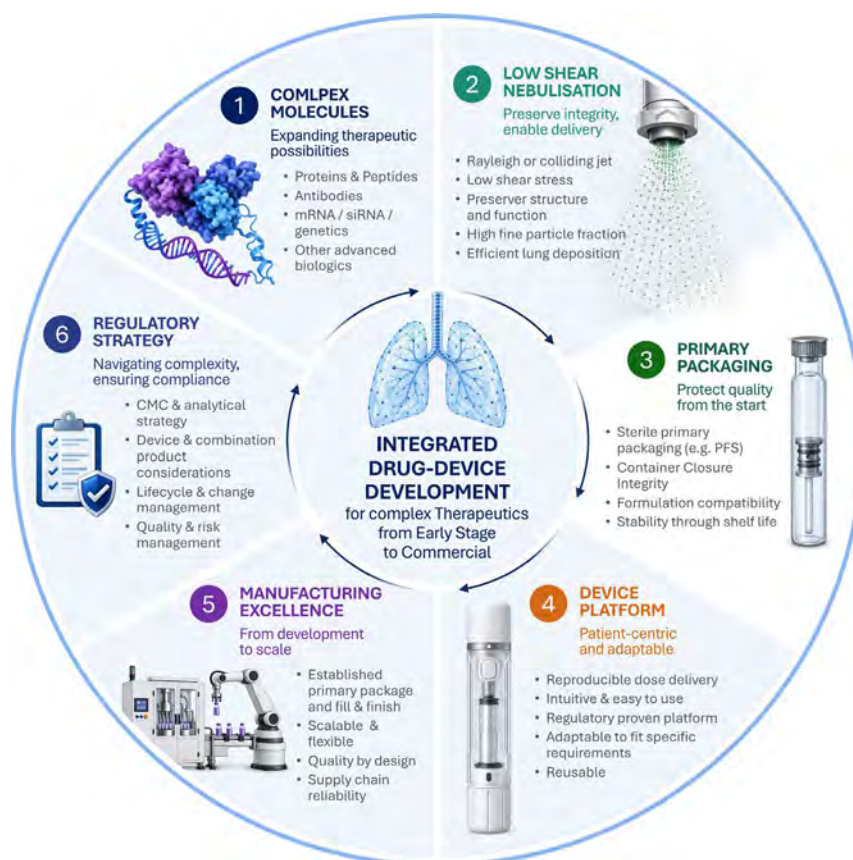


Figure 3: Integrated drug-device development for complex inhaled therapeutics. Bringing molecule, aerosolisation, packaging, device, manufacturing and regulatory strategy together from early development to commercialisation.

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