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ON

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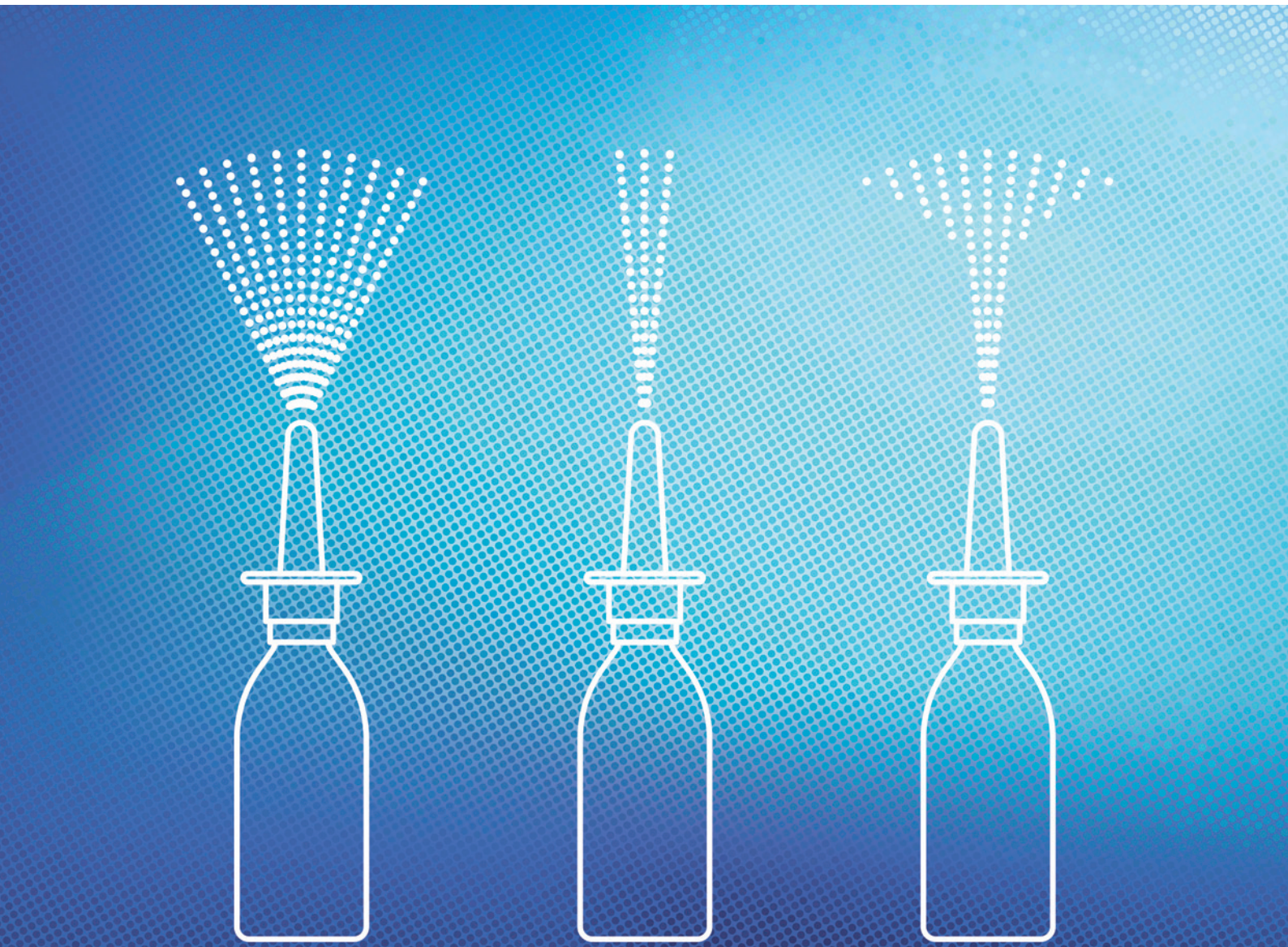
APRIL 13TH 2026

PULMONARY & NASAL DRUG DELIVERY



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PULMONARY & NASAL DRUG DELIVERY

ONdrugDelivery Issue N° 184, April 13th, 2026

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

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Systemic OINDP Delivery:
Innovation in the Pulmonary and Nasal Sectors

As patient-centric design and novel biologics continue to rise in prominence, the potential for rapid systemic delivery presented by pulmonary and nasal administration continues to make orally inhaled and nasal drug products an exciting and dynamic sector of the drug delivery world. In this issue of ONdrugDelivery, we cover some of the innovation taking place across the sector – including the possibilities of direct nose-to-brain delivery, next-generation nebulisers, soft mist inhalers (SMIs) and low-global warming potential propellants for pressurised metered dose inhalers (pMDIs).

Beginning the issue, **Bespak**, our Outstanding Sponsor, digs into the ongoing transition for pMDI propellants (Page 8). Detailing both the formulation and device design challenges presented by the leading low-global warming propellants and how the company has tackled them, Bespak's article offers key insights on this pressing topic.

Next, **Crux**'s Managing Director discusses the company's new Technology Centre in Bristol (UK) and the opportunities this major new facility unlocks for future project (Page 16). **Catalent** presents a CDMO-eye view of liquid nasal product development, from formulation considerations, through platform selection and all the way to scale-up and validation processes (Page 22). Then **Copley Scientific** explores the role of automation in pMDI testing, presenting case studies that demonstrate how automation can eliminate unnecessary variability in test results (Page 32).

Following on, we have a trio of articles discussing novel pulmonary devices. Kicking off this section, **Nebu~Flow** considers how its acoustic wave-based nebuliser addresses many of the challenges associated with nebulising biologics (Page 40). **PARI** and **BPTM** discuss the critical role human factors played in the development of PARI's eFlow® Integrated nebuliser (Page 46), and **GAPLAST** turns our attention to the role SMIs are poised to play in the future of the respiratory sector, and how its AirlessMotion® bag-in-bottle technology is positioned to support this exciting new device category (Page 52).

The second half of this issue dives into nasal drug delivery, beginning with an in-depth overview of the sector from **Kymanox**, talking through the challenges and strategies of nasal drug development (Page 58). Next up, highlighting the expansion of its offering into nasal in the wake of its acquisition of Renaissance Lakewood, **LTS** provides a thorough consideration of the untapped potential of nasal delivery for vaccines and systemic delivery, and what needs to be addressed to achieve that potential (Page 54). Lastly, pivoting the discussion to the role of nasal delivery in emergency therapies, particularly naloxone, **Nemera** concludes the issue with an explanation of how its UniSpray device opens the door to generic developers looking to expand the availability of this key therapeutic (Page 70).

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THE PHYSICS OF THE SWITCH: OPTIMISING pMDI DESIGN FOR LOW-CARBON LUNG DELIVERY

Thomas Daly and **Tony Mallett** of **Bespak** discuss the transition to low-global warming potential propellants, examining the vital adjustments to the whole inhalation system necessary to support effective and safe dosing without hydrofluorocarbons.

As the industry accelerates its transition away from hydrofluorocarbon propellants, the focus is no longer whether change will happen, but how to deliver it without compromising clinical performance or patient care. The 10th anniversary of the Kigali Amendment to the Montreal Protocol marks this defining moment for the inhalation sector.

Low-global warming potential (GWP) propellants exhibit distinct physicochemical properties that directly affect aerosolisation, formulation stability and lung deposition in pressurised metered dose inhalers (pMDIs). Achieving equivalent clinical performance therefore demands a detailed understanding of these differences, alongside targeted design interventions to manage the resulting changes in fluid dynamics within the device.

This transition represents one of the most significant operational shifts in inhalation therapy in decades. While comparable in scale to the chlorofluorocarbon-to-hydrofluoroalkane transition of the 1990s, today's challenge is distinct in its engineering impediments and design constraints. To ensure consistent dose delivery, critical hardware components

> "TODAY'S CHALLENGE IS DISTINCT IN ITS ENGINEERING IMPEDIMENTS AND DESIGN CONSTRAINTS."

must be precisely matched to the vapour pressure, density, viscosity and solvency of a propellant. Optimising these elements requires a rigorous, system-level approach to device design, ensuring that progress towards low-carbon solutions is achieved without compromising clinical performance or the quality of patient care.

THE PHYSICS OF THE SWITCH

The two primary candidates for next-generation low-GWP propellants are HFA-152a and HFO-1234ze(E). While both significantly reduce the carbon footprint compared with legacy propellants, offering a reduction in GWP of approximately 90% and 99.9% respectively, they behave differently inside a canister.[1]

The pMDI aerosol generation process consists of two distinct phases: droplet formation (Phase I) and aerosol maturation (Phase II). Both phases are heavily influenced by the physicochemical properties of the propellant, meaning that a change in propellant necessitates a re-evaluation of the entire system.

The critical factors driving these differences are saturated vapour pressure, liquid density, viscosity and surface tension. The new propellants exhibit distinct physical profiles. HFA-152a has lower density but operates at similar vapour pressure to current standards. HFO-1234ze(E) has similar density to existing propellants, but requires careful tuning to maintain dose consistency.

These properties ultimately influence the atomisation process. When the metering valve opens, the propellant flashes, blasting the liquid formulation into droplets. Research indicates that, because HFA-152a possesses relatively lower vapour pressure and higher surface tension, it tends to deliver larger initial droplets. This alteration in Phase I droplet formation can cascade into Phase II aerosol maturation, shifting the aerodynamic particle size distribution of the drug.

Furthermore, the thermal properties of the plume have an influence. Recent studies have measured the plume temperature at the position representing the tongue surface. HFA-152a was found to be the coldest, reaching temperatures as low as –27°C due to its specific boiling point and evaporation characteristics. This is significantly colder than legacy plumes. Without design intervention, such a cold plume could trigger the "cold Freon" effect in patients, leading to breath-holding or poor inhalation technique.[1]

> "FOR SUSPENSION FORMULATIONS, THE DENSITY DIFFERENCE BETWEEN THE DRUG PARTICLES AND THE LIQUID PROPELLANT IS CRITICAL."

Beyond the mechanics of the spray, the interaction between the propellant and the drug formulation inside the canister is governed by distinct interactions. For suspension-based formulations, the density difference between the drug particles and the liquid propellant is critical. According to Stokes' law, this difference drives the rate of sedimentation (settling) or creaming (floating). As such, the lower liquid density of HFA-152a presents unique stability challenges.

This low density appears to be problematic for suspension stability, as most micronised drug particles are denser than the propellant. However, HFA-152a also exhibits higher viscosity, which helps to mitigate this effect. Experimental data suggest that sedimentation times in HFA-152a can actually be longer than in legacy propellants, aiding dose uniformity. Conversely, formulations designed for denser propellants will require reformulation to maintain dose consistency.

For solution-based pMDIs, the chemical interaction is equally critical. HFA-152a acts as a stronger solvent for many lipophilic drugs and excipients than traditional propellants. This enhanced solvency enables higher drug loading but increases the risk of extractables and leachables from valve components.

> "BESPAK HAS BEEN AT THE FOREFRONT OF THIS OPTIMISATION, CONDUCTING EXTENSIVE RESEARCH TO ADAPT THE MARKET-LEADING BK357 VALVE PLATFORM FOR THE LOW-CARBON ERA."

ADAPTING VALVES FOR THE LOW-CARBON ERA

Bespak is at the forefront of this optimisation, conducting extensive research to adapt the market-leading BK357 valve platform for the low-carbon era.

One of the immediate challenges with HFA-152a is its compatibility with elastomeric seals. Due to its solvency profile, HFA-152a can interact with certain polymers, leading to the extraction of material components. Recent studies have highlighted that levels of specific leachables can be higher with HFA-152a if incompatible gaskets are used.[1]

Bespak has addressed this by optimising the BK357 valve with robust material configurations. Through rigorous material screening, specific elastomers – such as ethylene propylene diene monomer and bromobutyl – have been validated for use with these new propellants. These materials ensure robust seal integrity, preventing leakage and moisture ingress that could degrade the formulation over the product's shelf life.

Beyond materials, the physical dimensions of the valve and actuator often require adjustments. The aerosol performance, specifically the emitted mass and particle size distribution, is directly influenced by the expansion of the propellant as it exits the actuator opening.

Since the new propellants expand differently to their legacy counterparts, the actuator sump volume, orifice diameter and length may need modification to match the spray pattern and fine particle fraction of a reference product. For instance, studies have shown that HFA-152a, with its lower vapour pressure, may require a smaller orifice diameter to increase jet turbulence and form droplets more effectively, thereby matching the respirable dose of a legacy propellant. Bespak uses proprietary empirical models to tune these parameters, helping to ensure equivalent lung deposition to legacy propellants.

VISUALISING THE INVISIBLE

The refill event, when the metering chamber refills immediately after actuation, is a critical yet often overlooked facet of inhaler design. If the chamber does not refill completely or consistently, the next dose delivered to the patient may be inconsistent. Historically difficult to observe, this internal flow has now been modelled using computational fluid dynamics (CFD) and captured experimentally with unprecedented temporal and spatial resolution using high-speed X-ray synchrotron imaging.[2]

This high-speed X-ray imaging, conducted at the European Synchrotron Radiation Facility (Grenoble, France), has revealed that the refill process is far more chaotic than previously understood. When ethanol is used as a co-solvent – common in solution -based pMDIs – the flow behaviour becomes significantly more complex. The X-ray imaging revealed that ethanol-based formulations create a chaotic flow with high vapour bubble number density inside the metering chamber.

If a larger proportion of vapour remains in the metering chamber before the next actuation, it may result in a lower dose than intended for the patient. This insight is crucial for the propellant transition, because HFA-152a/ethanol mixtures have different properties to legacy mixtures.

Complementing the physical imaging, Bespak presented a study at DDL 2025 using CFD to simulate the refill dynamics of a metering valve using four different propellants. The results highlighted a divergence in performance driven by the physics of each propellant:

- HFA-152a exhibited the fastest refill, achieving an 88.3% liquid fill level within 300 ms. Its lower density allows it to flow rapidly into the chamber, compensating for pressure differentials.
- HFO-1234ze(E), by contrast, demonstrated a slower refill rate, reaching only 75.9% in the same timeframe, largely due to its higher density and lower saturation pressure.

The simulation confirmed that this variance can be compensated for by modifying the metering valve inlet diameter. By tuning this specific geometric feature, engineers can equalise the refill performance, ensuring consistent dosing regardless of the propellant chosen.

MAPPING THE DESIGN SPACE FOR SUSTAINABILITY

The utility of digital simulation extends beyond just fluid dynamics. In typical development programmes, tolerance limits are established through a labour-intensive process of trial and error. This is not only costly, but can also generate significant material waste.

Bespak has moved towards a "digital-first" approach by mapping the product design space *in silico*. By combining finite element analysis with statistical techniques, engineers can virtually adjust over 100 design inputs to predict device performance under thousands of tolerance combinations.[3] This approach allows the team to identify a safe zone where manufacturing variability will not compromise critical quality attributes such as leakage or shot weight.

The sustainability impact of this digital shift is measurable. In a recent proof-of-concept project, Bespak used this method to avoid approximately 5 tonnes of plastic waste that would have otherwise been generated through physical prototyping and testing.[3]

"THE GREEN TRANSITION IS NOT JUST ABOUT WHAT IS INSIDE THE CANISTER, BUT THE CANISTER AND VALVE THEMSELVES."

"BY TUNING THIS SPECIFIC GEOMETRIC FEATURE, ENGINEERS CAN EQUALISE THE REFILL PERFORMANCE, ENSURING CONSISTENT DOSING REGARDLESS OF THE PROPELLANT CHOSEN."

While the propellant accounts for the majority of a pMDI's carbon footprint, a truly holistic approach to sustainability must also consider the embodied carbon of the device hardware. The green transition is not just about what is inside the canister, but the canister and valve themselves.

Bespak has achieved a significant sustainability milestone by completing the first lifecycle assessment for a pMDI valve – specifically for its BK357 platform.[4] This assessment has enabled engineers to pinpoint carbon hotspots within the componentry, specifically identifying the energy-intensive metal components as primary drivers of embodied carbon.

Based on this assessment, Bespak is actively investing in a decarbonisation strategy focused on the supply chain. By exploring the substitution of standard alloys with high-quality recycled grades, the aim is to significantly lower the embodied carbon of the valve without altering component geometry or compromising assembly processes.

When combined with the transition to low-GWP propellants, this hardware optimisation offers a credible pathway to a truly low-carbon product. Furthermore, Bespak's manufacturing sites in the UK at Holmes Chapel and King's Lynn now obtain 97.5% of their electricity from renewable sources, further reducing the Scope 2 emissions associated with production.[5]

INDUSTRIALISING THE GREEN TRANSITION

Beyond technical considerations, this transition requires significant operational changes. HFA-152a is classified as a flammable gas, which necessitates crucial upgrades to manufacturing infrastructure, including ATEX-certified filling lines and specialised safety handling procedures. This requirement has created a bottleneck in the industry, as few legacy facilities are equipped to handle flammable aerosols at pharmaceutical standards.[5,6]

"THE FUTURE OF DRUG DELIVERY TO THE LUNGS IS LOW CARBON, AND THROUGH PRECISE ENGINEERING AND COLLABORATION, THE INDUSTRY IS READY TO DELIVER IT."

Bespak has positioned itself as a specialist inhalation CDMO capable of guiding partners through this complex landscape. The company has invested heavily in commercial-scale filling lines for both HFA-152a and HFO-1234ze(E) – an investment that is underpinned by a culture of safety and collaboration with suppliers and manufacturers to define best practices.

Advanced simulation of refill dynamics, robust seal materials and optimised actuator geometry enable devices to be both sustainable and clinically robust. The future of drug delivery to the lungs is low carbon, and through precise engineering and collaboration, the industry is ready to deliver it.

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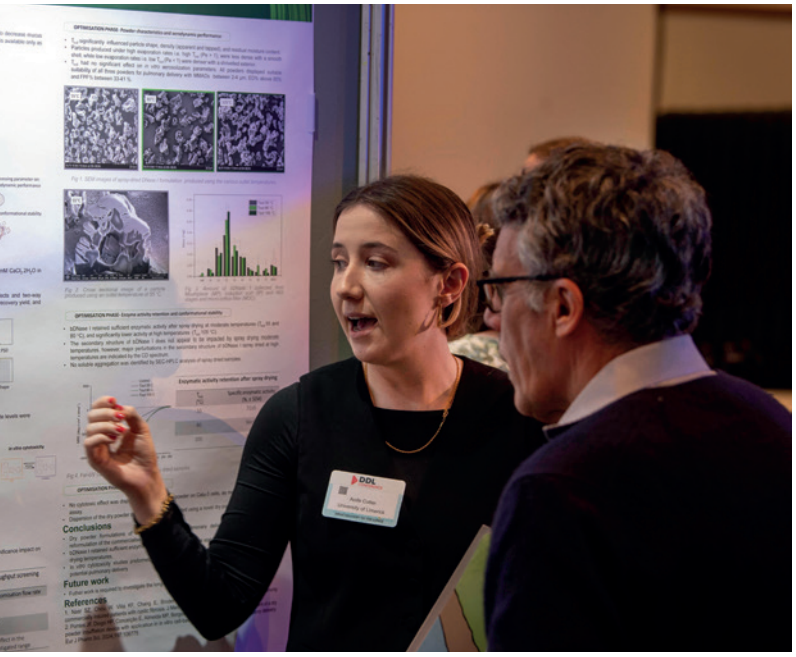

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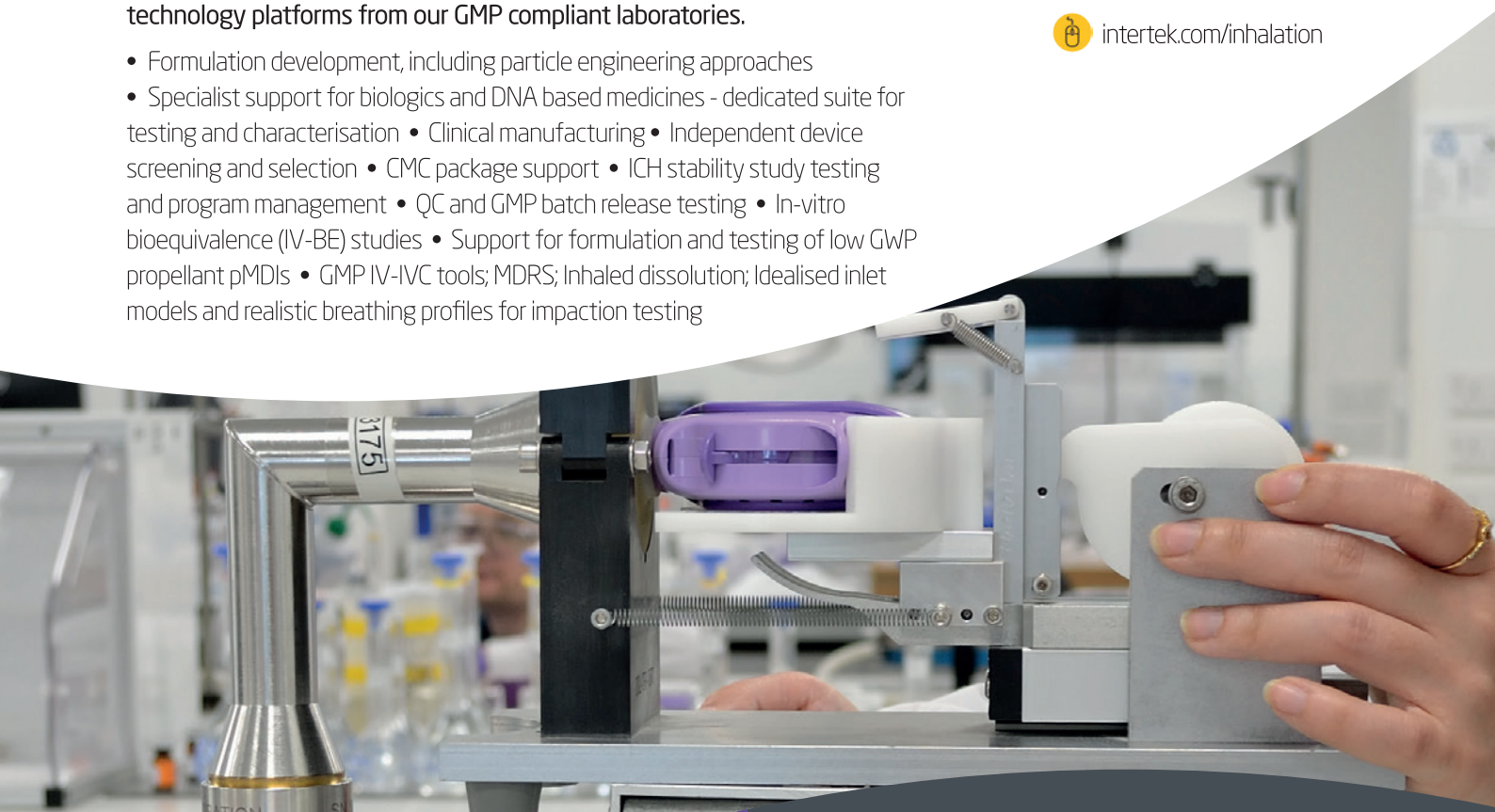

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Interview:
Inside The Crux Technology Centre

In this interview, **Stephen Gilmore** of **Crux Product Design** discusses the opportunities and capabilities unlocked by Crux's new Technology Centre located in Bristol, UK. Mr Gilmore provides an overview of the new capabilities provided by the facility and the potential it represents to the future of the company.

Q Crux recently opened its new Technology Centre in Bristol. What does this expansion represent for the company and the partners it works with?

A The opening of the Crux Technology Centre marks an important step forwards for our teams and the organisations we collaborate with across the healthcare sector. The investment reflects both the growth of Crux as a business and the increasing complexity of the programmes we support.

Figure 1: The Crux Technology Centre and Crux Headquarters.

Over the past decade we have seen a significant shift in expectations around medical device development. Devices are no longer judged purely on technical performance; they must also deliver a high level of usability, reliability and confidence for clinicians and patients. Achieving that requires deeper integration between user research, design, engineering and applied science.

The new Technology Centre expands the environments where this work takes place (Figure 1). Our teams now have access to larger human factors facilities, expanded laboratories and specialist spaces that allow us to develop devices at a larger scale. At the same time, it increases our capacity to work with partners on complex development programmes that require close collaboration across disciplines. For our clients, the benefit is clarity earlier in development – they can see how devices behave in realistic environments, gather meaningful usability evidence and make informed decisions with greater confidence as projects move forwards.

Q Human factors research appears to be a central feature of the new facilities – why has this area become so important in medical device development?

A Human factors has become fundamental to successful medical device development because it directly influences how effectively a device can be used and validated. In regulated

Figure 2: Usability research suite and viewing room in the Crux Technology Centre.

environments, usability is closely linked to risk management. Regulators expect pharmaceutical companies to demonstrate that devices can be used correctly by their intended users in real-life contexts. That requires structured research, evidence gathering and a clear link between user insight and design decisions.

At Crux, we view human factors as an integral part of engineering development rather than a separate activity. By observing how users interact with devices, we can identify opportunities to improve user ergonomics, interaction and workflow very early in the process. This approach helps to remove uncertainty; instead of relying on assumptions or obsolete data about how a device might be used, teams can observe real behaviour, capture evidence and refine the design accordingly. The result is a development pathway that is both more efficient and more aligned with regulatory expectations.

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As Managing Director of Crux, Stephen Gilmore sits on the board and provides strategic leadership across client programmes. With over 20 years' experience in regulated product development and more than a decade at Crux, he has helped guide the company's evolution into a leading consultancy, delivering medical and drug delivery devices for global pharmaceutical clients. His role spans programme governance and high-level decision-making, ensuring that complex development programmes are robustly led from concept to launch. He works directly with senior client stakeholders to manage risk, accelerate development and bring commercially successful, regulation-ready products to market.

Q How does the Technology Centre support usability research throughout the full device development process?

A The Technology Centre includes dedicated usability research rooms designed to support studies at every stage of development (Figure 2). Early-stage research often focuses on formative exploration, which may involve evaluating initial concepts, studying first impressions and identifying opportunities to refine the

"ONE OF THE MOST IMPORTANT ADVANTAGES OF THE CRUX TECHNOLOGY CENTRE IS THE WAY IT CONNECTS DIFFERENT DISCIPLINES WITHIN A SINGLE ENVIRONMENT."

way a device is handled or understood. At this point, the goal is to gather insights that can inform decisions before engineering or design development progresses, whereas later-stage studies move towards formal human factors validation. These studies are conducted within structured protocols and generate the evidence required for regulatory submissions.

Having purpose-built environments for both types of work allows us to maintain continuity across the development journey. The teams who capture early insights can support validation studies later on, ensuring that design decisions are clearly documented and supported by evidence throughout development.

Q The Technology Centre emphasises collaboration between research, engineering and design teams – how does that influence the pace and quality of development?

A One of the most important advantages of the Crux Technology Centre is the way it connects different disciplines within a single environment. Human factors research generates a continuous stream of insights about how devices are used, so that, when those insights flow directly into design and engineering development, design teams are able to respond quickly. Prototypes can be refined and reintroduced into testing environments within a short timeframe. This creates a development rhythm where observation, iteration and evaluation happen in close succession. It allows programmes to maintain momentum while still meeting the rigorous standards expected of regulated device development.

Q The expansion also increases Crux's dry lab capabilities – how does this support testing and validation for medical products?

A The new Technology Centre significantly expands our dry lab facilities, effectively doubling the space available for testing and validation work (Figure 3). These laboratories enable our teams to evaluate the performance of medical devices under controlled conditions using specialised equipment. This includes mechanical testing, device characterisation and detailed analysis that supports engineering development and verification activities.

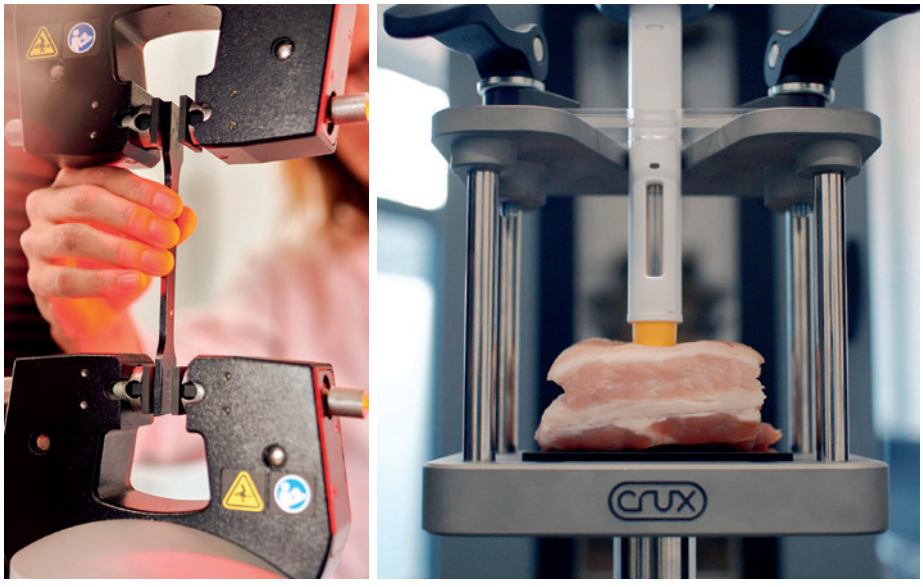

Figure 3: The Crux Technology Centre expands Crux's dry-lab capabilities.

Q One of the most distinctive spaces in the new Technology Centre is the surgical research suite – how does this help teams evaluate device performance?

A The surgical human factors suite allows us to recreate clinical environments with a high level of realism; that context is extremely valuable when studying how devices are handled during complex procedures. Within the space, we can simulate operating room conditions and observe how clinicians interact with devices while carrying out realistic tasks. Usability experts can study hand movements, device positioning, workflow and communication between surgical team members.

These observations often reveal insights that are difficult to capture in more traditional testing environments. Small design elements, such as grip shape, feedback mechanisms or device orientation, can influence how confidently a device is used during a procedure. Both research suites also include adjacent viewing rooms where clients and usability specialists can observe sessions live (Figure 4). That shared visibility allows the entire development team to see how devices perform in the hands of real users and to discuss potential improvements immediately after study sessions.

Q The Technology Centre represents a significant investment in Bristol – how does the expansion help Crux foster new talent?

A The decision to expand in Bristol reflects a long-term commitment to the region and to the engineering sector more broadly. By doubling our UK footprint, we have created space for a growing workforce – over the coming years we expect to continue expanding our team of mechanical engineers, designers, human factors specialists, applied scientists and life scientists.

Figure 4: Surgical research suite and viewing room in the Crux Technology Centre.

Equally important is the role the centre plays as a place for collaboration and exchange of ideas. The building includes a dedicated auditorium with capacity for more than 100 people, allowing us to host talks, industry discussions and guest speakers from across the sector. Bringing researchers, clinicians, engineers and technology leaders together in this way can help create valuable conversations around the future of medical device development.

Q The expansion also reflects broader growth across both the UK and the US. How does this international presence influence the way Crux works with partners?

A Our expansion reflects a deliberate strategy to strengthen our presence in two important regions for innovation. In the UK, the new Crux Technology Centre and the existing Crux Headquarters provide the infrastructure required to support a growing team and larger development programmes while remaining rooted in the region where the company was established. At the same time, our office in Kendall Square in Cambridge, Massachusetts (US) has developed rapidly. Being located within one of the world's most active technology and life sciences ecosystems places us close to organisations developing the next generation of healthcare technologies, allowing us to collaborate more closely with our partners. Many programmes now involve teams operating across regions, combining expertise to deliver solutions at a global scale.

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EXPANDING HORIZONS IN LIQUID NASAL DRUG DEVELOPMENT

Dr Alan Watts and **David Wilcox**, both of **Catalent Pharma Solutions**, examine the current product designs in the nasal market landscape and outline key technical and regulatory considerations for liquid nasal drug products.

Over the past two decades, liquid nasal dosage forms have evolved from simple antihistamine or decongestant sprays into highly engineered drug-device combinations capable of addressing diverse therapeutic needs. Initially focused on local indications such as allergic rhinitis or intranasal influenza vaccines, the modality now supports products requiring rapid systemic absorption, caregiver-administered emergency therapies and, increasingly, direct nose-to-brain delivery.

This expansion reflects advances in formulation science – including solubility enhancement, mucoadhesive polymers and stabilisation of biologics – paired with sophisticated multidose and unit-dose device technologies. Regulatory frameworks have also evolved to recognise the clinical and public health value of nasal therapeutics, reinforcing the need for robust chemistry, manufacturing and controls (CMC) strategies.

Drawing on experience across development, clinical supply and commercial manufacturing, a co-ordinated approach to early CMC strategy enables streamlined scale-up, risk mitigation and regulatory readiness.

INDICATIONS AND EMERGING MARKETS

Liquid nasal delivery spans locally acting therapies, rapid systemic rescue medications and central nervous system (CNS)-targeted products. Established indications, such as allergic rhinitis and intranasal influenza

"ACUTE PAIN MANAGEMENT PRODUCTS HIGHLIGHT THE NASAL ROUTE'S CAPACITY FOR RAPID SYSTEMIC ABSORPTION."

Traditional Markets		Emerging Markets		Upcoming (New) Markets	
Allergic rhinitis	Acute pain	Seizure rescue	Depression	Heart arrhythmia	Psychiatric agitation
Influenza vaccine	Opioid overdose	Migraine	Anaphylaxis	Traumatic brain injury	Metabolic disease

Table 1: Traditional, emerging and upcoming (new) markets for liquid nasal drug products.

vaccination, continue to represent substantial global volume. These products typically employ aqueous solution or suspension formulations delivered through high-precision multidose pumps. From a CMC standpoint, they require tight control of droplet size distribution (commonly Dv50 ~40–120 µm), spray pattern geometry, plume angle, priming/repriming behaviour and delivered dose uniformity across the container lifespan. Microbial control strategies – either preservative-based or preservative-free with sterile filtration and closed-tip systems – must support in-use stability. Extractables and leachables, container-closure integrity and ICH stability performance remain foundational development considerations.

Acute pain management products highlight the nasal route's capacity for rapid systemic absorption. The highly vascularised respiratory epithelium (~150–200 cm^2 surface area) supports onset within minutes for appropriately designed small molecules. For moderately lipophilic agents, such as butorphanol or ketorolac, absorption occurs primarily via passive transcellular diffusion. Formulation strategies typically involve solubility enhancement (co-solvents or cyclodextrins), pH optimisation to increase the unionised fraction and viscosity modifiers to balance mucosal residence time against mucociliary clearance (approximately 15–30 minutes).

Similar principles underpin intranasal naloxone for opioid overdose rescue, where reliable pharmacokinetics under real-world conditions are essential. These emergency-use products have shaped regulatory expectations for unit-dose systems, emphasising delivered dose accuracy, shot weight reproducibility, spray content uniformity, human factors validation and device robustness.

Seizure rescue therapies have expanded outpatient management through caregiver-administered intranasal benzodiazepines. Because compounds such as midazolam and diazepam exhibit limited aqueous solubility, formulations frequently rely on non-aqueous systems, solubilising excipients and viscosity-modifying polymers while minimising irritation and run-off. Clinical data demonstrate achievement of therapeutic plasma concentrations within approximately 10–15 minutes.[1]

Other CNS-directed therapies further illustrate the platform's evolution. Intranasal esketamine for treatment-resistant depression underscores the importance of deposition control and absorption kinetics. While the quantitative contribution of direct nose-to-brain transport remains debated, evidence supports the feasibility of olfactory and trigeminal pathways when formulation and device variables are optimised.[2]

Reproducible upper nasal cavity deposition depends on droplet size, plume dynamics and actuation consistency, with some programmes using mechanically assisted delivery technologies. Migraine therapies and emerging cardiovascular and emergency indications reflect continued innovation. Modern dihydroergotamine systems and calcitonin gene-related peptide receptors (CGRP)-targeted agents need predictable pharmacokinetics during acute episodes when oral absorption is compromised. Programmes in anaphylaxis and paroxysmal supraventricular tachycardia require ultrarapid systemic onset; for example, intranasal adrenaline (epinephrine) demands mitigation of oxidative degradation to achieve delivery performance comparable to autoinjectors.

Perhaps most transformative is the growing pipeline of peptides and proteins (Table 1). Large molecules face enzymatic degradation, limited epithelial permeability and rapid clearance. Strategies under investigation include mucoadhesive polymers, enzyme inhibitors, permeation enhancers and targeted deposition to the olfactory region. Intranasal insulin and glucagon-like peptide-1 analogue programmes exemplify efforts to enable needle-free metabolic therapies, though achieving reproducible bioavailability remains a primary technical hurdle. Collectively, these advances signal the continued expansion of nasal delivery as a versatile, systemic and CNS-drug delivery platform.

EARLY CMC AND DEVELOPMENT CONSIDERATIONS FOR LIQUID NASAL PRODUCTS

Early CMC strategy defines the technical and regulatory trajectory of a liquid nasal drug product. Unlike many conventional oral dosage forms, nasal products represent an integrated drug-device combination in which formulation properties, container-closure configuration and spray mechanics collectively determine clinical performance. Accordingly, early development should align formulation science, device platform selection, manufacturing strategy and analytical control within a unified target product profile.

"REPRODUCIBLE UPPER NASAL CAVITY DEPOSITION DEPENDS ON DROPLET SIZE, PLUME DYNAMICS AND ACTUATION CONSISTENCY, WITH SOME PROGRAMMES USING MECHANICALLY ASSISTED DELIVERY TECHNOLOGIES."

Platform Selection

One of the earliest strategic decisions is selection of a unit-dose, bi-dose or multidose presentation. Unit-dose and bi-dose systems are generally preferred for emergency-use or high-potency products because they simplify microbial control and eliminate in-use contamination risk. These systems must demonstrate tight control of delivered volume (typically ± 10% or less, depending on product requirements), shot weight reproducibility and spray geometry consistency across production lots. An example of a unit-dose system is shown in Figure 1.

Nemera's (La Verpillière, France) UniSpray (see this issue, Page 70) accurately delivers a single 100 µL dose in any orientation without priming. Multidose systems, which are more common for chronic indications, introduce additional CMC complexity, including preservative efficacy validation or implementation of preservative-free pump technologies that incorporate mechanical tip seals and one-way valve systems. Resyca's (Munich, Germany) Ultra Soft Nasal Pump, shown in Figure 2, uses Rayleigh spray technology to deliver a 45–70 µL fine, low-velocity plume, allowing for better nasal mucosal coverage and minimal dripping.[3]

Preservative-containing products require antimicrobial effectiveness testing (e.g. US Pharmacopeia <51>) and justification of preservative concentration relative to nasal tolerability and potential ciliary toxicity. Preservative-free multidose systems frequently require aseptic processing and validated container-closure integrity to maintain sterility assurance throughout labelled in-use periods.[4]

Figure 1: Unit-dose nasal device (Nemera's UniSpray).

Manufacturability must be evaluated in parallel with device selection. Nasal products are particularly sensitive to fill volume accuracy, crimping or stopper placement (for unit-dose systems) and torque control (for multidose pumps). Variability in fill volume directly affects delivered dose and spray characteristics. Decisions regarding terminal sterilisation feasibility versus aseptic processing are often dictated by formulation stability and excipient compatibility. Aseptic filling introduces higher environmental classification requirements (ISO 5/7), media fill validation and sterility assurance considerations but may be necessary for preservative-free products or heat-sensitive actives. Early compatibility studies assessing sorption, leachables, silicone oil interactions and elastomer extractables are essential to prevent late-stage reformulation or device requalification.

Product Quality Control

Analytical development is equally critical. Regulatory guidance emphasises characterisation of both formulation and device performance attributes, including impurities, pH, viscosity, osmolality, microbial limits, delivered dose uniformity (DDU), droplet size distribution (e.g. laser diffraction Dv10/Dv50/Dv90), spray pattern and plume geometry.[4] These attributes are directly linked to regional deposition within the nasal cavity and therefore to safety and efficacy. For suspension products, resuspendability, sedimentation rate and redispersibility must be quantified to ensure consistent dosing. Rheological profiling supports optimisation of mucosal residence time while minimising run-off and patient discomfort. Device-specific parameters – such as actuation force, stroke length and priming behaviour – should be incorporated into control strategies, particularly for combination products subject to human factors validation.

Early *in vitro* deposition testing using anatomical nasal cast models can provide predictive insight into regional deposition patterns, especially for programmes targeting the upper nasal cavity or potential nose-to-brain delivery.[5] Such data may inform droplet size optimisation, plume angle adjustments or selection of breath-powered delivery technologies.

Collectively, these early CMC decisions establish the framework for clinical success and commercial scalability. Proactive integration of formulation, device engineering, manufacturing controls and analytical characterisation reduces downstream risk, shortens development timelines and supports a robust regulatory submission strategy.

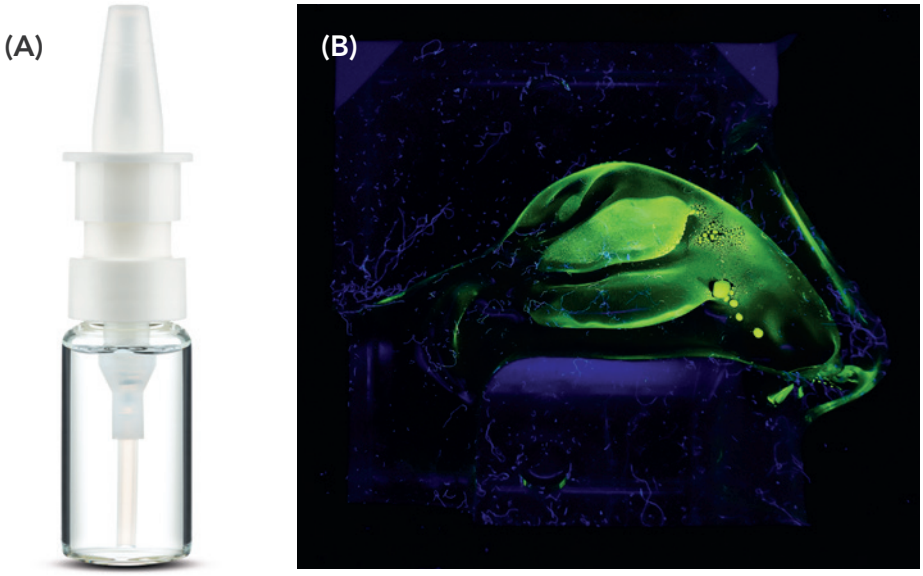

Figure 2: (A) Multidose nasal device: Resyca Ultra Soft Nasal Pump Spray. (B) Image of nasal epithelium coverage due to low-velocity fine mist.[3]

Excipient Function	Excipient Name	In Commercial Product?	Commercial Product Example
Absorption enhancer	Dodecyl maltoside	Yes	Valtoco®
	Alkylsaccharides (Intravail®)	Yes	Nayzilam®
	Chitosan	No	–
	Cyclodextrins (HPβCD)	Yes	Spravato®
	Bile salts (e.g. sodium deoxycholate)	No	–
Mucoadhesive/ residence enhancer	Chitosan	No	–
	Carbomer (Carbopol)	Yes	XHANCE
	Hydroxypropyl methylcellulose (HPMC)	Yes	Flonase
	Sodium hyaluronate	Yes	Ryaltris
Solubiliser (co-solvent)	Propylene glycol	Yes	Sprix®
	Ethanol	Yes	Lazanda
	PEG 400	Yes	Valtoco®
Preservative	Benzalkonium chloride	Yes	Flonase
	Phenylethyl alcohol	Yes	Nasonex
	Potassium sorbate	Yes	Patanase
Buffer/pH adjuster	Product stability	Yes	Flonase
	Weight loss	Yes	Zavzpret®
	Extractables and leachables	Yes	Spravato®
Tonicity adjuster	Sodium chloride	Yes	Narcan®
	Dextrose	Yes	Nayzilam®
	Mannitol	Yes	FluMist®
Antioxidant/stabiliser	EDTA (disodium edetate)	Yes	Flonase
	Sodium metabisulfite	Yes	Neffy®
	Ascorbic acid	Yes	Afrin®
Viscosity modifier	Microcrystalline cellulose + CMC (Avicel® RC)	Yes	Flonase
	HPMC	Yes	Nasacort® Allergy 24HR
	Carbomers	Yes	XHANCE

Table 2: Excipients used in liquid nasal drug products.

FORMULATION CONSIDERATIONS FOR LIQUID NASAL PRODUCTS

Formulation development for liquid nasal products requires a careful balance of chemical stability, mucosal bioavailability, manufacturability and patient safety. Nasal formulations are inherently complex due to the combination of physicochemical properties, device interactions and local tolerability requirements. Early formulation decisions and excipient selection (Table 2) directly impact downstream manufacturing, analytical characterisation and clinical performance.

Formulation Type

Solution formulations are often the first approach considered for nasal delivery due to their simplicity, dose uniformity and compatibility with multidose and unit-dose devices. However, these systems demand rigorous control of solubility, pH, viscosity and chemical stability to maintain product integrity throughout shelf life. Solubilising agents (e.g. cyclodextrins, polyethylene glycol), buffering systems to maintain physiological pH (typically 4.5–6.5) and antioxidants (e.g. ascorbic acid, sodium metabisulfite) are commonly incorporated to mitigate degradation by hydrolysis or oxidation.

Viscosity plays a pivotal role in droplet formation, spray plume geometry and droplet size distribution; optimal viscosity ranges are typically 1–10 cP for aqueous solutions to ensure reproducible atomisation while minimising run-off and nasopharyngeal deposition variability.[5]

Suspension formulations present additional technical challenges. The particle size distribution of the API, typically achieved through micronisation, is critical for dose homogeneity, redispersibility and reproducible pharmacokinetics. Stabilising excipients – such as cellulose derivatives, xanthan gum or polysaccharides – are used to prevent sedimentation, creaming or particle agglomeration over the labelled shelf life. The interplay between suspension viscosity, pumpability and long-term stability often necessitates iterative optimisation, including compatibility testing with the intended delivery device to ensure consistent dose delivery across the container lifespan.[1]

Preservatives and Bioavailability

Preservative strategy is another crucial determinant, particularly for multidose systems. Conventional preservatives such as benzalkonium chloride, phenylethyl alcohol, or potassium sorbate are effective but may cause local irritation, ciliary toxicity or regulatory concerns for long-term use. Consequently, there is a growing trend towards preservative-free multidose devices, which rely on aseptic manufacturing and mechanical tip-seal pump designs to prevent microbial contamination. The choice of preservative – or the decision to omit one – directly influences extractables and leachables profiles, container-closure material selection and the overall microbial control strategy.[4]

Bioavailability-modifying excipients are critical for products requiring rapid systemic absorption or enhanced CNS exposure. Absorption enhancers (e.g. chitosan, alkylsaccharides), mucoadhesive polymers and solubilising agents can increase residence time, facilitate mucosal uptake and potentially support nose-to-brain delivery. Selection of these excipients must balance efficacy, nasal tolerability and regulatory acceptability. The integration of formulation design with device engineering, analytical characterisation and human factors considerations is essential to achieve reproducible delivery and therapeutic performance.

Dara SYX-E-UDS Filling/D

- Max fill rate: 100 units/min
- Typical Capacity: 15M units/yr (3x5)
- Nitrogen sparging capabilities
- In-line visual inspection
- Low Bio-Burden: Filled under laminar flow hood

Figure 3: Unit-dose manufacturing line at Catalent: Dara SYX-E-UDS.

Ultimately, early formulation strategy must be informed by a combination of physicochemical profiling, stability studies, device compatibility testing and *in vitro* deposition modelling. These efforts ensure that liquid nasal products meet both regulatory and clinical requirements while maintaining manufacturability and patient safety.

CLINICAL AND COMMERCIAL PRODUCTION CONSIDERATIONS FOR LIQUID NASAL PRODUCTS

Transitioning a nasal formulation from development to clinical and commercial supply requires early alignment of scalable manufacturing processes, device integration and quality assurance strategies. Liquid nasal solutions and suspensions necessitate specialised filling technologies capable of accurately dispensing small volumes – often in the range of 50–200 µL per actuation – while maintaining dose uniformity and minimising product loss.

Commercial facilities commonly employ precision unit-dose filling systems, such as the Dara (Barcelona, Spain) SYX-E-UDS (Figure 3) and Groninger's (Crailsheim, Germany) DFVN 1000, or multidose platforms such as the Filamatic (Baltimore, MD, US) ProLINE. These are available at Catalent's nasal manufacturing site and incorporate high-accuracy metering, automated stopper placement and validated actuation mechanics to ensure consistent delivered dose and spray performance.

Scale-up and Validation

Scale-up from laboratory to commercial production introduces critical technical considerations. Formulation integrity must be preserved across larger batch sizes without altering rheological properties, droplet size distribution or suspension homogeneity. High-value or low-solubility APIs demand careful management of manufacturing losses during mixing, transfer and filling operations. Process analytical technologies (PAT), including in-line viscosity measurement, turbidity monitoring and near-infrared spectroscopy, can provide real-time quality assessment and support batch-to-batch consistency. Suspension products require rigorous control of particle size distribution throughout blending, holding and filling stages to prevent sedimentation or dose variability. Early generation of robust, scalable process parameters reduces the risk of late-stage reformulation or device requalification.

Validation and process characterisation are central to ensuring commercial readiness. Early identification of critical quality attributes – such as droplet size, plume geometry, DDU and microbial integrity – alongside critical process parameters for mixing, filling and device assembly, enables a risk-based validation strategy. Engineering and demonstration batches serve to confirm reproducibility, device-formulation compatibility and actuation performance under representative operating conditions.

"INTEGRATING FORMULATION SCIENCE, DEVICE ENGINEERING, ANALYTICAL CHARACTERISATION AND MANUFACTURING STRATEGY AT THE EARLIEST STAGES FOSTERS A COHESIVE, HIGH-FIDELITY PRODUCTION PROCESS."

Validation programmes must encompass the entire drug-device combination, including assembly operations, container-closure integrity and, where applicable, aseptic or sterilisation processes to meet regulatory requirements.

Integrating formulation science, device engineering, analytical characterisation and manufacturing strategy at the earliest stages fosters a cohesive, high-fidelity production process. By proactively addressing scale-up, PAT implementation and validation design, developers can ensure that clinical supply is robust, reproducible and aligned with commercial demands, ultimately reducing development timelines and mitigating risk in the pathway to regulatory approval.

CONCLUSION

Liquid nasal dosage forms are experiencing unprecedented growth, with products ranging from small molecules to peptides and biologics, and encompassing solutions, suspensions, emergency therapies and nose-to-brain applications. The complexity of these modalities demands a fully integrated CMC strategy, where early alignment of formulation, device selection, analytical methods, manufacturing processes and microbial control ensures robust, reproducible and scalable outcomes.

Experience across the full development lifecycle is critical for translating innovative nasal therapies from concept to commercial supply. By combining advanced formulation science, precision device engineering, and rigorous manufacturing and analytical practices, developers can mitigate risk, accelerate timelines and deliver reproducible clinical performance. As the nasal therapeutic landscape continues to expand, such co-ordinated approaches will be central to enabling the next generation of high-value, patient-focused nasal drug products.

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Alan Watts, PhD, is Director of Technology & Innovation for Pulmonary and Nasal Products at Catalent. He has nearly 15 years' experience in the development of inhalation products in industrial and academic settings. Prior to Catalent, Dr Watts was Associate Director of Pharmaceutical Development for Savara Pharmaceuticals, leading combination product development, and Research Assistant Professor at the University of Texas at Austin (TX, US), where he oversaw an aerosol research lab, taught pharmacy courses and co-invented a novel dry powder inhaler platform. Dr Watts has a PhD in Pharmaceutics from the University of Texas at Austin and a BS in Biomedical Engineering from Louisiana Tech University (LA, US).

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2026/27 Editorial Calendar

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APR/MAY Sustainability in Drug Delivery DEADLINE PASSED	**MAY** Delivering Injectables: Devices & Formulations DEADLINE PASSED	**JUN** Oral Drug Delivery DEADLINE: **May 21, 2026**
JUL Industrialising Drug Delivery DEADLINE: **May 28, 2026**	**SEP** Wearable Injectors DEADLINE: **Aug 6, 2026**	**SEP/OCT** Dual Chamber Delivery Systems DEADLINE: **Aug 20, 2026**
OCT Prefilled Syringes & Injection Devices DEADLINE: **Sep 3, 2026**	**OCT/NOV** Sustainability in Drug Delivery DEADLINE: **Sep 17, 2026**	**NOV** Pulmonary & Nasal Drug Delivery DEADLINE: **Oct 1, 2026**
DEC Delivering Gene & Cell Therapeutics DEADLINE: **Nov 5, 2026**	**JAN 2027** Prefilled Syringes & Injection Devices DEADLINE: **Dec 10, 2026**	**FEB** Oral Drug Delivery DEADLINE: **Jan 7, 2027**
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AUTOMATING MDI ACTUATION: PRECISION DATA WITH LESS EFFORT

COPLEY

Paul Martin of **Copley Scientific** considers how automation can enhance testing for metered dose inhalers by removing the variability in actuation technique introduced by manual operation, presenting two case studies that demonstrate this potential improvement in data quality.

The susceptibility of metered dose inhaler (MDI) performance to vary depending on actuation technique is an important source of variability in both testing and use. Patient-related variability is unavoidable, but analyst-related variability during testing need not be. Automating actuation reduces a significant and avoidable source of analyst-to-analyst variability in MDI testing, resulting in tighter, more precise data and clearer differentiation between handling effects and true product performance.

In practice, automated actuation reduces the risk of apparent out-of-specification (OOS) results and the need for repeat testing driven by handling variability rather than product performance. Furthermore, with more precise and repeatable data, it becomes easier to investigate the specific effects of actuation parameters and to distinguish those effects from changes in formulation or device design. The net impact is faster progress towards robust performance under conditions that are representative of patient use.

Current efforts to reformulate MDIs with low-global warming potential (GWP) propellants have increased the need for repeatable MDI testing. Changes in formulation properties, such as density and vapour pressure, can increase their sensitivity to variations in actuation technique, reinforcing the importance of tightly controlled testing when assessing comparability or interchangeability. Identifying and controlling such effects is crucial for making confident decisions on accelerated timelines.

Copley Scientific's Vertus® III is an automated shake, fire and flow control platform offering controlled and repeatable delivery for MDIs and nasal drug products. By setting, executing and recording specific actuation parameters, such as shake frequency, shake-to-fire delay and actuation hold time, Vertus III supports controlled studies that isolate which aspects of technique drive variability. The following case studies illustrate how this structured approach can support the investigation and optimisation of actuation technique and the development of more robust test methods, helping to ensure that observed variability reflects product performance rather than differences in operator technique.

HOW ACTUATION PARAMETERS INFLUENCE DOSE DISPERSION AND DELIVERY

To understand how actuation parameters influence MDI performance, it is useful to review their principles of operation. MDI formulations contain an API dissolved or suspended in a propellant or propellant-solvent mixture. The main components of an MDI device are:

- The cannister, which holds the formulation under pressure
- The metering valve, which measures out each dose
- The actuator mouthpiece, which delivers the aerosolised dose to the patient.

Pressing down on the cannister releases a defined metered volume through the actuator mouthpiece. The associated drop in pressure triggers rapid propellant expansion driving aerosol formation and delivery. When downward pressure on the cannister is released, the metering valve refills to prepare the next dose for delivery. This refill, and any associated "priming" behaviour, can be influenced by timing and storage orientation.

Actuation-related variability is generally greater for suspensions than solutions; solutions are inherently homogeneous, whereas suspensions may settle or cream depending on the physicochemical properties of the drug and formulation. Although users are instructed to shake an MDI prior to use, there is typically no specific guidance on how to achieve consistent API dispersion. Key sources of variability include:

1. Shaking, and the time between shaking and firing
   - Shake speed, angle and duration
   - Delay between shaking and firing.

2. Metering valve refill and priming behaviour
   - Actuation force profile (force/time) applied to release the dose
   - Time between repeat actuations and whether it is sufficient to refill the metering chamber
   - Storage orientation during testing, which can influence drainage and loss of prime.

These mechanisms can affect critical quality attributes (CQAs), including:

- Total emitted dose (TED)
- API concentration in the TED relative to the intended homogeneous dispersion
- Aerosolisation dynamics and particle size distribution, influencing the respirable fraction.

Since these CQAs underpin product comparability assessments, controlling actuation conditions is central to robust MDI testing.

HOW AUTOMATED ACTUATION IMPROVES THE QUALITY AND VALUE OF TEST DATA

Published studies demonstrate that actuation-related variability can be significant. For example, a study of five commercially available MDIs reported that, for some products, delays of just 60 s between shaking and firing resulted in delivered doses ≥ 300% relative to the label claim (LC),[1] but only for some – not all – of the MDIs tested. Three produced excessively high delivered doses, one a sub-LC dose and the fifth, a solution-based MDI, showed no discernible change. Actuation-related variability can be both significant and difficult to predict.

In a controlled laboratory setting, training and aids such as timers and metronomes can improve repeatability. However, given the complex interacting mechanisms at play, manual actuation can introduce sufficient variability to obscure subtle but important product-related effects. Reduced sensitivity compromises the value of test data for:

- Understanding its susceptibility to individual aspects of the actuation technique
- Identifying strategies that reduce variability for different patient populations
- Confirming parity between test and reference products when interchangeability is the objective.

"ACTUATION-RELATED VARIABILITY IS GENERALLY GREATER FOR SUSPENSIONS THAN SOLUTIONS; SOLUTIONS ARE INHERENTLY HOMOGENEOUS, WHEREAS SUSPENSIONS MAY SETTLE OR CREAM DEPENDING ON THE PHYSICOCHEMICAL PROPERTIES OF THE DRUG AND FORMULATION."

"AUTOMATING ACTUATION REDUCES UNCONTROLLED VARIABILITY IN DOSE DELIVERY, ENABLING RIGOROUS DoE STUDIES. THE RESULTING DATA CAN SUPPORT OPERATOR TRAINING, INFORM INSTRUCTIONS FOR USE AND STRENGTHEN THE QUALITY OF REGULATORY SUBMISSIONS."

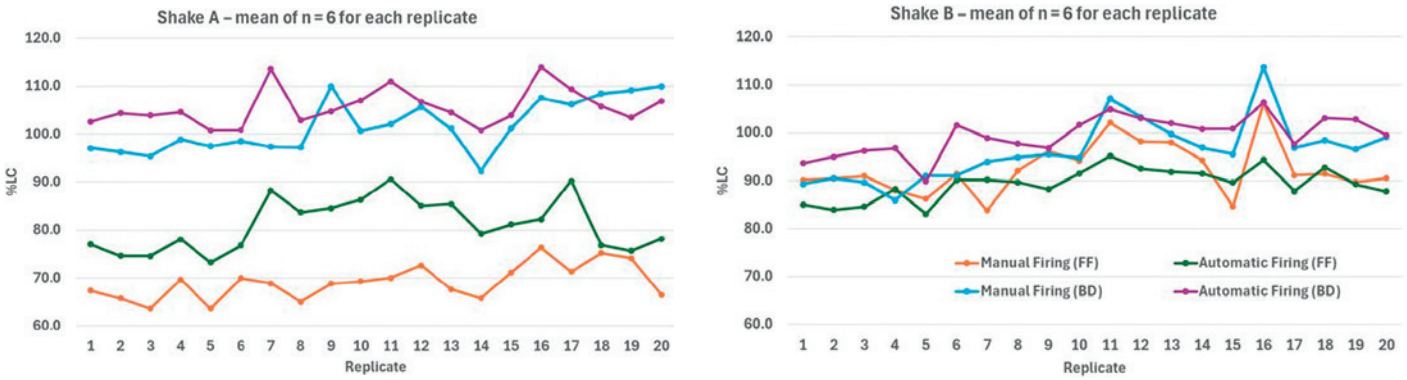

Figure 1: Through-life delivered dose data show that FF delivery is more susceptible than BD to shake, hold and fire variability (Shake A – left, Shake B – right). Shake B produces more consistent FF dose delivery closer to LC. (Originally presented at DDL 2025 and reproduced with kind permission of the authors.)

Automating actuation reduces uncontrolled variability in dose delivery, enabling rigorous design of experiment (DoE) studies. The resulting data can support operator training, inform instructions for use and strengthen the quality of regulatory submissions. The following case studies illustrate these benefits.

CASE STUDIES

Isolating the Impact of Human Factors in MDI Testing

This case study demonstrates how automated actuation improves MDI data quality – especially for suspension-based products – and differentiates shake profiles with respect to dose consistency, establishing a secure basis for operator training and test method development. Figure 1 summarises delivered dose uniformity results for Symbicort (AstraZeneca), a dual API MDI containing budesonide (BD) in solution and formoterol fumarate (FF) in suspension.[2] Tests were carried out using two different shake, hold and fire profiles – Shake A and Shake B (Table 1) – with both manual actuation and automated actuation using Copley Scientific's Vertus III+. Six MDIs were tested for each shake method (24 in total). Shots were collected at beginning (10), middle (5) and end of life (5) for each test.

These results show that the delivered dose of the BD solution was relatively insensitive to the applied shake, hold and fire profile. In contrast, the FF suspension was sensitive, with Shake B clearly preferable for delivering the LC. A proposed rationale for this is that the formulation is prone to creaming or foaming, with the susceptibility minimised by the shorter shake time and longer delay of the Shake B profile.

	Shake A	Shake B
Shake time	5 seconds	1 second
Wait time	None	3 seconds
Actuation time	2 seconds	2 seconds

Table 1: Shake, hold and fire profiles for Shake A and Shake B. (Originally presented at DDL 2025 and reproduced with kind permission of the authors.)

For FF using Shake A, manual actuation produces greater variability and a shift in mean relative to automated actuation (Figure 2). This suggests that the Shake A parameters are not robust for this product. With the Shake B parameters, the manual and automated data were more closely aligned, but automation still produced tighter and more consistent data. Automation also reduced variability in the

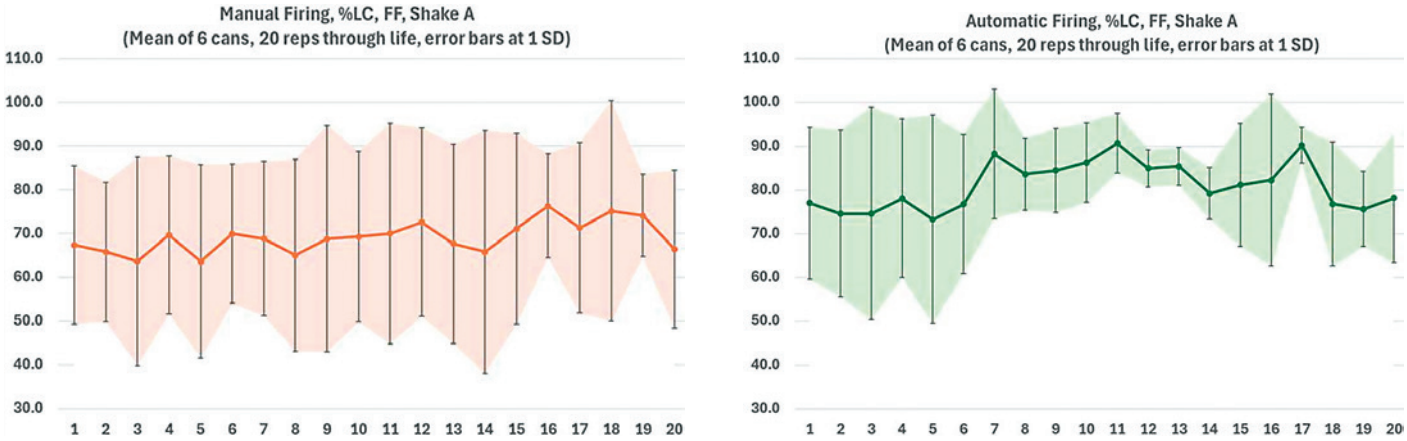

Figure 2: Under Shake A, automated actuation reduces the variability of the FF delivered dose relative to manual actuation, with tighter clustering around the mean. (Originally presented at DDL 2025 and reproduced with kind permission of the authors.)

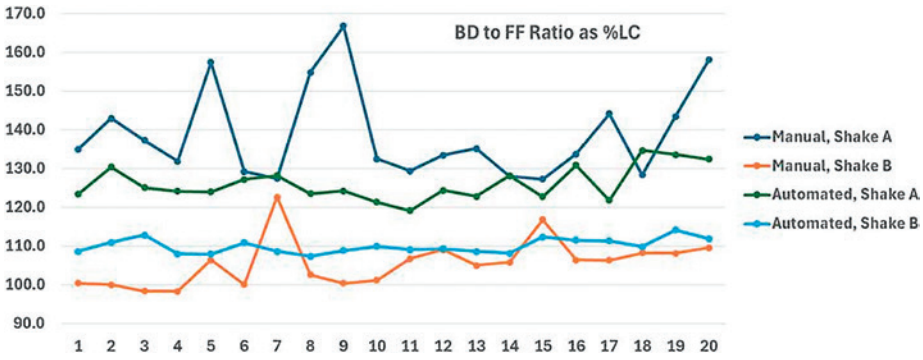

Figure 3: Automated actuation improves the consistency of BD:FF delivered dose ratio. (Originally presented at DDL 2025 and reproduced with kind permission of the authors.)

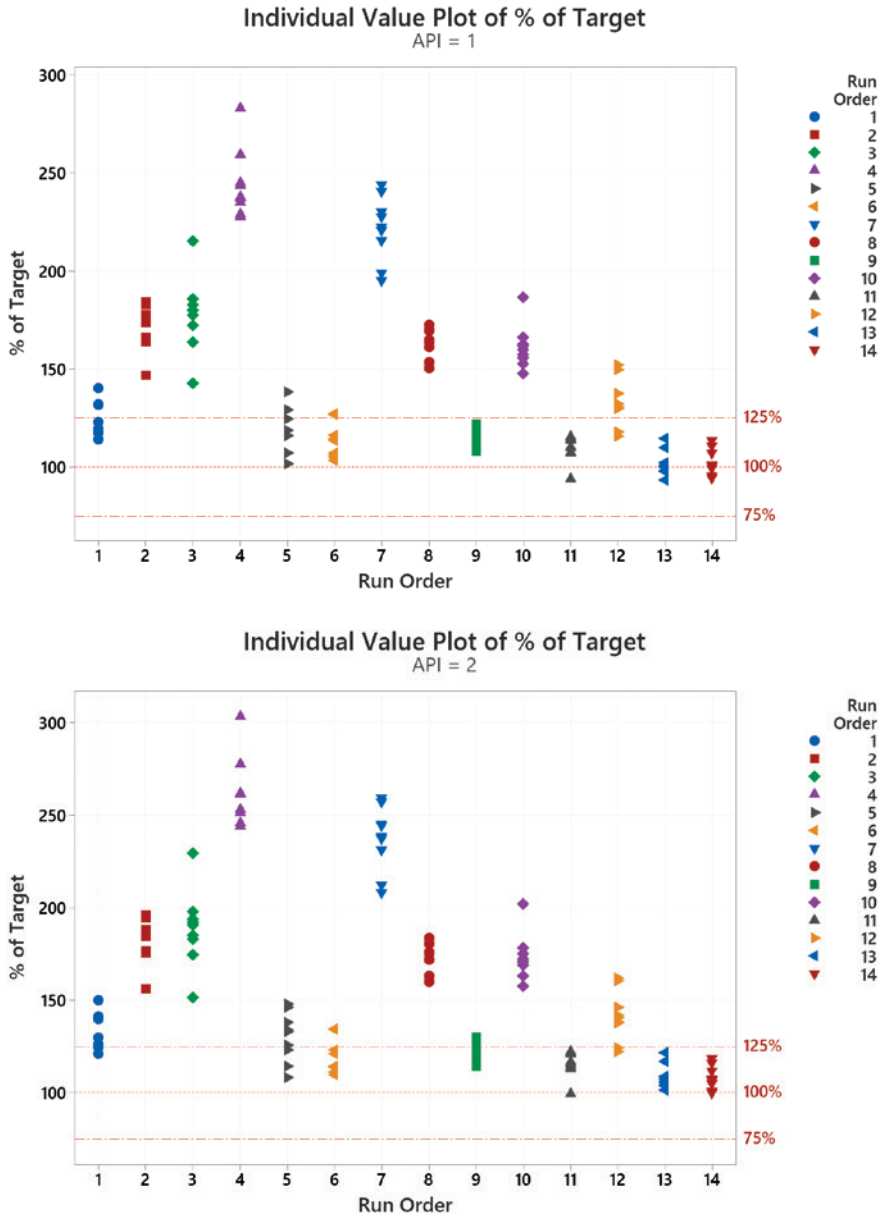

Figure 4: DoE results identify actuation conditions (runs 13 and 14) that produce delivered doses closest to LC for a novel low-GWP dual-active MDI (API 1 – top, API 2 – bottom). (Originally presented at DDL 2025 and reproduced with kind permission of the authors.)

BD data (data not shown), although to a lesser extent, which is consistent with the lower susceptibility of solution-based MDIs to actuation variability.

For this dual API product, the BD:FF ratio (Figure 3) can be a sensitive indicator of dispersion consistency. Under Shake B parameters, ratio consistency was strong, with a relative standard deviation (RSD) of 1.7%, while individual API RSDs were higher (7.2% RSD for FF, 6.8% RSD for BD). This suggests that, with Shake B, metered doses are close to homogeneous in composition, with both APIs trending together.

A key conclusion from this study is that automated actuation in combination with an optimal actuation profile (Shake B) is an effective way of reducing variability to ensure robust testing and enable the study of inherent variability relating to device metering and product performance.

Assessing the Influence of Actuation Technique on Dose Delivery for a Low-GWP MDI

This case study demonstrates how automated actuation can be used to quantify the susceptibility of an HFA 152a-based MDI to variability in specific actuation parameters and to identify robust analytical methodologies to support early-stage product development. Figure 4 and Table 2 show data from a DoE study evaluating the impact of actuation parameters on dose content uniformity for each API from a dual-API, ethanol-free MDI formulated with HFA152a (a low-GWP propellant).[3]

Four parameters were investigated:

- Shake speed (1 or 2 Hz)
- Shake duration (5 or 10 s)
- Shake to fire delay (1, 2 or 3 s)
- Actuation hold time (0 or 1 s).

For each condition, three doses were collected from each of three devices at the beginning of unit life. Samples were collected into a standard dose uniformity sampling apparatus in accordance with relevant pharmacopoeial guidelines, using automated actuation for dose delivery (Vertus® +).

Runs 4 and 7 produced the highest delivered doses, exceeding 200% of LC

Standard Order	Run Order	Shake Speed (Hz)	Shake Duration (s)	Shake-to-Fire Delay (s)	Actuation Hold Time (s)
5	1	2	10	~2	1
7	2	2	5	~3	1
13	3	1	5	~2	1
12	4	1	5	~3	1
3	5	2	5	~3	0
9	6	2	5	~1	1
1	7	1	10	~3	1
10	8	1	10	~3	0
8	9	1	10	~1	0
4	10	1	10	~1	1
14	11	2	10	~2	0
6	12	1	5	~2	0
2	13	2	5	~1	0
11	14	2	10	~1	0

Table 2: DoE settings used to evaluate the impact of actuation parameters on dose content uniformity. (Originally presented at DDL 2025 and reproduced with kind permission of the authors.)

for both APIs. In contrast, runs 13 and 14 produced delivered doses closest to target at ~102% and ~108% of LC for API 1 and 2, respectively. Runs 13 and 14 shared a higher shake speed (2 Hz) and the shortest combined time for shake-to-fire delay (1 s) and actuation hold time (0 s). Differences relative to LC between the two APIs were consistent with differences in their density and, by extension, settling rate.

More generally, the study identified shake speed, shake-to-fire delay and actuation hold time as statistically significant factors for delivered dose, while shaking duration was not significant within the tested range. These findings are consistent with the practical expectation that vigorous shaking followed by immediate firing minimises the risk of settling in sedimenting formulations. Minimising hold time further improves dosing consistency by increasing the probability of sampling a more homogenous formulation prior to the next actuation.

A key observation is that the trends are driven by small timing differences, on the order of just 1 s. Executing this run order with that level of precision would be challenging using manual actuation; automated actuation therefore enables generation of method-development data that would be difficult to obtain reliably using manual actuation. For development programmes in which bioequivalence and comparability decisions depend on sensitive measurements, this can materially reduce risk.

STEP-BY-STEP TO THE BENEFITS OF AUTOMATION

For laboratory managers, the value of automation is usually measured in two ways: data quality and throughput. This article focuses on a single task – actuation – and shows how controlling actuation parameters reduces an avoidable cause of variability. However, with automation, the broader opportunity is cumulative; when repeatable actuation is combined with automation across additional steps and supported by connected data handling, laboratories can strengthen:

- Data integrity and traceability of test conditions
- Method robustness and transferability
- Speed and defensibility of OOS investigations.

In laboratories where dose variability leads to repeat testing or difficult investigations, controlling actuation is

"IN LABORATORIES WHERE DOSE VARIABILITY LEADS TO REPEAT TESTING OR DIFFICULT INVESTIGATIONS, CONTROLLING ACTUATION IS A LOGICAL FIRST STEP."

a logical first step. Establishing defined and documented actuation conditions removes a significant cause of variability and strengthens confidence in every result generated.

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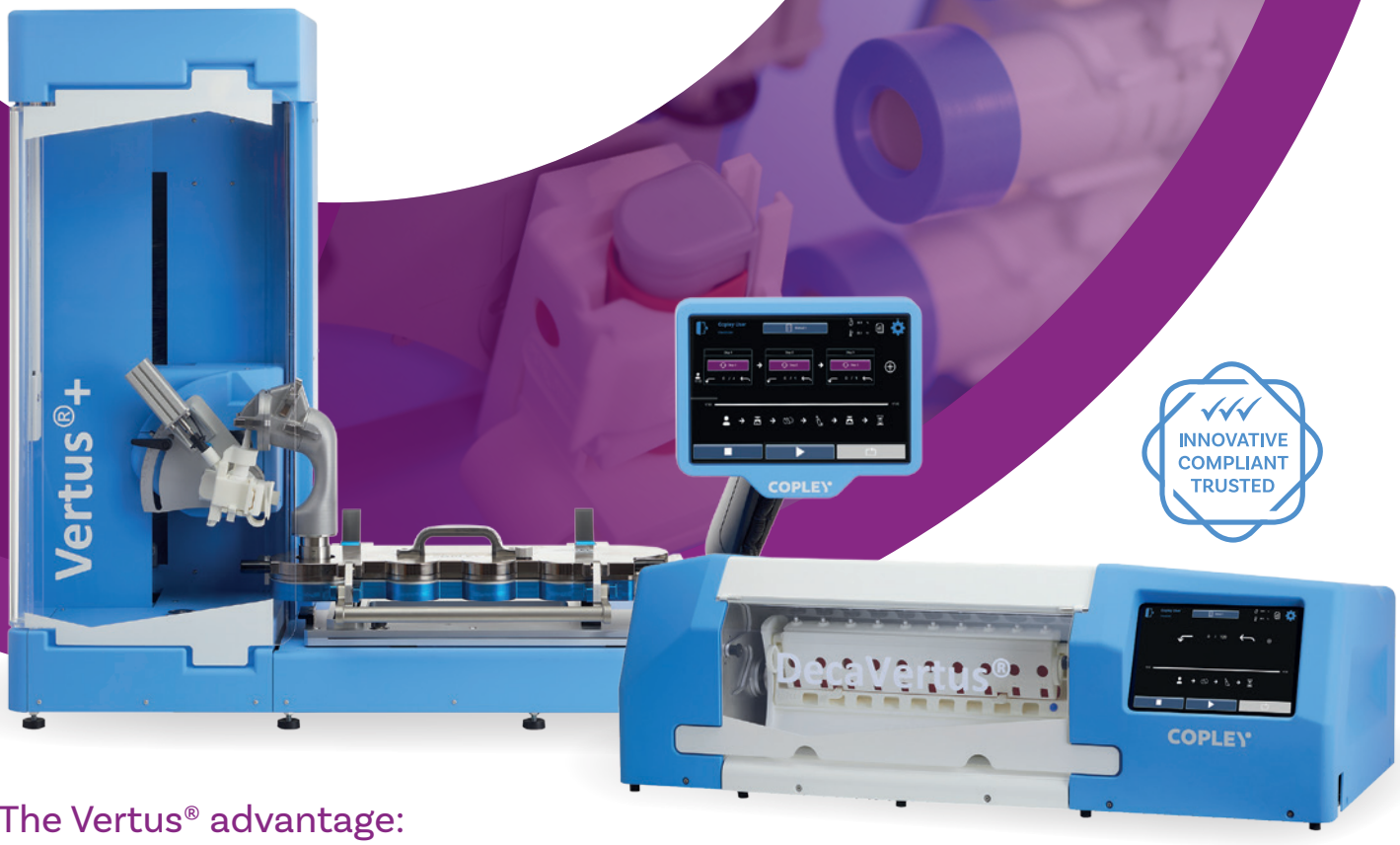

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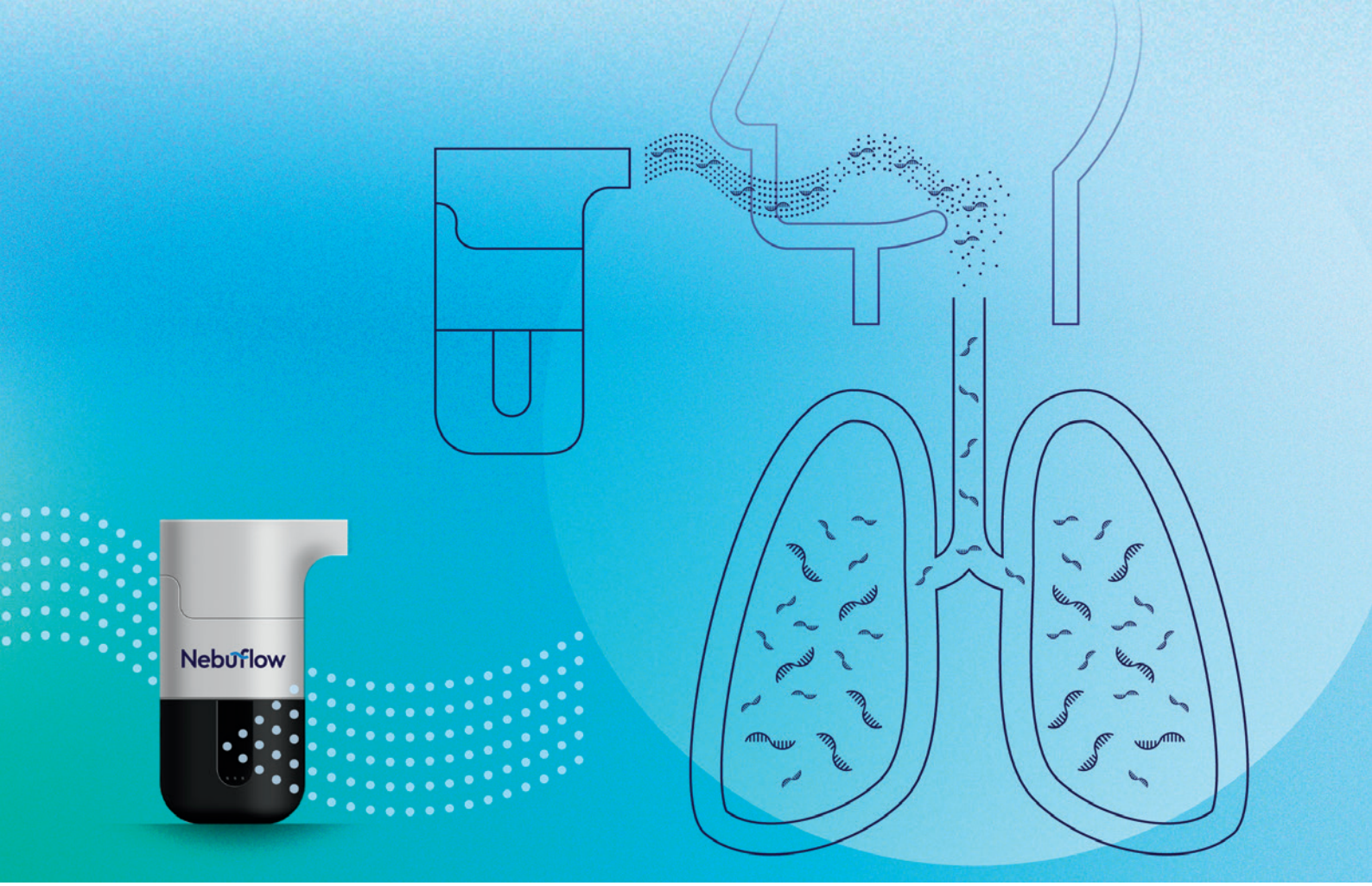

ACOUSTIC WAVE PLATFORM NEBULISER FOR INHALED DELIVERY OF BIOLOGIC THERAPIES

Nebuflow

Dr Elijah Nazarzadeh of **Acu-Flow Limited** (trading as **Nebu~Flow**) reports on the applications of Nebu~Flow, an acoustic wave-based nebuliser platform, addressing the challenges associated with drug delivery to the lungs via more efficient aerosolisation, enabling precise inhaled delivery of life-changing treatments.

The ability of biologic medicines to specifically target the underlying mechanisms of a wide range of diseases has driven substantial interest and investment in their development. This momentum facilitated the rapid development and approval of the first messenger RNA (mRNA)-based vaccines during the covid-19 pandemic, highlighting the potential of novel therapeutic platforms and encouraging a more optimistic outlook for future drug development.

Despite these advances, the number of approved biologic therapies remains relatively limited, particularly for respiratory disorders. Currently, the approved treatments for such conditions are primarily monoclonal antibodies, administered via intravenous or subcutaneous injection. In contrast, RNA-based therapeutics are still emerging, with only 25 approved globally. Only a few of these novel therapeutics have been formulated, let alone approved for inhalation, a promising delivery route for biologics that offers high local drug concentration with reduced systemic exposure.[1]

Beyond the conventional formulation, stability and pharmacokinetic considerations associated with biologic drug development, additional challenges arise when developing these therapies for inhalation. In particular, device compatibility and aerosol performance requirements – such as achieving an optimal aerodynamic particle size distribution – present significant barriers.

Inhalation drug delivery systems generally rely on the dispersion of either dry powder or liquid formulations. Currently, the majority of RNA-based therapeutics under development for respiratory indications are formulated as liquids.[2–4] This route typically requires fewer development steps than dry powder formulations and is often preferred in early-stage development, particularly for clinical evaluation.

Nebulisers are primarily used for pulmonary delivery of liquid medicines, applying energy to the formulations to generate respirable aerosols. However, this process can subject sensitive biologics to mechanical shear, thermal stress and interfacial forces, potentially leading to degradation, denaturation or loss of functional activity.

Vibrating mesh nebulisers are currently among the most widely used platforms in research and early development of RNA therapeutics, but even these advanced devices can have limitations. Reported challenges include shear-induced damage to large biomolecules, finite mesh lifetime due to vibrational wear, clogging of mesh apertures and the need for extensive cleaning and maintenance.[5–7]

In contrast, Nebu~Flow® technology uses acoustic wave energy to aerosolise liquid formulations. With this platform, acoustic waves are generated on the surface of a piezoelectric substrate and transferred into the liquid along their propagation path, resulting in controlled aerosol formation.

Current evidence indicates that the technology can address many of the key mechanical and performance constraints of conventional nebuliser systems. In previous studies, Acu-Flow Limited demonstrated the capability of Nebu~Flow to generate fine aerosols with a fine particle fraction exceeding 90% for formulations containing small interfering RNA (siRNA). More recent investigations have shown that the platform can be tuned, enabling aerosol generation under reduced shear conditions. Furthermore, the system employs an energy transfer approach free of coupling layers, making the nebulising engine readily replaceable. This potentially eliminates the cleaning limitations associated with conventional mesh-based devices.[8–10]

The evaluated formulations span a range of molecular sizes and structural complexities, including antisense oligonucleotides (ASOs), conjugated siRNA, mRNA and plasmid DNA, as well as fragile liposomal and lipid nanoparticle (LNP) delivery systems. All studies were conducted within clinically relevant concentration ranges, based on previously reported data for each formulation.

SMALL RNA-BASED MOLECULES

Both ASOs and siRNAs are short, synthetic nucleic acid therapeutics, typically fewer than 25 nucleotides in length, designed to modulate gene expression. Advances in chemical modification strategies have improved their structural stability, cellular uptake and resistance to nuclease degradation. Nevertheless, recent studies have indicated that nebulisation may induce oxidative stress, strand cleavage or conformational alterations in nucleic acid therapeutics, particularly under conditions involving elevated shear or interfacial stress.[11]

Antisense Oligonucleotides

Danvatirsen, a chemically modified, 16-mer, single-stranded, antisense gapmer targeting signal transducer and activator of transcription 3 (STAT3) mRNA, was selected as a model ASO. The compound was nebulised at clinically relevant concentrations (≥20 mg/mL). Aerosol samples were collected using a Next Generation Impactor (NGI) and evaluated for both structural integrity and biological activity.

Structural characterisation was performed using liquid chromatography-mass spectrometry (LC-MS). Analysis demonstrated no detectable structural modifications in the nebulised ASO compared with the non-nebulised reference (Figure 1), indicating preservation of molecular integrity following aerosolisation.

Biological activity was assessed in A431 epidermoid carcinoma cells using a STAT3 enzyme-linked immunosorbent assay (ELISA) to quantify target knockdown. Dose-response curves for all nebulised samples met predefined system suitability

(A)

(B)

Details	R^2	Potency (%)	Ratio A	Effective Asymptote Ratio	Slope Ratio	Pass/Fail
Nebulised 1	0.99	99	1.14	1.18	0.79	PASS
Nebulised 2	1	87	1.22	1.25	0.92	PASS
Nebulised 3	1	129	1.01	1.01	0.94	PASS
Positive 1	1	137	1.02	1.03	0.84	PASS
Positive 2	0.99	105	1.07	1.09	0.87	PASS

Figure 1: (A) Summary of purity and phosphorus-sulphur:phosphorus-oxygen ratio for all nebulised samples, compared with controls. (B) Results of ELISA showing potency levels of nebulised samples, compared with non-nebulised danvatirsen. Scrambled ASO was used as a control.

criteria (including R^2 values, asymptote ratios and slope ratios) and all samples satisfied assay acceptance requirements. Relative potency values ranged from approximately 87–129% compared with the non-nebulised reference, with variability consistent with the non-validated status of the assay (Figure 1B).

Importantly, all nebulised samples demonstrated clear STAT3 knockdown activity, confirming retention of functional potency following aerosolisation. Positive controls performed as expected, and non-nebulised reference samples exhibited relative potencies of 137% and 105%.

Small Interfering RNA

Chemical conjugation strategies, such as ligand attachment, are widely used to enhance siRNA stability, cellular uptake and pharmacological performance. In this study, a chemically modified, trivalent N-acetylgalactosamine (GalNAc)-conjugated siRNA was nebulised at a concentration of 100 µg/mL. This model system enabled assessment of both nucleic acid integrity and potential shear-induced detachment of the conjugated ligand following Nebu~Flow nebulisation.

The process involved size-fractionated aerosol sampling (<5 µm) conducted using a parafilm-modified NGI. Aerosol collected from all NGI stages was then pooled to generate one representative sample per nebulisation run. Structural integrity of GalNAc-siRNA was assessed using gel electrophoresis.

Bioactivity was evaluated by incubating nebulised samples with primary mouse hepatocytes at concentrations of 1 nM and 4 nM for 48 hours. Following incubation, cells were lysed and mouse transthyretin mRNA expression levels were quantified using TaqMan quantitative PCR and normalised to glyceraldehyde-3-phosphate dehydrogenase expression. The 4 nM condition served as a full-knockdown control (>95%), while the 1 nM concentration was selected to detect any reduction in activity attributable to nebulisation.

Gel electrophoresis analysis of triplicate samples generated using the Nebu~Flow nebuliser demonstrated identical banding patterns between nebulised samples and positive controls (Figure 2). The observed bands corresponded to intact GalNAc-siRNA, which migrated at a higher apparent molecular weight than unconjugated siRNA, confirming preservation of the conjugated structure following aerosolisation.

Functional assessment demonstrated >95% knockdown at 4 nM and >90% knockdown at 1 nM, indicating no measurable loss of biological activity, even at low concentrations.

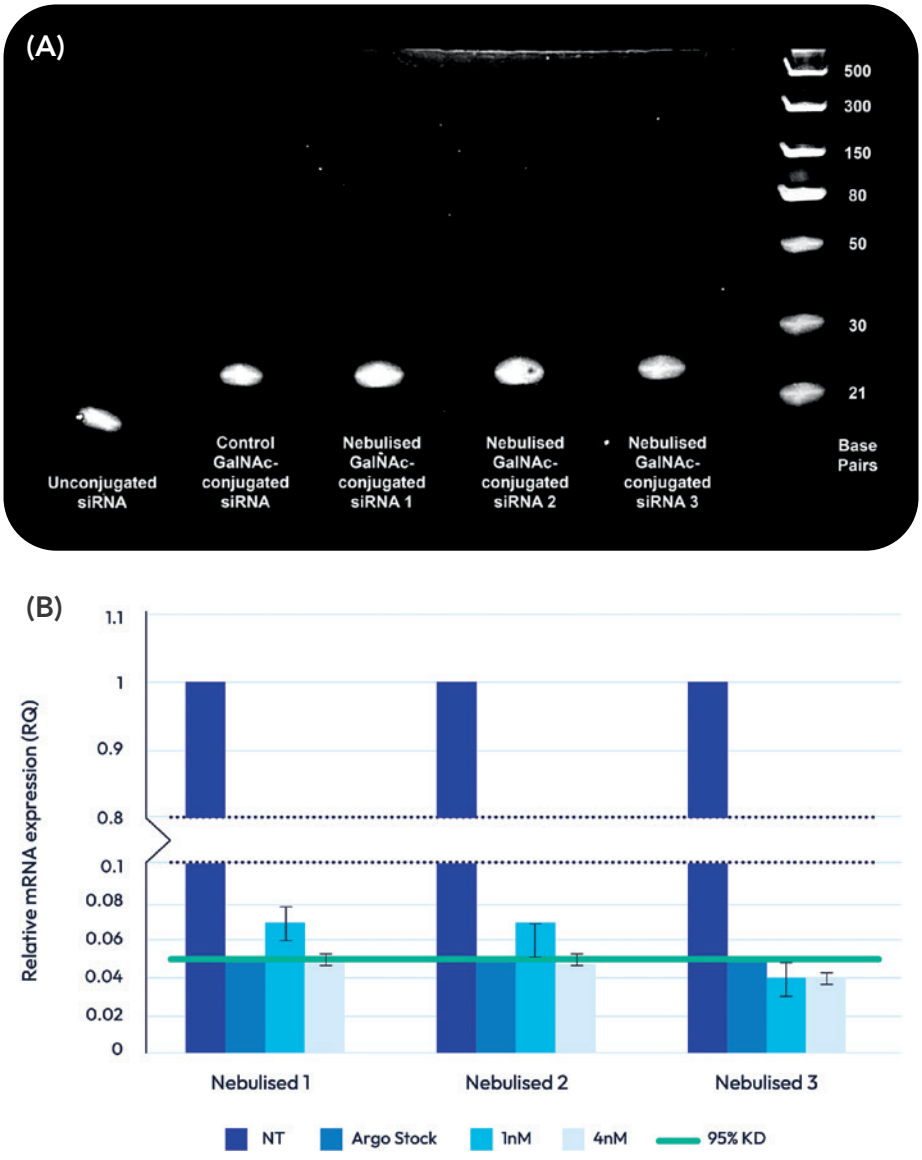

Figure 2: (A) Integrity of nebulised GalNAc-conjugated siRNA assessed via non-denaturing polyacrylamide gel electrophoresis (n=3). (B) Knockdown efficacy of nebulised GalNAc-conjugated siRNA in primary mouse hepatocytes with 3 replicates.

LARGE RNA-BASED MOLECULES

Shear forces generated during nebulisation are frequently implicated in fragmentation of large nucleic acids. Shear sensitivity increases with molecular length; therefore, plasmid DNA (>2,500 base pairs) was selected as a model to evaluate mechanical stress associated with aerosolisation. A commercially available vibrating mesh nebuliser was included as a benchmark comparator.

Structural characterisation of plasmid DNA before and after nebulisation was performed using a bioanalyser, enabling quantification of DNA strand size distribution (Table 1). Samples nebulised using the Nebu~Flow platform showed a ~1% reduction in the proportion of large plasmid species, compared with a

Sample	>3kb (%)	1-3kb (%)	<1kb (%)
Non-nebulised	19.7	11.6	68.7
Nebu~Flow	18.57	15.97	65.46
Mesh	16.53	23.03	60.44

Table 1: Extracted data from bioanalyser, showing the concentration of different sizes of Plasmid DNA fragments for non-nebulised (control) and nebulised samples from Nebu~Flow and a mesh nebuliser.

"THESE RESULTS INDICATE THAT THE NEBU~FLOW PLATFORM IMPOSES LOWER SHEAR STRESS RELATIVE TO CONVENTIONAL MESH NEBULISERS, RESULTING IN REDUCED FRAGMENTATION OF LARGE NUCLEIC ACID CONSTRUCTS."

>3% reduction observed with the mesh nebuliser. Additionally, mid-size fragment populations increased by ~4% following Nebu~Flow nebulisation, compared with >10% in samples processed using the mesh device.

These results indicate that the Nebu~Flow platform imposes lower shear stress relative to conventional mesh nebulisers, resulting in reduced fragmentation of large nucleic acid constructs.

LIPID CARRIERS FOR ENHANCED TRANSFECTION OF BIOLOGICS

Biologic therapeutics, particularly large nucleic acids such as mRNA, require delivery systems to facilitate cellular uptake and enhance transfection efficiency. These delivery vehicles are typically lipid-based carriers, including liposomes and LNPs. Liposomes, composed of phospholipid bilayers, are generally larger and structurally more fragile than LNPs, making them a relevant and sensitive model for assessing shear-induced damage during aerosolisation.

In this study, liposomes encapsulating green fluorescent protein mRNA were formulated using the LipidBrick® system (Sartorius, Göttingen, Germany) according to the manufacturer's protocol. The formulations were nebulised using the Nebu~Flow acoustic wave nebuliser platform and a commercially available vibrating mesh nebuliser as a comparator. The aerosol was then collected and condensed in a low binding vial. Post-nebulisation characterisation was performed using dynamic light scattering with a Zetasizer (Malvern Panalytical, Malvern, UK) to determine hydrodynamic diameter (Z-average), polydispersity index (PDI) and zeta potential. Encapsulation efficiency (EE) was quantified using a RiboGreen assay.

Sample	Z-average (nm)	PDI	Zeta Potential (mV)	EE (%)
Non-nebulised	186.3±15.6	0.11	8.5±2.0	98.9±0.3
Nebu~Flow	202.2±6.8	0.12	6.7±1.1	98.4±0.1
Mesh	276±41.9	0.36	-3.3±7.2	73.0±20.9

Table 2: Physical characteristics of liposomes before and after nebulisation. The Nebu~Flow nebuliser had the lesser impact, with no loss in mRNA load, compared with the non-nebulised sample. The mesh nebuliser caused a large change in liposome size and over 20% loss in mRNA load.

Nebulisation with the Nebu~Flow platform resulted in a minimal increase in liposome size (~15 nm), whereas samples processed using the mesh nebuliser exhibited a substantially larger size increase (~90 nm). The PDI of Nebu~Flow-treated samples remained close to 0.1, consistent with a monomodal and homogeneous size distribution. In contrast, samples aerosolised using the mesh nebuliser displayed markedly elevated PDI values, indicating significant disruption and heterogeneity in liposome populations.

These findings were further supported by changes in zeta potential and EE. Mesh-nebulised samples exhibited a shift toward more negative zeta potential values and a >25% reduction in EE, suggesting substantial mRNA leakage and carrier destabilisation. Free mRNA is unlikely to provide therapeutic benefit due to rapid degradation and poor cellular uptake.

Collectively, these results demonstrate that aerosolisation using the Nebu~Flow nebuliser platform preserves liposome structural integrity and mRNA encapsulation to a significantly greater extent than conventional mesh nebulisation, supporting its suitability for the aerosol delivery of fragile lipid-based mRNA formulations (Table 2).

CONCLUSION

Unlocking the potential of inhaled RNA therapeutics will depend on the development of nebuliser technologies capable of addressing the challenges of aerosolising structurally sensitive biomolecules. Nucleic acid therapeutics are inherently vulnerable to shear, interfacial stress and potential oxidative degradation during aerosol generation. Their sensitivity increases with molecular size and structural complexity, particularly for conjugated siRNA, large plasmid DNA and lipid-encapsulated mRNA formulations.

The findings presented here demonstrate that the Nebu~Flow acoustic wave-based nebuliser platform efficiently aerosolises a broad spectrum of RNA-based therapeutics while consistently preserving their

structural integrity and biological activity:

- For chemically modified ASOs, nebulisation using clinically relevant doses resulted in no detectable structural alteration by LC-MS and maintained full biological activity in a STAT3 knockdown assay.
- GalNAc-conjugated siRNA retained structural integrity and demonstrated preserved functional potency in primary hepatocytes, achieving >95% gene silencing at benchmark concentrations.
- For large plasmid DNA, the Nebu~Flow platform imposed substantially lower shear stress compared with a conventional vibrating mesh nebuliser, resulting in reduced fragmentation of high molecular weight nucleic acids.
- In lipid-based mRNA formulations, key determinants in delivery and therapeutic efficacy – liposome size distribution, surface charge characteristics and EE – were maintained with Nebu~Flow, whereas the comparator mesh device induced significant carrier disruption and mRNA leakage.

By providing a gentler and more tuned approach to aerosolisation, capable of supporting the inhaled delivery of shear-sensitive nucleic acid therapeutics across a wide molecular size range, Nebu~Flow may represent a promising platform to enable the clinical translation of inhaled RNA-based biologics.

ACKNOWLEDGEMENTS

The work described in this article is the result of a collaborative effort across the Nebu~Flow team. The author would particularly like to acknowledge Kiing Seng Wong, Niel Fullarton, Sarina Saeidi, and Ivona Ivanova for their outstanding contributions to the conceptual development, design and execution of the programme.

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"UNLOCKING THE POTENTIAL OF INHALED RNA THERAPEUTICS WILL DEPEND ON THE DEVELOPMENT OF NEBULISER TECHNOLOGIES CAPABLE OF ADDRESSING THE CHALLENGES OF AEROSOLISING STRUCTURALLY SENSITIVE BIOMOLECULES."

Dr Elijah Nazarzadeh

Elijah Nazarzadeh, PhD, is the Founder and Chief Scientific Officer of Acu-Flow Limited (trading as Nebu~Flow). Dr Nazarzadeh has a PhD in Fluid Mechanics from King's College London (UK). During his career, he has provided scientific consultation to a number of companies in the field of colloids and interface science. He developed the Nebu~Flow technology while working as a postdoctoral researcher at the University of Glasgow (UK) and led its development and commercialisation activities, then founding Acu-Flow Limited in 2019. Dr Nazarzadeh received a Lee Lucas Award from the Institute of Physics (UK) for his exceptional efforts in the development of Nebu~Flow technology.

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A NOVEL HUMAN FACTORS APPROACH FOR A NEW PLATFORM-BASED, BREATH-TRIGGERED NEBULISER

Simon Bucher of **PARI Pharma** and **Dr Amy MacDonald** and **Dr John DeFoggi** of **BPTM** explain how human factors engineering is at the centre of the development of PARI's breath-triggered eFlow® Integrated nebuliser, and consider how this approach preserves scientific rigour while avoiding redundant testing and ensuring efficient resource allocation.

Human factors (HF) engineering prioritises the user experience throughout product development with the aim of developing patient-centric devices that optimise usability, improve adherence and minimise risks associated with use. Effective patient-centric nebuliser devices are invaluable in respiratory disease management, with a wealth of evidence demonstrating their many benefits, including enhanced drug delivery efficiency, better compliance, reduced symptom burden and improved patient satisfaction.[1,2]

DEVELOPING A PATIENT-CENTRIC NEBULISER DEVICE PLATFORM

Within a platform approach, a shared core technology is defined that serves as the foundation for multiple applications. In this case, the nebuliser functions as a drug delivery device with a standardised core architecture that remains consistent across products, while certain components or performance parameters can be adapted to accommodate different APIs, therapeutic areas or specific treatment requirements.

This approach enables pharmaceutical companies to use the same fundamental nebuliser platform to develop their own combination product and mitigate risk by reducing development efforts, regulatory complexity and time to market. While this preserves sufficient flexibility to meet drug- and indication-specific requirements, this approach creates unique HF challenges for the device manufacturer when developing a new platform product for a large therapeutic category. This is particularly relevant in the respiratory field, where rare diseases play an important role, especially if highly specific user characteristics need to be targeted.

At the time of platform development, however, none of the pharmaceutical partner, final drug product and target indication are known. The platform therefore requires broad usability across diverse patient groups.[3,4]

In addition, pharmaceutical companies typically generate proprietary HF data for their own combination products. Limited data-sharing between agencies and pharmaceutical companies – even when using the same platform device – combined with the regulatory expectation of available test data with the intended patients often weakens confidence in early HF data generated at a platform level. As a result, pharmaceutical companies tend to incorporate comprehensive, time-consuming and costly usability assessments into their development programmes that often re-evaluate previously addressed issues.

Optimising this process through early identification of both usability risks and meaningful user characteristics has the potential to improve time to submission and eliminate redundant formative testing throughout the regulated pathway. Pharmaceutical companies rely on minimising development risk and accelerating time to market by selecting an appropriate nebuliser device for their drug products.

As demonstrating safe and effective use in HF summative studies is part of the NDA process, they must have confidence that the respective nebuliser is appropriate for their specific patient population based on the HF activities already conducted. This presupposes that the previously generated tests and supporting evidence are demonstrably applicable to their intended patient population, and that these data can be provided by the manufacturer and incorporated within the pharmaceutical companies' regulatory documentation. Consequently, pharmaceutical companies can integrate the device more seamlessly into their drug product and focus their development efforts on the user interface specific to their combination product, such as co-packaging and labelling.

However, regulatory authorities such as the US FDA increasingly expect manufacturers to clearly delineate how a new platform product differs from similar cleared comparators or other versions of the same platform product.[5,6] Such comparative justification can enable the agency to conduct a more efficient and focused review by identifying product-specific risks, novel features and relevant regulatory considerations. To achieve this, PARI has initiated a new approach that generates usability data during device platform development in a format that can be efficiently incorporated into combination-product HF programmes, thereby minimising redundant testing cycles.

When developing the new breath-triggered eFlow® Integrated nebuliser platform,[7] PARI established a comprehensive HF strategy. By prioritising a more robust user characteristics assessment (UCA) over individual disease labels, PARI ensures that the device meets the needs and characteristics of a diverse target population with varying respiratory conditions.

> "BY PRIORITISING A MORE ROBUST UCA OVER INDIVIDUAL DISEASE LABELS, PARI ENSURES THAT THE DEVICE MEETS THE NEEDS AND CHARACTERISTICS OF A DIVERSE TARGET POPULATION WITH VARYING RESPIRATORY CONDITIONS."

HF-CENTRED DEVELOPMENT OF PARI'S eFLOW® INTEGRATED NEBULISER

Understanding human functional capabilities and limitations is fundamental to designing safe and effective medical devices. It provides device manufacturers with the context and general range of what their intended user population has the potential capacity to do. However, an individual's ability to use a device ultimately depends on the specific combination of their personal user characteristics. Disease conditions, therapeutic interventions and patient age represent critical variables that can substantially influence product use, user interaction and overall performance in both clinical and home settings. In recognition of these factors, the FDA requires usability and HF testing to be conducted with representative intended users under conditions that reflect the anticipated context of use.

Accordingly, PARI adopted a broad respiratory-focused approach to systematically characterise shared and divergent patient attributes across relevant indications. This strategy was intended to identify commonalities that may support platform-based development while also delineating clinically meaningful differences that could potentially affect usability, risk profiles or performance outcomes.

INTEGRATION OF USER CHARACTERISTICS ASSESSMENT INTO TRADITIONAL HF TESTING

PARI conducted literature reviews and expert interviews with pulmonologists to map shared and divergent functional patient characteristics across respiratory indications, including chronic obstructive pulmonary disease, cystic fibrosis, interstitial lung disease (ILD), idiopathic pulmonary fibrosis, bronchiolitis obliterans syndrome and pulmonary arterial hypertension. This research provided initial evidence that respiratory diseases share a broad set of physiological and psychological patient capabilities (i.e. persistent and progressive respiratory symptoms, cognitive impairment, reduced strength and

mobility). Figure 1 shows how disease-specific and non-specific symptoms affect physical and cognitive impairment in ILD.

The identified characteristic commonalities were then translated into definable user characteristics that could impact handling of the device (e.g. hand strength, pinch force, executive function, pulmonary function, etc). PARI subsequently incorporated UCA into the traditional workflow of HF simulated-use study design – an additional assessment of the individual test participants prior to the actual simulated use within the test session. Systematic measurements of user characteristics within formative studies were conducted using validated tools to ensure that the device design adequately reflected the needs of the intended population and to steadily build a data set with UCA to strengthen the outcomes of the literature research. Besides basic health assessments (such as measurements of height, weight, blood pressure and body temperature), these measurements included physical parameters such as hand size, grip strength and dexterity (Figure 2).

Pulmonary function testing was performed using spirometry without the administration of bronchodilators to measure baseline respiratory capacity. In addition, oxygen saturation was measured via pulse oximetry. Cognitive function was evaluated using the Mini-Mental State Examination – Second Edition, Standard Version (MMSE-2:SV) and the Behavior Rating Inventory of Executive Function (BRIEF-A). Finally, quality of life was assessed using the St George's Respiratory Questionnaire.

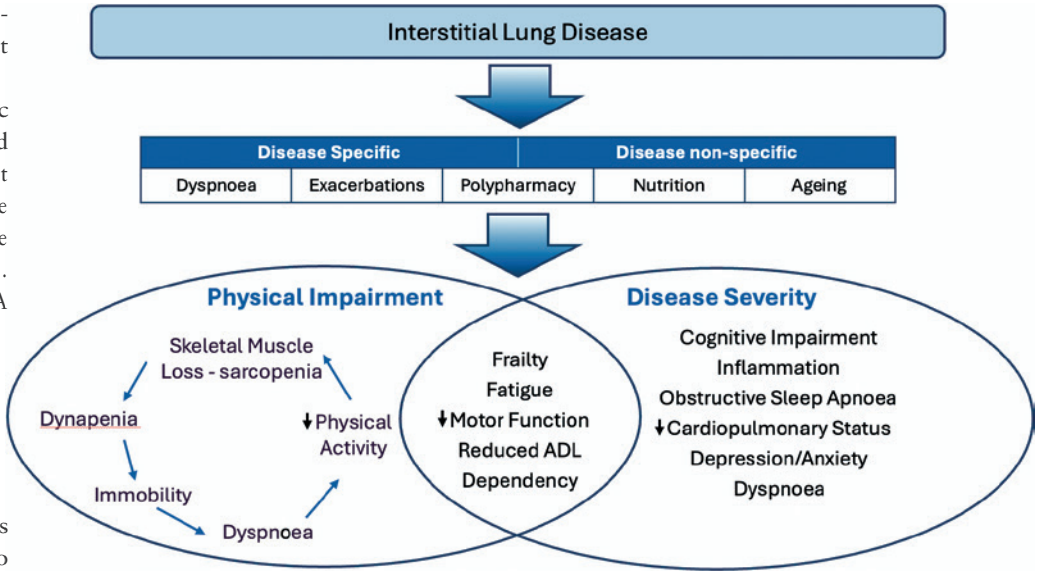

Figure 1: Physical impairment and disease severity in ILD – adapted from Hanada *et al*, 2023.[8]

Overall, the UCA methodology offered several key benefits and applications for device development. It supported improved design decisions through a comprehensive understanding of relevant user capabilities and limitations. It also provided deeper insights for root cause analyses and enabled targeted interventions to mitigate identified risks. Figure 3 provides an excerpt from a user characteristics sheet comparing an individual's UCA data (adjusted to, for example, age, gender, dominant hand, education) with the normative population. In the example, the cognitive assessment (BRIEF A) revealed clinically significant scores ($T \geq 65$), indicating some degree of executive dysfunction in these areas. The individual's hand grip strength was average, while pinch forces and 9 HPT times were very low (≤ 5th percentile). Although grip and pinch values fell within acceptable ranges for successful device use, they were still below typical healthy individuals.

If these factors and respective limitations are known, the results of the usability test and root cause assessments can be interpreted in a different manner and contextualised within the broader population. The occurrence of use errors can thereby be assessed more accurately regarding whether they represent a generalisable issue affecting the entire target user population or are attributable to a subset of users with specific characteristics. With reference to the example shown in Figure 3, potentially observed challenges related to device handling must be considered in a differentiated manner, as the individual exhibits impairments in dexterity and muscular strength.

Figure 2: Validated tools such as the 9-hole peg test (left), grip force (middle) and hand size measurements (right).

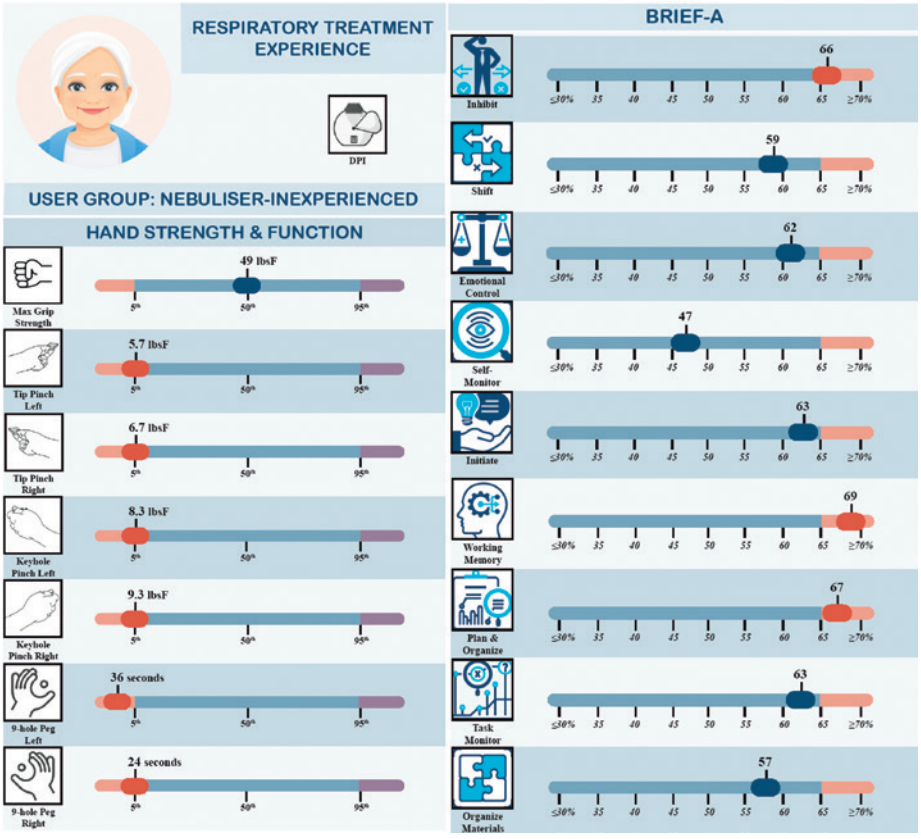

Figure 3: Excerpt of an individual's UCA data sheet.

An additional, but unexpected benefit observed in practice is the reduction of test-related anxiety among participants, potentially leading to more reliable assessment outcomes. Overall, these advantages contributed to patient-focused drug-device development and promoted patient-centred design principles.

HOW THE eFLOW INTEGRATED NEBULISER DEVELOPMENT BENEFITTED FROM UCA

The integration of the UCA helped to create a more robust device design of the eFlow Integrated nebuliser by considering physical limitations early on. Even with a relatively small sample size, a broad range of hand dimensions, strength levels and related parameters was captured during formative testing. This indicated that the study cohort sufficiently represented the variability found in the respiratory population, providing confidence that the device had been evaluated with representative users of its target patient group. For example, insights into physical impairments and dexterity issues led to several iterations of the mouthpiece geometry, ensuring that the parts were of a sufficient size (evaluated through hand measurements and dexterity testing) and with acceptable assembly forces (evaluated by hand grip and pinch forces) to be easily and effectively handled.

> "THE INTEGRATION OF THE UCA HELPED TO CREATE A MORE ROBUST DEVICE DESIGN OF THE EFLOW INTEGRATED NEBULISER BY CONSIDERING PHYSICAL LIMITATIONS EARLY ON."

However, a more significant challenge emerged regarding cognitive decline. A prior review of the literature had suggested that individuals with chronic respiratory conditions may experience greater cognitive impairment compared with healthy individuals of the same age. This tendency was also reflected in the measured user characteristics of the test participants. Findings highlighted that cognitive limitations were more prevalent and more advanced than initially anticipated. Importantly, because these insights were obtained early in the development process, they enabled targeted design measures to address cognitive challenges. For example, findings related to executive function impairment informed multiple refinements to the presentation and labelling of device components. As a result, patients are guided through the initial assembly and preparation steps in fewer, clearly structured tasks, thereby minimising working memory demands (Figure 4).

The user experience at first exposure to the nebuliser is particularly critical, as it establishes the foundation for motivation

Figure 4: Multiple stages of presenting the nebuliser parts during first exposure.

Figure 5: eFlow Integrated nebuliser with breath-guiding feedback.

"THE USER EXPERIENCE AT FIRST EXPOSURE TO THE NEBULISER IS PARTICULARLY CRITICAL, AS IT ESTABLISHES THE FOUNDATION FOR MOTIVATION AND LONG-TERM ADHERENCE."

and long-term adherence. This is especially challenging if the drug product is then later co-packaged with the nebuliser. The overall system complexity increases even further, as users typically do not differentiate between the device and the medication. Instead, they perceive and interact with it as an integrated, holistic product whose components must function seamlessly together. Additional co-packaged consumable items, such as drug inserts and labelling, can, in turn, be overwhelming for the user. In this context, clear and effective guiding of the user regarding the correct workflow by limiting the tasks and instructions is essential.

USER CHARATERISTICS DATA SET TO STREAMLINE APPROVAL PROCESSES OF DRUG-DEVICE COMBINATION PRODUCTS

PARI's development of a new nebuliser platform based on the UCA approach is expected to provide pharmaceutical partners with increased confidence in early development decisions. By applying a robust, systematic and scientifically grounded methodology to identify user characteristics that may influence safe and effective use, PARI can help its partners address potential use-related risks proactively.

This structured approach enables evidence-based design optimisation and facilitates more informed strategic decisions throughout development. Traditionally, pharmaceutical companies invest substantial time and financial resources in re-evaluating device-specific use tasks. However, previously generated UCA-based usability data from PARI can be shared transparently with pharmaceutical partners and used as supportive evidence for regulatory submissions. For example, use scenarios such as cleaning and disinfection or following the breath-guiding feedback (Figure 5) during inhalation may not need to be revalidated if documented evidence already demonstrates that these use steps were previously evaluated with participants representative of the intended patient population. Here, explicit confirmation of representativeness through UCA is key.

If such evidence exists and is supported by well-structured study designs, this novel approach offers significant benefits for both regulatory authorities and manufacturers. By avoiding redundant testing while maintaining full data transparency,

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resources can be allocated more efficiently without compromising scientific rigour. Importantly, the available resources can then be directed towards the assessment and mitigation of combination product-specific risks. This enables a more meaningful evaluation of aspects that are truly critical to safe and effective use performance with a clear emphasis on patient-centred outcomes.

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HOW SOFT MIST INHALERS WILL BREATHE NEW LIFE INTO DRUG DEVELOPMENT

This article is based on a whitepaper originally published by GAPLAST GmbH

Kasim Yilginc of **GAPLAST** discusses the expanding importance and influence of the respiratory sector within pharmaceutical pipelines, including the role that soft mist inhalers are poised to play in improving patient outcomes and how the company's AirlessMotion® bag-in-bottle technology can support the development of these inhalation devices.

The prevalence of respiratory diseases is increasing around the world, particularly in high-income regions. According to the Global Burden of Disease Study 2017, 544.9 million people had a chronic respiratory disease in 2017, representing an increase of 39.8% from 1990 and a global prevalence of 7.1%.[1] With key risk factors including smoking, household air pollution and ambient particulate matter, it is no wonder that lung diseases are becoming increasingly widespread.

Chronic obstructive pulmonary disease (COPD), a debilitating and progressive disease characterised by persistent respiratory symptoms and airflow limitation, remains the most prevalent chronic respiratory disease worldwide, accounting for 55.1% of chronic respiratory indications among men and 54.8% among women. Of all countries, the UK has the highest rate of COPD; according to the latest data from the UK Department of Health & Social Care, COPD-related mortality rates recently increased in England from 42.8 people per 100,000 in 2020–2022 to 43.9 per 100,000 in 2021–2023.

Combined with epidemiology figures from GlobalData (London, UK), which forecast the total prevalence of COPD across 16 major pharmaceutical markets to increase from 15% in 2023 to 16% by 2033 in men and from 12% to 13% in women, it is clear that chronic respiratory conditions are becoming an increasingly important global health concern. In fact, according to the WHO, COPD is the third leading cause of death worldwide.

Fortunately, the pharmaceutical industry continues to expand its R&D efforts in novel respiratory therapies, with the US FDA approving 14 non-new molecular entities since 2015, according to GlobalData's drugs database. In 2024 (Figure 1), the industry commenced 1,215 new clinical trials studying respiratory conditions, marking a 36% increase from 2014. As of January 2025, there were 1,823 drug candidates under development for the treatment of respiratory diseases, including 124 products in Phase III trials and 23 in the pre-registration stage.

The respiratory disease pipeline currently reflects a range of therapies and modalities, with a relatively even divide between biologics and small molecules. Most investigative therapies are administered via injection (35.4%), with the other major routes being oral (31.1%) and inhalation (29.8%). Of these, only the inhalation route offers a direct route to the lungs, enabling lower API doses and potentially fewer side effects. Inhalable corticosteroids, for example, have become a mainstay of daily asthma treatment due to their improved safety profile when compared with oral alternatives.

INHALABLE RESPIRATORY THERAPIES – THE CURRENT PIPELINE

According to GlobalData, the majority of inhalable respiratory therapy candidates are in the preclinical stage of development (Figure 2). As of Jan 2025, there was a roughly equal number of candidates in Phase I and II trials (67 and 68, respectively), with less than half of that in Phase III. Within that, the leading indications for inhalable respiratory therapies are COPD and asthma, with a high number of therapies also under development for cystic fibrosis and idiopathic pulmonary fibrosis (Table 1).

Indications	Number of drugs
COPD	88
Asthma	83
Cystic fibrosis	53
Idiopathic pulmonary fibrosis	52
Bronchiectasis	27

Table 1: Inhalable respiratory therapy pipeline by indication (Source: GlobalData, Pharmaceutical Intelligence Center).

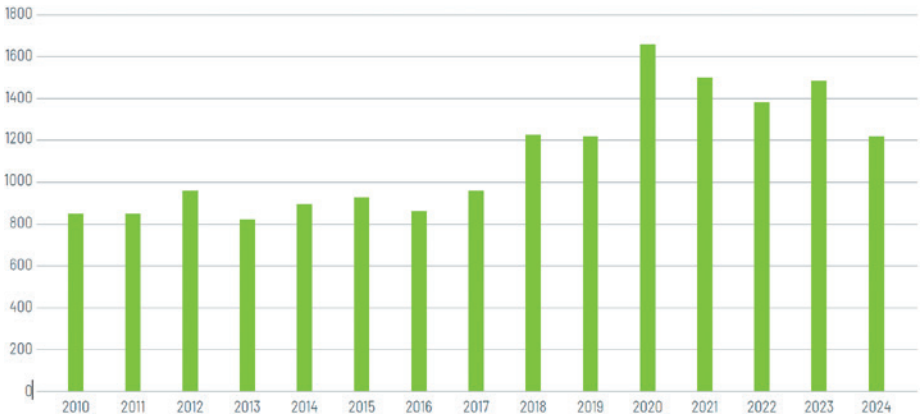

Figure 1: Respiratory clinical trials by start year (Source: GlobalData, Pharmaceutical Intelligence Center).

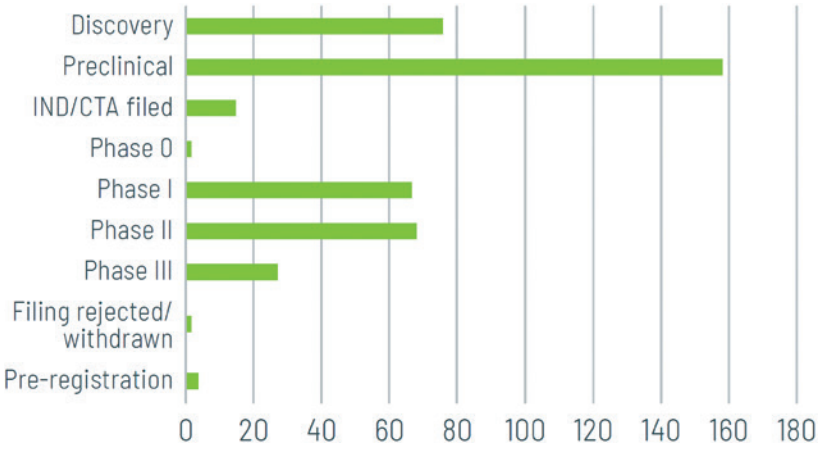

Figure 2: Inhalable respiratory therapy pipeline by development stage (Source: GlobalData, Pharmaceutical Intelligence Center).

While inhalable therapies have traditionally favoured small molecule formulations, such as corticosteroids, a significant proportion is comprised of biologic candidates, representing 41.1% of the total pipeline. Small molecules make up the largest share, at 48.2%, with 30 oligonucleotide products accounting for the remaining 10%. When it comes to mechanisms of action, most of the inhalable therapies are receptor agonists or antagonists, with other common mechanisms being explored, including enzyme inhibitors, ion channel activators, and protein and peptide inhibitors.

"WHILE INHALABLE THERAPIES HAVE TRADITIONALLY FAVOURED SMALL MOLECULE FORMULATIONS, SUCH AS CORTICOSTEROIDS, A SIGNIFICANT PROPORTION IS COMPRISED OF BIOLOGIC CANDIDATES, REPRESENTING 41.1% OF THE TOTAL PIPELINE."

A few examples of inhalable biologics in Phase III trials include an alpha-1 proteinase inhibitor for emphysema (Grifols, Barcelona, Spain), which is prepared from human plasma, and the Broncho-Vaxom vaccine (OM Pharma, Geneva, Switzerland), which is under development for the treatment of recurring wheezing and allergic asthma. Beijing Tri-Prime Genetic Engineering Co (Beijing, China) currently has a Phase III product manufactured using recombinant DNA technology, meanwhile Molgradex (Savara, Langhorne, PA, US), a recombinant protein candidate, is currently undergoing clinical testing for unspecified lung diseases.

THE EVOLUTION OF INHALABLE DEVICES

As the pharmaceutical pipeline evolves, with an increasing number of respiratory biologics under development, there have also been significant advancements in the delivery technology used to administer these medications. Pressurised metered dose inhalers (pMDIs) have been a mainstay of inhalable drug delivery for decades, with well-known products including the Easi-Breathe (Teva) and Autohaler (Teva). More recently, however, dry powder inhalers (DPIs) and soft mist inhalers (SMIs), such as Respimat (Boehringer Ingelheim), have been growing in popularity. Environmental concerns are a key part of the story, as DPIs and SMIs offer the significant advantage of not requiring a propellant, contributing to a significantly more environmentally friendly approach to respiratory treatment.

However, greenhouse gas emissions are not the only reason pharmaceutical manufacturers are showing increasing interest in alternative inhaler technologies. SMIs are frequently considered to be significantly easier to use than traditional inhalers, requiring less co-ordination between actuation and inhalation, supporting improved outcomes in two key ways. Firstly, SMIs offer an easier experience for patients, which can help to solve adherence challenges, ensuring more consistent usage of the product. Secondly, as studies have shown, SMIs can also increase the amount of medication that reaches the lungs per actuation.

"SMIs ARE FREQUENTLY CONSIDERED TO BE SIGNIFICANTLY EASIER TO USE THAN TRADITIONAL INHALERS, REQUIRING LESS CO-ORDINATION BETWEEN ACTUATION AND INHALATION, SUPPORTING IMPROVED OUTCOMES IN TWO KEY WAYS."

For example, one study that investigated the deposition of fenoterol in the lungs and oropharynx after delivery from three different inhaler devices – an SMI, a pMDI and a pMDI with spacer – found that the SMI device deposited 39.2% of the product in the whole lung, while the pMDIs with and without a spacer deposited just 11% and 9.9%, respectively. For the pMDI, 71.7% of the administered drug deposited in the oropharynx. Inhalational technique errors, which are estimated to occur in approximately 90% of pMDI users, could be playing a key factor in this effect.[2]

The "soft", slow-moving mist achieved with SMIs is also much gentler on the throat than the forceful spray of a pMDI. This factor contributes to less irritation and coughing with the newer technology, indicating that it could be well suited to the delivery of fragile biologic compounds, such as mRNA. Finally, SMIs are small and highly portable, with no requirements for the addition of a spacer or holding chamber.

A CHANGING MARKET

There are currently 67 marketed products in the US, EU and UK that feature inhaler technology, not including generics. In 2023, these products were estimated by GlobalData to generate total global sales of US$9.55 billion (£7 billion), with the highest grossing product – Symbicort Turbohaler (AstraZeneca), a DPI – making $2.36 billion in 2023, accounting for 24.7% of the market. Other blockbusters include Seretide/Advair (GSK), available in both pMDI and DPI devices, which generated $1.41 billion revenue in 2023, and Spiriva (tiotropium bromide) Respimat (Boehringer Ingelheim), an SMI that achieved sales of $1.39 billion the same year. In addition to Spiriva, which received FDA approval in 2001, other key SMI products include Striverdi (olodaterol) Respimat (Boehringer Ingelheim), first approved by the FDA in 2013, and Spiolto/Yanimo (tiotropium bromide/olodaterol) Respimat (Boehringer Ingelheim), approved in 2015 in nine European countries and by the FDA.

According to GlobalData, an average of five patents are expected to expire each year until 2030. In 2025, Aerobec auto-inhaler (Teva), Duaklir Genuair (Covis Pharma, Amsterdam, the Netherlands) and Arnuity Ellipta DPI (GSK) are all expected to expire. When it comes to Boehringer Ingelheim's portfolio of SMI products, expiries are expected in early 2027 for Stirvedi and Spiolto/Yanimo, while the constraining patent expiry of Spiriva in the US is anticipated in 2026.

With this date now just a few years away, several companies are expected to pursue generic formulations; the high costs of the branded products have created a strong demand for generic counterparts. However, there are many challenges involved with replicating both the APIs and the specific inhalation devices. Meanwhile, with dosage form information unavailable for pipeline products, there are currently limited data to support the entry of new molecular entity SMI products into the market.

Nevertheless, with a considerable body of evidence to suggest that SMIs can help formulators optimise drug delivery to the lungs, while also improving the inhaler experience for patients, SMIs are becoming an increasingly appealing technology for drug developers looking to make their product stand out on the market. As such, it is equally likely that companies will look to reformulate existing marketed drugs into SMIs as a method of extending the product's lifecycle before expiry.

FUTURE TRENDS

Future developments and innovations are inevitable in this field, from innovative nozzle designs that enable targeted delivery of specific drugs, such as biologics, to digitalised SMIs that make use of electronic breath actuation and real-time dose verification data. Inhaler technology is expected to be explored far beyond the field of respiratory diseases, particularly as investigation into cannabis-related medications for pain management and mental health conditions increases. Yet, behind all these exciting innovations, is the container closure system at the heart of the system – and without it, even the most advanced SMIs and the innovative drug-device combinations cannot fulfil their promise.

One company that understands the crucial role of the cartridge inside out is GAPLAST, a provider of drug delivery technologies and components and inventor of the AirlessMotion® bag-in-bottle system (Figure 3). The company's AirlessMotion bag-in-bottle technology is a patented drug delivery system that has proven itself in the medical and pharmaceutical industries. It is a packaging system that provides high protection against chemical, physical and microbiological contamination, with options spanning 5–1,250 mL to meet the diverse needs of its customers. Also available as a 5 mL cartridge, this multilayered container closure system can be adapted to the requirements of various SMI devices and formulation compatibilities.

Figure 3: GAPLAST's AirlessMotion cartridge for SMIs with optional cap.

The technology follows the same basic principle that all SMI devices are built around – as the cartridge's flexible inner bag contracts, the internal volume is pushed out and administered via the device's inhalation system as a fine spray mist. The amount of extracted liquid can be defined according to customer requirements, and unique colours and volumes are also possible upon customer request (Figure 4).

Figure 4: The AirlessMotion bag-in-bottle technology can be adapted to the needs of various SMI designs.

One of the most important features of the product is its impressive barrier properties, which play a critical role in maintaining the sterility and stability of the product. Optimised barrier properties are particularly important when it comes to sensitive drugs such as biologics, standing GAPLAST in good stead to support the future wave of inhalable drugs currently in development. GAPLAST has been working with the bag-in-bottle technology for over 35 years, which has enabled the company to create a very strong oxygen and water barrier to protect the product.

Another advantage of the AirlessMotion bag-in-bottle design is that it can achieve very consistent dosages. This is because its inner pouch collapses in a safe and predictable manner that showcases a high repetition rate, so the contained fluid is always kept at the same height as the volume of the inner pouch decreases. This guarantees even dosages throughout the entire device lifecycle up to the last drop, without any propellant.

"OPTIMISED BARRIER PROPERTIES ARE PARTICULARLY IMPORTANT WHEN IT COMES TO SENSITIVE DRUGS SUCH AS BIOLOGICS, STANDING GAPLAST IN GOOD STEAD TO SUPPORT THE FUTURE WAVE OF INHALABLE DRUGS CURRENTLY IN DEVELOPMENT."

Looking ahead, the continued evolution of inhaler technology is set to transform patient outcomes in the respiratory sector and far beyond. Particularly as the development of biologics gathers pace, with ever more manufacturers expected to consider patient-friendly inhaler technologies such as SMIs, the availability of reliable container closure systems with precise dosage control and exceptional barri er properties cannot be underestimated. With decades of experience, proven technologies and a history of innovation, GAPLAST is poised to deliver the cartridge solution these companies need to help their patients breathe easy.

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Expert View

INTRANASAL DRUG DELIVERY: FORMULATION, DEVICE DESIGN AND CHARACTERISATION STRATEGIES

Dr Matthew Owen of Kymanox reviews the formulation and device challenges, designs and considerations that are shaping the nasal delivery market.

Intranasal drug delivery has evolved into a clinically established route for both local and systemic therapies, with growing interest in targeted nose-to-brain applications.[1] Once primarily associated with topical decongestants and corticosteroids, the nasal route is now used for rapid systemic delivery, rescue medications, peptides and central nervous system (CNS) therapeutics.[2–5] This progression reflects advances in formulation science, device engineering and an improved understanding of nasal physiology.

The nasal cavity can be broadly divided into vestibular, respiratory and olfactory regions (Figure 1). The vestibule primarily serves as an entry zone, with minimal contribution to absorption of drug product. The respiratory region, which includes the inferior, middle and superior turbinates, accounts for most of the functional surface area and is the principal site of systemic absorption. The nasal cavity provides several inherent advantages for drug delivery: rapid absorption due to high vascularisation, avoidance of first-pass hepatic metabolism and non-invasive administration that supports patient adherence.[6,7] In addition, anatomical connections to the brain via the olfactory pathway and a network of nerves, known as the trigeminal pathway (Figure 2), present an opportunity for CNS targeting that can bypass the blood–brain barrier.[1,2,8] Direct transport via the olfactory and trigeminal pathways is believed to contribute to CNS drug exposure, whereas drugs reaching the brain via systemic circulation must cross the blood–brain barrier. A drug that is swallowed may undergo gastrointestinal absorption and first-pass metabolism, minimising effective nasal bioavailability.

Despite these advantages, intranasal product development presents distinct technical challenges. The nasal cavity is a dynamic and protective environment characterised by limited dosing volume (approximately 100–150 µL per nostril), rapid mucociliary clearance, enzymatic activity and significant inter- and intra-patient variability.[9] Therefore, effective development requires co-ordinated optimisation of formulation properties, regional deposition and device performance.

"THE NASAL CAVITY PROVIDES SEVERAL INHERENT ADVANTAGES FOR DRUG DELIVERY: RAPID ABSORPTION DUE TO HIGH VASCULARISATION, AVOIDANCE OF FIRST-PASS HEPATIC METABOLISM AND NON-INVASIVE ADMINISTRATION THAT SUPPORTS PATIENT ADHERENCE."

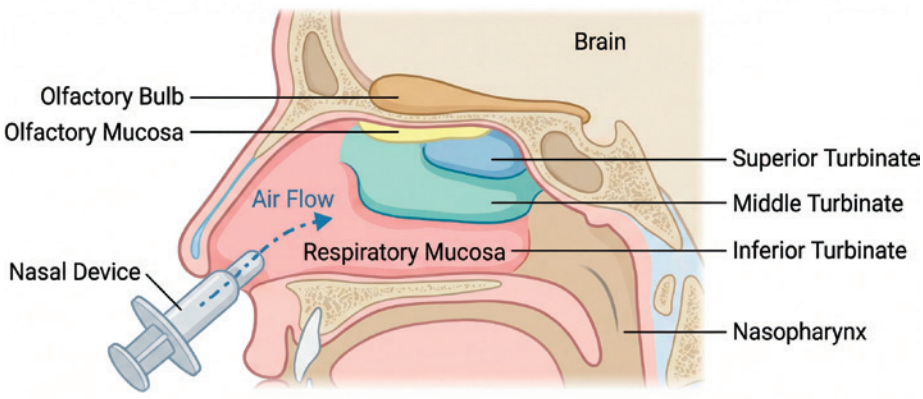

Figure 1: Anatomical descriptions for nasal cavity delivery.

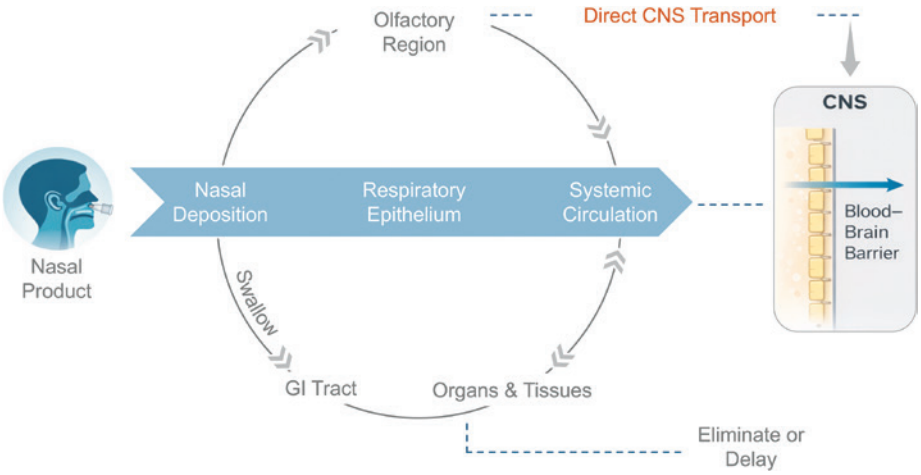

Figure 2: Targeted intranasal delivery pathways.

FORMULATION CONSIDERATIONS

Aqueous Liquid Nasal Sprays

Systemic delivery of therapeutics via the intranasal route is highly dependent on the physical and chemical properties of the formulation, nasal physiology and geometry. The key hurdles lie in the workable surface area, the rheological properties of the mucus layer, presence of enzymes and ciliary clearance.[8–10] For systemic delivery, most of the formulation will deposit on the respiratory mucosa, which has an active surface area of approximately 150–180 cm^2, depending on the measurement method.[11]

The viscosity of the mucus layer can influence diffusion and residence time. Healthy mucus exhibits relatively low viscosity, but this can increase under diseased conditions, potentially affecting drug diffusion and clearance.[12] Therefore, formulation flow behaviour and permeation into the mucus layer are important considerations, particularly with mucociliary transport.

Permeation enhancers can be added to the formulation to increase epithelial permeability and improve transmucosal transport. If extended residence time is desired, particularly for larger biomolecules, hydrophilic compounds, or CNS-targeted therapies, mucoadhesive compounds may be incorporated to prolong local retention.[13–15]

Other formulation factors include pH and tonicity modifiers. The local pH of the nasal mucosa is slightly acidic (5.5–6.5) in healthy humans and may become more alkaline (>7) in diseased states, such as rhinitis.[16] The formulation pH should be as close to physiological conditions as is feasible. Maintaining near-physiological pH supports ciliary function, minimises irritation and helps to preserve mucosal integrity.[17]

In terms of osmolality, the nasal mucosa is isotonic (approximately 290 mOsm/kg). Most nasal formulations are designed to approximate isotonic conditions to minimise changes in mucosal hydration, ciliary beat frequency and irritation.[18,19] Hypertonic formulations may induce stinging, watering, sneezing or increased mucus secretion, potentially accelerating clearance.[20]

The addition of a preservative may be necessary to prevent microbiological contamination if the drug product is not produced in an aseptic environment or sterile filtered.[21] Preservative selection depends on formulation pH and compatibility to ensure antimicrobial effectiveness and stability. As with all excipients, there are patient risks and side effects with each selection, especially with irritants and use with a targeted population such as children.[17,21,22] Table 1 highlights critical key attributes and typical formulation additives.

Dry Powder Nasal Products

Dry powder-based nasal products represent an alternative approach with specific advantages and constraints. Powder formulations are often less compositionally complex than liquid sprays and, in some cases, may consist primarily of APIs with minimal excipients. Nasal powders are also advantageous for molecules with limited aqueous solubility or stability, such as biologics.[23]

Attribute	Purpose	Typical Excipients
Permeation Enhancer	Improve permeability in viscous mucosa through typical paracellular or transcellular transport	• Alkyl saccharides (dodecyl maltoside, etc.) • Cyclodextrins (β-cyclodextrin, etc.) • Diethylene glycol monoethyl ether • Fatty acids (oleic acid, etc.) • Phospholipids (C16, C14, etc.) • Surfactants (PS20, PS80, etc.)
Mucoadhesive	Adhere to mucosa to minimise and prevent clearance	• Cellulose compounds (carboxymethyl cellulose, hydroxymethyl cellulose, etc.) • Polyethylene glycol polymers • Thiolated polymers • Poloxamers
pH Modifier	Target physiological pH to prevent irritation	• Buffers • Acids (HCl, etc.) • Bases (NaOH, etc.)
Osmolality Modifier	Target isotonic/low hypotonic environment	• Sugars (dextrose, sucrose, etc.) • Salts (NaCl, KCl, etc.)
Preservative	Prevent microbial growth and increase shelf life	• Benzalkonium chloride, chlorobutanol, benzyl alcohol, etc.

Table 1: Critical key attributes of liquid nasal sprays.

A key difference from liquid systems is the engineering of the powders. The powders are commonly engineered using processes such as spray drying,[24,25] which involve equipment configurations to ensure the desired particle size, morphology, dispersibility and inter/intra-active location. For nasal delivery, particle size distribution and aerodynamic behaviour are critical due to deposition and pulmonary safety considerations.[13,14,25] For example, a powder with geometrical size distribution of 10–50 µm may still present a smaller aerodynamic diameter if the tap density is low, which increases the risk of unintended pulmonary deposition (<10 µm). Unintended pulmonary deposition may introduce additional safety considerations and should be minimised through particle engineering strategies.[26]

Typical nasal powder formulation may include APIs, permeation enhancers, salts and/or sugars, that are similar to excipients used in liquid systems.[1,3,10] An additional key consideration is moisture control. Excipients should exhibit minimal hygroscopicity, so the manufacturing processes should minimise moisture exposure.[25,27] Elevated moisture content can negatively affect powder dispersibility and reduce delivered dose performance.[28] Dry powder systems often demonstrate improved chemical stability relative to aqueous formulations and may support an extended shelf life under appropriate storage conditions.[29]

DEVICE SELECTION AND SPRAY PERFORMANCE

There are many forms and brands for unit-, bi- and multidose nasal device formats. Examples of US FDA-approved unit-dose products include Narcan (naloxone hydrochloride; Emergent BioSolutions, Gaithersburg, MD, US), RiVive (naloxone; Harm Reduction Therapeutics, Bethesda, MD, US), Zavzpret (zavegepant; Pfizer) and Neffy (adrenaline (epinephrine) – ARS Pharmaceuticals, San Diego, CA, US).

FDA-approved bi-dose products include niche products such as Spravato (esketamine – Janssen Pharmaceutical) and recently CARDAMYST (etripamil) was approved by the FDA for Milestone Pharmaceuticals (Quebec, Canada) using a bi-dose format. There are many multidose nasal over-the-counter medicines, such as Flonase (fluticasone; Haleon, Weybridge, UK) and Nasonex (mometasone furoate; Organon Pharma, Jersey City, NJ, US). For nasal powders, unit-dose devices are common, an example being BAQSIMI (glucagon; Amphastar Pharmaceuticals, Rancho Cucamonga, CA, US).

Dose strength selection and intended nasal target region are critical design considerations. Most devices are engineered to promote deposition within the respiratory mucosa to facilitate transmucosal systemic absorption (Figure 3).[10,11,15,30,31]

For systemic delivery, the respiratory epithelium, including the inferior, middle and superior turbinates, is the primary target. To promote broad coverage, plume width (W) should be relatively wider with a shorter plume length (L), generating a broader plume angle (φ). Spray velocity (v) should be sufficient to achieve deposition without excessive impaction.[32,33] Droplet sizes are typically engineered to promote nasal deposition while minimising inhalation risk. Proper device orientation remains important to ensure consistent and reproducible deposition within the respiratory region, which comprises the majority of the active target area.

For nose-to-brain targeting, the olfactory regions represent less than 5% of the total surface area. Therefore, design controls in the device and dosing need to be established for maximum coverage.[17,30] For instance, to increase the probability of olfactory deposition, the device and head placement should be tuned, such that the direction of the resulting spray is fine targeted to the olfactory region. A narrower plume angle and controlled velocity may reduce anterior impaction and improve olfactory targeting. Droplet size must be optimised to balance regional targeting with safety considerations.[10,15,30]

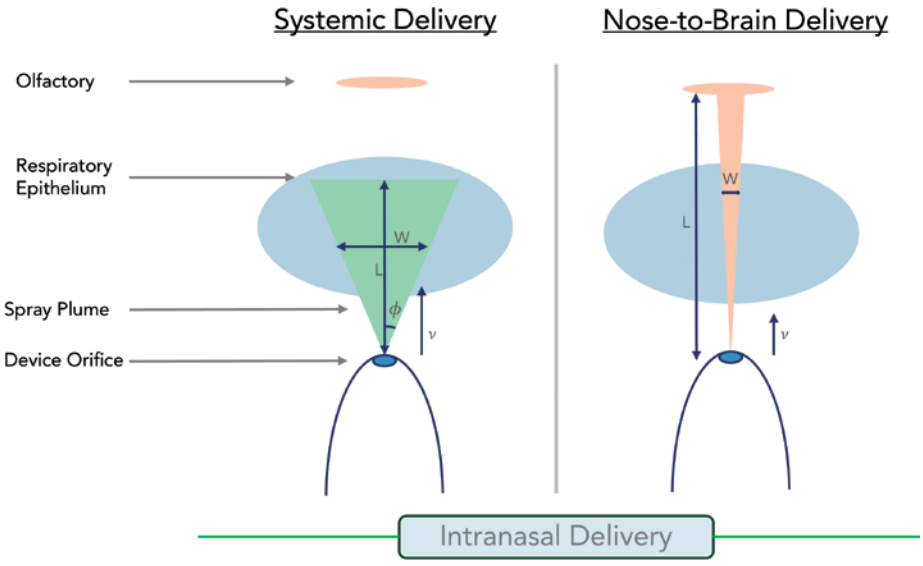

Figure 3: Plume characteristics for systemic and nose-to-brain delivery.

In Vitro Anatomical Models

An important tool for performance evaluation is the *in vitro* anatomical nasal cast model. These models are typically derived from single or average human anatomies using cyclic tomography datasets. They enable the quantification of regional deposition in areas of the nasal cavity, such as the vestibule, turbinates, olfactory and nasopharynx.[34] Standard models are often constructed from rigid materials, such as polymers or stainless steel; however, a more representative nasal cavity would simulate a mucosal-like surface. This is typically achieved by using a viscous polymer or a combination of viscous polymer and surfactant.[35] Such models significantly streamline product development and support formulation-device optimisation prior to clinical evaluation.

Characterisation and Performance Testing

The typical testing regimen includes both bulk formulation testing and device performance evaluation. These are usually

Domain	Test	Liquid Nasal Spray	Nasal Powder	Clinical and Regulatory Relevance
Chemistry – Identification, Assay and Strength	Assay of active (HPLC/UPLC)	✓	✓	Label claim verification
	Related substances and impurities (HPLC/UPLC)	✓	✓	Degradation and stability monitoring
	Assay of critical excipients (HPLC/UPLC/GC)	✓	✓	Label claim confirmation
	pH	✓	N/A	Nasal tolerability and stability assurance
	Osmolality	✓	N/A	Mucosal compatibility
	Moisture content	N/A	✓	Powder flow and stability control
	Blend uniformity	N/A	✓	Dose homogeneity assurance
Physical Characterisation (Bulk)	Viscosity	✓	N/A	Flowability and spray performance
	Particle size distribution (laser diffraction)	N/A	✓	Spray performance and dispersion control
	Density (bulk/tapped)	✓ (Bulk)	✓ (Tapped)	Manufacturability and fill consistency
	Appearance	✓	✓	Visual quality control
	Foreign particulate matter (HiAC/microscopy)	✓	✓	Particulate safety assurance
	Residual solvent	✓	✓	Patient safety assurance
Microbiological Control	Bioburden	✓	✓	Prefill microbial safety
	Preservative content	✓	✓	Microbial integrity control
Device Performance	Delivered dose	✓	✓	Dose accuracy
	Pump delivery	✓	✓	Dose precision and reproducibility
	Dose content uniformity	✓	✓	Dose uniformity assurance
	DSD (Dv10, Dv50, Dv90)	✓	N/A	Deposition control and respirable fraction safety
	Aerodynamic particle size distribution (APSD)	N/A	✓	Deposition control and respirable fraction safety
	Spray pattern/plume geometry	✓	✓	Nasal cavity coverage
	Actuation force	✓	✓	Actuation consistency and patient usability
	Nasal cast modeling	✓	✓	*In vitro* deposition characterisation
Stability	Product stability	✓	✓	Shelf-life determination
	Weight loss	✓	✓	Container-closure integrity
	Extractables and leachables	✓	✓	Toxicological risk mitigation

Table 2: Integrated bulk and device characterisation strategy for nasal spray and nasal powder products.

performed in parallel or before formulation-device performance testing, such as assays of active and excipients (Table 2).

A key difference between liquid and dry powder systems is the emitted particle size distribution. For liquid sprays, droplet size distribution is commonly measured via laser diffraction, which is the size distribution over a stable region in the timeframe of the spray. The key reporting parameters include Dv10, Dv50, Dv90, span and percent volume less than 10 µm.

These metrics characterise droplet distribution and support pulmonary safety assessments. This technique could be used for nasal powders, but the common practice is to use impaction techniques, such as next-generation impaction.[36,37] Deposition across stages, including induction port or nasal inlet/globe, pre-separator, collection cups and final external filter, enables the calculation of the mass median aerodynamic diameter, fine particle fraction/dose and emitted dose. Using the size cut-offs from these stages enables the determination of the pulmonary safety risk of the nasal powder.

FUTURE OUTLOOK AND CONCLUSIONS

Intranasal drug delivery has become a practical and clinically established route for systemic and CNS-enabling treatments. As outlined, successful development requires careful alignment between formulation properties, particle or droplet engineering, device design and understanding of nasal anatomy. Small changes in viscosity, moisture content, plume geometry or particle size can meaningfully impact deposition and overall product performance. For both liquid sprays and dry powders, bulk chemistry and device function are tightly connected and must be developed together.

Looking forward, progress in this space will likely come from better integration of formulation and device development, along with more predictive *in vitro* tools, such as anatomically relevant nasal casts and computational modelling. Interest in peptides, biologics and other complex molecules will continue to push innovation, particularly for powder-based systems where stability metrics are advantageous. At the same time, variability in nasal physiology and the challenges of regional targeting, especially for CNS delivery, remain important areas for continued focus.

Overall, intranasal delivery is located at the intersection of formulation science, device engineering and nasal physiology. As these disciplines become more tightly co-ordinated, the nasal route is positioned to play an increasingly important role in rapid systemic therapies and future brain-targeted treatments.

ABOUT THE COMPANY

Kymanox is a life science professional services firm dedicated to accelerating the development and delivery of modern medicines. With expertise in design, development and testing; biologics and advanced therapies; quality and compliance; facilities and manufacturing services; and combination products, Kymanox helps clients to navigate and de-risk critical challenges across the product's lifecycle. From preclinical to post-market support, the company's global team brings deep knowledge in science, engineering and compliance, supporting patented solutions, ensuring seamless scale-up and delivering operational readiness from concept to commercial production.

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REFRAMING THE ROLE OF NASAL SPRAYS IN AN INCREASINGLY PATIENT-CENTRIC DRUG DELIVERY LANDSCAPE

Eric Kaneps of **LTS** looks at the reality of nasal drug delivery for liquid formulations and considers how advances not only open new opportunities but can also be seen in the context of a groundswell of momentum around non-invasive, patient-centric delivery. Mr Kaneps reflects on how this shift in dynamics, coupled with a shift in mindset, is opening the door for pharmaceutical companies to expand their drug delivery options and fully optimise the development pathway for their molecule.

In science, progress is predicated on the evaluation of hard evidence. As humans, however, we are hardwired to occasionally fall back on defaults, assumptions and heuristics to make sense of a complex world.

Because of this evolutionary trait, rather than reassessing and recalculating every situation, we rely on labels as shortcuts to meaning. They act as signals, triggering associations in our brain to help accelerate understanding and streamline decision making, easing our cognitive burden in the process. However, problems arise when those associations are inaccurate, incomplete or become outdated. Where fresh eyes would expand and update our perspective, labels can keep our understanding within the parameters of legacy thinking. Or, to borrow from Oscar Wilde, "to define is to limit".

In drug delivery, it can be argued that the term "nasal" is burdened with this fate. Driven by its capabilities in a wide range of therapeutic areas and despite rapid

> "DESPITE RAPID EVOLUTION IN RECENT YEARS, NASAL CONTINUES TO BE STRONGLY ASSOCIATED WITH LOCALLY ACTING TREATMENTS FOR ALLERGIC RHINITIS AND DECONGESTION."

evolution in recent years, nasal continues to be strongly associated with locally acting treatments for allergic rhinitis and decongestion.

With decades of experience in this space, the LTS Nasal and Sterile Drug Products division has engaged first-hand in the development of nasal drug delivery, consistently advocating nasal spray systems as a patient-friendly and effective delivery pathway for addressing important unmet patient needs.

THE DEFINING EARLY YEARS OF NASAL DEVICES

Looking at the history of liquid nasal sprays, perhaps it is easy to understand why we have arrived at this point. When they transitioned out of laboratories and into the commercial landscape in the 1950s and 1960s, drugs delivered via the nose were almost exclusively targeted for rhinitis and decongestion. Early market-approved products formalised the notion of the nasal route in the context of vaporised or atomised medicine, something that had previously been explored for medicinal purposes for hundreds if not thousands of years. In doing so, these devices defined the strong associations of nasal delivery with particular therapeutic areas.

Fougera Pharmaceuticals' (Melville, NY, US) Tyzine (tetrahydrozoline hydrochloride) and Bayer's Afrin® (oxymetazoline) were early examples of liquid-based nasal sprays designed to relieve nasal congestion by narrowing blood vessels in the nasal passages. Other major brands and generic alternatives followed, continuing to expand the market for nasally administered decongestants. Then, in later decades, corticosteroids were formulated as nasal sprays to alleviate the symptoms of allergic rhinitis and sinusitis, thus providing a preferable, topical alternative to systemic delivery.

Today, these segments are major contributors to a global nasal spray market worth an estimated US$32.43 billion (£24.33 billion) in 2025.[1] While this scale, allied to the longevity of these products, makes it understandable that nasal delivery has become strongly associated with the symptomatic treatment of decongestion and rhinitis, the reality is far more diversified. In recent decades, advances in nasal devices and formulation technologies have improved the nasal delivery landscape, driven by enhanced knowledge of nasal physiology and its benefits as a platform for addressing many of the shortcomings of parenteral and oral delivery.

> "MOMENTUM TO DEVELOP NASALLY DELIVERED VACCINES HAS CONTINUED TO BUILD IN THE FOLLOWING DECADES, WITH CLINICAL TRIALS FOR A RANGE OF RESPIRATORY AND NON-RESPIRATORY DISEASES."

Evidence of this can be seen in a variety of places: intranasal opioids and triptans for rapid relief of migraine, headache and breakthrough cancer pain; benzodiazepines for treatment of epileptic seizures; intranasal metoclopramide liquids as an alternative to oral dosing for nausea and vomiting; nicotine nasal sprays for rapid systemic absorption in smoking cessation; sprays for heart-related indications; and even intranasal treatments for dry eye disease.

A NON-INVASIVE VEHICLE FOR VACCINES

Further advances in nasal delivery have been seen in the field of vaccines. In 2003, the first nasal spray vaccine was approved in the form of FluMist (MedImmune, Gaithersburg, MD, US), extending the boundaries of such devices beyond short-term symptom relief and into the territory of systemic immunity. This demonstrated the ability to provide equal protection via a safer, more practical and less painful method than injections, enhancing receptivity among needle-averse and more sensitive target groups, such as children.

Momentum to develop nasally delivered vaccines has continued to build in the following decades, with clinical trials for a range of respiratory and non-respiratory diseases, including HIV, tuberculosis and hepatitis B.[2] In the wake of the covid-19 pandemic, research into nasal vaccines and anti-viral treatments accelerated and expanded in scope, with researchers seeking to exploit the benefits of mucosal immunity at the primary site of entry for many pathogens. Injectable products such as Sputnik V (Gam-COVID-Vac; Gamaleya Research Center, Moscow, Russia) have since received approval for application with a nasal applicator, while iNCOVACC (BBV154; Bharat Biotech, Hyderabad, India) and Pneucolin (dNS1-RBD; Beijing Wantai Biological Pharmacy Enterprise, Beijing, China) are examples of vaccines developed specifically for nasal delivery.[3]

Extensive work continues in this area. One such example is a Phase II randomised clinical trial of an azelastine nasal spray, which revealed that this commonly available over-the-counter (OTC) antihistamine provides pre-exposure prophylaxis against SARS-CoV-2 and other respiratory pathogens.[4]

And, most recently, a major breakthrough was reported by Stanford Medicine (Stanford, CA, US) researchers and collaborators, who shared promising findings from a study in mice regarding a nasally delivered vaccine formula that protects against a wide range of bacteria, allergens and respiratory viruses, including SARS-CoV-2, thus opening the door to the possibility of a nasally delivered "universal vaccine".[5]

SYSTEMIC DRUG DELIVERY AND PATHWAYS TO THE BRAIN

Furthermore, the non-invasive, rapid onset benefits of nasal delivery have also established this drug pathway in the field of emergency treatments. Narcan® (naloxone hydrochloride; Emergent BioSolutions, Gaithersburg, MD, US), a nasal spray for overcoming opioid overdoses, was first fast-tracked onto the market as a prescription drug in 2015 and was subsequently approved in the US in 2023 for OTC non-prescription use, underlining its importance in tackling illicit overdose use.[6] Its success paved the way for other emergency nasal treatments. This includes the delivery of benzodiazepines such as

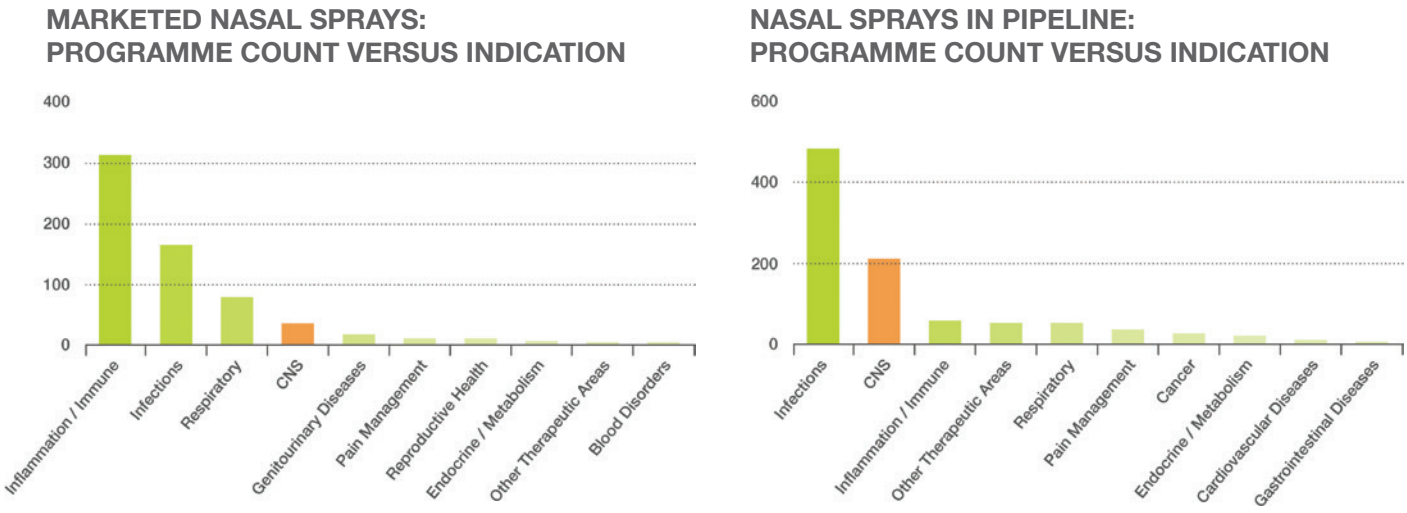

Figure 1: Distribution of marketed nasal spray products and pipeline programmes by therapeutic indication. Currently marketed products are largely focused on inflammation/immune and infectious diseases, with relatively few CNS therapies. In contrast, CNS indications represent the second largest category in the development pipeline, suggesting a rapidly increasing interest in intranasal drug delivery for CNS disorders.

Nayzilam (midazolam; UCB, Brussels, Belgium) for epileptic seizures, and Neffy (adrenaline (epinephrine); ARS Pharma, San Diego, CA, US), which was approved in August 2024 as a nasal spray treatment for anaphylaxis, by both the US FDA and the EMA (where it is marketed as EURneffy).[7]

Designed to be absorbed via the nasal mucosa for systemic effect, these emergency cases underline the strengths of nasal delivery in providing rapid relief via simple administration methods to patients who are potentially unable to co-operate. This contrasts injections, where the barriers to administration are far higher for caregivers who might still be hesitant in emergency situations, even after training on the handling of syringes.

In the case of Narcan, nasal administration leads to systemic absorption of the API, enabling it to reach the brain, where it displaces opioids that have bound to the same receptors. Spravato® (esketamine; Janssen Pharmaceuticals), a blockbuster drug for treatment-resistant depression, is another case of a nasally delivered systemic therapy acting on receptors in the brain. Various other examples, including insulin to alleviate symptoms of Alzheimer's disease as well as treatments for Parkinson's disease and multiple sclerosis, all serve as evidence of the growing interest in nasal delivery across a range of central nervous system (CNS) indications.[8–10]

More widely, the ability of nasal sprays to bypass the blood-brain barrier entirely via the olfactory/trigeminal nerve holds significant potential for treatments targeted at CNS conditions. Here, a broad range of active substances and various molecule types are under investigation, notably preclinical/clinical testing to explore nasal delivery of nucleic acid-based therapeutics (such as small interfering RNA and messenger RNA) using nanotechnology (Figure 1).[11]

ANSWERING UNMET NEEDS AND ADDRESSING SHORTCOMINGS

Innovations such as these are made possible by ever-deepening knowledge of the nasal physiology, but they are also the product of clear focus on meeting patient needs, both in terms of medical outcomes and the preference for convenient, non-invasive administration. Indeed, one study has shown that 88% of participants prefer EURneffy nasal sprays over traditional adrenaline autoinjectors.[12] In this context, nasal delivery can be seen as the endpoint of a development process that begins with a set of ideal requirements for how an API can be delivered, rather than making decisions on delivery based on preconceived ideas or typical formats of oral and parenteral delivery (Figure 2).

Unlike oral dosage forms, nasal delivery does not directly result in reduced efficacy through first-pass metabolism in the liver or gut wall and there are no complications associated with swallowing. Unlike injectable dosage forms, there is no problem with needle-related pain or fear of needlestick injuries. In addition, the burden associated with cold-chain storage requirements is either greatly reduced or removed entirely.

Of course, many factors must be considered when it comes to decision making around optimising delivery, but advances in non-invasive technologies, such as nasal sprays, mean that patient-centricity can increasingly be accommodated as a priority rather than something to be considered or optimised at a later stage of development. LTS's nasal expertise spans the entire product development cycle, with

"THE ABILITY OF NASAL SPRAYS TO BYPASS THE BLOOD-BRAIN BARRIER ENTIRELY VIA THE OLFACTORY/TRIGEMINAL NERVE HOLDS SIGNIFICANT POTENTIAL FOR TREATMENTS TARGETED AT CNS CONDITIONS."

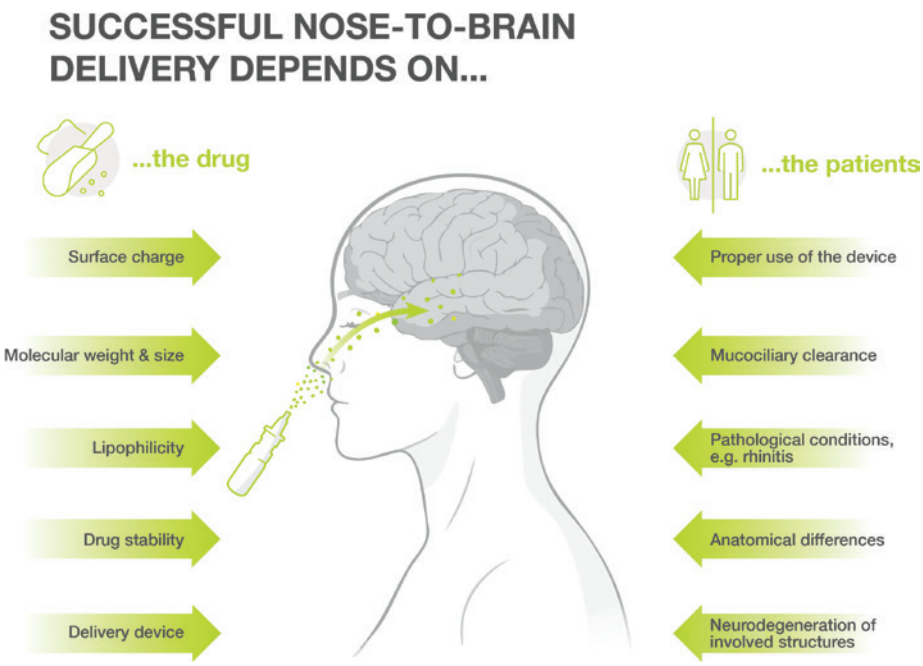

Figure 2: Factors influencing nose-to-brain delivery.

services in formulation science and spray testing complemented by device design/development and scale-up manufacturing capabilities for unit-dose, bi-dose and multidose devices.

These capabilities in nasal drug delivery are one important strand of a wider portfolio of non-invasive drug delivery technologies, which also incorporates transdermal therapeutic systems, oral thin films, micro-array patches and on-body delivery systems. While each route offers distinct benefits, these delivery platforms are all united by the fact that they all mitigate pain and are readily accepted by patients. In most cases they can also be self-administered or administered easily by caregivers in non-clinical settings, including the home. This fits with the healthcare sector's wider ongoing ambitions to reduce resource burden and costs while introducing far greater levels of patient convenience.

A DIVERSE DELIVERY LANDSCAPE OFFERS NON-INVASIVE OPPORTUNITIES

Such benefits show how the maturation of non-invasive technologies has significantly expanded the range of options for transporting an API to its target site in the body. Pharma partners today have far more choice in the delivery pathway available to their molecule. And with the full breadth of capabilities offered by LTS, they can access the necessary expertise to specify the optimal route and then to guide development through complex clinical and regulatory phases. This ensures that when a drug reaches the market, it does so in a form that truly supports sustained compliance with the dosing regimen.

"SUCH BENEFITS SHOW HOW THE MATURATION OF NON-INVASIVE TECHNOLOGIES HAS SIGNIFICANTLY EXPANDED THE RANGE OF OPTIONS FOR TRANSPORTING AN API TO ITS TARGET SITE IN THE BODY."

In summary, there is a strong body of evidence to suggest that the landscape of drug delivery has been redrawn in the decades since intranasal devices first appeared on the market as approved products. To some, the label "nasal spray" continues to conjure mental images of decongestants and rhinitis treatments, or that nasal is categorised singularly as an alternative to oral dosage forms or injections. But these limited definitions could stifle the future potential of promising molecules during critical early development stages.

At a time when the needs and wishes of patients are so central to effective, sustained and convenient models of treatment, it is arguably the time for mindsets to shift and for legacy thinking to be re-evaluated. By starting with a refreshed, broad-based view of the current drug delivery horizon, development pathways can be optimised, outcomes can be improved and unmet patient needs can be answered. Whether for locally acting or systemic drugs, whether delivered to the respiratory tract or the brain, and whether for chronic conditions or emergency treatments, nasal drug delivery must be appreciated in its full scope and in the broader direction of non-invasive, patient-centric delivery to ensure its huge potential is realised for patients of the future.

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Eric Kaneps serves as the Vice-President of Sales & Marketing at LTS Nasal and Sterile Drug Products and has been in this role since 2018. Mr Kaneps has over 25 years of experience in sales, business development and account management in the pharmaceutical industry. Mr Kaneps worked at DPT Laboratories as the Director of Business Development from 2001 to 2016. In this role, he transitioned the OTC/Consumer Health-based business towards pharmaceutical-based nasal and sterile products, which became the foundation for Renaissance Lakewood (now LTS Nasal and Sterile Drug Products). In between his roles at the Lakewood site, he was Senior Vice-President of Business Development for Pharma-Tech Industries, a CMO that specialises in prescription and OTC ingestible and topical powder products. Mr Kaneps holds a BSBA in International Business & Economics from The Ohio State University, US.

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DE-RISKING DEVICE SELECTION – WHY CHOOSE UNISPRAY FOR NALOXONE RESCUE APPLICATIONS

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Elsie Thomas of **Nemera** explains why UniSpray is a robust nasal platform for generic naloxone, based on an evidence-driven approach that combines usability studies, threshold analyses and interchangeability assessments, and how it ensures safe and reliable performance, intuitive use, and regulatory acceptability in real-world opioid overdose rescue situations.

Naloxone nasal sprays, such as Narcan® (Emergent, Gaithersburg, MA, US), are lifesaving over-the-counter products designed for the rapid reversal of opioid overdoses, including those caused by heroin, fentanyl and prescription pain medications. They act within minutes to restore breathing and their widespread public availability has expanded dramatically in recent years as part of public health overdose-prevention strategies.

Developing generic versions of naloxone nasal sprays is essential to ensure broader accessibility at a lower cost (Figure 1). However, as Narcan is a complex drug-device combination product, manufacturers must demonstrate far more than just pharmaceutical equivalence; they must also prove that the intended users – often in

Figure 1: Patient using UniSpray.

"UNISPRAY CAN ENABLE INTUITIVE, RELIABLE, ERROR-FREE USE ACROSS A REPRESENTATIVE POPULATION – A FUNDAMENTAL REQUIREMENT FOR COMBINATION PRODUCTS PRESCRIBED FOR EMERGENCY AND RESCUE SITUATIONS."

high-stress emergency situations – can use the device safely and intuitively, without additional training compared with the reference listed drug (RLD), in this case Narcan.

Generic developers frequently rely on platform unit-dose devices offered by nasal device manufacturers. Originally, these platforms may have been designed for other molecules or indications and therefore may exhibit structural differences compared with the RLD. Determining whether such differences introduce use-related risks requires a rigorous, evidence-based methodology combining usability evaluations, threshold analyses and interchangeability assessments.

Nemera has applied these approaches with UniSpray to de-risk device selection and support regulatory readiness for generic naloxone applications.

USABILITY STUDIES – CAN USERS OPERATE THE DEVICE SAFELY AND INTUITIVELY?

Usability studies determine whether intended users can perform all critical steps correctly – without prior training – under simulated real-world conditions. In a study using UniSpray:

- 20 participants aged 26–75 years completed six administrations each (three on a dummy, three self-administered)
- A total of 100% of participants successfully activated the device and completed all essential steps
- Users could not or did not attempt to remove the plunger after activation, confirming the robustness of the integrated safety mechanism.

These results demonstrate that UniSpray can enable intuitive, reliable, error-free use across a representative population – a fundamental requirement for combination products prescribed for emergency and rescue situations, such as naloxone nasal sprays for opioid overdoses.

THRESHOLD ANALYSIS – DO DESIGN DIFFERENCES INTRODUCE NEW USER RISKS?

Threshold analysis is a structured, comparative assessment used by generic drug manufacturers to determine whether any differences between a platform device and the RLD introduce use-related risks; it includes:

- **Physical Comparison:** Nozzle geometry, plunger design, finger flange, materials, shape and contours

Figure 2: UniSpray by Nemera.

- **Task Analysis:** Mapping each user action to identify any step potentially impacted by design variations
- **Instructions for Use and Label Comparison:** Ensuring that no ambiguity or additional instructions are required.

While assessing UniSpray as a suitable platform for generic naloxone, the threshold analysis identified one visible difference: the absence of the "arch" that frames the Narcan RLD device plunger, removed to reduce the quantity of single-use plastic in the device (Figure 2).

This feature was evaluated comprehensively, and Nemera demonstrated that it provided no critical user benefit for gripping, positioning, activation or dosing. The analysis confirmed that users can operate a device without the arch at the same performance level.

INTERCHANGEABILITY ASSESSMENT – CAN RLD USERS SWITCH WITHOUT ADDITIONAL TRAINING?

Interchangeability evaluations determine whether someone familiar with the RLD can transition safely to the platform device without further training – a key regulatory expectation for naloxone generics. These assessments typically include:

- Comparison of user interface elements (hand posture, actuation gesture and nozzle placement)
- Alignment of primary container and functional performance, ensuring dose delivery consistency
- Evaluation of potential confusion points, especially when visible differences exist
- Regulatory review of threshold analysis outcomes.

For UniSpray, US regulatory authorities concluded that the identified differences between each device did not affect essential design attributes nor introduce risk. As a result, no comparative use

human factors study was deemed necessary, confirming UniSpray as a functionally suitable candidate platform for naloxone generics. This significantly reduces development burden, cost and timelines for generic applicants.

AN EVIDENCE-BASED PATHWAY SUPPORTING GENERIC NALOXONE DEVELOPERS

When implemented together, usability studies, threshold analyses and interchangeability assessments provide a comprehensive, science-driven foundation ensuring that a nasal unit-dose device is:

- Safe
- Intuitive
- Robust and consistent during real-world handling
- Functionally equivalent to the RLD
- Acceptable for regulators.

For naloxone rescue applications – where seconds matter and users may be untrained, stressed or panicked – this integrated approach helps developers to de-risk platform selection and regulatory submissions, avoid unnecessary human factors studies and accelerate time-to-market for affordable, lifesaving generics.

The integration of usability insights, threshold analysis and interchangeability assessments enables a precise understanding of how design differences translate into real-world performance – ensuring that devices remain safe and reliable even when visible structural variations exist.

"THE INTEGRATION OF USABILITY INSIGHTS, THRESHOLD ANALYSIS AND INTERCHANGEABILITY ASSESSMENTS ENABLES A PRECISE UNDERSTANDING OF HOW DESIGN DIFFERENCES TRANSLATE INTO REAL-WORLD PERFORMANCE."

Beyond naloxone rescue applications, this evidence-based methodology also supports the broader portfolio of ear, nose and throat solutions offered by Nemera. Nasal platforms, from multidose sprays to unit-dose rescue devices, are developed with the same scientific rigour, ensuring robust performance, patient-centric usability and compatibility with bioequivalence pathways across a wide range of molecules. For NDA or ANDA programmes, Nemera supports pharma partners by providing end-to-end services in human factors, analytical testing, device selection and regulatory support, while reducing development risks and accelerating approval timelines.

Elsie Thomas

Elsie Thomas is Marketing Category Manager for the Ear, Nose and Throat (ENT) Franchise at Nemera. Based in Lyon, she leads strategic marketing initiatives for nasal drug delivery systems, supporting both established products and new combination product developments. Her experience spans pharmaceutical devices, bioequivalence-driven generic programmes and global go-to-market strategies, working closely with R&D, regulatory and commercial teams. In her role, Ms Thomas contributes to portfolio positioning, customer-centric value propositions and the launch of innovative nasal delivery solutions for international markets.

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GAPLAST is a 35-year-old family-owned manufacturer based in Germany, specialising in primary packaging for pharmaceutical, medtec and dermocosmetic applications. Its portfolio includes airless Bag-in-Bottle systems, inhaler cartridges, desiccant closures and drug-device components. The company's services range from product ideas and development to series production under strict regulatory and GMP standards.

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LTS develops and manufactures drug delivery systems for pharma partners, with a focus on transdermal therapeutic systems, oral thin films, micro-array patches, wearable injectors, nasal and sterile dosage forms. Its systems are applied in more than 40 marketed products.

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Nebu~Flow is a start-up medical device company transforming inhaled drug delivery with a new class of nebuliser technology. Nebu~Flow aerosolises a wider range of drug formulations than conventional devices, including novel therapies such as biologics, peptides and RNA therapeutics, that lack effective routes to the lung. Nebu~Flow is currently developing the product and seeking collaborators for product development.

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Nemera is a drug delivery device solutions and combination product services provider that puts patients first to enable the design and manufacture of devices that maximise treatment efficacy. Nemera is committed to the highest quality standards, from early device strategy to state-of-the-art manufacturing. Nemera works closely with customers to ensure the success of their combination products.

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