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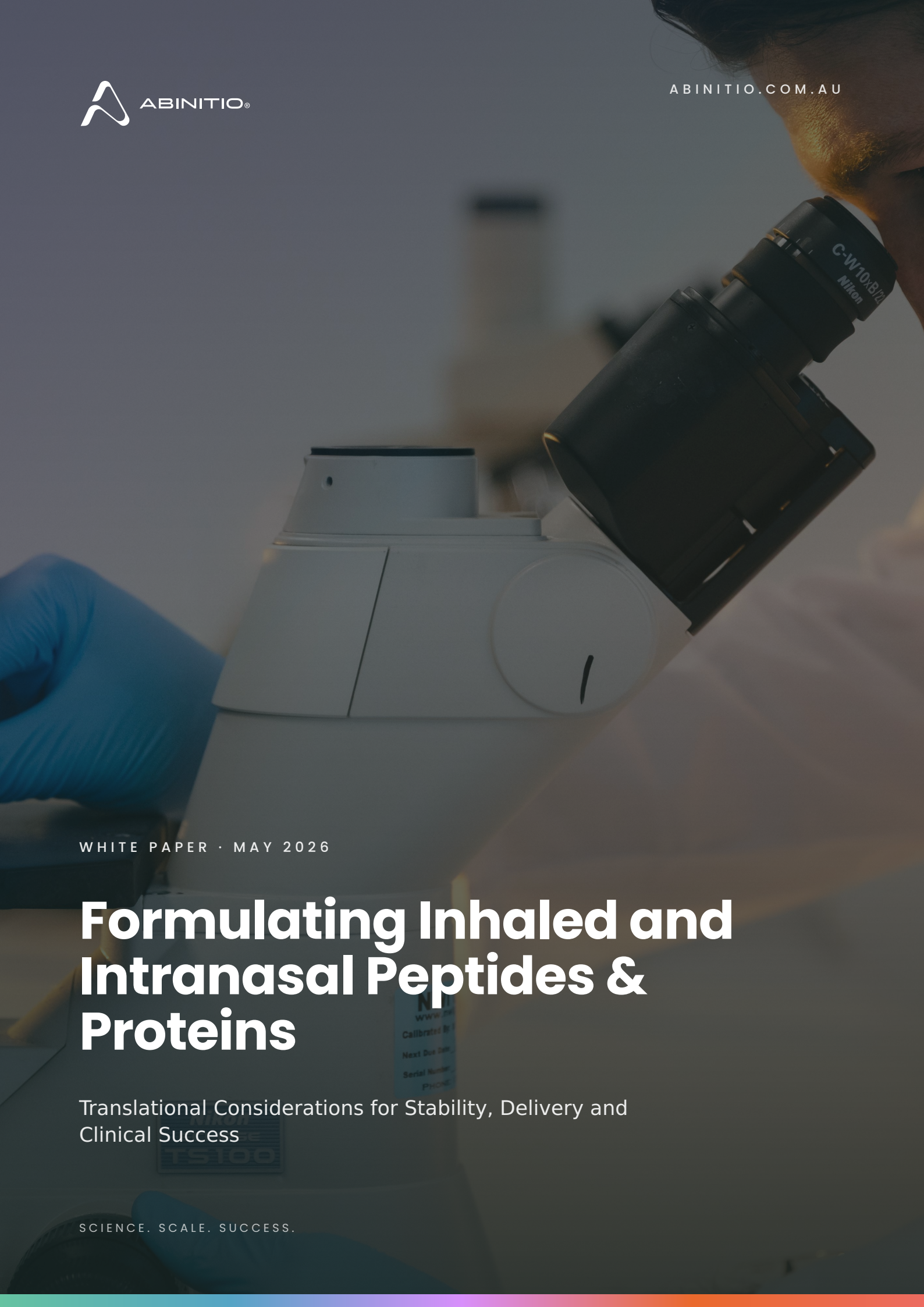

WHITE PAPER · MAY 2026

Formulating Inhaled and Intranasal Peptides & Proteins

Translational Considerations for Stability, Delivery and Clinical Success

SCIENCE. SCALE. SUCCESS.

EXECUTIVE SUMMARY

Structurally fragile. Highly sensitive. Exceptionally difficult to deliver.

Peptides and proteins are rewriting the future of medicine, but a molecule can only achieve real patient outcomes if it can be successfully stabilised, scaled, and delivered.

The pharmaceutical landscape is experiencing a profound paradigm shift driven by peptide- and protein-based therapeutics. Spanning metabolic diseases, respiratory medicine, oncology, vaccines and precision therapeutics, these macromolecules represent the next frontier of therapeutic innovation. However, despite major advances in molecular discovery, successful translation of these therapies remains highly dependent on formulation and delivery strategy.

Inhaled and intranasal administration routes are attracting growing interest as non-invasive alternatives to injectable therapies. These delivery routes offer significant advantages, including rapid absorption, improved patient compliance, localised targeting, avoidance of first-pass metabolism, and potential access to systemic or central nervous system pathways. Yet the same biological complexity that makes peptides and proteins therapeutically powerful also makes them exceptionally difficult to formulate and deliver effectively.

> “ The limiting factor for clinical success is no longer the therapeutic molecule itself, but the surrounding delivery architecture that enables the molecule to remain stable, bioavailable, manufacturable, and clinically effective.

Unlike traditional small molecules, peptides and proteins are structurally fragile and highly sensitive to environmental stress. Factors such as aerosolisation, moisture exposure, shear forces, interfacial stress, and enzymatic degradation can significantly compromise stability, biological activity, and clinical performance. As a result, the successful development of inhaled and intranasal biologics requires a highly integrated approach that combines formulation science, device engineering, analytical characterisation, manufacturing strategy, and translational development.

This white paper explores the major considerations involved in the formulation of inhaled and intranasal peptides and proteins, with particular focus on stability, delivery architecture, device integration, and translational readiness.

From promising molecule to viable medicine

As non-invasive routes gain strategic importance, the difference between a promising biologic and a clinical product increasingly lies in the engineering of the delivery architecture that surrounds it.

The pharmaceutical industry is undergoing a significant transition toward biologic and complex therapeutic modalities. Peptides and proteins are increasingly being utilised due to their high specificity, potent biological activity, and ability to target previously inaccessible pathways. At the same time, advances in biotechnology, recombinant manufacturing, and precision medicine are accelerating the development pipeline for biologic therapeutics.

Despite these advances, formulation and delivery continue to represent major barriers to successful clinical translation. Many biologics still rely on injectable administration because oral delivery remains challenging due to poor gastrointestinal stability and limited membrane permeability. However, chronic injectable therapies present their own limitations, including poor patient compliance, discomfort, cold-chain complexity, and healthcare administration burdens.

As a result, non-invasive delivery approaches such as pulmonary and intranasal administration are gaining increasing strategic importance. The respiratory tract offers an attractive route for both local and systemic drug delivery due to its large surface area, extensive vascularisation, and relatively permeable epithelial barriers. Similarly, the nasal cavity provides rapid absorption kinetics, convenience of administration, and the potential for direct nose-to-brain transport pathways.

While these routes offer substantial opportunities, they also introduce unique technical and translational challenges. In many cases, the limiting factor for clinical success is no longer the therapeutic molecule itself, but rather the surrounding delivery architecture that enables the molecule to remain stable, bioavailable, manufacturable, and clinically effective.

> “ The limiting factor for clinical success is no longer the therapeutic molecule itself. It is the surrounding delivery architecture.

A different formulation problem from small molecules

Peptides and proteins possess complex higher-order structures that are highly sensitive to their environment. Formulation must protect biological activity at every step, from manufacturing through administration.

The formulation of peptides and proteins differs fundamentally from traditional small molecule pharmaceutical development. Small molecules are generally chemically stable, structurally simple, and relatively tolerant to manufacturing and environmental stress. In contrast, peptides and proteins possess complex higher-order structures that are highly sensitive to their surroundings.

Minor changes in temperature, pH, moisture content, ionic strength, or mechanical stress may induce denaturation, aggregation, hydrolysis, oxidation, or irreversible loss of biological activity. These degradation pathways are particularly problematic in inhaled and intranasal delivery systems, where molecules are exposed to substantial physical stress during aerosol generation and administration.

Nebulisation, spray atomisation, dry powder dispersion, and pump actuation all generate shear and interfacial stresses capable of destabilising fragile biologic structures. In some cases, the delivery process itself may induce aggregation or structural unfolding before the molecule even reaches the target tissue.

This challenge becomes even more complex when considering the need for long-term stability during manufacturing, storage, transportation, and patient use. Accordingly, formulation development for inhaled and intranasal biologics is not simply about solubilising an active pharmaceutical ingredient. Rather, it involves engineering an entire protective environment around the molecule that preserves its integrity throughout the product lifecycle.

Engineering a protective environment around the molecule

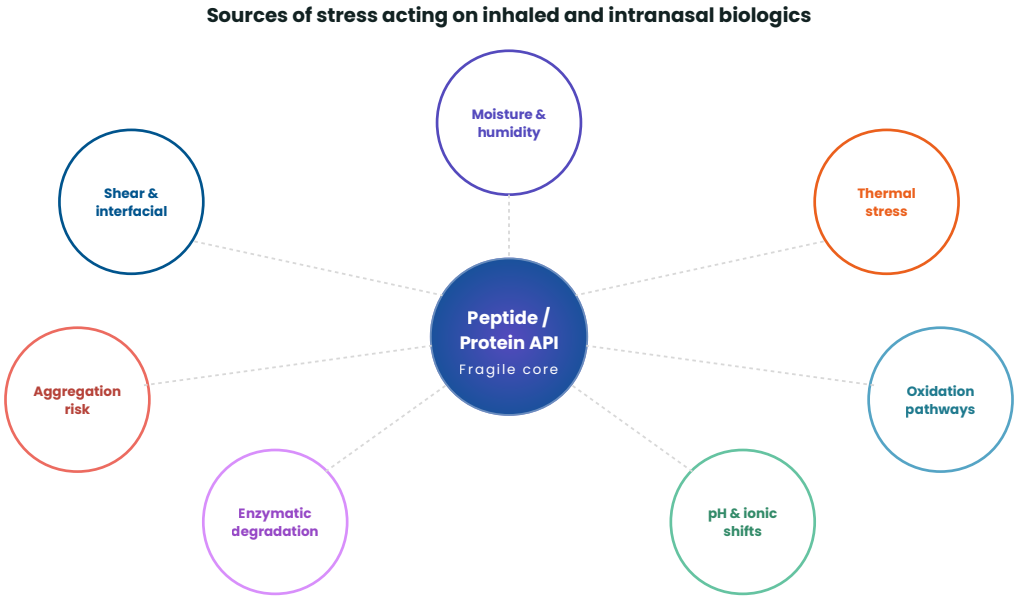

FIGURE 1 · COMMON STRESS PATHWAYS TARGETED BY FORMULATION DESIGN

Stability represents one of the most critical determinants of success for inhaled and intranasal biologics. Both physical and chemical degradation pathways must be carefully controlled throughout development.

Physical instability commonly manifests as aggregation, precipitation, adsorption to surfaces, or structural unfolding. Aggregation is particularly problematic because it may not only reduce therapeutic potency but also alter aerodynamic behaviour and increase immunogenicity risk. Even low levels of aggregation can significantly impact dose reproducibility and patient safety.

To mitigate these risks, formulation scientists employ a wide range of stabilisation strategies designed to preserve molecular integrity during manufacturing, storage, aerosolisation, and administration. Traditional excipients such as sugars, amino acids, and surfactants continue to play important roles in protecting proteins and peptides against interfacial and dehydration stress. Sugars such as trehalose and sucrose are commonly used to stabilise proteins during drying processes by preserving hydrogen bonding networks and reducing molecular mobility, while amino acids such as leucine and glycine may improve powder dispersibility and minimise aggregation tendencies. Surfactants may further reduce surface-induced denaturation during aerosol generation.

Beyond these conventional approaches, buffer selection is often a critical yet underestimated component of biologic stability. Proteins and peptides are highly sensitive to pH fluctuations, ionic strength, and local microenvironmental changes, all of which may influence conformational stability, aggregation propensity, and degradation kinetics. Carefully optimised buffer systems therefore serve not only to maintain pH, but also to minimise chemical degradation pathways such as deamidation, hydrolysis, and oxidation. Commonly utilised systems may include phosphate, citrate, acetate, histidine, or tris-based buffers, depending on the specific stability profile of the molecule. Importantly, buffer behaviour may also change during drying processes such as spray drying or lyophilisation, where local pH shifts can occur as water is removed, further emphasising the need for careful formulation optimisation.

Nanoparticles, dry powders and water activity

Modern stabilisation strategies extend well beyond conventional excipients. Nanoparticle carriers, packaging engineering and water-activity control all contribute to a molecule's clinical performance.

Nanoparticle-based stabilisation and delivery systems represent another rapidly advancing area within biologic formulation science. Lipid nanoparticles, polymeric nanoparticles, liposomes, nanogels, and hybrid carrier systems are increasingly being investigated not only as delivery vehicles, but also as protective environments for fragile peptides and proteins. By encapsulating or associating the biologic within a nanoparticle matrix, these systems may shield molecules from enzymatic degradation, moisture exposure, oxidation, and shear stress during aerosolisation. Nanoparticles may also improve mucosal penetration, prolong residence time, enhance absorption, and enable controlled or targeted release profiles. In pulmonary and intranasal delivery, nanoparticle systems may further facilitate uptake across epithelial barriers while preserving biological activity.

Chemical stability presents an additional layer of complexity. Peptides and proteins remain vulnerable to oxidation, deamidation, hydrolysis, disulfide scrambling, and enzymatic degradation throughout their lifecycle. These pathways may be accelerated by moisture exposure, elevated temperature, interfacial stress, or unfavourable pH conditions. Consequently, careful optimisation of excipient compatibility, water activity, packaging systems, and storage conditions becomes essential.

For dry powder systems in particular, moisture management is critically important. Water uptake can dramatically alter particle morphology, induce agglomeration, reduce aerosol performance, and accelerate degradation kinetics. As a result, inhaled biologic formulations often require highly engineered packaging systems with stringent humidity protection to preserve long-term stability and product performance.

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Particle engineering for deep-lung deposition

Successful pulmonary delivery is an exercise in aerodynamics as much as biology. Particle size, density and dispersibility dictate where the dose lands and whether it works.

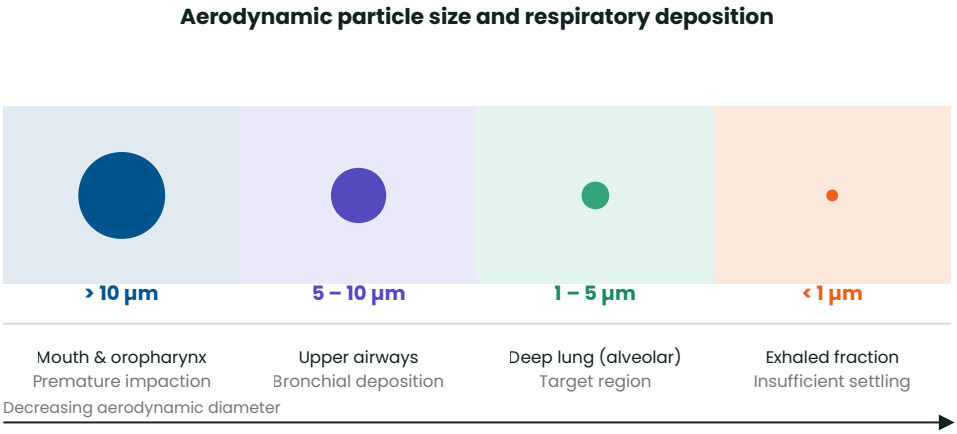

FIGURE 2 · APPROXIMATE RELATIONSHIP BETWEEN AERODYNAMIC DIAMETER AND DEPOSITION SITE

Pulmonary delivery offers one of the most promising non-invasive routes for biologics due to the unique physiology of the lungs. The alveolar region provides an exceptionally large absorptive surface area combined with thin epithelial barriers and extensive vascularisation, enabling rapid systemic uptake of appropriately engineered molecules.

However, achieving effective pulmonary delivery requires precise control over aerosol performance and particle engineering. Unlike oral or injectable formulations, inhaled products must be carefully designed to achieve deposition within specific regions of the respiratory tract. Particle size, density, morphology, and dispersibility all directly influence aerodynamic behaviour and clinical performance.

Typically, particles intended for deep lung deposition require aerodynamic diameters between approximately one and five microns. Particles outside this range may either deposit prematurely within the upper airways or be exhaled before deposition occurs. Consequently, particle engineering technologies such as spray drying, freeze drying, and thin-film freezing play central roles in inhaled biologic development.

At the same time, pulmonary delivery devices themselves significantly influence formulation performance. Dry powder inhalers, nebulisers, soft mist inhalers, and metered dose inhalers each expose biologics to different forms of stress and aerosolisation dynamics. Nebulisers, for example, may subject proteins to prolonged liquid-phase instability and repeated shear exposure, while dry powder systems require highly controlled powder flow and moisture protection.

This interdependence between formulation and device means that inhaled biologic products cannot be developed in isolation. Instead, successful translation requires simultaneous optimisation of the molecule, formulation, device platform, and manufacturing process.

SECTION 04 · INTRANASAL DELIVERY

A non-invasive route with rapid kinetics, and unforgiving constraints.

Mucoadhesion, permeability and patient variability

Intranasal delivery has emerged as another highly attractive route for peptides and proteins, particularly for therapies requiring rapid systemic exposure or direct access to central nervous system pathways. The nasal cavity provides a highly vascularised environment capable of relatively rapid absorption while avoiding gastrointestinal degradation and hepatic first-pass metabolism.

Nevertheless, the nasal route presents its own physiological barriers. The available administration volume is relatively small, mucociliary clearance rapidly removes foreign material, and enzymatic activity within the nasal cavity may degrade sensitive biologics before absorption occurs.

As a result, intranasal formulations often require strategies to improve both residence time and permeability. Mucoadhesive systems, permeation enhancers, in situ gelling technologies, and nanoparticle carriers are increasingly being explored to overcome these limitations.

Powder-based intranasal systems are also gaining considerable attention due to their improved stability profiles relative to liquid formulations. By reducing water activity, dry powders may minimise hydrolytic degradation while also increasing nasal residence time. However, these systems require careful optimisation of particle engineering, spray performance, and device compatibility to ensure reproducible dosing and patient usability.

Importantly, intranasal delivery introduces additional considerations around deposition patterns and patient variability. Differences in nasal anatomy, breathing patterns, disease state, and administration technique may significantly affect product performance. Consequently, human factors and device usability become important aspects of translational development.

Manufacturing and Translation

One of the most underestimated challenges associated with inhaled and intranasal biologics is the transition from laboratory feasibility to scalable manufacturing. Many formulations that perform successfully during early-stage research encounter significant barriers during scale-up, GMP production, or long-term stability assessment.

Manufacturing processes such as spray drying may expose biologics to thermal stress, rapid dehydration, and interfacial forces that destabilise the active molecule. Batch reproducibility, sterility control, powder consistency, and process robustness all become critical factors influencing commercial viability.

Comprehensive analytical characterisation therefore plays a central role throughout development. Stability-indicating methods, aggregation analysis, particle sizing, aerodynamic performance testing, biological activity assays, and moisture analysis are all essential components of a robust translational programme.

In many cases, failure of inhaled or intranasal biologics occurs not because the molecule lacks therapeutic potential, but because formulation, device integration, or manufacturability challenges emerge too late in development.

FUTURE OUTLOOK

Integrated platforms, not isolated strategies

The future pipeline of advanced therapeutics will increasingly include peptides, proteins, RNA therapeutics, gene therapies, and other complex biologics. As these therapies continue evolving, demand for non-invasive delivery systems is expected to increase substantially.

Emerging technologies such as advanced biomaterials, controlled-release systems, precision particle engineering, and AI-assisted formulation optimisation are likely to further accelerate the field. At the same time, there is growing recognition that successful biologic products require integrated translational platforms rather than isolated formulation strategies.

Ultimately, the future leaders in inhaled and intranasal biologics will likely be those capable of integrating molecular discovery, formulation science, device engineering, analytical characterisation, and scalable manufacturing into cohesive therapeutic systems.

Conclusion

Inhaled and intranasal delivery represent transformative opportunities for peptide- and protein-based therapeutics. However, these routes also magnify the inherent fragility and complexity of biologic molecules.

Successful translation depends on far more than identifying a promising therapeutic candidate. Stability, aerosol performance, device compatibility, manufacturability, and delivery architecture all play critical roles in determining whether a biologic can ultimately become a clinically successful medicine.

As the biologics sector continues expanding, formulation science and translational delivery engineering will increasingly define the difference between promising molecules and viable therapeutic products.

> “ The next frontier is not simply discovering new molecules. It is engineering formulations that can reliably translate into real patient outcomes.

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ABOUT ABINITIO

One partner. The whole path from molecule to market.

ABINITIO is an Australian pharmaceutical R&D and GMP manufacturing organisation specialising in advanced drug delivery, inhalation therapeutics, intranasal therapeutics, biologics formulation, particle engineering, and translational pharmaceutical development.

We deliver a seamless, integrated model covering the three critical pillars of the development lifecycle, built around fragile, complex molecules and the patients who depend on them.

PILLAR 01

Science

Advanced R&D and formulation optimisation for complex, fragile molecules, including peptides, oligonucleotides, proteins, and RNA-based therapeutics.

PILLAR 02

Scale

State-of-the-art particle engineering and GMP manufacturing solutions, including spray drying, freeze drying, and inhalation product manufacture.

PILLAR 03

Success

End-to-end clinical trial readiness and regulatory support, integrating analytical, manufacturing, and translational development under one roof.

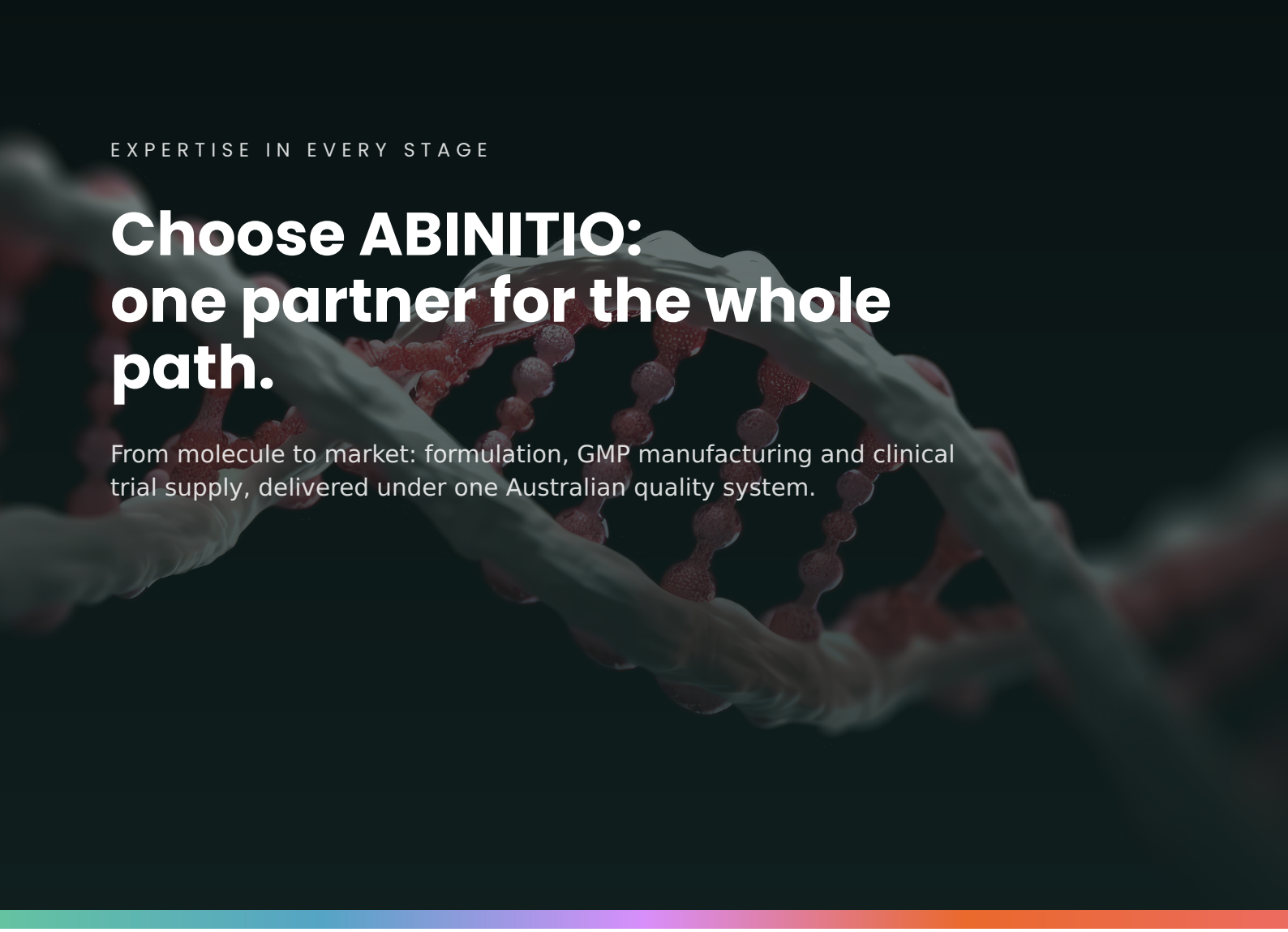
Capabilities at a glance

Our specialised capabilities encompass a diverse range of complex dosage forms, including topical, oral, nasal, respiratory, and nebulised systems, engineered for both human and veterinary applications.

Whether the requirement is feasibility-stage formulation, scale-up of a sensitive biologic, or full clinical trial supply, ABINITIO offers integrated R&D, GMP and clinical support under a single quality system.

Science. Scale. Success.

Learn more about our integrated path from molecule to market at abinitio.com.au.



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