Why it is Time to 'Think Different' about Nasal Delivery of Biologics

Whether it's a case of the stars aligning or elements combining, there are plenty of phrases to summarise the power that is unleashed when separate forces unite in a single, shared purpose.

These moments of confluence are fertile territory for creativity and innovation. Indeed, as Steve Jobs said, it's when you connect the dots together that you can "synthesize new things".

For pharmaceutical companies, there are two current market forces receiving greater attention considering the pandemic that have the potential to create such a frisson where they collide: the increasing emphasis on biologic entities and the growing appreciation for the benefits of nasal drug delivery.

Combining the two for the intranasal delivery of biologics, however, is a sweet spot that continues to evade many pharmaceutical firms thanks to a variety of challenges.

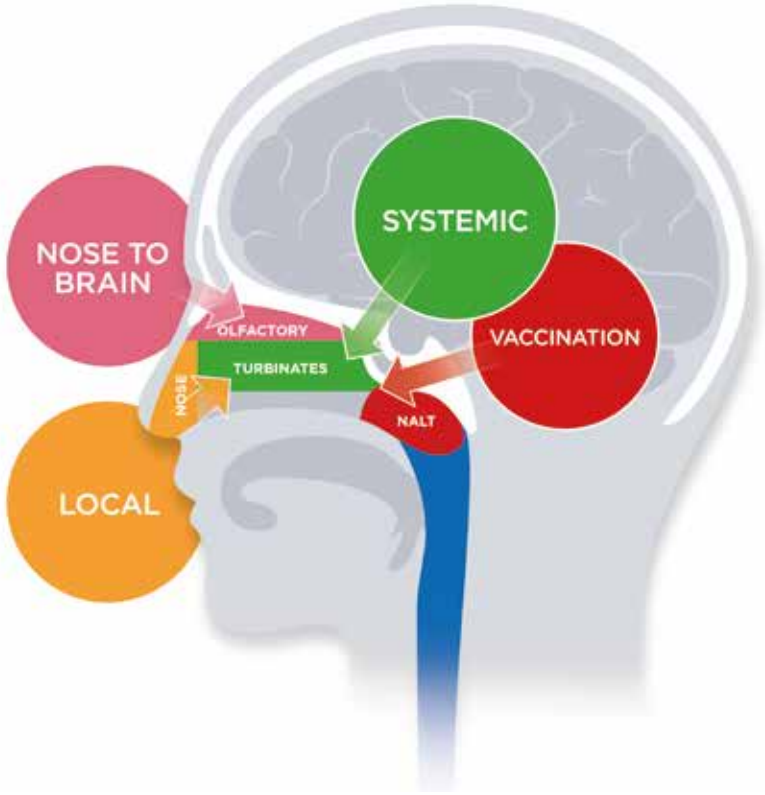
In this article we will discuss the reasons why both biologics and nasal delivery are continuing to attract attention. In particular, we will look at the demand for prophylactic therapies to protect populations against the ongoing threat from SARS-CoV-2, and the benefits of targeting these therapies locally in the nasal cavity.

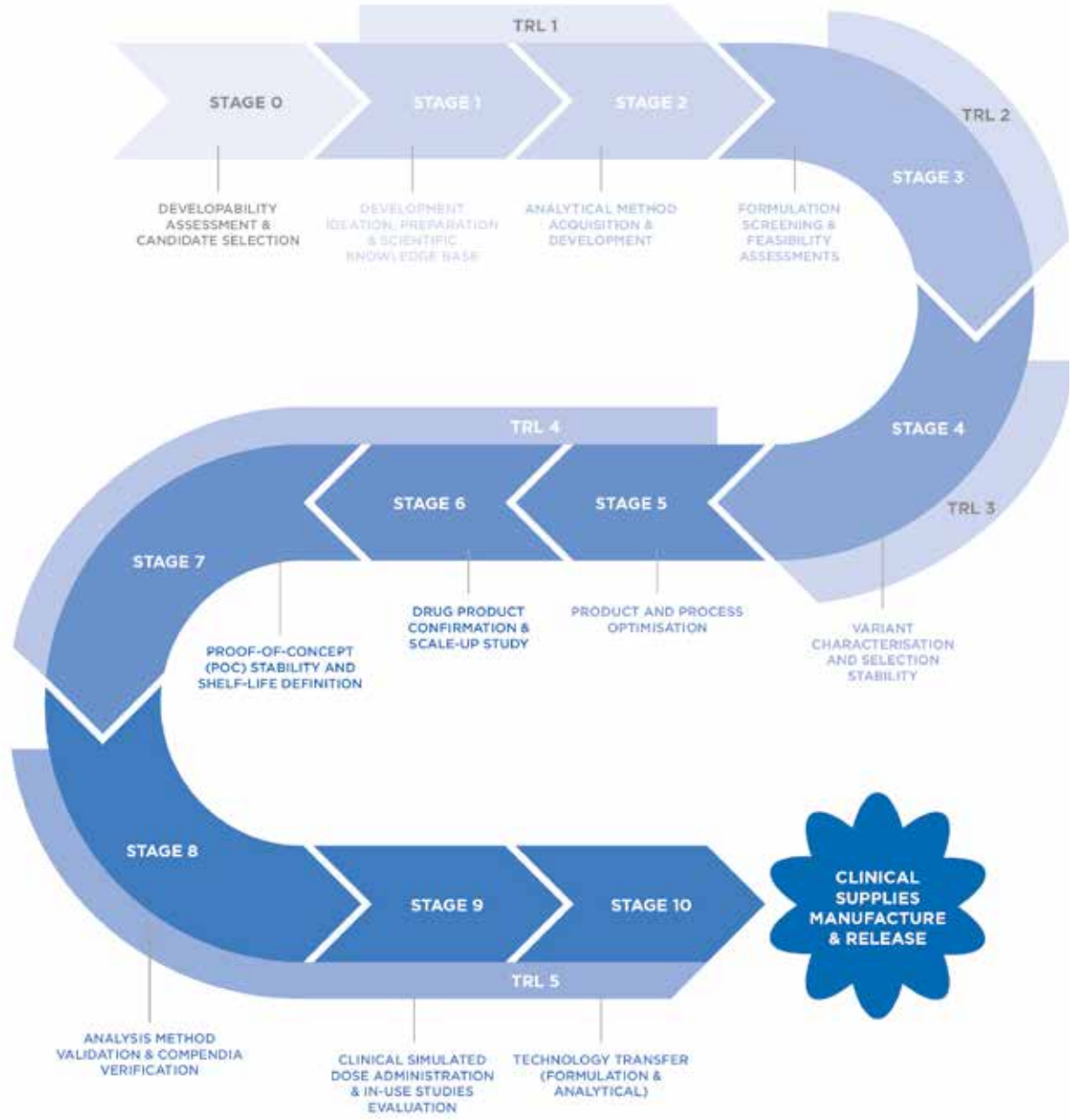
We will also consider the various formulation difficulties associated with these complex proteins and macromolecules, as well as the breadth of physiological barriers presented by nasal delivery. We will then explore how formulation science and technology are enabling these challenges to be overcome, achieving maximum deposition and retention in the nasal cavity, and more promising outcomes for patients.

Finally, we will argue the importance of pharma partners aligning their efforts with drug and device delivery partners early in the process to accelerate and de-risk development at every stage, from formulation through to clinical trial and regulatory submission, while also considering how data and connectivity can be employed to optimise the product lifecycle and sustain ever better patient outcomes.

On January 30, 2020, the Director-General of the World Health Organization (WHO), Dr. Tedros Adhanom Ghebreyesus, declared the COVID-19 outbreak a public health emergency of international concern (PHEIC) – the organisation's highest level of alarm.

At that point, there were just two antivirals in development to treat the novel coronavirus. Just 41 days later, when the WHO characterised the outbreak as a pandemic, the combined number of antivirals, vaccines and treatments in development had jumped to 74. According to the latest available data, that figure now stands at over 850 and continues to grow.[1,2]





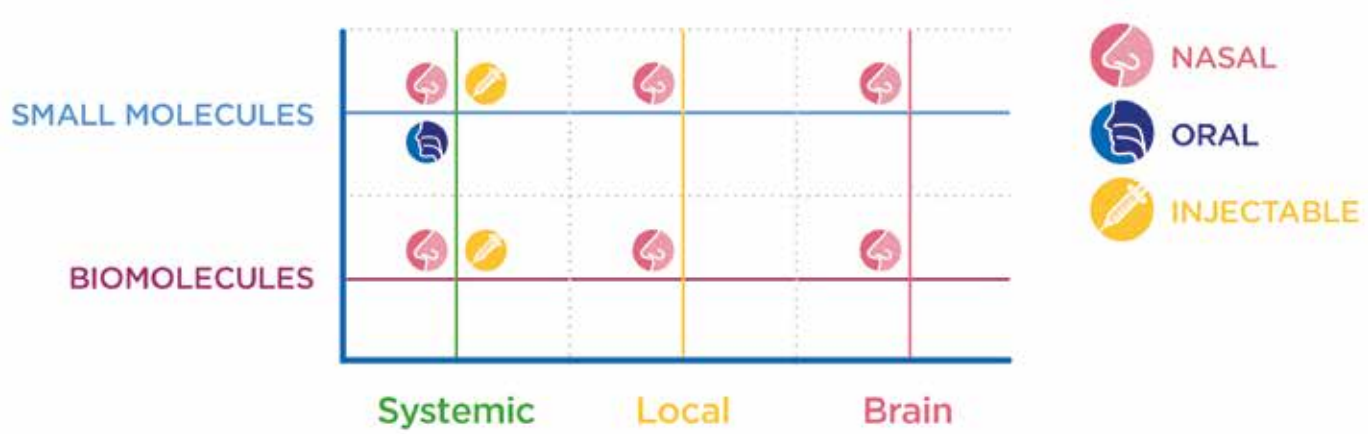
This dynamic rise provides evidence of the high level of activity that has been sustained within the pharma and biotech sector in response to the immediate global emergency of COVID-19. As such, it represents a notable spike on a graph that was already on an upward trajectory for many years prior to the pandemic. This growth been driven by the success of biologics in tackling the ongoing burden associated with chronic conditions, including cancer and autoimmune diseases, as well as an increased focus in biosimilars as patent expiration brings increased generic competition to the sector.

The rise of biologics is borne out by various data points. According to market analyst Frost & Sullivan, emerging biotechnology companies have grown their contribution to global drug discovery and early development outsourcing by more than 80% since 2018 – in a market worth $19.65 billion in 2020, and estimated to grow at a compound annual growth rate of 6.4% to 2026.[3] Data from IQVIA confirms this trend, highlighting the fact that small molecules have declined 12% since 2014 on a real net per capita basis, while biologics have increased by 50%.[4]

Comparisons between small and large molecules in terms of market performance might provide helpful context, but it's important to acknowledge that these are not like-for-like products in terms of their physical properties.

Chemically synthesized small-molecule APIs offer a more robust proposition while, in contrast, the delicate, complex proteins of large-molecule biologics must be produced in aseptic conditions and handled with extreme care to ensure they remain stable on their pathway to the patient. The difference in their nature means that different characterisation techniques are also required for chemical and biological entities, including the analytical methods used for quantification and in determining stability.

The properties of biologics also have implications for the method of drug delivery. Small molecules are predominantly delivered in oral forms because of their ability to withstand the uncompromisingly harsh conditions present in the gastrointestinal (GI) tract to deliver required levels of bio-availability. The same cannot be said of biologics, however,



whose sensitive properties make them prone to degradation in the GI tract, and whose size complicates the process of molecules passing through cells in the gut lining via intestinal permeability.

The result is that injection and infusion remain the preferred delivery routes for biologics to offer the necessary protection based on the pharmacokinetic properties of the API. It is acknowledged, however, that parenteral drug delivery is not preferred by arguably the most important stakeholder in the process: the patient.

As routes of self-administration go, having to self-inject or even using an auto-injector device present a much poorer patient experience compared with the convenience of other delivery mechanisms. And while the injection process might be managed on the patient's behalf by a healthcare professional (HCP) within a clinical setting, for some (or many) patients, there is no escape from the discomfort of a needle-stick– something that can trigger anxiety and fainting in those affected by needle phobia – and indeed the risk of needle-stick injury for the HCP.

A further consideration of parenteral administration is that it results in systemic delivery. This may be desired, but it precludes situations where a topical and targeted pharmacodynamic effect would be beneficial. From a pharmacokinetic perspective, the direct and rapid nature of drug absorption also introduces the risk of systemic adverse effects as the formulation generates unwanted bioavailability beyond its intended location. Taken together, the combination of these factors has placed increasing focus on methods of drug delivery that are able to achieve the dual objectives of offering compliance with the pharmacological properties of biologics but also overcoming the downsides associated with oral and parenteral administration.

Nasal administration is an example of a drug delivery route that sits happily in both these camps, presenting biotechnology and pharmaceutical companies with a robust platform for patient-centric innovation with biologics. Its potential has been amplified over the course of the pandemic, with COVID-19 acting as a catalyst for interest in treatments targeting the nasal cavity.

For patients, nasal inhalation might not quite offer the convenience of oral administration routes, but it is far more readily accepted than injection or many other parenteral routes. It offers simple and pain-free administration, with the potential for patients to self-manage their medication using portable devices.

Because molecules are deposited in the highly vascularised nasal cavity, there are no concerns associated with the potency of a dose being reduced by first-pass metabolism in the GI tract, and the effects can be both local and systemic. In the case of tackling SARS-CoV-2, for example, nasal administration introduces the potential for vaccines to generate a local and mucosal immune response through targeting of the antigen-presenting cells situated in the nasopharynx-associated lymphoid tissue (NALT). It also provides an appealing route for the delivery of locally acting prophylactic therapies to neutralise the virus directly in the nasal cavity or for the convenient administration of vaccine therapies designed to introduce – or maintain – a level of immunity.

Employing nasal delivery for biologics brings various advantages, therefore, but it is not without its challenges and considerations. Indeed, there is a paradox at play in that the fundamental characteristics of proteins and peptides – their size and complex tertiary structure – are both the factors behind their success, in terms of improved potency and selectivity, and the factors behind some of their major weaknesses, such as poor absorption and stability.[5]

Not only susceptible to degradation at ambient temperature and adsorption into packaging materials, biologics also display sensitivity to *in vivo* conditions, reacting negatively to temperature and acidity as well as the presence of enzymes such as proteases and peptidases, which can impact on permeation.

This sensitivity extends to biologics' relationship and interaction with the excipients that might be employed to address areas of stability. Preservatives and other excipients used as constituents in 'typical' formulations of nasally inhaled small-molecule APIs may, in the case of biologics, trigger difficulties such as protein agglomeration and precipitation. Consideration must also be given to the toxicology of the mucoadhesives and absorption enhancers necessary for achieving the desired exposure and transfer of large molecules at the nasal mucosa, and for defending against mucociliary clearance.[6]

The superior molecular mass of proteins, in combination with their hydrophilic properties, also results in limited permeation across biological tissue in comparison with small molecules.

The issue of scale also translates into formulations comprising biologics having a different sensitivity to aerosolization and shear stress, which carries implications for particle distribution and deposition.

For biotech and pharmaceutical companies, these various challenges in formulation and delivery must therefore be considered and addressed to deliver on the promise of intranasal biologic development. Looking at formulation science in particular, there are numerous strategies available to tackle and manage issues such as stability.

Lyophilization, for example, can address difficulties associated with macromolecular drugs in liquid form, with powder dosage forms not only offering greater chemical stability, but also extending the product's shelf-life. Various methods are used to transform the drug into powder form, including freeze drying and the widely used spray drying. More recently, supercritical fluid-assisted spray drying has emerged as a promising alternative to conventional spray drying, since it facilitates the production of smaller particles that are dissolved more quickly by the nasal mucus, improving bioavailability and reducing the risk presented by mucociliary clearance.[7]

For scientists working in the pharma supply chain, it is crucial that they understand the importance of supporting biotech and pharmaceutical partners with deep expertise in areas such as this, providing access to technologies and development tools that optimise biologic API molecules for nasal delivery.

Through early-stage pre-formulation studies, assessment can be made of the drug product's stability, with particular attention paid to the compatibility of excipients. This lays down essential foundations for further evaluation of stability and integrity in the formulation stage, ultimately influencing the level of efficacy achieved by the end product.

Using a combination of *in vitro* characterisation via nasal cast deposition and *in silico* physiological-based pharmacokinetic (PBPK) modelling, analysis can then be carried out on the predicted performance of the formulation regarding deposition, retention and absorption in the nasal cavity. These methods elicit data relating to factors such as spray pattern, plume geometry, droplet spray distribution and spray content, providing three-dimensional analysis to support regulatory submissions.

Many providers in the supply chain are already able to help partners look further down the product lifecycle, for example, drawing on advances in connected technology to consider the potential for 'connected' nasal devices to emerge over time. Particularly for patients managing chronic conditions, including mental health conditions affecting the Central Nervous System (CNS), such devices facilitate valuable communication via a smartphone interface, making data on medication use available to healthcare providers.

As we have shown, arriving at this point in the future is dependent on carefully navigating a complex and multi-layered development pathway when it comes to intranasal biologics. This, again, underlines the importance of taking an integrated approach to formulation and device development, consolidating an appreciation of API and device characteristics as well as patient behaviour and necessities.

It is also clear, however, that significant potential exists within this relatively vacant space. Whether helping defend populations against the clear and present danger of COVID-19, tackling chronic autoimmune conditions or delivering molecules to the CNS to treat neurodegenerative diseases, it is only by thinking differently and exploring the potential that exists at the intersection of biologics and nasal drug delivery that those opportunities will be realised. Furthermore, it is only by taking an integrated approach that the development cycle can be kept to a minimum and the patient benefits can be felt as quickly as possible.

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