Conversations with... Gemma Budd, on Nasal Drug Product Development

Discussing strategies for successful navigation of the path from discovery to Investigational New Drug Application (IND) for orally inhaled and nasal drug products (OINDPs)

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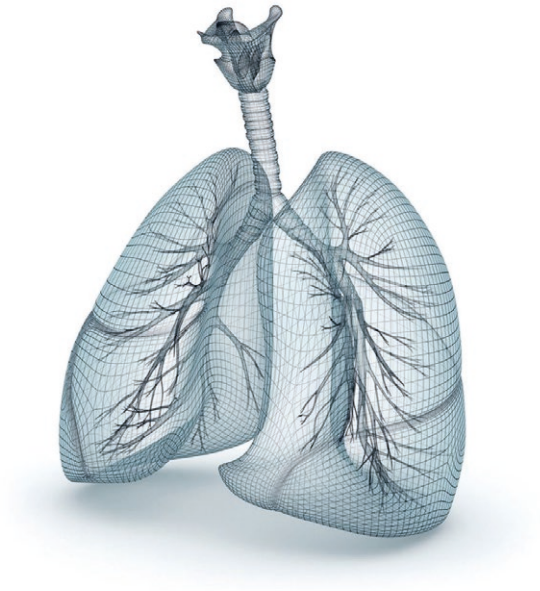
OINDPs are often referred to as combination products. Can you explain that term and its implications for development?

The term reflects that OINDPs are a unique combination of drug and device regulated jointly as a pharmaceutical product and supplied to the patient as such. We're not talking about a medical device that the patient uses with different drugs. Drug and device together define the performance, and development consequently necessitates a holistic approach, with optimization of the device and formulation in tandem to achieve target performance.

OINDPs are further differentiated from other combination products, such as injectables, by their very high dependence on patient technique and capability. Consideration of the patient is therefore an additional factor in development. For example, the requirement to inhale deeply may challenge patients prescribed an inhaler for a respiratory disease, due to compromised lung functionality, so being able to quantify the impact that may have on drug deposition in a diseased patient can make a real difference to formulation and device selection. In another example, for a rescue medication simplicity is key; a minimal number of handling steps is highly desirable. There are no regulatory requirements for disease-specific testing but taking account of factors such as breathing profiles and lung physiology from the outset ultimately increases the likelihood of achieving clinical efficacy; both *in vitro* testing and modelling can be useful in this regard.



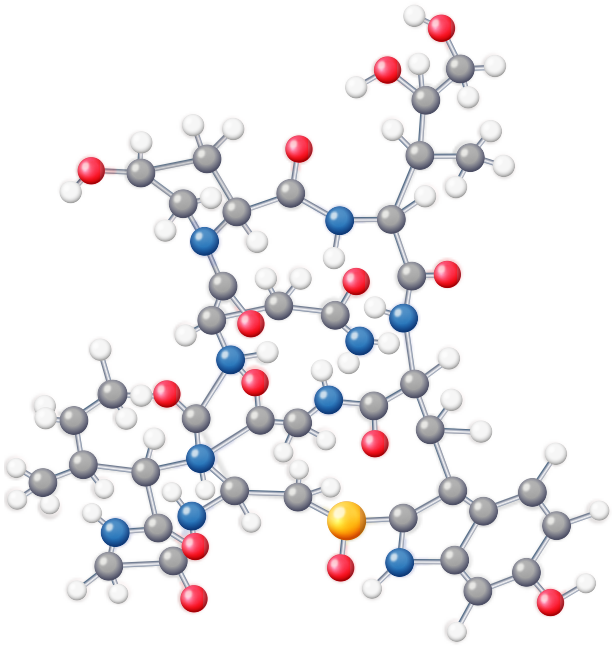
What types of molecules are currently filling the OINDP development pipeline?

In the pulmonary space, developers are looking beyond Asthma and Chronic Obstructive Pulmonary Disease (COPD) to therapeutics for lung-related diseases such as cystic fibrosis and pulmonary hypertension which are still treated primarily with tablets, injectables or by intravenous infusion. The motivation is more effective drug delivery to the site of action - often of existing drug molecules - to achieve better efficacy with fewer off-target effects.

With nasal drug delivery we're seeing more new molecules, notably biologics. Examples include peptides, RNA/DNA based molecules and antibodies and other proteins, primary

targets being therapeutics for diseases of the central nervous system (CNS) and airborne viruses. There is evidence that intranasal delivery may enable by-passing of the blood brain barrier, offering potential to achieve a better balance between therapeutic efficacy and side effects for drug delivery to the CNS. That said, differentiating nose to brain from systemic delivery is complex. I'd expect to see this area far more established in 5 to 10 years' time, possibly with a differentiated regulatory pathway with respect to toxicity and safety studies.

With respect to anti-virals, interest triggered by the COVID-19 pandemic has not waned, rather there is growing recognition of the more general benefits of using intranasal delivery to tackle airborne viruses. Intranasal vaccines have potential to trigger a local immune response in the nasal mucosa to complement the protection offered by systemic immunity. Prophylactics may be valuable to stop diseases at the point of entry, limiting their spread, while targeted therapeutics may, more generally, prove a good choice for ongoing treatment.



The traditional areas of application for OINDPs – asthma, COPD, and hayfever – are awash with genericization but it's worth mentioning the reformulation that is going on for pressurized metered dose inhalers (pMDIs). The need to switch to lower global warming potential propellants is a major influence on anyone working in this area, especially for companies with aggressive net zero targets to meet.

Where should developers start? Can you highlight some early key decisions that need to be addressed?

Scoping the fundamental physicochemical characteristics of the drug molecule is a good place to start. Quantify solubility, permeability, degradation pathways and, for biologics, stability, to provide a foundation for formulation. Establish what your molecule is capable of and what its deficiencies are to get product development off on the right track.

Thinking about dosing requirements early on is helpful even if you can only get a ballpark estimate - 50µg or 50mg? Dose has a defining impact on development strategy with larger doses mitigating towards powder delivery.

Delivering high doses with nasal liquid formulations is a challenge due to the necessity to work within the drug's limit of inherent solubility and stability in solution. Formulating at high concentrations also pushes up viscosity, particularly for biologics, potentially compromising spray performance and / or leading to agglomeration or precipitation of the drug. However, lower drug concentrations mean larger dose volumes, and potentially multiple actuations per dose. This is not desirable from a patient adherence perspective and in addition the nose poorly tolerates high liquid loading. Doses above 100 - 200µL are often associated with losses due to swallowing or dripping. On the other hand, powders can be formulated at very high drug concentrations to avoid these issues and demonstrate better retention times due to an ability to withstand mucociliary clearance, and for biologics also offer the substantial additional benefit of greater stability.

Dosing also highlights areas of significant challenge. If the requirement is for a high dose to be delivered into the bloodstream, then how are you going to get sufficient drug to the target site? Formulation without carriers or enhancers will help to keep the number of actuations to a minimum but may negatively impact aerosolisation performance or bioavailability. By contrast, for small doses, adding carriers isn't an issue, but limits of detection for analytical techniques may be an issue. Can you establish the methods required to support development?

Focusing on the device, what factors are most influential in guiding choice?

The decision to formulate as a powder or a liquid is a primary factor. Beyond that, selecting devices with a precedence of market use is the preference for both new molecules and reformulation since that reduces risk. That said, there are areas where existing options are limited – nasal powders being a prime example – and the benefits of working with a new device will be compelling. For example, we're currently working on a multidose device for nasal powders to fill a recognized gap in the market.

The intended patient demographic is also a factor. A device already established with the target population is excellent as you'll know patients can use it safely and as intended. More broadly, matching ease-of-use and training to patient needs is important for long-term success. Preserve devices for emergency use for applications that merit them – rather than routine delivery for chronic conditions - since they typically carry a higher price tag due to the more exacting specifications and tolerance associated with delivering the required reliability and precision.

From a technical perspective, device choice can help significantly with dose targeting so deposition profile is also a consideration. For intranasal delivery, optimizing devices for deposition in either the turbinates for systemic delivery, or the olfactory region for nose to brain delivery, is an active area of development.

And with respect to the formulation, what techniques and strategies can be particularly helpful there?

Overall, the goal is to keep the formulation as simple as is possible whilst addressing the inherent limitations of the drug molecule. How, when and where you invest formulation time and effort as you work towards this goal is crucial. Focusing attention on where it will count, ahead of Phase I clinical trials, can make a major difference to your chances of success and the cost of assessing them.

Leveraging relevant disease models can be highly informative and accounting for the nuances of inhaled or intranasal delivery is vital. The nose and lungs are designed to prevent the ingress of contaminants into the body with multiple barriers to uptake ranging from poor accessibility to minimal fluid levels and mucociliary clearance. Appropriate disease modelling will highlight the biggest hurdles to success for an individual molecule.

It's possible to go into Phase I trials with the simplest of formulations – a drug and buffer – and for pulmonary delivery, to begin with a nebulizer, letting the patient inhale the dose at low concentration formulation over a long period. This approach will accelerate you into the clinic but not necessarily to market. The drug may fail because of factors such as low permeability that can ultimately be addressed through formulation. It's smarter is to assess how the molecule is most likely to fail – modelling data will help here - and develop the formulation as far as is necessary to address that issue. In essence, maximize the chances of success without over-investing too early.

This is where a knowledgeable partner can pay dividends if OINDP-specific in-house expertise is limited. At Nanopharm we work solely with OINDPs so we're adept at working out how to get the information needed for an IND without incurring unnecessary time and expense.

What about meeting regulatory requirements? Are there any issues that cause widespread problems?

The combination nature of OINDPs makes for more complex regulatory requirements than for simpler dosage forms and it's important to be clear on IND requirements. For example, there is no need to go as far as performing all of the drug product characterisation (DPC) studies in the guidance for Chemistry, Manufacturing and Controls at Phase I; that phase of work can be abbreviated and is really intended for late phase and setting commercial drug product specifications However, working with CROs/CDMOs with experience to know what is or isn't needed, and how to justify deviations from the guidance, is important so you do not inadvertently cut corners or indeed do too much.

Lack of approved functional excipients is probably one of the most limiting factors for delivery through the nose or lungs (as opposed to for local action). For a repurposing/ reformulated drug targeting the 505(b)(2) abbreviated pathway there may not be any appetite to take a new excipient to the regulator, and for generics this wouldn't be possible if a Q1/Q2 product is needed. This means choice may be limited if you want to use permeation enhancers, for example, though they are steadily entering the clinic and ultimately the market. With a new molecular entity, where you're faced with tox studies anyway, then it might be worth broadening the net and seeing what is achievable. The industry is going to need new excipients to push the OINDP envelope, and higher value disease targets, notably disorders of the CNS, will make it easier to justify the associated investment.

And finally, any last tips or advice?

Recognizing the specialized nature of OINDPs and their development is the first step towards success. Being an expert in pharmaceutical development is not enough when it comes to these uniquely challenging and valuable products. Complex mechanisms and behavioral nuances can make or break a product and the risks are correspondingly high. That said there is a growing body of expertise to accelerate and de-risk OINDP development and the potential prizes are significant. With the right partner OINDP commercialization can be lucrative whether for repurposing or introducing a new drug. Investing wisely and well, at the right time, is the key to success.