Intranasal Drug Product Development—From Formulation to Scale-Up Manufacturing

Pharmaceutical Technology spoke with experts from Catalent on intranasal drug product development—its benefits, applications, best practices and more.

Kiran Amancha, Ph.D.
Group Leader
Inhalation Product Development
Catalent

Jan Neelissen, Ph.D.
Associate Director
DMPK Advisory Services
Catalent

David Wilcox
Director
Inhalation Product Development
Catalent

PHARMTECH: What are some characteristics of active pharmaceutical ingredients (APIs) that make them good candidates for systemic absorption after intranasal administration?
NEELISSEN: In terms of physiochemical properties, APIs should be low-molecular-weight (< 300 Da), non-polar drugs, have good permeability, be active in low doses (< 10 mg) and have good solubility at physiological pH. In addition, APIs that are unstable in gastrointestinal (GI) fluids or have high first-pass metabolism after oral dosing are considered as possible candidates for intranasal administration.

PHARMTECH: How can physiologically based pharmacokinetic (PBPK) modeling tools help predict drug absorption and guide formulation development?
NEELISSEN: Using the physicochemical properties of the API and *in silico* predictions or measurements of key parameters such as permeability and solubility, PBPK modeling can be used to predict fraction absorbed through the nasal mucosa and help determine if the API is a suitable candidate for intranasal delivery. If oral pharmacokinetic data is available, PBPK modeling can be used to estimate the intranasal dose needed to match the systemic exposure following oral administration. PBPK modeling can guide formulation strategy, for example, by determining if the formulation should be solution-based or powder-based by predicting the expected exposure following administration of each type.

PHARMTECH: What are the benefits of intranasal drug administration? What are typical applications/indications?
NEELISSEN: First, it avoids first-pass loss and avoids degradation in the GI fluid, both of which are potential issues associated with oral delivery. Second, it offers ease of administration and fosters better patient compliance for those with difficulties swallowing tablets. And third, intranasal drug administration ensures rapid drug absorption and quick onset of action. It offers the potential for direct access to the brain via olfactory and trigeminal nerves, thus avoiding the blood-brain barrier in addition to reducing side effects owing to lower systemic exposure. It can be used in treatments for migraines, headaches, break through cancer pain, hormone replacement therapies, smoking cessation, epilepsy, cardiovascular indications and more.

PHARMTECH: What are best practices for intranasal drug product formulation design?
AMANCHA AND WILCOX: The formulation of a nasal drug product needs to be designed to support the required product performance attributes to achieve the desired release and absorption within the nasal cavity. First, establish if solubility and/or permeability is/are limiting factor(s) of the API's bioavailability. The majority of nasal liquid formulations are aqueous-based and given the high percentage of poorly soluble APIs in development, it may be necessary to select a vehicle or solvent system that enhances the solubility of the API. Solubilizers/surfactants/co-solvents are evaluated to enhance the solubility of the API and should have limited irritant and toxic effects on the local tissues at the levels used in the formulation. If it is a permeability issue, the bioavailability of both small and large molecules can be enhanced using permeation enhancers.

Once the solubility and permeability issues of the API have been defined, formulators should start thinking about how to increase the residence time of the API in the nasal cavity. The residence time of the drug formulation within the nasal mucosa can be increased with the use of bio-adhesive agents. Optimum viscosity needs to be selected to prevent delayed release but at the same time enhance the residence time for optimum drug absorption while not impacting spray performance or manufacturability, i.e., filling, of the drug product.

From the perspective of chemical stability, intranasal formulations can be optimized to maintain stability and potency of the drug. The stability of the API can be enhanced using stabilizers, such as chelating agents and antioxidants, in the formulation. Nasal powders confer better stability compared to liquid products. In addition, the development strategy should also ensure that the formulation is compatible with both the manufacturing equipment and, throughout the shelf-life of the drug product, the device components.

PHARMTECH: What are some key considerations when developing an intranasal product? What types of nasal drug delivery devices are there?

AMANCHA AND WILCOX: Intranasal products can be used to treat both acute and chronic indications. The common types of nasal drug delivery devices include powder devices and liquid devices. These devices are available as unit-dose or bi-dose, which are typically used for acute indications, and multi-dose delivery systems for chronic conditions. Fill volumes depend on the application with volumes up to 120 µL for unit-dose devices and up to 30 mL for a multi-dose device. For nasal powders, fill weights typically vary from 10 – 25 mg. Device selection depends mainly on the indication, and the expected dosing frequency.

For solution formulations, there are several key considerations such as API solubility/stability/permeability, which can impact potential dose, solution stability, osmolality, bioavailability, and pH or propensity to cause local irritation. The viscosity of the formulation is critical, as it affects the performance of the spray pump, influences residence time of the drug at the site of absorption and impacts device filling during manufacturing.

For powder formulations, powder flow is an important attribute when considering the small quantities of powder to be filled into each device. The physical stability of the powder is an important characteristic, as are the size, shape and surface properties of the powder particles, as these factors can all impact the redispersion or aerosolization of the powder and, as a result, the performance of the drug product.

PHARMTECH: What are some best practices in manufacture and scale-up?

AMANCHA AND WILCOX: In designing the manufacturing process for a nasal product, it is important to follow a systematic approach based on ensuring adherence to the critical quality attributes (CQAs) defined for the drug product, as these ensure its safety and efficacy. Scientific knowledge and risk assessments should be used to identify the material attributes and process parameters that will impact these CQAs development studies, which often involve Design of Experiments (DoE) to establish the criticality of the parameters identified. As the process is scaled, risk assessments, such as failure modes and effects analysis (FMEA), should be conducted to identify any high-risk attributes and implement a control strategy to ensure that CQAs of the drug product are achieved.

In the case of liquid unit-dose and bi-dose products, the manufacturing process involves preparation of bulk drug product solution, filling of the solution into a vial, insertion of a plunger into the filled vial and final assembly of the filled vial into the nasal actuator device.

For production of the drug product solution, custom-made vessels provide control of mixing (speed and duration), pH, temperature and the vessel headspace. Filling and assembly equipment should be designed to provide accurate and precise control over the required tolerances for filling, plunger insertion and assembly operations. For preservative-free unit- and bi-dose systems, bulk product sterile filtration or terminal sterilization may be employed during manufacturing to prevent microbial contamination.

For more information watch the webinar Intranasal Drug Delivery-Identifying Challenges and New Product Opportunities.