Trends in nasal delivery

Challenges and opportunities in the development of intranasal products

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Expanding therapeutic opportunities

One trend in intranasal drug delivery involves the expansion into a variety of treatment areas beyond allergic rhinitis and seasonal allergies, the traditional targets of nasal sprays. Interest in intranasal drug delivery among academics, regulators, and the pharmaceutical industry has experienced steady growth in recent years as the result of a broadening recognition that delivery of drugs via the nasal route offers a variety of new medicinal and business opportunities. Researchers have recognized intranasal delivery's potential for treating diseases as wide-ranging as diabetes, Alzheimer's disease, and obesity.

Intranasal drug delivery offers a number of new therapeutic opportunities, and pharmaceutical companies are exploring the benefits of the intranasal route for large molecule drugs and biologics such as insulin and vaccines that traditionally required injection because of their poor absorption and/or metabolism when administered orally. Due to the easily accessible vascular beds and large surface area of the nasal mucosa, intranasal drugs can be absorbed directly into the bloodstream, bypassing the gastrointestinal (GI) metabolism and avoiding GI side effects.

Furthermore, the anatomical and physiological properties of the olfactory region in the nasal cavity may provide a way to bypass the blood-brain barrier and deliver drugs for neurological conditions such as Parkinson's disease and Alzheimer's directly to the central nervous system. Direct absorption of drugs delivered intranasally may also achieve faster onset of action, which is particularly critical for treating acute conditions, including migraine, epileptic seizures, and breakthrough cancer pain. The presence of lymphatic tissue in the nasal mucosa suggests the potential for nasal vaccine delivery because the lymphatic tissue is involved in generating the immune response to invading microorganisms.

Co-development of drugs and devices

Another recent trend involves the increasing drive towards an earlier integration of design and development programs for the device and the formulation. Companies have been working on ways to overcome sometimes seemingly competing requirements for intranasal products. For example, the need for resistance to microbial contamination may suggest the use of preservatives in the formulation, but the use of certain preservatives has been shown to cause irritation of the nasal mucosa. In cases like this, some developers have turned to specialized delivery devices to eliminate the need for preservatives.

Changing a formulation's ingredients can change its properties, necessitating adjustments to a delivery device's design. For example, in order to improve the active ingredient's bioavailability, a developer might employ custom-tailored excipients such as bioadhesives, permeation enhancers, and nasal enzyme inhibitors. The formulation might also include nanoparticles or microspheres as drug transporters to increase the formulation's retention time and adhesion to the nasal mucosa or its stability, solubility, or absorption across cell membranes. However, adding excipients and/or drug transporters may produce unintended consequences such as changed aerodynamic properties, which may in turn lead to unacceptable deposition patterns or aggravation of underlying respiratory conditions.

The answer to such challenges often lies in approaching the active+formulation+device system as a whole and creating solutions that simultaneously take into account all aspects of the product, basing the development on an explicit risk assessment and risk management program. For example, the emergence in recent years of disposable single-use nasal sprays and closed-air pumps that isolate the product from the ambient air has allowed formulators to consider preservative-free systems. Developers must also consider their choice of materials for the device in conjunction with their selection of formulation ingredients to ensure appropriate stability upon storage, including consideration of potential chemical and/or thermal degradation of the active ingredient and interaction of the formulation and device components that could potentially lead to leachables.

Pharmaceutical companies are continuing to focus on co-developing devices with drug and/or biologic

Some guidelines relevant for nasal sprays, nasal metered dose inhalers (MDIs), and nasal dry powder inhalers (DPIs)

US Food and Drug Administration (FDA)

FDA/CDER. Draft Guidance for Industry. Sinusitis: Designing Clinical Development Programs of Nonantimicrobial Drugs for Treatment (2006).

FDA/CDER. Draft Guidance for Industry. Allergic Rhinitis: Clinical Development Programs for Drug Products (2000).

FDA/CDER. Draft Guidance for Industry. Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action (2003).

FDA/CDER. Guidance for Industry. Integration of Dose-Counting Mechanisms into MDI Drug Products (2003).

FDA/CDER. Draft Guidance for Industry. Inhalation Drug Products Packaged in Semipermeable Container Closure Systems (2002).

FDA/CDER. Guidance for Industry. Nasal Spray and Inhalation Solution, Suspension, and Spray Drug ProductsChemistry, Manufacturing, and Controls Documentation (2002).

FDA/CDER. Guidance for Industry. Sterility Requirement for Aqueous-Based Drug Products for Oral InhalationSmall Entity Compliance Guide (2001).

FDA/CDER. Draft Guidance for Industry. Allergic Rhinitis: Clinical Development Programs for Drug Products (2000).

FDA/CBER. Container Closure Systems for Packaging Human Drugs and Biologics Chemistry, Manufacturing and Controls Documentation (1999).

FDA/CDER. Draft Guidance for Industry. Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation (1998).

FDA/CDRH. Reviewer Guidance. Nebulizers, Metered Dose Inhalers, Spacers, and Actuators (1993).

European Agency for Evaluation of Medicinal Products (EMEA)

EMEA/CPMP. Note for Guidance on Requirements for Pharmaceutical Documentation for Pressurized Metered Dose Inhalation Products, CPMP/QWP/ 2845/00 (2002).

EMEA/CPMP. Draft Points to Consider on the Requirements for Clinical Documentation for Metered Dose Inhalers (MDI), CPMP/EWP/4151/00 (2002).

EMEA/CPMP. Draft Note for Guidance on the Clinical Investigation of Medicinal Products in the treatment of Asthma, CPMP/EWP/2922/00 (2001).

EMEA/CPMP. Note for Guidance on Dry Powder Inhalers, CPMP/QWP/158/96 (1998).

Health Canada (including Joint Health Canada/EMEA guidances)

Health Canada and EMEA. Pharmaceutical Quality of Inhalation and Nasal Products (2006) and EMEA/CHMP/QWP/49313/2005 Corr. (2006). Also adopted by Australia.

Health Canada. Submission Requirements for Subsequent Market Entry Steroid Nasal Products for Use in the Treatment of Allergic Rhinitis (2007)

US Pharmacopoeia (USP) and European Pharmacopoeia (EP)

USP. Chapter <601> Aerosols, Nasal Sprays, Metered Dose Inhalers, and Dry Powder Inhalers (in-process revision), Pharmacopeial Forum 29 (4) 1176 (2003).

USP. Chapter <905> Uniformity of Dosage Units USP27-NF22 p. 2396 (2003) (final revisions appearing in USP28-NF23, 2004).

USP. Chapter <1111> Microbial Contamination Limits for Non-Sterile Drug Products. Pharmacopeial Forum 28 (3) 916 (2002). Also in Pharmeuropa 13.1 (2002).

EP. Nasalia. 0676, Nasal Preparations, in European Pharmacopoeia 1997, 3rd ed. (Council of Europe, Strasbourg, 1996, ISBN 92-871-2991-6), 1763-1765 (1997).

International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS)

IPAC-RS. Good Manufacturing Practices Guideline for Suppliers of Components to Orally Inhaled and Nasal Drug Products (2006).

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

ICH Q1A(R). Revised Guideline Stability Testing in New Drug Substances and Drug Products (2001).

ICH Q1D. Guideline Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products (2002).

ICH Q1E. Step 2 Draft Guideline Evaluation of Stability Data (2002).

ICH Q3B(R). Step 2 Draft Revised Guideline Impurities in New Drug Products (1999).

ICH Q3B. Guideline Impurities: Residual Solvents (1997).

ICH Q6A. Guideline Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances and Decision Trees (1999).

ICH Q8. Pharmaceutical Development (2005).

Q8 Revision 1 (Annex) (2007).

ICH Q9. Quality Risk Management (2005).

ICH Q10. Pharmaceutical Quality Systems (2007).

formulations to minimize pulmonary deposition by achieving an appropriate aerodynamic particle size distribution. The size of aerosolized particles or droplets depends both on the device characteristics and on the formulation's physicochemical properties, such as viscosity and surface tension for liquid formulations or bulk particle size and surface morphology for dry powder formulations. Therefore, in order to design an intranasal product that will generate droplets or particles large enough to avoid being carried into the lower respiratory tract or the lungs, developers must consider factors related to both the device and the drug. Several recently introduced "blow-in" devices, which take advantage of the reflex closing of the airway passage between the nasal and oral cavities when air is blown out of the mouth, offer an alternative way to prevent pulmonary deposition.

Developers of intranasal products have also been working to optimize the patient's experience of the product, which relies on the mechanical operation of the device as well as the delivery of the formulation. The mechanical design of the device affects the patient's use in terms of actuation force and other ergonomic factors. Directionality of the spray, perceived temperature, and the force of the spray as it enters and spreads in the nasal cavity also influence the patient's perception of the product. For passive dry powder inhalers, designers are minimizing the airflow resistance of the device in order to minimize the inhalation force required for aerosolization. In addition to the geometrical and mechanical design of the delivery device, the adhesive forces between powder particles and between the powder and the surfaces of the container closure system must be considered.

New regulatory approaches

Regulatory approaches to intranasal products have continued to evolve along with scientific and technological developments and in response to economic and societal factors. To provide guidance for product developers and to establish a common baseline for product registration, the FDA, EMEA, Health Canada, the US and European pharmacopeias, as well as a number of international organizations, have issued a number of guideline documents and monographs pertinent to in-vitro characteristics of intranasal products and associated delivery devices over the past decade (see sidebar). A smaller number of disease-specific clinical development program guidelines for conditions such as sinusitis or allergic rhinitis treated with intranasal products have also appeared.

Current regulatory thought favors an increasingly comprehensive approach to development programs, especially in the US, where the traditional lists of tests and specifications prescribed by guidances are being replaced by a Quality-by-Design (QbD) approach. QbD gives sponsors an opportunity and a responsibility to establish process and product parameters that will assure acceptable quality and clinical performance. This process requires early assessment, and regular re-assessment, of most critical aspects of the product, testing methods, manufacturing processes, and controls. These assessments rely on general scientific research and understanding, and take into account historical information from development, manufacturing, and patient feedback for similar products and devices. Multi-factorial experiments that probe the impact of ranges and interactions of various factors of the device, formulation, analytical methods, and manufacturing processes are then used to modify initial designs.

Regulators and industry representatives from a number of countries continue to discuss regulatory requirements and best development practices for intranasal products in forums like the biannual conference organized by the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS), an international association of innovator and generic companies that develop, manufacture, or market orally inhaled and nasal drug products. For example, at the 2008 IPAC-RS conference, representatives from industry and regulatory agencies will discuss current practices, past experiences, and future directions.

A comparison of the existing US and European regulations for pharmaceuticals, including nasal medicinal products, will also take place to facilitate a dialogue to advance mutual understanding of the global regulatory and manufacturing environment. Among other current topics of discussion are the lessons learned from the ICH Q8, Q9, and Q10 guidelines, especially as they apply to intranasal and orally inhaled products, issues involved in working with suppliers of devices and device components, and the potential for environmentally responsible ("green") chemistry, manufacturing, and engineering of drug delivery products.

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