Emerging Trends and Opportunities in Orally Inhaled Drug Products

Pharmaceutical Technology sat down with Carolyn Berg, Vice President of Business Development, Inhalation, Catalent, and Carla Vozone, Vice President of Strategy Innovation and Partnerships, Catalent, to discuss innovations in orally inhaled drug products, in particular dry powders for inhalation.

Carolyn Berg
Vice President
Business Development, Inhalation
Catalent

Carla Vozone
Vice President Strategy
Innovation and Partnerships
Catalent

PHARMACEUTICAL TECHNOLOGY: What trends are you seeing in orally inhaled therapeutics?

BERG: One of the most significant trends we see is the growing pipeline of products and molecules. Looking forward, from 2021 - 2030, we are predicting a 20% growth year-over-year—the most we've seen in the past two decades. This reaffirms the potential clinical benefit of the orally inhaled route of administration. Dividing the market into small and large molecule segments, small molecules account for 65% of pipeline programs while large molecules account for 35% of programs.

In the small molecule segment, both nebulizer and dry powder inhaler (DPI) modalities are growing, with more interest in the development of DPI programs as compared to nebulization programs. Traditional inhalation-delivery products, such as metered-dose inhalers (MDIs), are decreasing. Most new MDI drug products are in the generic space, and only a handful of companies are utilizing MDIs for the development of novel drug products, one example being inhaled cannabinoids. The MDI space has been relegated to a largely generic play with relatively little R&D.

In the large molecule segment, we are seeing a plethora of R&D focused on large molecule therapies for delivery in nebulizers and DPIs. While nebulized products account for most of the programs, both modalities are exhibiting growth. Most large molecule programs are at the pre-clinical or early developmental phases, whereas small molecule programs are spread throughout all phases of development, from pre-clinical to phase 3.

We are also seeing a greater number of DPI devices being approved for market. There are many types of multi-dose DPI (mDPI) devices now, but only a few years ago, the market was largely dominated by GlaxoSmithKline's Diskus® device. In the past three years, we have seen more mDPI devices approved and commercialized, from Teva, Mylan, Hikma/Vectura and GSK.

The emerging trend in inhalation devices, however, is not in the mDPI space but in the capsule-based single-dose DPI (sDPI) space. This is true for both repurposed drugs undergoing 505b(2) regulatory assessment, and New Molecular Entities (NMEs). Capsule-based sDPIs are attractive to developers because they are substantially less complex and more cost effective to produce than their multi-dose counterparts. When designing the clinical program, capsules are beneficial in that they provide flexibility in the dose-ranging of the clinical trials by offering both single-capsule inhalation and multiple-capsule inhalation using the same device.

Developing a new mDPI is extremely complex, slow and introduces regulatory and clinical risk into a drug-development program. However, these risks can be mitigated using previously approved off-the-shelf sDPI devices.

Another trend observed in the inhaled-delivery pipeline is that it is driven primarily by small- to mid-size emerging biopharmaceuticals (EBP). EBPs represent 71% of the inhalation pipeline and the bulk of these companies are located within the U.S. (55%) and the EU (25%). Historically, big pharma dominated development of orally inhaled treatments for traditional respiratory indications such as asthma and chronic obstructive pulmonary disease (COPD). Today, we are seeing the rise of EBPs with inhalation programs more focused on niche respiratory and neurological indications. These smaller innovators tend to partner with Contract Development and Manufacturing Organizations (CDMOs) to accelerate their programs—from formulation development to commercialization.

PHARMACEUTICAL TECHNOLOGY: What is driving the shift toward DPI products for manufacturers and patients?

BERG: The shift is mainly due to three factors: (i) the emergence of macromolecules and biologics; (ii) the focus of the pipeline on complex diseases that require higher drug doses; and (iii) adoption of newer manufacturing technologies such as spray drying to produce inhalable powder.

Macromolecules and biologics. The first biologic was approved in 1981: insulin. For the first three decades following, two to three new biologics were approved per year. From 2014 – 2020, there was on average 10 biologics approved per year. As a result, there is a huge increase in the emergence of biologics for all sorts of indications, some of which are especially well-suited for pulmonary delivery such as lung cancer and viral/bacterial infections. Large molecules can be formulated as DPI, rendering them more stable and obviating the need for cold-chain storage.

Higher drug doses. Treatments for traditional pulmonary indications are usually delivered in the microgram range due to their local effect in the lungs. When analyzing the shift toward new indications—pulmonary infections and other diseases—higher drug doses are usually required to be delivered to the lung to achieve the required blood concentration for a systemic effect.

New technologies. In the past, nebulization was the preferred option for doses over 150 mg. However, it is not the most patient-friendly, due to administrative difficulties. For example, one of the first approved large-molecule pulmonary products that used inhalation via nebulization was Pulmozyme® (dornase alfa), a mucolytic for cystic fibrosis (CF) patients. This medication must be stored under refrigeration, so even if a patient has a portable nebulizer, the cold-chain requirements add substantial complexity and inconvenience to administer the drug. This is where newer manufacturing technologies such as spray drying come into play—by eliminating lactose and using novel excipients, drugs can be formulated with a 90+% drug load, thus accommodating substantially larger doses. These innovations have paved the way for many more molecules to be delivered via DPI. Tobramycin is a great example of this. It was originally launched as a nebulized drug, treating Pseudomonas infections in CF patients, and then reformulated as a spray dried powder for administration in a portable capsule based sDPI device.

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PHARMACEUTICAL TECHNOLOGY: What is driving the development of new inhalation drug products for new indications?

BERG: Pulmonary inhalation is a proven route of delivery for the treatment of local and systemic indications—local for respiratory/lung diseases; systemic for neurological, metabolic and other diseases. Respiratory diseases are self-explanatory, but even these have expanded from traditional to CF, pulmonary arterial hypertension, idiopathic pulmonary fibrosis and others. Systemically, there are various products that have made it through clinical development and have shown efficacy by pulmonary inhalation such as inhaled insulin for Type 1 and 2 diabetes, inhaled levodopa for Parkinson's disease and inhaled antipsychotics for agitation.

Inhalation therapies are also proven to treat infectious diseases (bacterial, fungal and viral). Pseudomonas, staphylococcus infections resistant to methicillin (MRSA) or methicillin sensitive (MSSA), non-tuberculosis mycobacteria (NTM), Aspergillus and others—require almost chronic use of antibiotic/anti-fungals and have substantial side effects when taken orally. If reformulated into an inhalable form, they have the potential to increase efficacy by providing increased pharmacokinetic (PK) and pharmacodynamic (PD) effects due to greater bioavailability at the site of the infection, with fewer side effects.

Inhaled drugs are also in development for neurological disorders such as Alzheimer's disease, depression, anxiety, migraine headaches and pain. Again, we are moving from the theoretical, "Can the pulmonary route be used to treat neurological conditions?" to the proven, "Yes, it is highly effective, convenient and safe." There are a lot of biological drugs being developed for lung cancers, and some of these are in the pulmonary delivery route. In summary, the pulmonary route of administration, especially via dry powders, offers patients many potential benefits over traditional routes such as intramuscular or oral.

PHARMACEUTICAL TECHNOLOGY: What are some key considerations when developing inhaled drug products?

VOZONE: There are three elements to the inhalation drug-development triangle: the patient, the device and the drug formulation.

The patient. Establishing the target product profile (TPP) along with considering the disease and patient population is paramount for a successful development strategy. Understanding whether the drug acts locally, such as with asthma or COPD, or systemically, such as with neurological or metabolic indications, and what the likely therapeutic dose is will all determine the selection of the device and the formulation design. Age and the condition of the patient are also considerations: What is the dexterity of the target population? Are they able to coordinate their breath with the device's aerosolization? Will they be able to effectively inhale and consistently achieve the desired emitted dose?

The device. The device is the vehicle used to effectively deliver the drug to the patient's airways to achieve the desired efficacy. For pulmonary delivery, there are three device options: MDIs, DPIs and nebulizers. Each offers different advantages and limitations depending on multiple variables, for example, the drug stability, the dose, the lung regional deposition it is intended for, as well as the patient considerations indicated before. The advancement of digital inhalers raises a few different considerations related to data integrity and mechanical compatibility, adding to the multi-faceted development complexities of inhaled drug-device combinations.

The drug formulation. Formulation is dependent on the molecule's physico-chemical properties, the daily dose necessary for efficacy and safety and the selected device system. Highly potent drugs that are administered in relatively low doses (<5 mg) are typically formulated with carrier-based lactose DPIs or delivered as a solution or suspension using an MDI. Examples of these are corticosteroids, long-acting β-adrenoreceptor agonist (LABA) or long-acting muscarinic receptor antagonist (LAMA). Certain therapies, such as anti-infectives or CNS, typically require higher drug doses (>5 mg) to attain systemic bioavailability and the desired efficacy, which normally requires delivery of the drugs through nebulization. Formulation of dry powders for inhalation has evolved to include aerodynamic particles that are engineered in a porous, low-density structure that achieve high fine-particle doses (high-respirable fractions) despite their relatively large geometric particle-size distribution. Spray drying is the established particle engineering technology that produces high drug-payload particles for inhalation and enables a patient-friendly DPI alternative to nebulization. There are also important considerations in terms of the stability of the drug in the device selected. Dry powders for inhalation tend to be more stable because they are solids versus the liquid formulations used in nebulization or MDIs. Stability not only matters at the time of manufacturing but over the shelf life of the product, so that both aerosolization performance and efficacy performance can be maintained.

PHARMACEUTICAL TECHNOLOGY: What are some recent advancements in inhalation powder formulation and manufacturing techniques?

VOZONE: Lactose-based formulation for inhalation with a typical drug loading of 10% to 20% has been the mainstay of drug delivery via DPI for many years. More recently, there has been a need to administer drugs in higher doses, and there is a trend toward powder formulations that can carry more drug. Instead of lactose-based formulations, advanced formulation platforms use excipients to engineer particle morphology and manipulate density to form inhalable particles of the drug that, after spray drying, have the right aerodynamic properties. Spray drying a complex mixture of drugs and excipients that produces the right aerodynamic particle sizes is having a tremendous impact on the industry and will continue to be adopted in the future. The main platforms in commercial products—PulmoSphere®, Technosphere® and Arcus®—are enabling the creation of more products that can now be aerosolized by dry powder.

PHARMACEUTICAL TECHNOLOGY: What future innovations do you predict for inhaled therapy?

VOZONE: Pulmonary and nasal delivery are attractive as non-invasive alternative routes of administration for systemic delivery of biological drugs (peptide and protein-based therapeutics) and newer modalities such as nucleic acids, virus-like particles (VLPs) or cell therapies. Biologics and new therapeutic modalities currently represent 32% of the pipeline of inhaled and nasal new drugs. The level of innovation this delivery route has seen in recent years is extraordinary. It has been accelerated by COVID-19 therapies, especially with the administration of vaccines through the nasal or lung route as well as the administration of anti-infectives to the respiratory tract.

In the last three years, the number of biologics or new modalities within inhalation and nasal delivery has increased by almost 90%. These drugs are very different in terms of formulation requirements and developmental considerations. While most of the programs select nebulization for pulmonary delivery, this device option may degrade the molecules and trigger conformational changes to the proteins caused by the physical stresses in the aerosol formation. In response, the industry is looking at alternative platforms that can stabilize proteins, monoclonal antibodies (mAbs) and mRNA, as a powder, for pulmonary delivery.

Future processing technologies will likely produce powders using process parameters that can stabilize fragile macromolecules using lower temperatures and gentler processing conditions. In parallel to these technologies, innovation will be centered around formulations that can deliver biopharmaceuticals and new modalities to the airways in a safe, consistent and efficacious manner, furthering the potential of pulmonary delivery as an attractive, non-invasive alternative route of administration for local and systemic delivery.