

# Inhalation Drug Delivery - Understanding Basic Steps Involved in Pressurized Metered Dose Inhalation (pMDI) Development

## INTRODUCTION:

Drug delivery via the inhalation route is an efficient, safe and efficacious method for local and systemic administration of certain therapeutic agents. Many inhaled therapeutics are delivered to the lung tissue to elicit a local response, typically for asthma or other lung disorders. However, because of the large surface area and high vascularity of the lungs, it is also an excellent route of administration for systemic drug delivery. In recent years, researchers began developing inhalation products containing proteins and peptides (e.g. insulin and calcitonin), opioids, vaccines, hormones and other therapeutic agents intended for local and systemic absorption.

Inhalation drug delivery is advantageous for local delivery due to a reduction in systemic side effects. It is also advantageous for systemic delivery due to rapid and complete absorption by the alveolar capillaries as well as prevention of hepatic first pass metabolism. Ideal drug candidates for this route of administration should be relatively potent (i.e. low dose), safe for pulmonary administration (i.e. not a pulmonary irritant) and should have chemical characteristics that allow for solubilization and absorption within the lung.

Development of inhaled therapeutics presents numerous challenges for researchers and commercial manufacturers. This white paper will provide insight into the aspects of formulation development, packaging development and analytical development associated with inhaled drug delivery as it relates to pressurized metered dose inhalers (pMDI).

## RATIONALE:

### *Formulation Development*

The typical components of a pMDI formulation include the active pharmaceutical ingredient (API), a cosolvent (e.g. alcohol), surfactants and the propellant. The final formulation should contain a safe and efficacious API, contain minimal levels of excipients, be free of microbial contamination, contain particles of API in the size range necessary for effective pulmonary delivery and be stable for the intended shelf life.

A propellant is utilized to create an aerosol of drug particles following actuation of the pMDI device. Historically, the propellants used were chlorofluorocarbons such as CFC-11, 12 and 114. Because of the global warming and ozone depletion potential of CFC based propellants, they have been replaced by less environmentally harmful hydrofluoroalkane based propellants such as HFA-134a and 227. HFA propellants have low inhalation toxicity and high chemical stability but are poor solvents for APIs, which necessitates formulation of suspensions rather than solutions in most cases. Combinations of HFA-134a and HFA-227 can be used to provide better solubility, appropriate aerosol velocity and density of the suspension (i.e. suspension settling). A cosolvent, which is typically ethanol, is used to help dissolve the API in the propellant, lower the vapor pressure of the propellant system and improve miscibility of surfactants in the propellants. A surfactant may be included to aid in valve lubrication, improve homogeneity of the dispersion or enhance the solubility of the API in the propellant/cosolvent system. Typical surfactants, which are allowed by the FDA, include oleic acid, lecithin and sorbitan trioleate. Other excipients used in pMDI dosage forms include pH modifiers (e.g. buffering agents), preservatives and antioxidants.

Because of the specialized nature of inhalation drug delivery and risk for pulmonary toxicity, there are very few excipients that are allowed by the FDA in inhalation products. The development scientist should review the FDA's inactive ingredient guide to determine acceptable excipients and their concentrations. Introduction of a new excipient or using allowed excipients at higher than allowed levels can dramatically increase time to market and overall cost of development.

### *Packaging Development*

The performance of pMDI drug products is equally dependant on the primary packaging components as it is on the formulation. The packaging components used in pMDI drug products include the canister, valve, actuator and optionally a spacer. Each component is critical to the overall stability and performance of the drug product and should be selected based on the desired formulation and performance characteristics.

Canisters act as a reservoir for the formulation and can be made from glass, plastic, stainless steel and most commonly aluminum. The surface of aluminum canisters can be treated to prevent interaction of formulation components with the aluminum, which can improve stability. The canisters can be anodized, coated with epoxy or acrylic materials and can

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range in size from 5-28µm. The typical neck diameter is 20mm.

The valve and associated housing acts as a seal for the canister and controls the volume of drug dispensed during each actuation. Valves for other aerosols, such as sunscreens or foams, are typically continuous in nature. However, pMDI valves incorporate a metering chamber which delivers a specific volume during each actuation. The metering chamber can range in volume from 25µL to 100µL and is tailored to a desired dose delivered through the valve.

An actuator is utilized to activate the valve and direct the aerosol toward the patient's mouth. The shape of the actuator can affect the spray pattern and droplet/particle size of the aerosol and should be designed for optimum performance. Due to the high velocity of the emitted dose and interpatient variability observed during actuation, a spacer may be incorporated to improve performance of the device, thereby improving clinical efficacy.

### *Analytical Development*

Like other dosage forms, analytical characterization is important to ensure a stable and effective product. Similar to other aerosol solutions and suspensions the Food and Drug Administration (FDA) and United States Pharmacopeia (USP) analytical requirements include appearance, identification, potency, impurities, microbial limits, extractables, leachables, pressure testing (leak testing) and alcohol content (if used in the formulation). The net fill weight of the formulation must be determined and controls put in place to ensure consistent fill weight during filling. Specialized analytical techniques which must be developed include aerodynamic particle size distribution, dose content uniformity, dose content uniformity through container life, shot weight, plume geometry and spray pattern. The analytical techniques used to characterize the performance of pMDI drug products must be validated according to requirements from FDA, USP, International Conference on Harmonization (ICH) and the European Pharmacopoeia (EP).

The aerodynamic particle size distribution is most commonly measured using cascade impaction and may be different than the geometric particle size distribution that would be measured using laser light diffraction. This analytical technique simulates the flow of particles in an air stream at velocities similar to what is expected in the human lung. This method determines where in the lung the drug particles will impact and be available for absorption or therapeutic activity. A cascade impactor is a series of stages containing pores of ever decreasing diameter from the first stage to the final stage. As the air flows through the impactor, the diameter changes increase the air velocity at each stage, causing impaction of drug particles of a specific diameter range at each stage. The individual stages are assayed and a particle size distribution is generated from the concentration of drug at each stage. This technique is very specialized and requires significant training to ensure the analyst is precise in each measurement.

Plume geometry and spray pattern are determined using an optical instrument which takes high speed images of the emitted dose. The images are used to calculate the angle of the aerosol plume and diameter at a specified distance as it exits the actuator. These measurements are used to determine actuator design based on the formulation characteristics, as the density and viscosity can affect the spray pattern.



It is important that the pMDI deliver a consistent dose throughout the life of the container or specified number of actuations. For example, if the pMDI is developed to deliver 30 doses, the emitted dose at each actuation must be consistent over the entire 30 doses. Dose content uniformity is used to determine the emitted dose of a single actuation, whereas, dose content uniformity through container life determines the

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maximum number of doses that can be delivered by the device at a certain fill volume, which must be greater than or equal to the number of labeled doses. Once the number of required doses is determined, the quality control test will evaluate up to the labeled number of actuations, typically measuring dose content uniformity of 10 actuations spread over beginning, middle and end.

### Process Development

Following initial formulation development and packaging component selection, it is imperative that a robust process be developed to routinely and consistently manufacture the drug product. As with other pharmaceutical drug products, it is important that the process be developed with the commercial product and commercial process in mind (i.e. Quality by Design). The formulation and propellant can be added to the canister separately (dual phase filling) or together (single phase filling) which may require special equipment and process modifications, depending on the method used.

Initial process development conducted on manual filling equipment allows for quick process optimization. Manual filling is feasible for development and early phase clinical trials. Once the product matures to late stage clinical and/or commercial, the final process must be developed using high speed, automated equipment. To ensure that any excursions away from target parameters will not affect the performance of the final drug product, critical processing parameters of the filling and device assembly are identified and evaluated at the minimum, target and maximum requirements.

### CONCLUSION:

Development of inhalation products can be very challenging, but once commercialized, can be very rewarding. Navigating through the various stages of development can be made easier by partnering with a contract development and manufacturing organization, like DPT, who understands the process and are experts in pMDI development.

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