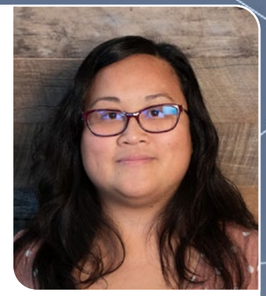
SPEAKER SPOTLIGHT:

Advancing Inhalation Drug Delivery

Revolutionary change in manufacturing strategies and device designs for new modalities are currently driving the inhalation industry forward. To achieve greater acceleration within this field, challenges in each stage of drug product development need to be faced and overcome. Susan Hoe joined us to discuss her priorities and the future of the industry in the lead up to the 3rd Annual Inhalation & Respiratory Drug Delivery USA Congress, 17 – 18 March 2020, San Diego USA, where she will be speaking on "Challenges and Opportunities with Excipients in Inhalation Drug Product Development".



SUSAN HOE

Associate Director, Inhalation Product Development, AstraZeneca

Susan Hoe is an Associate Director for Inhalation Product Development at AstraZeneca, located in South San Francisco, CA. She currently leads preclinical and early phase development of inhaled biologics, and spray dried formulation platform development within the company. Since joining Pearl Therapeutics (now AstraZeneca) in 2014, Susan has supported product development for Bevespi Aerosphere, Breztri Aerosphere, and PT027 programs, in addition to her work driving the establishment of an inhaled biologics pipeline within AstraZeneca. Prior to 2014, Susan conducted post-doctoral research into inhaled bacteriophage therapy, and spray dried formulation design via predictive in silico modelling, at the University of Alberta, Canada under Professor Reinhard Vehring. She holds a PhD in Pharmaceutical Science and Bachelor of Pharmacy from the University of Sydney, Australia.

What are your current priorities within biopharmaceutical development for inhalation drug delivery?

The current priority is to advance as many new modalities as quickly as possible through clinical development, to 'validate' these molecules against their target and via this route of administration, and gather enough data early on to make some initial decisions on what types of modalities are suitable for inhalation and which need more work and can be deprioritized. There is still much to learn and understand about the DMPK and PD of these biomolecules, and the inhalation safety profile of these molecules for patients with preexisting respiratory disease is still in question.

Another priority is executing an appropriate device and manufacturing strategy for these new modalities. These biomolecules necessitate an investment in infrastructure to potentially support entire franchises at the commercial scale, infrastructure which is currently lacking within most pharmaceutical companies and is in question for CMOs specializing in inhalation. There is also a need to rethink device design, as these molecules are being formulated in ways that have additional requirements that current devices cannot or struggle to deliver (e.g. moisture protection, high payload delivery).

What have been the biggest challenges that you have had to overcome within this field?

The major challenge has been to define the development strategy in this area that has limited regulatory guidance and very little published safety data. The most conservative approach is to adopt appropriate requirements from both inhalation product development and large molecule injectables development, however this creates an immense amount of work to generate data, some of which is potentially unnecessary. It also significantly limits avenues for inhalation product development, which in turn may lead to molecules being terminated prematurely, however patient safety is paramount and application of injectable biomolecule requirements mitigates business and patient risk. This is an area that continues to be debated, and without conclusive patient safety and tolerability data it is difficult to assess the risk level.

What are some priorities for your work within this field over the next year?

Similar answer to Question 1 - Progressing several biomolecules to Phase 1 and generate safety and tolerability data not only for the biomolecules, but also for the formulations, which contain novel excipients for the inhalation route.

Another priority is to expand our understanding of particle formation models and drying kinetics to spray dried formulations containing biomolecules, and how this correlates to the physical properties of the subsequent powder. Properties such as moisture sensitivity, hygroscopicity, aerosol performance, powder density, and so on are key to drug product performance. Since the device and manufacturing strategies are currently in design or open to redesign, there is a lot of interplay between how a formulation is selected and the viability of the biomolecule as a commercial product. There is no defined decision tree that says modality X has to use formulation Y, and device Z, in order to be acceptable. The aim is not to create something like this, but rather to

> *"Improvements in animal models predicting the safety, efficacy, and DMPK of inhaled biomolecules will have a major impact on the progress of inhaled biomolecules development."*

create a general set of guidelines for each modality. Reinvestigating particle formation modeling, how the biomolecules are distributed on the particle surface, and what impact this has on the final drug product, is a key priority.

Looking forward, what future innovations do you anticipate that will progress inhaled therapy development?

The industry is primarily focused on monoclonal antibodies, but we are already seeing new classes of engineered proteins entering pre-clinical or early clinical development with certain liabilities mutated out of the protein sequence (e.g. for molecular stability, improved binding affinity, improved specificity, improved manufacturability). Given that the formulation options for inhalation are still rather limited, protein engineering innovations are a key aspect to consider in deriving a viable inhaled drug product. This may be more of a wish than an anticipation, but improvements in animal models predicting the safety, efficacy, and DMPK of inhaled biomolecules will have a major impact on the progress of inhaled biomolecules development. De-risking pre-clinical development will open up the biomolecules pipeline.

How do you expect goals of carbon footprint reduction may affect manufacturing and strategy within this industry?

For the inhalation industry as a whole, carbon footprint reduction is an issue already affecting strategy. Global warming concerns within the general population has been discussed as a potential reason for doctors to prescribe DPIs over pMDIs. There has been a recent announcement by Chiesi to transition to lower global warming potential propellants in their pMDIs. The total carbon footprint of pharmaceutical-grade propellants are dwarfed by the footprint of other industries, however as regulations on propellant manufacture tighten, the use of HFA-134a and HFA-227ea propellants may rapidly become cost-prohibitive and the supply chain strategy could also weaken should suppliers choose to exit the market. Another aspect that I don't see discussed much is how the development of biomolecules in dry powder format could potentially achieve carbon footprint reduction by eliminating the cold chain. Spray drying, freeze drying, are energy intensive processes, but are transient. Biomolecules in liquid require refrigeration and/or freezing from beginning to end (drug substance to fill-finish, storage in warehouses, shipment, storage in hospitals or at home).