Paving the Way to Better Inhaled Drug Delivery

Christopher Gruenloh, Research Fellow, GMP Lab, PPD Laboratory Services, Thermo Fisher Scientific, gives us his rundown on the current state of play for inhaled drugs and how the pharmaceutical laboratory is evolving to accommodate new developments

PMPS: **In what area of inhalation technology have you seen the most development and investment in the last five years?**

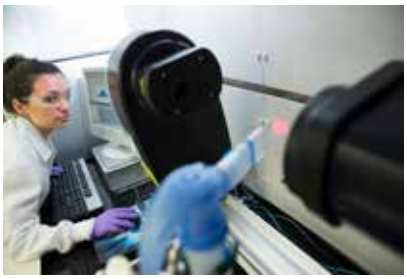
Christopher Gruenloh: Exciting progress has been made in bringing more affordable, and hence more accessible, respiratory medicines to the market, with the first FDA approval of a generic inhaled medicine achieved by Mylan for its copy of Advair Diskus (fluticasone propionate, salmeterol xinafoate) dry powder inhaler in January 2019. This feat was accomplished after more than a decade of R&D activities, and following the FDA's publishing of product-specific guidance documents that laid out a general pathway with requirements for the approval of these medicines.

Following this first success, multiple companies have subsequently won FDA approval for generic versions of albuterol sulfate and levalbuterol used in rescue inhalers, and most recently a generic budesonide/formoterol fumarate MDI used as a controller medicine. In the past few years, the FDA, through its guidance, has indicated the agency may be willing to consider Q3 data on microstructure (e.g., morphologically directed Raman spectroscopy and inhaled dissolution techniques amongst others) for some products in lieu of the traditional weight of evidence approach that includes costly clinical endpoint studies.

As the agency expresses some openness to the regulatory approval pathway, there is excitement in the field regarding the opportunity to develop, validate, and use new characterisation techniques that will ultimately shepherd in the next generation of generic inhalation products.

How do you see inhaled formulations changing in the future, and what are we likely to see?

For decades the orally inhaled and nasal drug product (OINDP) community has focused on the development of medicines to treat chronic diseases like asthma, COPD, and allergic rhinitis. The development paradigm for these diseases involves daily treatment, using a multidose inhaler or nasal spray that typically contains enough medicine for treatment over a period



of one to several months. While some gaps still exist in successfully treating these chronic diseases, the standard of care is well established. Looking forward, the development paradigm for OINDPs appears to be evolving to include new therapeutic modalities (e.g., proteins, nucleic acids, bacteriophages, and viral vectors for gene therapy), as well as disease targets outside the nose and lungs (e.g., nose-to-brain and cardiovascular delivery).

Medicines being developed with the new therapeutic classes and targets

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have target product profiles that differ from the multidose drugs used to treat asthma, COPD, and rhinitis, leading to a resurgence in usage and sophistication of the nebuliser for lung delivery. Today's nebulisers are smaller and more portable than the prototypical jet nebuliser of the past, with use of vibrating meshes to successfully deliver fragile biological drugs. Breath-actuated or 'smart' nebulisers not only minimise medication losses, but also have the capability to limit aerosol delivery to the desired portion of the patient's inspiratory profile.

From your point of view, what are the key opportunities to look out for in the inhaled drug sector?

I am incredibly excited about the potential opportunity to deliver viruses (e.g., bacteriophages and viral vectors for gene therapy) to the respiratory tract to treat opportunistic infections like pseudomonas aeruginosa, and hereditary diseases such as cystic fibrosis. Development and approval of such products would be life-changing for patients who suffer from these diseases. As an analytically-based aerosol scientist, I'm also intrigued by some of the challenges posed by these therapeutic modalities. Bacteriophages and viral vectors (e.g., adeno-associated and lentiviral vectors) are nanoparticle-sized colloidal systems that probably act more like true solutions than they do as suspensions. Several challenges arise pretty quickly when working with these systems, as noted in the following questions:

1. Can I safely work with these biological agents from a biosafety risk assessment consideration?

2. How do the thought process and risk assessment change when considering that exposure to fugitive emissions from an inhalation device may cause permanent genetic change?

Then, once you figure out how to safely work with these therapeutics:

1. Does aerosolisation change the activity/efficacy of the viral product?

2. What are the best tools to characterise this colloidal system: size exclusion chromatography, dynamic light scattering, plaque assays, droplet digital PCR, and/or analytical ultracentrifugation?

3. What detection methodology should be associated with delivered dose and APSD testing?

As more of these types of products are developed, I expect we'll experience additional paradigm shifts for both technologies and regulations driven by the needs of these new therapeutics.

In what ways can better analysis of inhaled products support patients and end users?

I've already mentioned the colossal success of some trailblazing generics companies that are bringing the first generation of generic inhaled drugs to the market. Although this is a great accomplishment, it was achieved through a combination of 'brute force' approaches and extreme

dedication by these companies to meet a perceived inflexible set of regulatory requirements. While many companies have not been successful here, I'm hopeful of a future in which appropriate analytical tools can be developed that will establish links between the drug as measured in the vial, and their action at a molecular level in the lungs or nose. One example of that progress includes the use of morphologically directed Raman spectroscopy to measure the particle size distribution of an active ingredient suspended with an excipient in a chemically specific manner. The approval of this nasal spray without the requirement for efficacy studies provides a reason to believe advances in characterisation methods can be valuable in the future.

Do inhalation drug products represent the future of drug delivery, and what therapeutic areas could see greater investment in the future?

There will always be a need for drug delivery to the lungs. Specifically for diseases of the respiratory tract, the merits of topical delivery to the site of action cannot be surpassed by other forms of administration. There are also well-known arguments (large surface for absorption, avoidance of first pass metabolism, etc.) for using the inhalation route to deliver drugs systemically.

Reflecting back on the challenges faced during the development and short-lived commercialisation of inhaled insulin in the 2000s, and the few numbers of other drugs being studied via this route since then, underscores the challenges involved. With all this said, I am optimistic that at least one of the several inhaled therapeutics being developed in support of cardiovascular indications will be successful.

Christopher Gruenloh is a research fellow in the **PPD Laboratory Services** GMP Lab of Thermo Fisher Scientific, where he supports development and implementation of analytical solutions to meet the needs of clients who are developing OINDPs. Chris' research interests include the delivery of biologics to the respiratory tract and better controlling sources of variability in OINDP testing platforms. Chris is a member of the AAPS Inhalation and Nasal Community's Leadership Team and represents the company as an associate member of IPAC-RS. Chris has a PhD in analytical chemistry from Purdue University, US.