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INTERTEK'S CENTRE OF EXCELLENCE FOR INHALED AND NASAL BIOLOGICS

Here, Chris Vernall, Business Development Director, Intertek Pharmaceutical Services, discusses the significance and difficulties of biologics in the inhalables sector, and how Intertek's Centre of Excellence for Inhaled and Nasal Biologics provides valuable services for those developing products in this area.

THE SIGNIFICANCE OF INHALED BIOLOGICS

Inhaled biologics have been forecast to grow in importance due to the fact that inhalation presents a highly attractive route for the administration of various classes of large molecule, particularly for the treatment of respiratory diseases. The major driver here is the potential for local, targeted delivery to the lung, opening up new treatment pathways for diseases such as cystic fibrosis, asthma and lung cancer. Delivery directly to the lung is likely not only to be more efficacious, but also to require less of the active ingredient compared with other routes of delivery.

Systemic delivery of biologics is also possible via the lungs or the nose. Drug delivery via these routes is more convenient and less painful compared with other routes of administration for biologic drugs, which are generally administered intravenously.

CURRENT STATE OF THE MARKET

There are a small number of inhaled biopharmaceuticals currently on the market, these being Pulmozyme® (dornase alfa) from Genentech, a nebulised cystic fibrosis (CF) treatment and Mannkind's Afrezza® (insulin) dry powder. There are several others in development including peptides, e.g. Bio-11006 (BioMarck) – a novel peptide chain for lung cancer and ARDS; bacteriophages, e.g. AB-PA01 (Ampliphi BioSciences) – for drug-resistant P aeruginosa lung infections; and oligonucleotides, e.g. AZ1419 (AZ/DynaVax) – for asthma.

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WHAT ARE THE MAJOR CHALLENGES?

The complexity of biologics and the difficulty of delivering a drug to the lungs and the nose means that this area of pharmaceutical development is particularly challenging. Biologic drugs have complex structures fundamental to their function and are much larger than classical small molecules. They are susceptible to a wide range of degradation routes, which can impact the safety and efficacy of the drug.

Protein structures have limited stability and can easily unfold under only mild stress. Aggregation, where the protein self-associates, is one of the most common issues, whereas fragmentation, deamidation, hydrolysis, oxidation, isomerisation, succinimidation, deglycosylation, disulphide bond formation/breakage and other crosslinking reactions can all play their

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"The Intertek Centre of Excellence for Inhaled Biologics deploys a strategic programme of orthogonal analytical methods which aim to fully characterise the biological entity, but also establish whether the device delivery mechanism has adversely affected parameters such as structure, purity and the activity in line with the ICH Q6B Guidance."

part in degradation. In addition to this, inhaled and nasal products require specific testing to assess delivered dose uniformity from the device and the particle size of the drug emitted.

In regulatory terms, inhaled and nasal biologics will require characterisation as per ICH Q6B, as well as the specific respiratory testing outlined in documents such as the EMA guideline on the pharmaceutical quality of inhalation and nasal products (June 2006) or the US FDA metered dose inhaler (MDI) and dry powder inhaler (DPI) products quality considerations guidance (April 2018).

HOW CAN INTERTEK HELP OVERCOME THESE DEVELOPMENT CHALLENGES?

Intertek has over 30 years' experience in biologics characterisation, from small peptides up to monoclonal antibodies and conjugated species, and has provided contract testing, formulation and clinical manufacturing services for inhaled and nasal drug products for a similar period of time. The Intertek Centre of Excellence for Inhaled Biologics (Figure 1) deploys a strategic programme of orthogonal analytical methods (Table 1) which aim to both fully characterise the biological entity and establish whether the device delivery mechanism (e.g. actuation through an inhaler) has adversely affected parameters, including structure, purity (aggregation, fragmentation etc.) and the activity (potency), in line with the ICH Q6B Guidance.

Figure 1: Laboratory at Intertek's Centre of Excellence for Inhaled and Nasal Biologics.

Analysis	Methods
Structural Characterisation and Confirmation	Amino acid composition (e.g. by AAA) Protein sequencing & terminal amino acid sequencing (e.g. by MALDI-MS and HPLC-MS/MS) Peptide mapping (e.g. by HPLC-MS)
Higher Order Structural Analysis	Secondary structure (e.g. by CD, AUC and FT-IR) Tertiary structure (e.g. by NMR, Fluorescence, DSC)
Purity and impurities	Content assay and impurities (e.g. A280, SDS-PAGE, LC-MS, CIEF, CE) Aggregates (e.g. AUC, DLS, SEC-MALS)
Potency and biological activity	Biological response or *in vitro* model (e.g. cell-based assay, ELISA)

Table 1: Analytics for biologics.

Intertek's team of expert formulation scientists have extensive experience in product development of nasal or nebulisation solutions, suspensions and dry powders. For biologics, initial formulation work is focused on excipient selection and device compatibility. Liquid formulations will need to include suitable surfactants, anti-oxidants and buffers. If a dry powder formulation is considered, lactose is often not a suitable carrier and a spray dried matrix may need to be considered. Intertek routinely supports this area of formulation development for large molecules, alongside device screening

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to support an optimal combination product.

With the expansion of Intertek Pharmaceutical Services' facilities in the UK (Melbourn and Manchester), including increasing the footprint of its laboratories and continual investment in technologies and recruitment, its Centre of Excellence for Inhaled and Nasal Biologics is well positioned to meet the challenges of this growing market. Intertek understands that this complex class of drug products offers multiple potential benefits and have therefore developed the advanced toolset needed across formulation, product characterisation and drug delivery to accelerate development processes.

ABOUT THE AUTHOR

Chris Vernall is the Business Development Director at Intertek Melbourn. He is an analytical chemist by training and holds a Masters Degree from Loughborough University. Mr Vernall started his career at Pfizer, as a Materials Scientist working on novel inhaled compounds, before moving to Nanopharm where he worked in formulation, specifically with DPIs and MDIs. He then made the move to Intertek Melbourn as a Senior Analyst, before taking up a role in Business Development. He started in his Director role in April 2017.

ABOUT THE COMPANY

With over 25 years of experience in supporting clients' orally inhaled & nasal drug product development, Intertek Melbourn provides product performance testing, method development/validation, stability, CMC support, formulation development and clinical manufacturing capabilities. The company's services are designed to provide the right information at the right time ensuring total quality assurance for products and processes. Intertek Pharmaceutical Services' network of more than 1,000 laboratories and offices and over 43,000 people in more than 100 countries, delivers innovative and bespoke assurance, testing, inspection and certification solutions for its customers' operations and supply chains across a range of industries worldwide.

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