How to Harness the Benefits of Inhalation When Re-formulating Biologics

The biologics market is growing rapidly, and is on track to be worth $719.14 bn by 2030, up from $366.6 bn in 2021.[1] This growth is being driven primarily by the rising prevalence of chronic diseases, such as cancer, diabetes, and heart disease, which demand sophisticated diagnostics and therapeutic treatments.[2]

Many of these life-changing biologics – used to treat conditions such as rheumatoid arthritis, Crohn's disease, and cancer – are reaching blockbuster status, providing treatment for millions of chronic disease patients around the world. However, many of these therapies were brought to market during the first wave of innovation, and their patents will expire in the coming years. With exclusivity only lasting approximately 20 years, 230 biologics are expected to fall out of patent in the next few years up to 2025.[3,4]

After the loss of exclusivity biopharma companies will be able to develop generic versions of these treatments to compete with the original branded product. This is already reflected in the biosimilar market, which is expected to reach $143.6 bn in 2031, growing at a compound annual growth rate of 24.7% from 2021.[5] The biosimilar product will be cheaper than the original, leading to the original innovator losing market share. If pharmaceutical companies want to compete with standard generic products, they will have to reformulate their product to extend its life cycle.

Reformulating an existing drug product's route of administration can extend exclusivity. This, coupled with breakthrough innovation in targeted therapies for chronic and orphan lung diseases, means that companies are shifting towards delivery via the respiratory tract. In this article, Bernhard Müllinger, General Manager and COO, Resyca® and Kris Brosig, Director of Business Development discuss the current challenges of inhaled biologics, exploring how formulation and device innovation may be the answer to overcome them.

The Benefits of Biologic Reformulation

Traditionally, biologics have been administered parenterally, relying on healthcare professionals (HCPs) to deliver these essential medications to patients. Diversifying the delivery route of biologics to self-administered alternatives, such as oral, inhaled, or self-administered injectable drugs, can help reduce the load on HCP resources while improving patient convenience. This is because medication can be taken at home rather than in a clinical setting. In addition, up to 10% of the population suffers from injection anxiety.[6] Moving away from injectables, coupled with easing treatment access, can help to improve patient adherence, moving towards more patient-centric healthcare.

Choosing a Delivery Method for Biologic Reformulation

There are many options for administering a drug product, and biologic oral solid dose (OSD) formulation is a method that has also gained interest in recent years. As with formulating any drug product, there are challenges that need to be overcome. For orally administered biologics, this stems from the fact that they must travel through the gastrointestinal tract to be absorbed by the body and reach the desired target. Biologics are sensitive materials that undergo degradation under acidic conditions and when exposed to stress. Drug formulations must make the biologic robust enough to survive the stress associated with each route of administration or encapsulate it for protection. Recent advancements in formulation technology have led to breakthroughs in this area, enhancing product stability and bioavailability even for molecules with a larger molecular weight. Nevertheless, oral administration may not be suitable for all biologic drug products, and so other methods of delivery are also being investigated.

Inhaled biologics are of particular interest as they promote patient centricity, delivering the drug directly to the target site within the lungs, or other parts of the respiratory system, such as the nasal passage or upper airways. With pulmonary diseases still being a leading cause of mortality globally, novel drug products and biologic reformulation are being investigated for inhaled delivery, allowing administration direct to the desired part of the respiratory system.

Inhaled biologics offer numerous advantages that make them a viable option for biologic administration:

- **Reduced side effects:** Inhaled biologics reduce off-target toxicity that leads to adverse effects at locations within the body other than the desired target.[7]
- **Large absorption area:** The substantial absorption area (130 m^2) of the respiratory system aids drug product bioavailability, reduces dosage requirements, and offers similar permeability to the small intestinal mucosa.[8]
- **Improved efficacy:** For local treatment, inhaled biologics have shown improved efficacy compared with traditional parenteral delivery.[9]
- **Enhanced nervous system targeting:** Potential delivery of biologics to the central nervous system would result in rapid response upon administration.[10]

Although inhalation offers a number of benefits, inhaled biologics are still in the early stages of development, and a number of challenges must be overcome to successfully use this method to produce, or reformulate, a drug product.

The Challenges Associated with Inhaled Biologics

Biologics remain highly sensitive and complex materials, and therefore a number of challenges need to be addressed to develop inhaled biotherapeutics. Inhaled biologics as a segment remains in its infancy, and so it has had, as yet, limited regulatory exposure.

This limited regulatory exposure may lead to additional scrutiny when seeking approval, as there is still ambiguity regarding dosing, efficacy, and safety that needs to be addressed, and will require extensive analysis and evidential documentation.

Many challenges arise throughout the development, formulation, and delivery of a desired biologic, requiring innovative solutions to ensure success. This is the case for both novel biologic treatments and reformulated products.

When developing and formulating an inhaled biologic, challenges to overcome include:

- **Bioavailability issues:** Molecules with a large molecular weight have limited permeability across the membrane and despite the large absorption area, this is also true for inhaled biologics. This poses questions about possible drug build-up in the lungs, leading to toxicity and potential immunogenicity.

- **Formulation and delivery challenges:** A large number of excipients are used when formulating a drug product for parenteral delivery. However, for an inhaled product it is imperative that the formulation allows for aerosolised delivery of the active ingredient, ensuring delivery to the target area of the respiratory system. Consideration must be given to stability of the molecule over the shelf life of the product in the combination device and also stabilising the molecule to ensure any delivery shear forces do not adversely impact the activity of the molecule. This means novel excipients may need to be added to the formulation, which can add an additional hurdle to regulatory approval, and is considered on a case-by-case basis.[12] In addition, both the active component and the excipients used must be compatible with the device materials.

With over 40 inhaled biopharmaceuticals currently in the early phases of the drug development pipeline, overcoming the inhaled biologic challenges is a priority.[13] The limited range of possible inhaled dosage forms – from MDIs to nebulisers and dry powder inhalers (DPIs) – add to the complexity, as the biologic formulation must be adapted to meet the needs of these formats.

Advances in Inhaled Devices and Formulation

Drug product formulation plays a large part in overcoming the challenges associated with biologic drug products. Adding excipients into the product formulation can be used to help overcome the bioavailability and sensitivity issues while also helping to better formulate a drug for aerosolised delivery.

The design of the delivery device – either nasal or oral form – can be a powerful tool to overcome drug development and delivery challenges. Although in the past devices required extensive product customisation to ensure effective, safe, and efficacious delivery, recent innovations in soft mist inhaler (SMI) technology have significantly reduced customisation needed for a specific biologic formulation, reducing project costs and accelerating timelines. These next-generation SMIs and nasal sprays produce a slow-moving aerosol cloud that can provide more effective targeted delivery while minimising stress and damage to the biologic.

SMIs with novel spray technologies are well suited to deliver sensitive compounds as they limit the shear stress exposed to the drug during delivery. This is particularly important for sensitive biologics (e.g. mRNA) or sensitive formulations such as lipid nanoparticles (LNPs). Using novel spray technologies can reduce degradation and aggregation of biologicals upon administration.

In addition, easy alteration of the spray cone angle of these innovative devices enhances delivery precision, expertly targeting the desired site at high doses while enhancing design uniformity, both of which can result in improved drug performance. The enhanced therapeutic performance per inhalation leads to lower dosage requirements – 20 times smaller than for parenteral delivery – making this mode of delivery much more cost effective. The novel design of these new SMI technologies also requires less pressure to actuate than traditional devices, making them even easier to administer.

Working with Experts

We are at the very beginning of the inhaled biologic story. This means that we have few resources to guide new drug development or re-formulation projects to regulatory approval. Nevertheless, the rewards of pioneering this approach to successfully deliver essential medication to patients via the respiratory tract are many.

Forming a supportive partnership with an expert in inhaled biologic formulation and in innovative devices – such as SMIs – can ease this process. Access to a bank of knowledge and expert advice will help drive a project forward at speed so companies can stay ahead of the patent expiry curve and ensure future exclusivity – or bring their new biologic to market with the best chance of success.

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