

Optimising Device Design for New-generation Biologics

New waves of biological drugs may vastly improve treatment for many diseases, but not without adapted delivery devices for effective subcutaneous administration. There is a need for innovative drug delivery devices that accommodate higher viscosity and higher-volume formulations, typical of new biologics and biosimilars.

The increase in subcutaneous injection as a route of administration for drug delivery is the result of converging trends in the pharmaceutical and healthcare sectors. Since the 1990s, the pharmaceutical industry has made significant advances in biological drug development, with the latest wave of research focusing on oncology treatment. Meanwhile, healthcare systems have worked to enable home administration on a wider scale; this helps to alleviate pressure on hospitals and facilitates treatment for patients, especially those with chronic illnesses which may require frequent medication delivery. Since subcutaneous administration is more suitable for this purpose than intravenous delivery, the subcutaneous route for biotherapeutics is now well-established for many conditions, including diabetes and autoimmune diseases. Furthermore, access to these highly effective – but often costly – drugs is widening as biologics patents continue to expire and allow less expensive biosimilars to be introduced to the market.

Critical to the continued success of subcutaneous administration is the design of drug delivery devices. This is starting to become more important with the increasing

focus on reformulating even intravenous drugs for subcutaneous administration where possible. Biologics for subcutaneous delivery present a particular challenge for device development due to their molecular structure, and as new generations of biologics are created, there is a need for greater innovation to maintain safe and effective delivery as well as maintain ease of use for the patient.

The Viscous Nature of Biologic Formulations

Since biological drugs are made of large, complex protein molecules, the solutions tend to require injection and can have greater viscosity than chemically-based medicines, which can present challenges. When they are administered in increasingly higher volumes, this can create further challenges. For instance, as monoclonal antibodies (MAbs) often have high dose requirements, they are formulated at high concentrations and this causes viscosity to increase exponentially. This high-viscosity, high-volume combination poses a challenge for drug delivery design, particularly as new biologics are now surpassing previous design parameters. Standard prefilled syringes and safety devices have typically been designed for 1ml fill volumes, with a viscosity usually under 10cP. The emergence of higher viscosity drugs, typically biologics, has made drug delivery device modification imperative. From a patient perspective, there is also a clear benefit in enabling less frequent injections; however, this poses additional challenges in requiring larger volumes and potentially higher viscosity formulations.

Strategies for Reducing Viscosity

Methods of reducing viscosity, although potentially advantageous, can create new obstacles. For instance, excipients can lower viscosity but may alter the characteristics of the original formulation. There are varying attitudes to excipient use among pharmaceutical companies. In a recent survey, a third of respondents (35%) said their firms were highly likely to consider using excipients with biologics to improve subcutaneous absorption and dispersion, whereas 11% of respondents said their firms were highly unlikely to do so.¹ Another solution is to lower the concentration of the

drug. This increases the required volume of the dose, so companies must also factor in that the recommended maximum volume for a single subcutaneous injection is 2–3ml.

Wearable injectors can enable self-administration of volumes over 2ml, as they allow highly concentrated drugs to be diluted into larger volumes and administered subcutaneously over longer periods. However, uptake of these has been low to date, despite a plethora of products available and in development. Wearables need to be kept in place on the injection site for a period of time to allow time for drug delivery and where worn for extended periods, may be visible or impact areas of daily life such as showering or swimming. As a result, many patients may prefer single periodic injections, even if they are required more frequently. There is certainly scope for the development of safe, easy-to-use wearable injectors, particularly in diabetes management, but only 40% of respondents in the survey mentioned above reported their companies were ‘actively’ developing on-body injection devices for higher-volume subcutaneous administration.

The Impact of Viscosity on Drug Delivery

To ensure that viscosity does not negatively impact effective subcutaneous drug delivery, human factors specialists and design engineers must consider a number of factors. Firstly, biologics tend to be stored at low temperatures, which increases viscosity.



This, along with increased patient comfort, is one reason why prefilled syringes containing biologics, which are typically refrigerated for storage, need to be removed in time to reach room temperature before use. Secondly, for manual injection, injection force should ideally not exceed 10 N, but this can be difficult to achieve if drug viscosity is too high. A further consideration is injection time, which increases with viscosity. Human factors observations suggest that typically patients have difficulty holding a device in place for over 10–15 seconds during dose delivery, so ideally the full dose must be delivered within this duration.

Lastly, while larger gauge needles facilitate delivery of higher viscosity formulations, pain on injection can cause patients to remove the device before the full dose is delivered. 29G or 27G needles are commonly used for subcutaneous injections, or even 25G needles; any smaller gauge and larger needle diameter than this may cause pain during the injection procedure. For more viscous drugs, thin-wall needles have been developed and are commonly used to help improve the flow of the drug in needles of a small diameter. Since the level of pain and the difficulty of injection can have implications on patient compliance, the ergonomics and design of the delivery device are increasingly important for higher viscosity drugs.

Adapting Injection Devices for Higher Viscosity and Volume

Manufacturers are now developing syringes for fill volumes up to 2.25ml to accommodate high-viscosity drugs, and the delivery devices designed for these new syringes should provide a positive patient experience. Prefilled safety syringe devices allow patients to control injection speed and force, and possibly the level of pain, which is important for biologic drugs for all the reasons outlined above. Ease of use ranks highly in patients' priorities so new-generation devices should avoid introducing new techniques

or instructions for use as far as possible, to avoid confusing users. The design must take into consideration patients with impaired strength or dexterity limitations, who may find biologics particularly difficult to inject, and ensure that the device is comfortable to hold and that the plunger is easy to depress. A further critical factor to consider is that with biologics typically requiring dosage volumes of up to 2ml, patients must be able to clearly see the contents of the syringe before administration, to check for drug clarity and that the full dose has been delivered. Ensuring that the plunger cannot be removed from the device is another way of ensuring full-dose administration, as removable plungers can cause leakage.

Failure to carry out robust human factors testing across the intended user population may result in a failed regulatory submission, and ultimately delay getting the combination product to market. The primary container for the drug, as well as the delivery device, must therefore be part of the product development process from the very beginning, to ensure that both the final combination product passes usability testing, and that all the components are compatible. Not only is the drug delivery device critical for patient adherence, ensuring that users obtain maximum benefit from a therapy, but its design features and associated benefits may also give manufacturers an additional advantage in a competitive market.

The Merits of Intuitive Design in Biologics Delivery

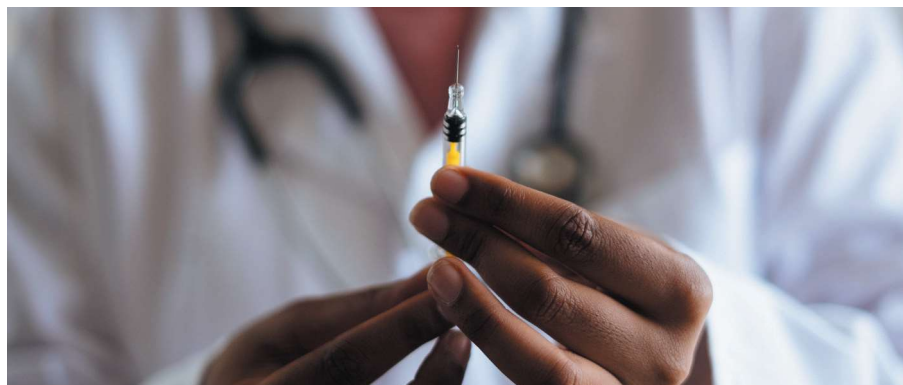
Enabling effective subcutaneous administration of new-generation biologics, which can be higher in volume and viscosity, requires careful consideration of patient and manufacturer requirements. Home administration has significant benefits for patient quality-of-life, while reducing increasing pressure on healthcare systems. However, patient adherence may be impacted if drug delivery devices



cannot maintain comfort and ease of use. Manufacturers must strive to maintain intuitive design and injection technique, appropriate for healthcare professionals and patients alike. Simple design is beneficial for all stakeholders; simplicity makes products less intimidating for users, but also facilitates production and assembly for manufacturers. Achieving this simplicity is by no means straightforward – especially considering the characteristics of biologic formulations – but the benefits on offer make this a worthwhile endeavour.

REFERENCES

1. Owen Mumford Pharmaceutical Services, in partnership with Pharma Intelligence, INJECTABLE COMBINATION PRODUCTS: Industry Insights On The Challenges Of Meeting A Growing Global Need, August 2020



**George
l'ons**

George is currently Head of Product Strategy and Insights at Owen Mumford, having worked for the former OEM and now Pharmaceutical Services division of the organisation since 2006. His current focus is on deciphering the rapidly changing pharmaceutical and biotech sectors in relation to their needs for combination products. In his previous roles in business development, he worked closely alongside R&D to develop devices for a variety of global pharmaceutical and diagnostic clients. Prior to Owen Mumford, George worked for Abbott in EMEA marketing roles in Germany, focusing on their diabetes business.