Article

Wearable Large Volume Injectors Hold Promise for Success in Commercialization of Biologics

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ABSTRACT

With so many biologics in development and no patient-centric way to deliver them, it was inevitable that innovative delivery solutions would emerge that enable a new pharmaceutical product to meet two top criteria for successful commercialization: satisfy patient demands for easy drug administration without disruption to their everyday lives, and address health system demands for lower costs and more value. The solution lies in combining biologic drugs with the more advanced large volume wearable injectors to enable patients to self-inject even the most viscous formulations and volumes of up to 50 mL with ease and comfort in their homes or workplaces.

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GROWTH MARKET FOR COMBINATION PRODUCTS: BIOLOGICS DELIVERED BY WEARABLE LVIS

The pipeline for the pharmaceutical industry will continue to be driven by the development of biologics and biosimilars. Since most biologic formulations are highly viscous due to their molecular composition, they are frequently administered in large volumes via intravenous (IV) infusion and, by necessity, in the healthcare facility setting.

In a 2016 Accenture survey of more than 200 executives at leading pharma companies in the United States and Europe, 85% of respondents said their companies plan to increase spending on patient-centric capabilities over the next 2 years.[1] For administration of biologics, easy-to-use wearable LVI's that are based on pain-free injection technology provide this patient-centricity—among other benefits.

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INCREASE IN PROMISING NEW BIOLOGICS AND BIOSIMILARS TO TREAT MULTIPLE DISEASE STATES

Biologics and biosimilars encompass an array of products such as vaccines, blood components, somatic cells, gene therapy, as well as recombinant therapeutic proteins. Over the past 20 years, several biologics have demonstrated proven efficacy and safety as evidenced by first-in-class therapies such as bevacizumab, rituximab, trastuzumab, and imatinib that are used to treat a wide variety of autoimmune diseases and certain types of cancer. While these previously approved products are projected to have continued high sales, hundreds of new experimental biologics have entered the pipeline and comprise more than 50% of products undergoing pharma development.[2] According to the National Institutes of Health clinical tests database, there are more than 900 biologics currently being studied in clinical trials in multiple therapeutic areas for numerous

disease states, with the largest growth occurring in the therapeutic areas of cancer (and cancer-related conditions), infectious disease, and autoimmune disorders. In addition, increasing emphasis has been placed on developing biologics to treat rare diseases.[3] All signs indicate that the trend for increased development, approval, and use of biologics will continue into the foreseeable future.

VISCOSITY AND VOLUME CHALLENGES WITH BIOLOGICS

From the perspective of treatment administration, the main challenge of biologics resides in their molecular complexity, in many cases their long-chain protein composition that results in a dense, highly viscous solution. Given the high viscosity of most biologics, and the fact that biologics are not suited for oral administration, these products have traditionally been administered intravenously (IV) as a 1- to 2-minute bolus injection or diluted and infused continuously or at specific intervals over longer periods of time, depending on the specific biologic product and therapeutic indication. Preparing an IV requires a high degree of technical skill and can be more challenging with elderly or cognitively challenged patients. Intravenous injections also carry a risk of systemic infection and require medical observation for side effects including infusion site reactions. For these reasons, IV administration of biologics must be performed by trained staff at the hospital or physician's office. The entire process for IV infusion of biologics is therefore inconvenient for the patient and represents a substantial time and resource burden to the healthcare facility.[4]

The subcutaneous route may be the optimal method of administering most biologics and has distinct advantages over other injection methods. While skilled personnel are required to administer IV and IM injections, subcutaneous injections are routinely self-administered by patients.[5,6] Subcutaneous injections use short, small bore needles that are more comfortable and have a comparatively lower risk of infection or other complications. For patients requiring multiple, daily doses, subcutaneous injections can be administered at several alternative sites.[6] When administered through the subcutaneous route, biologics are transported through the capillaries and lymphatic system, with the result being a sustained and slower systemic absorption that avoids the immediate, sharp peak concentrations.

SUBCUTANEOUS INJECTION OF BIOLOGICS: OVERCOMING THE VOLUME CHALLENGE

While the subcutaneous route may present advantages for administering many biologic therapies, subcutaneous injections are limited in the amount of drug product that can be delivered and tolerated by the patient in a single injection. In most cases, the volume of bolus subcutaneous injection is limited to 1-2 mL. One approach to circumvent these volume limitations includes increasing the concentration of the active ingredient in the formulation. However, one of the main constraints in biologic formulation development is the exponential relationship between the concentration and formulation viscosity. For large protein biologics such as monoclonal antibodies (mAbs), volume and bioavailability constraints must be addressed before subcutaneous injections can be used in place of intravenous dosing regimens. Monoclonal antibodies often have high dose requirements and as a consequence must be formulated at very high concentrations, which typically result in highly viscous drug products. These highly viscous formulations cannot be readily injected, particularly when smaller-gauge needles are used to reduce the patient's pain or discomfort.[7,8]

Achieving optimal therapeutic concentrations is often limited by manufacturing processes and other constraints such as pH and osmolality, along with the use of certain excipients.

Given that these formulation properties need to be kept within specified ranges to prevent patient discomfort and injection-site reaction, increasing the administered volume of drug product is left as the only practical option to deliver a larger dose. There are limitations, however, to how rapidly a volume of drug can be injected subcutaneously. While there is wide variation in the optimal injection time among individual drug products, and although information regarding the relationship between injection volume and speed is limited, it is understood that subcutaneous space cannot tolerate rapid injection of increasingly large dose volumes, as tissue disruption and site reaction occur. Furthermore, if the subcutaneous injection is rapid and the volume is too large, the product may leak outside the body through the injection site, thereby reducing the bioavailability relative to the total dose. Finally, patient self-administration using a manual subcutaneous injector is not practical due to the fact that the larger volume requires longer injection time and increases the difficulty for the patient to hold the device at the injection site.

WEARABLE LARGE VOLUME INJECTORS (LVIS): AN ELEGANT SOLUTION

With the continued increase in marketed biologic products, the new wearable LVI delivery systems are now able to improve the bioavailability of biologics and overcome their inherent concentration, viscosity, and volume challenges. These systems are patient-centric devices that simplify the self-administration of large volumes (> 1 – 2 mL) in a controlled manner. Understanding subcutaneous tissue pressure has been critical for designing injection devices that are acceptable to patients, especially during potentially lengthy administrations of biologic therapies. A recent study found that patient discomfort is related to increased pressure and mechanical strain in the subcutaneous space, which is more directly related to increasing flow rate than to volume.[9] These new systems overcome the large-volume injection challenges by allowing the patient to administer increased volumes into the subcutaneous space more slowly. By extending the subcutaneous injection time, LVIs increase patient comfort and expand the possibilities for large volume self-injection.[9,10] Due to the need for longer duration of injection, these devices are temporarily attached to the body at an appropriate injection site.

Current wearable LVIs range in size, dimension, complexity, and functionality. Some wearable LVI devices use computer-based systems integrated with electric or electrohydraulic motors that offer a variety of pre-programmed dose administration settings. The working parts of other simpler LVI devices are purely mechanical yet allow for a wide range of injection volumes and flow-rate settings, and provide injection pause features and patient data collection using wireless technology. Some LVI devices utilize prefilled syringes while the most advanced, from Enable Injections, use standard vials or syringes along with a platform technology for automated mixing, reconstitution, and warming of refrigerated drug product. It also delivers the largest doses, up to 50 mL. Most LVI devices are designed to adhere to the injection site skin using an adhesive and are small, unobtrusive, and disposable.

Since LVI devices are built to simplify the self-administration of a subcutaneous injection over relatively longer periods of time, numerous human factors considerations have been incorporated into their designs. Foremost among these include ease of use, patient comfort, and discretion. To simplify patient device operation, LVIs utilize clean ergonomic designs and can typically be operated using an intuitive 3-step process consisting of placement, activation, and injection initiation. Patient comfort is a top concern with wearable LVIs. These subcutaneous devices use small bore needles that are never visible to the patients, incorporate pause and flow-rate control features to allow for patient control and comfort. Another important safety feature includes automatic needle retraction to prevent accidental needle sticks to patients and caregivers. As patients prefer discretion during self-administration, most LVIs are designed with a low profile with smooth edges to that allow them to be easily and safely concealed beneath clothing over extended periods of time.

WIDER IMPLICATIONS OF WEARABLE LVIS: A HAND-IN-GLOVE FIT WITH THE NEW HEALTHCARE PARADIGM

The new model for healthcare is one that drives down costs by reducing the time and resource burden on healthcare facilities by promoting efficiencies including individual self-care under the right conditions. Wearable LVIs fit neatly into this new paradigm. A time-and-motion study undertaken in eight countries reported significant time savings for both healthcare professionals and patients through the use of subcutaneous versus the IV route of administration. These findings suggest a potential for reduced waiting times, greater appointment availability, and improved efficiency of oncology units with use of the subcutaneous formulation. Furthermore, compared with IV drugs, the majority of participants in the study considered subcutaneous drugs clinically safer and more cost-effective, resulting in higher patient satisfaction.[10]

In many cases biologics will continue to be administered by healthcare professions in a hospital or other point-of-care setting using the IV or subcutaneous route of administration as the situation dictates. However, the introduction of wearable LVIs will allow a large segment of patients to discretely self-administer their high volume biologic treatment subcutaneously in a safe and efficacious manner, and in the process reduce the time and resource burden on healthcare facilities.

CONSIDERATIONS IN CHOOSING A WEARABLE HIGH VOLUME SUBCUTANEOUS DELIVERY DEVICE

The process for determining the appropriate biologic product and patient population for use of a wearable LVI is multifaceted and will need to be carefully considered by healthcare professionals. Healthcare specialists will

need to select the right system and device to deliver the chosen biologic using the optimum treatment protocol for a particular patient. Treatment administration variables include injection frequency, dose volume, drug viscosity, delivery rate, and duration.[11] Human factor considerations include pain reduction, portability, and convenience, each of which influence treatment compliance and preference rates among the target patient populations. Physicians will of course need to assess individual patient factors to determine the appropriate candidates for self-administration of a biologic using LVIs.

Other external and device-related aspects that might impact the selection of an LVI system include the range of doses used to treat a specific patient population, the requirement for small or incremental dose adjustments, specific ergonomic or ease of use considerations, and the need for refrigeration. Prior to subcutaneous injection, many biologic products need to be warmed to room temperature, which represents an inconvenient 30-minute step. Consequently, there is a need for a delivery system capable of transferring the highly viscous product while rapidly warming the drug to room temperature.[12]

Today's more sophisticated drug delivery devices are differentiated from legacy injection systems in several important ways. Some novel systems currently make use of standard vials and syringes and in the process minimize the drug stability issues frequently observed in new container closer development. In conjunction with the use of vials and syringes, the new injection systems automatically warm the drug as the injector is filled, thus reducing the usual wait time required when using a refrigerated drug product. The newest systems also automate the mixing and reconstitution of lyophilized drugs, which removes patient variability and error from the mixing process. In terms of minimizing pain and improving patient comfort, the new injection systems use the smallest needle possible and allow the patient to pause the injection or make adjustments in flow rate. Although capable of injecting large volume biologics up to 50 mL, the injectors themselves are small and designed with a low profile that can be discreetly worn on the body beneath loose clothing, which allows freedom of mobility. The newer devices incorporate the latest in simple data-capture technology, which can be used to monitor the patient's adherence to therapy and promote compliance.

PHARMA-DEVICE PARTNERSHIPS

Given the projected increase in development of biologics coupled with innovations in biologic delivery systems that may increase patient autonomy and reduce healthcare costs, a natural partnership is underway between drug and medical device companies. In the US, FDA regulations point toward a path to approval that includes biologics and their associated delivery systems as drug/device combination products, with both the biologic and device components requiring approval under biologic license application (BLA) process. Since the biologic regulatory pathway requires a rigorous clinical program, LVI devices can be leveraged to achieve success by providing flexible dose administration and data gathering capability during early phase pharmacokinetic studies. The BLA itself will need to contain extensive device design information and provide summaries of device-focused human factors studies. Synergistic drug and device company partnerships that effectively play to each other's strengths under a comprehensive strategy should lead to regulatory marketing approval, commercialization, and future improvements to lifecycle management of the combination products. Ultimately, the innovator pharmaceutical companies require an elegant solution for the delivery of their biologic product that medical device companies provide.

SUMMARY

Development, approval, and use of wearable large volume injectors (LVIs) for subcutaneous delivery of biologics facilitates self-administration, increases patient comfort and compliance, and reduces cost and resource burdens in harmony with the new healthcare paradigm that emphasizes outcomes. Current market forecasts predict robust growth for LVI device companies, with projections of up to $8.1 billion by 2025. Biologics, when combined with these patient-centric delivery devices, hold promise to provide greater success in commercialization.

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