Upsizing Auto-injectors for Patient Independence with New Treatments

Innovations in auto-injector design mean treatments requiring larger volumes or higher doses, such as those for chronic disease and even cancer, could soon be safely self-administered by patients at home

Gary Calderwood at SHL Medical

By shifting injections from clinics to living rooms, auto-injectors have revolutionised the delivery of low-volume parenteral drugs. They have made self-administration simple and safe, in turn improving the patient experience and supporting treatment adherence.

The number of drugs available in single-use auto-injectors has increased dramatically since the mid-2000s. There are currently over 90 auto-injector combination products, with global sales approaching 300 million units.[1] This growth has largely been due to a greater push to enable patient autonomy, comfort and safety in administering self-injectable medicines, coupled with the rise of chronic conditions associated with changing demographics and the introduction of biologics to treat these. These conditions include type 2 diabetes, rheumatoid arthritis, psoriasis, atopic dermatitis and obesity.

Unserved Patient Groups

Despite this growth, the applicability of auto-injectors remains constrained by the capacity of their primary containers. Most auto-injector combination products have injection volumes of 0.1 to 1.0ml. As a result, patients with conditions requiring higher doses are yet to enjoy the benefits of at-home treatment offered by subcutaneous (SC) self-administration. For them, intravenous (IV) infusion in a hospital setting remains the only option.

In oncology, in particular, there is growing interest in transitioning from IV to SC administration by using enzyme-assisted drug formulations. Injection site absorption enhancers and drug delivery device innovations are also making the SC self-administration of larger volumes possible. This is an exciting prospect for biotech, as new cancer therapies and molecules account for nearly 40% of the industry's development pipeline.[2] Changing to SC administration would reduce costs, time of delivery and adverse systemic effects, ultimately increasing patients' treatment adherence and quality of life.

Early evidence suggests that, although the rapid injection of large volumes in SC tissue may result in varying degrees of leakage, site reactions and discomfort, it is generally well tolerated.[3-5] In addition, several technologies have been proposed to overcome such limitations. These are able to minimise intermolecular interactions to reduce the viscosity of high-concentration formulations, to form fluid suspensions, or to modify the SC space to facilitate the delivery of a larger volume of fluid, such as transient permeation.[6]

Given the feasibility of delivering treatments with higher-dose SC injections, the priority becomes designing and manufacturing user-friendly auto-injectors that can safely store and administer these larger volumes.

Pre-filled Syringes as Primary Containers

Increasing administration volumes is not merely a matter of scaling up existing auto-injector designs. Typical auto-injectors comprise a pre-filled syringe (PFS) with a staked needle as the primary drug container. By integrating PFSs with staked needles, pharma companies have created two- and three-step self-injection devices that do not expose the user to the needle. This innovation has facilitated the development of drug brands that are both clinically effective and user-friendly.

More than 98% of single-use, PFS-based auto-injectors hold a dose volume of 1.0ml or less. In recent years, a number of drugs with higher injection volumes have been released in auto-injectors with PFSs holding up to 2.25ml. With

indications including atopic dermatitis, high cholesterol and other chronic conditions, these have demonstrated that administering higher-volume SC injections with auto-injectors in a home setting is practical.[1]

Despite their usefulness as primary containers for biologics, PFSs present challenges in maintaining the stability of protein-based molecules or complex monoclonal antibodies. These issues become more serious as dose size increases, arising from factors such as the presence of silicone oil used to lubricate the glass barrel, tungsten residue from manufacturing, and contact materials like adhesives and needles.[7-9]

One critical limitation is siliconisation, as silicone oil-water and air-water interfaces can lead to protein aggregation and particle formation in the drug itself.[7] High-temperature baking of silicone can effectively reduce silicone migration and protein aggregation while preserving the injection system's functionality. However, achieving uniform silicone layers on parenteral containers through baking requires temperatures exceeding 300°C, which can compromise the bonding force between the staked needle and the glass barrel.[10]

A Cartridge-based Solution

Cartridges are a promising answer to the unconventional challenges presented by the emerging needs in SC drug delivery. Already a trusted primary container in the pharma industry, cartridges feature several properties well matched to the needs of sensitive biologics, such as the absence of tungsten. In contrast to PFSs, cartridges lack a staked needle and have limited material in direct contact with the drug, offering further stability advantages and making them better suited for high-temperature baking to minimise protein aggregation and particle formation.

> *Advances in auto-injector design are making it possible to use cartridges as the primary container, while also delivering a user experience as safe and simple as that of two-step, staked needle devices*

However, traditional, cartridge-based solutions are poorer when it comes to user accessibility because, unlike PFSs with staked needles, they require users to attach the needle manually before injection. This additional step increases the risk of contamination and needle-stick injuries, in turn worsening the patient experience and medication adherence.

Fortunately, advances in auto-injector design are making it possible to use cartridges as the primary container, while also delivering a user experience as safe and simple as that of two-step, staked needle devices.

A Needle Isolation Technology for More User-friendly Devices

One innovation has been the development of a sterile self-contained cannula unit with patient and non-patient ends, in order to eliminate the need for users to attach the needle manually. In this approach, a pre-installed needle is housed, or 'isolated', within the cap of the device (**Figure 1**). As the user unscrews the cap, the non-patient end moves backwards to pierce the cartridge septum, thereby opening the fluid path and automatically priming the injector (**Figure 2**). The patient end of the needle stays hidden at all times by a sliding cover, which also activates the auto-injector when pushed against the injection site.

This technology allows the cartridge to function like a conventional PFS with a staked needle, ensuring the needle is completely shielded before and after injection. The cannula unit also supports complete control of the cannula gauge and length, enabling precision targeting of injection depth and time.

In addition, while swabbing the cartridge septum is recommended as a precaution for some cartridge-based injection systems, the architecture of the septum in this new approach makes this unnecessary. This is supported by a multi-phase bioburden study, which found no evidence of microbial growth in auto-injectors incorporating the needle isolation technology.[11]

The integration of the needle isolation cannula system into devices has

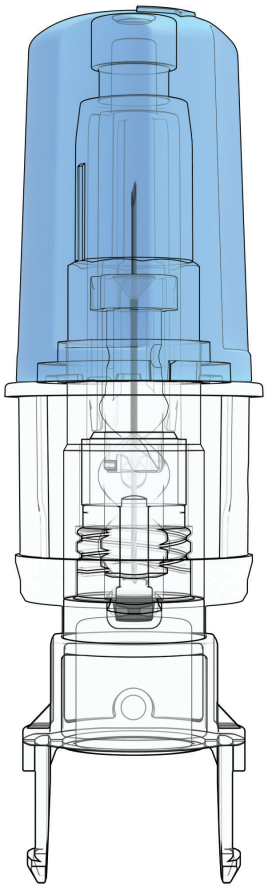

Figure 1 A close-up image of a cannula unit utilising the needle isolation technology. The sub-assembly is a sterile unit that houses the needle within the cartridge-based auto-injector

already proven successful with regulators and the market. The first cartridge-based auto-injector built with the technology received FDA approval in 2017 and became commercially available the following year. This combination product has delivered millions of doses to patients worldwide since its launch, underlining its viability in terms of manufacturing, usability and end-user safety.

Reaching 5.0ml and Beyond

The development of auto-injectors with isolated needle cannula units provides a safe and straightforward user experience while also opening up new possibilities for large-volume and high-dose SC drug delivery. Critically, these larger volumes will be able to accommodate speciality formulations, such as lyophilised drugs and suspensions.

Now, auto-injector technologies are available in 3.0ml and 5.0ml formats, specifically targeting therapy areas that require higher injection dosages and volumes. Despite its increased capacity, the device is compact and comparable to successful lower volume auto-injectors.

The expansion of auto-injectors for volumes of up to 5.0ml and beyond represents a significant step forward in patient-friendly drug delivery. Further technical investigation is necessary to better understand the influence of variables such as injection time, drug volume, viscosity and depth, but it is clear that large-volume, high-dose SC auto-injectors are feasible.

By pushing the boundaries of device development and leveraging the advantages of cartridge-based systems, particularly through integration with the needle isolation technology, important strides are being made in the device development side of combination products. Collaboration between the medtech and pharma industries will be crucial for exploring the potential of large-volume devices in the burgeoning SC drug delivery market.

References

1. *MIDAS, IQVIA data set, 2022.*
2. *I Lloyd (2022) 'Pharma R&D Annual Review 2022 – Navigating the Landscape', Citeline Informa Pharma Intelligence.*
3. *D V Doughty et al (2016) 'Understanding Subcutaneous Tissue Pressure for Engineering Injection Devices for Large-Volume Protein Delivery', J Pharm Sci, 105(7), 2105-2113.*
4. *W D Woodley et al (2021) 'Clinical Evaluation of an Investigational 5ml Wearable Injector in Healthy Human Subjects', Clin Transl Sci, 14(3), 853-869.*
5. *W D Woodley et al (2022) 'Clinical Evaluation of Large Volume Subcutaneous Injection Tissue Effects, Pain, and Acceptability in Healthy Adults', Clin Transl Sci, 15(1), 92-104.*
6. *A V Badkar et al (2021) 'Subcutaneous Delivery of High-Dose/Volume Biologics: Current Status and Prospect for Future Advancements', Drug Dec Devel Ther, 15, 159-170.*
7. *A Gerhardt et al (2014) 'Protein aggregation and particle formation in pre-filled glass syringes', J Pharm Sci,103(6), 1601-1612.*
8. *J S Bee et al (2009) 'Precipitation of a monoclonal antibody by soluble tungsten', J Pharm Sci, 98(9), 3290-3301.*
9. *L S Jones et al (2005) 'Silicone oil induced aggregation of proteins', J Pharm Sci, 94(4), 918-927.*
10. *S Funke et al (2016) 'Optimization of the bake-on siliconization of cartridges. Part II: Investigations into burn-in time and temperature', Eur J Pharm Biopharm, 105, 209-222.*
11. *A Hartl and L Guimond (2022) 'Addressing Primary Container Challenges in Autoinjector Drug Delivery: Interim Results of a Multiphase Bioburden Study for a Cartridge-Based Autoinjector', 2022 PDA Universe of Pre-Filled Syringes and Injection Devices Conference presentation.*

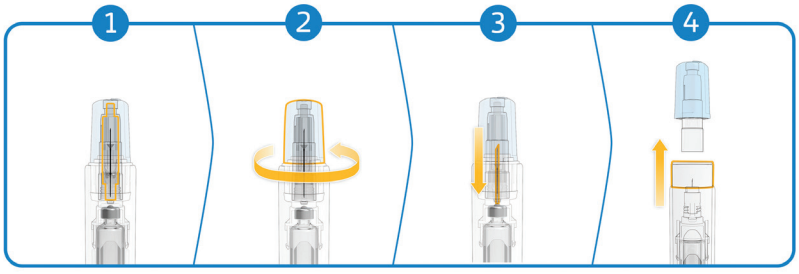

Figure 2 An overview of the needle isolation technology: 1 The closed system. 2 Twist off the needle cap. 3 The non-patient end of the cannula moves backwards to pierce the cartridge septum and open the fluid path. 4 Needle cap removal, with the needle remaining hidden throughout the injection process

Gary Calderwood is a product manager at **SHL Medical**. He leads on the development and life cycle management of the company's device technologies. Previously, he was a senior design engineer at SHL. He holds a higher degree in Medical Design Compliance and a BSc in Product Design.