DIRECTIONS FOR WEARABLE ON-BODY INJECTOR SYSTEMS AND BEYOND

Here, Matt Parker, Karthik Chellappan and David Cottenden, PhD, all Senior Consultants – Drug Delivery at TTP, discuss the current state of play for large-volume injection and look into the challenges that on-body delivery systems currently in development will need to overcome to find success in a changing marketplace.

With the continuing movement of disease management into patient's homes, injection device design will have to answer a changing set of demands – from dose volume and form factor to sustainability and cost per dose, as well as "platform-ability" and value-add – that will challenge existing partnership models in the industry (Figure 1). Future platforms could even borrow from the design of Nespresso coffee machines to accommodate a wider range of drugs.

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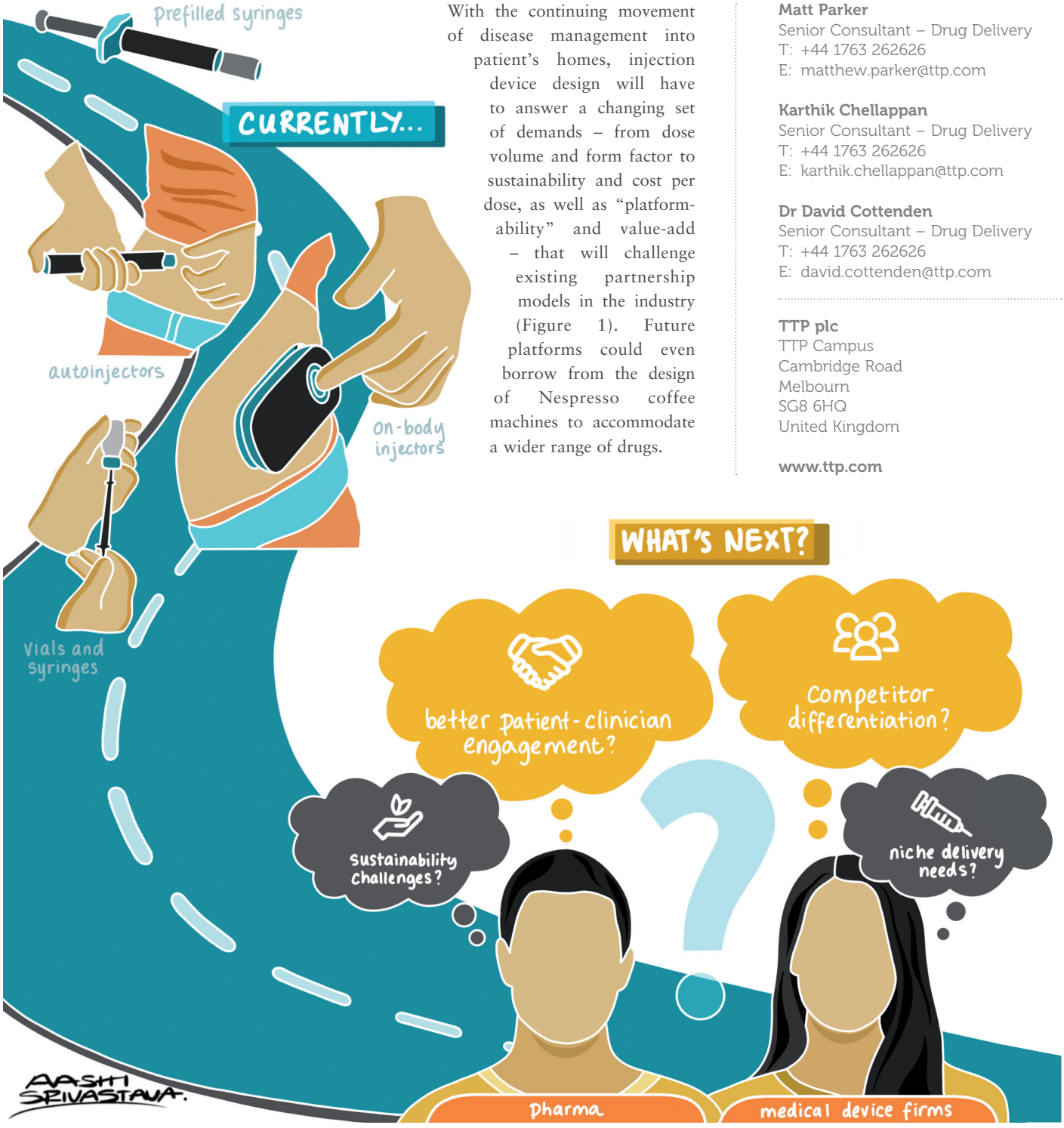

Figure 1: From the present to the future – a changing set of needs in injectable drug delivery.

THE CONTEXT FOR LARGE-VOLUME INJECTION

So far, two main trends have driven the development of injectable drug delivery devices:

- The growing share of biologic drugs in pharmaceutical pipelines, causing a shift away from oral towards injectable delivery
- Treatment moving from in-clinic to at-home, creating a need for more "patient-friendly" solutions than traditional vial-and-syringe or prefilled syringe presentations.

In the smaller-volume injection space, this has led to a proliferation of autoinjector systems. These typically deliver volumes of 1–2 mL and offer a convenient and patient-friendly means of delivering therapies, due to few use steps, sharp safety, hidden needles and low dexterity requirement. However, many therapies present formulation challenges to achieving these volumes, either due to stability concerns or viscosity. As such, there is increasing demand for devices capable of delivering larger doses, ranging from 3 to 100 mL, or even more. Indeed, several vendors, including SHL (Zug, Switzerland) and Ypsomed (Burgdorf, Switzerland) recently announced 5 mL autoinjectors.

The fundamental limitation of this class of devices is time, or how long a user can reasonably be expected to hold the device against their skin to complete a delivery. If the user lifts the device before completion, or too soon after, they will cause a wet injection where the therapy will not be correctly delivered.

For standard injectable primary packaging, the maximum delivery pressure is generally set by the strength of the glass vial. Infusion time is therefore dominated by the flow resistance of the needle. The relationship between viscosity, volume and delivery time is described by a Poiseuille flow model.

For example, 5 mL of a 30 cP viscosity drug with a standard 27G needle leads to an expected delivery time in excess of two minutes, and over 45 seconds even with thin-wall needles.

Many patients find it difficult to continue after even 30 seconds, so the scope for extending the autoinjector format is clearly limited. Furthermore, physiological modelling of pain (nociception), suggests that delivery of larger volumes of viscous drugs could also be unbearably painful within these timeframes.

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One alternative is to use several autoinjectors to deliver the total dose. But sequential injections present other known challenges for patient compliance. Increasing the frequency of dosing from weekly to daily also presents similar compliance challenges and may not provide the required pharmacokinetic performance.

WEARABLE INJECTORS TO THE RESCUE?

On-body delivery systems (OBDSs) – provide another route around the time challenge. By adhering the delivery device to the skin, the need to hold the device steady is removed, thereby enabling the delivery of larger doses. This realisation has prompted the development of at least ten large-volume wearable device platforms from a range of device manufacturers. These large-volume injection (LVI) solutions range from single-use mechanical to reusable electromechanical systems. Multiple companies are developing and commercialising these devices, including:

- Ypsomed (see this issue, p 6)
- West Pharmaceutical Services (PA, US)
- BD (see this issue, p 22)
- Sensile Medical, since acquired by Gerresheimer (see this issue, p 28)
- Nemera (see this issue, p 62)
- Enable Injections (see this issue, p 37)
- Sorrell, since acquired by LTS (see this issue, p 52)
- CCBio (see this issue, p 66)
- Subcuject (Hellebaek, Denmark)
- Sonceboz (see this issue, p 46)
- Weibel, since acquired by SHL.

But despite the proliferation of LVI devices available for license, few have launched. Neulasta (pegfilgrastim), by Amgen (CA, US), has been on the market in a repurposed Omnipod (Insulet, MA, US) device since 2015. However, while wearable, this is only a 0.6 mL device. Amgen has also launched Repatha (evolocumab) in the West SmartDose 3.5 mL (5 minute wearable) in 2016, with AbbVie (DE, US) following in 2020 with Skyrizi (risankizumab) and, as of 2023, scPharmaceuticals (MA, US) are close to market with Furoscix (furosemide) in West's 10 mL SmartDose. There have been some US FDA hold-ups relating to the manufacturing, testing, labelling and features of the Furoscix combination product, demonstrating the challenges of developing and launching in this market.

However, despite few launches to date, many of the companies developing these devices have announced partnerships with pharma clients. Numerous clinical trials of OBDSs are ongoing, further highlighting the interest from pharma in LVI.

Due to their increased part count, the cost of these systems is thought to be at least an order of magnitude higher than for autoinjectors. Increased complexity is apparent both in terms of the time and cost of R&D, as well as in the difficulties encountered by pharma when working with medical device partners to accommodate therapy-specific delivery requirements. In addition, high upfront licensing costs often limit the applicability of the current generation of OBDSs to a broader range of therapies.

A CHANGING LANDSCAPE

While the aforementioned trends continue, new ones are making themselves felt. In particular, OBDSs are facing challenges from a greater demand for sustainable medical devices and delivering value in the context of changing reimbursement models.

Delivery Volume

The demand for higher volumes does not seem to be plateauing, not at 5 mL, or even at 10 mL. While West's SmartDose 10 is one of the larger devices close to market, new therapy areas, including immunology

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and oncology, are driving a need for even larger-volume devices. Multiple manufacturers are responding by adopting 20 mL primary pack sizes for their pipeline devices – Sorrel (20 mL), Sensile (up to 20 mL), Sonceboz (up to 20 mL) and Enable Injections (up to 50 mL). This trend is likely to continue.

Another important driver for volume is in enabling therapies that were previously delivered via the intravenous (IV) route to be reformulated for subcutaneous (SC) infusion at home. An example here is Abbvie's Skyrizi, where the initial doses are delivered via IV infusion but subsequent doses are delivered by an OBDS.

Flexibility and Adaptability

In addition, future drug pipelines will demand greater flexibility from injector platforms. Challenges include the co-administration of multiple drugs, varying viscosities, complex reconstitution and mixing steps, weight-based dosing and stability. To date, the majority of devices have been optimised around a specific use-case – a specific volume, user interaction (prefilled or patient-filled) – or require the adoption of a specific dose container.

In terms of industry partnerships, this currently leaves pharma with the choice to either "lock-in" to the constraints of a specific partner's device or maintain relationships with a suite of vendors with different offerings. A platform capable of accommodating all of the diverse and varied requirements of future pipelines is yet to be developed. Additionally, for medical device companies, supporting multiple pharma partners in the development stage represents significant overhead, adding cost and time to development. Flexible and adaptable technologies that robustly address these challenges would be highly desirable.

Sustainability

The majority of systems in development are single-use disposable devices. However, given that the majority are complex electro-mechanical systems, the sustainability impact is significant. The volume of autoinjectors disposed on an ongoing basis is already recognised as problem and, with growing demands for sustainability, the industry should avoid a repeat with OBDSs. Growing societal pressures suggest that future platforms will need to be designed from the bottom up for sustainability.

Additional Value

By enabling new drugs to be delivered at home, OBDSs already add value for healthcare providers. Some of the existing devices already have a connectivity solution to connect with apps and mobile devices. Future devices may have to satisfy additional, more complex requirements, such as for dose and delivery verification.

WHAT MAY THE NEXT GENERATION LOOK LIKE?

Accommodating Larger Dose Volumes

The volume that can be delivered via the SC route is limited by the make-up of SC tissue. SC infusions of 20 mL of immunoglobulin therapies (SCIg) are routinely delivered over longer infusion times. Co-formulation or co-delivery with hyaluronidase permits the SC infusion of ever larger volumes. Facilitated SCIg delivery can allow up to 700 mL to a single site.[1]

However, the biomechanics of the skin is not the only consideration in device design. Increasing volume increases the size and weight of the device, especially if glass primary dose packaging is being used. There is a practical limit for what is tolerable to be worn on-body before other formats start to make more sense. Insulin infusion pumps, for example, use a separate cannula and are carried on the waist. For very high volumes, ambulatory pumps may become an option, albeit the user interactions are significantly more complex than the "stick and press" interface of many OBDSs.

Improving Sustainability

The carbon footprint of patients travelling to a clinic often eclipses the footprint of individual devices, meaning that at-home therapy already represents a net carbon saving.[2] However, the footprint of a single-use, connected, electromechanical device is significant. This can be addressed through reduced material use and increasing circularity.

Considering sustainability from the ground up may result in very different device architectures, in particular with a disposable and reusable component. The former will likely contain the dose, needle and fluid path, as well as the adhesive; while the latter includes the energy source, control electronics and drive engine. Sensile and Nemera, among others, are taking this approach with their devices.

Design for sustainability is also linked to cost-per-dose performance. Cost modelling indicates that reusable-disposable architectures can achieve a cost per dose comparable to a regular autoinjector when considered over a year of monthly treatment.

Adapting to the Needs of Diverse Therapies

Platform approaches to device development bring benefits in terms of time-to-market and risk against a background of diversified drug pipelines. Modular designs can mitigate the technical risks of needle insertion, drive engines and power across varying device form factors. However, flexibility is often limited by the selection of a primary pack, which represents a significant qualification effort, particularly for larger volume formats that enable the delivery of a variety of combinations.

However, there is room for technologies that simplify the adaptation of platforms to various requirements, such as volume, viscosity and dose preparation. For example, the Owen Mumford (Woodstock, UK) Aidaptus autoinjector platform has a self-adjusting design to automatically accommodate different fill volumes without requiring a change in device or parts. It is likely that there will be a rise in "platformable" wearable injectors that adopt similar approaches to accommodate variation in fill volume, viscosity and flow rate.

Inspiration can even come from platforms outside of drug delivery. Nespresso's Vertuo coffee machines encode the brew parameters in a barcode on-pod. This allows coffees with new brewing requirements to be released to distributed machines without updating them. Encoding delivery parameters into the dose-containing disposable element could similarly reduce the revalidation required to adapt the delivery system to new therapies, increasing the system's potential as a platform.

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Providing Additional Value

Finally, the changing scope of reimbursement in many geographies is creating a demand for platforms that provide additional value beyond delivery. With many newer drugs, sensing and remote monitoring will be essential for healthcare providers and pharmacists, who will need to play an increasingly active role in disease management. By integrating sensors and connectivity into devices, administration events can be tracked and reported. Timely intervention is required to ensure that patients keep to their dosing schedule, but also to manage treatment-associated reactions or adverse events and keep doses in the optimal therapeutic windows.

With the rise of reusable devices, medication authentication is also a critical concern. Wearables equipped with authentication mechanisms, such as barcodes, near-field communication and unique identifiers, can help patients verify the legitimacy of the medication being administered and prevent unapproved therapies from being delivered. Additional sensors may also help support the logistics of delivery, for example, by verifying the cold-chain storage of a temperature-controlled medication, or by verifying that a dose has warmed to the correct temperature prior to delivery.

Connected devices provide a unique opportunity to support disease management and engage patients with their therapies. Through real-time data collection and analysis, these devices can provide personalised insights and reminders to patients, encouraging patients to adhere to their medication schedule. However, uncertainties in the commercial viability of pharma-contract manufacturer partnership models need to be addressed before the full clinical potential of connectivity can be unlocked.

CONCLUSION

The trends behind the rise of autoinjectors and proliferation of OBDSs continue unabated. OBDSs that move the delivery of drugs to the home setting hold great promise, but it seems likely that future platforms will have to address a new set of technical and commercial challenges. As dose volumes and viscosities increase, filled-device weight will become a greater consideration in design and may prompt alternative form factors, energy sources and delivery strategies. To meet societal demands for greater sustainability, devices could be split into hybrid (reusable-consumable) architectures. Despite this, the user workflow needs to be kept simple; human-centric and behavioural design will be essential to maximise adherence and to empower patients to manage their condition at home.

Hybrid architectures and larger primary packs will also raise new technical challenges, such as transferring power between components (mechanical, electrical or other) and verifying dose authenticity. Finally, the addition of sensing and connectivity will provide additional opportunities to build solutions that empower patients to monitor their condition. These demands will test existing partnership models and accelerate innovation in future platform technologies.

ABOUT THE COMPANY

TTP is an independent technology company. Its combination of science and engineering means that it has the know-how to help solve the toughest challenges and get technology to market fast. The company's consultants are empowered to collaborate with clients, and each other, in a truly agile way. This has been a cornerstone of the company's success for over 30 years, allowing TTP to develop and deliver thousands of pioneering products and services. From start-ups to blue chip organisations, what unites TTP's clients is their desire to make brilliant things happen.

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ABOUT THE AUTHORS

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