Phillips Medisize
a molex company

EMERGING TRENDS IN WEARABLE DRUG DELIVERY

In this article, Tony Bedford, Director, Front-End Innovation, Phillips-Medisize, discusses the current state of the fledgling on-body injector market, including the difficulties of competing with autoinjectors in the <5 mL space, the potential on-body injectors have in oncology and Phillips-Medisize's own developments in the on-body injector field.

Even prior to the launch of the first wearable injector outside of insulin, the drug delivery industry has been anticipating significant uptake in the use of such novel devices, with forecast compound annual growth rates of over 25% for the next ten years.[1] In reality, the on-body injector (OBI) market for non-insulin is a fledgling, experimental one, and we are yet to see a consistent trajectory that it will follow, with only two "true" wearable (non-insulin) devices on the market and no new product launches since 2016.

Even the nomenclature used to describe wearable injectors seems to be suffering from an identity crisis, with multiple acronyms and descriptors being used – large volume injector (LVI), patch pump, OBI (as used in this article) and on-body delivery system (OBDS), which has been adopted for an upcoming standard by the ISO,[2] to name but a few.

"Even the nomenclature used to describe wearable injectors seems to be suffering from an identity crisis, with multiple acronyms and descriptors being used."

AUTOINJECTORS ERODING POSSIBLE OBI MAKET SHARE

With that reality check stated, we can speculate on a few emerging trends that might allow this new breed of subcutaneous drug delivery device to carve out a niche for itself, beginning with a potential increase in the likely "sweet spot" volume of drug to be delivered. A number of OBIs in development have focused on volumes below the 5 mL mark, but the likelihood of their widespread adoption is seemingly being eroded by a steady increase in the popularity of self-administered autoinjectors and, in particular, the advent of autoinjectors capable of delivering up to 2.25 mL of liquid.

"A number OBIs in development have focused on volumes below the 5 mL mark, but the likelihood of their widespread adoption is seemingly being eroded by a steady increase in the popularity of self-administered autoinjectors."

Anecdotally, it is feasible for a patient to receive two consecutive

Tony Bedford
Director, Front-End Innovation
T: +44 1223 297075
E: Tony.Bedford@molex.com

Phillips-Medisize
The Vitrum Building
St John's Innovation Park
Cowley Road
Cambridge
CB4 0DS
United Kingdom

www.phillipsmedisize.com

doses from 2.25 mL autoinjectors provided sufficient training and instructions are in place, although questions remain with respect to the practicalities and patient comfort of doing so. Issues that may need to be overcome include:

- Ensuring that patients are sufficiently trained to use both autoinjectors (in the case of a pack of two equalling a single dose) rather than mistakenly considering one to be a spare.
- Avoiding under-dosing through wet injections (where the autoinjector is lifted away from the skin prior to completion of delivery).
- Absorption and pain issues caused by repeated injections at the same site.

These issues could be addressed through the use of an OBI. Nevertheless, the availability of proven autoinjector technology may make <5 mL a challenging playing field for OBIs. That said, there may be plenty of opportunities for delivering volumes in excess of 5 mL, and one such opportunity is emerging in immuno-oncology.

FROM INTRAVENOUS TO SUBCUTANEOUS

For some time, the possibility of switching drug formulations from intravenous (IV) to subcutaneous (SC) delivery has been considered to be a driving force for the OBI market, as the volumes resulting from such a switch are likely to be much higher than any autoinjector or prefilled syringe can accommodate. That said, there is a precedent in oncology for nurse-administered delivery of SC drugs from a large syringe, for example MabThera SC 1400 mg (Roche, Basel, Switzerland), which is delivered as a fixed dose of approximately 11 mL. Although evidence of this type of switching is limited, there are some eye-catching programmes in early-phase clinical trials.

A small number of successfully launched PD-1 and PD-L1 "checkpoint inhibitors", intravenously delivered anti-cancer drugs that stimulate the immune system, have undergone positive Phase I research evaluating a switch to an SC formulation. This includes Merck & Co's (Kenilworth, NJ, US) Keytruda (pembrolizumab) which is already one of the best-selling drugs globally – and with further approvals likely, Keytruda's revenue is set to increase well beyond the US$11.1 billion (£8.3 billion) achieved during 2019.[3] At this early stage, an accurate prediction of SC liquid volume is not possible, but estimates in the 5–20 mL range are entirely plausible for this and other reformulated SC drugs in this category, making them prime candidates for administration via OBI devices that can accommodate and deliver these larger payloads.

COVID-19 AND ONCOLOGY

The ongoing and seemingly open-ended uncertainty caused by the covid-19 pandemic may also influence the direction of travel for oncology drugs and wearable drug delivery devices. Cancer patients have been finding their surgery or treatment postponed or even cancelled as healthcare providers pool their resources to fight the coronavirus,[4] whilst some patients will have chosen to stay away from clinics simply because of the risks involved. Although it is probably too early to tell what the impact of this situation is, it is likely to result in an increased number of tragic outcomes.

In the UK, NHS England has rolled out a programme permitting convenient, non-hospital based treatments for cancer patients,[5] which could be an early indication of the type of changes that come to pass in healthcare provisioning as a result of covid-19. One such change could be the adoption of OBIs for the delivery of oncology drugs; aside from the aforementioned MabThera there are other cancer treatments already available for SC administration in addition to the checkpoint inhibitors and other maintenance therapies currently undergoing clinical trials. Deploying these in an OBI could help mitigate pandemic-related risks through fewer touchpoints with frontline staff and less travel for patients, should the difficulties caused by covid-19 either stay with us for an extended period or facilitate a permanent change in the way we obtain certain healthcare provisions.

However, it must be acknowledged that the uptake of OBIs in the oncology sector is not straightforward; as with any healthcare practitioner, the protection afforded by oncologists to their patients includes maintaining the utmost safety in their treatment, as cancer drugs can be highly toxic and patients are often very unwell. Some cancer drugs demand direct supervision by a healthcare practitioner during at least the first course of treatment.

One advantage that OBIs could offer in this instance is the reduction of time spent in-clinic, with faster set-up times and shorter delivery durations than IV administration, whilst maintaining the increased safety that in-clinic treatment permits – or, for drugs considered suitable for self-administration, eliminating the requirement for the healthcare practitioner to be present altogether, along with the economic burdens associated with in-clinic treatment.

"A small number of successfully launched PD-1 and PD-L1 "checkpoint inhibitors", intravenously delivered anti-cancer drugs that stimulate the immune system, have undergone positive Phase I research evaluating a switch to an SC formulation."

PREFILLED OR USER-FILLED AND DEVICE COMPLEXITY

With the OBI market still in its infancy – at least as far as launched, marketed products are concerned – there is not much evidence to point to an industry "preferred" configuration. Devices launched (and in development) range from simple, spring-driven piston-based systems to sophisticated electromechanical solutions, and employ drug containers ranging from fill at point-of-use reservoirs to compatibility with standard primary containers.

From an automation standpoint, there is an obvious bias towards devices that are designed to use primary containers that are compatible with standard filling processes. Couple this to usability requirements, whereby minimal user interaction is considered preferable, and a clear trend is emerging for prefilled and preloaded devices offering a use sequence that is close to the simplicity of the two-step autoinjector.

Following that trend, Phillips-Medisize is currently engaged with a leading biotechnology company for the late-stage development of one such prefilled OBI for SC drug delivery. The electronic-enabled combination product comprises of a single-use disposable delivery device and prefilled container that can either be affixed to the patient's body via an adhesive patch or worn near the infusion site. The entire product is replaced every two days and more product launches of this nature are anticipated in the short-to-medium term.

> "Phillips-Medisize has been developing its own OBI device that addresses several of the trends thus far discussed."

Prefilled is by no means the only viable solution though – user-filled devices come with challenges of their own, as sterility must be maintained until the time of use – as a clear need for devices that are filled at the point of use is also emerging. The Neulasta® Onpro™ (Amgen, Thousand Oaks, CA, US), which launched in 2015 for post-chemotherapy neutropenia treatment, is a direct descendent of the user-filled Omnipod® device (Insulet Corporation, Acton, MA, US) for diabetics, and has shown that there is acceptance of reservoir-based OBIs, albeit for a very specific use case.

The potential for OBIs in the oncology sector, as covered in this article, could also present opportunities for fill-at-point-of-use reservoir-based devices. Stability concerns are reduced, as it is expected that the drug would not be in contact with the primary container or reservoir for sustained periods. This configuration would allow a healthcare professional to fill a device with a flexible weight-based dose, creating a need for bolus injectors that can fully evacuate a payload. Additionally, fill-at-point-of-use OBIs would permit lyophilised drugs to be delivered shortly after reconstitution.

PHILLIPS-MEDISIZE'S PROTOTYE OBI

Phillips-Medisize has been developing its own OBI device that addresses several of the trends thus far discussed (Figure 1). By incorporating electronically-enabled, delayed (if required) bolus delivery from a <1 mL reservoir, the delivery duration of Phillips-Medisize's OBI can be programmed to be from around 10 seconds up to 45 minutes without any need for changes to the drive system components. The device has been designed initially for fill-at-point-of-use with healthcare settings in mind – greater throughput, minimal contact time and the ability to administer away from clinic are all possible. However, Phillips-Medisize is exploring the possibility of a cartridge to suit the trend towards prefilled devices.

Currently at the prototype stage, the Phillips-Medisize device also addresses the trend towards increasing volumes, having been conceived with modularity in mind. The selected drive system is able to deliver a wide range of volumes and viscosities, the key variable being the duration of delivery set against absorption rates – for example, 5 mL of 20 cP liquid could be delivered in less than a minute.

Returning to the complexity of OBIs, it is inevitable that the more features and functions a device has, the higher the cost of goods will be. This will also be affected by the choice of drive system (including activation, drug expulsion and needle insertion). Predicting what may be an acceptable device cost is challenging, not least because each application is likely to come with a very different set of needs and parameters (such as unit volume manufactured, selling cost of the drug and the characteristics of the drug), but industry chatter does suggest that cost is a factor that has hampered the uptake of OBIs thus far. Consequently, the final trend

Figure 1: Philips-Medisize's OBI, which uses electronically-enabled delivery, is able to deliver a wide range of volumes and viscosities of SC formulation.

we must consider is the emergence of significantly lower cost OBIs that could heighten interest in this as-yet fledgling market by making them more competitive with autoinjectors for delivery volumes addressable by both device types. It certainly feels as though we are still at the beginning of an exciting journey.

ABOUT THE COMPANY

Phillips-Medisize, a Molex company, is an end-to-end provider of innovation, development, manufacturing and post-launch services to the pharmaceutical, diagnostics, medical device and speciality commercial markets. Post-launch services include a connected health app and data services. Backed by the combined global resources of Molex and its parent company Koch Industries, Phillips-Medisize's core advantage is the knowledge of its employees to integrate design, moulding, electronics and automation, providing innovative high-quality manufacturing solutions.

REFERENCES

1. *"Large Volume Wearable Injectors Market (5th Edition), 2020–2030: Focus on Bolus, Basal and Continuous Delivery Devices". Roots Analysis, 2020.*
2. *"ISO/DIS 11608-6: Needle-based injection systems for medical use – Requirements and test methods – Part 6: On-body delivery systems". International Organization for Standardization, 2020.*
3. *"Merck Announces Fourth-Quarter and Full-Year 2019 Financial Results". Bloomberg, Sept 2020.*
4. *Stone W, "Cancer Patients Face Treatment Delays And Uncertainty As Coronavirus Cripples Hospitals". Kaiser Health News, Apr 2020.*
5. *"Convenient modern cancer treatment for patients during covid-19 pandemic". NHS England, June 2020.*

ABOUT THE AUTHOR

Tony Bedford is Director, Front-End Innovation at Phillips-Medisize and has been involved in the design and development of medical devices for 25 years. With a background in product design, his broad experience covers everything from innovation and market strategy to clinical research and product launch, with a focus on understanding market, stakeholder and user needs. Prior to joining Phillips-Medisize, Mr Bedford held project management and business development roles in the consulting industry, working on a wide range of device programmes. He has specialised in drug delivery devices for a number of years.

Phillips Medisize
a molex company

Leading the Way in Medical Devices and Connected Health

Phillips-Medisize, a Molex company, is committed to serving pharmaceutical, diagnostics and medical device customers by creating technology and products to improve people's lives.

We operate innovation centers in North America, Europe and Asia, and manufacturing sites at 26 locations in 10 countries.

With over 5,500 employees working in a quality-conscious culture, we take you safely and quickly through the process of bringing your medical product to market.

www.phillipsmedisize.com