



AN INTRODUCTION TO YPSODOSE FOR THE LARGE-VOLUME INJECTION OF BIOLOGICS

In this article Ian Thompson, Vice-President Business Development at Ypsomed, describes self-injection device trends for larger injection volumes and introduces YpsoDose, a new prefilled large-volume wearable injector being developed by Ypsomed Delivery Systems.

Worldwide, pharmaceutical companies are focusing on biologic therapeutics, many based on monoclonal antibodies. Due to their molecular characteristics they are usually administered parenterally and, when self-injected, subcutaneously. Injections are infrequent – typically weekly, biweekly or monthly and there is a demand for less frequent injections e.g. every two, three or six months. The trend to fewer injections, ranging from traditional peptides/hormones to antibody therapies, means that larger doses and thus larger injection volumes are required.

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These larger volume injections are mainly being considered for treating autoimmune diseases such as rheumatoid arthritis, psoriasis and IBD/Crohn's, but also for new therapeutics such as the PCSK-9s recently launched for the treatment of hyperlipidaemia. Looking into the future

the potential for new drugs for treating Alzheimer's, and immuno-oncology therapies to control already treated cancers, will further increase demand for larger volume infrequent self-injections.

TRADITIONAL 1 ML AUTOINJECTORS & NEW 2.25 ML AUTOINJECTORS

Since the introduction of prefilled syringe (PFS)-based disposable autoinjectors around a decade ago, the majority of devices have been based on the 1 mL-long PFS and there are now over 10 different devices on the market. For a number of years there was a general acceptance that 1 mL was the maximum volume that could comfortably be delivered by an autoinjector. With the increased need for higher payloads and following clinical testing this no longer holds true and the 2.25 mL PFS is now accepted as the standard primary container for injection volumes in the 1-2 mL range.

Based on the demand for less frequent injections, the interest in 2.25 mL prefilled syringe-based autoinjectors is growing significantly. The injections are often for slightly viscous drugs with injection times in the 10-15 second range.

Ypsomed is covering this demand with the YpsoMate 2.25, which serves patients with an easy and convenient two-step automatic injection. While the standard YpsoMate 1 mL version has been industrialised and is being customised for over 15 customers, the new YpsoMate 2.25 mL version has been adopted by first customers and is in development for clinical studies (Figure 1).



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Figure 1: YpsoMate® 1 mL and YpsoMate® 2.25 mL two-step customisable autoinjectors cover injection volumes up to 1 mL and 1-2 mL.

THE WEARABLE INJECTOR FOR VOLUMES ABOVE 2 ML

For volumes above 2 mL, which require longer injection times, there is a need for large-volume wearable injectors. This implies a disposable injection device that is worn and connected to the body with an infusion set or ideally attached directly to the skin with an integrated fluid path and needle system. Compared to an infusion pump, which performs drug infusions over hours or days, the large-volume wearable injector is intended to administer 2-10 mL or an even greater volume of drug typically within 2-15 minutes.

In the large-volume injector field there are a number of wearable device concepts available and in development covering a broad range of specifications including: prefilled but not assembled; fillable; prefilled and preassembled; mechanical; electromechanical; cartridge-based and collapsible container-based systems. It is clear that there will be a range of devices required to cover different drug and patient needs. Learning from both previously developed and current offerings, it is also clear that the key focus in the area of biologics is in the 2-10 mL injectable volume space requiring prefilled and preassembled, electromechanical, cartridge-based, connected wearable injectors.

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AUTOINJECTOR OR WEARABLE INJECTOR?

For drugs with longer pharmacokinetic half-lives, pharma companies need to weigh up the pros and cons between more frequent injections from an autoinjector and less frequent injections from a wearable injector. Whether an autoinjector or wearable injector is selected for a particular therapy depends on a number of factors. Autoinjector technologies are established and proven and the prefilled syringe drug reservoir is typically also available for use by healthcare professionals (HCPs) or patients, in the form of a bare syringe or in combination with a safety syringe system. While an autoinjector typically contains a prefilled syringe, a skin-worn wearable injector requires a different drug reservoir –

typically a cartridge, combined with a sterile fluid path and needle system.

Many more questions are being asked. For example, what is preferred by patients, four 10-second autoinjections per month or one 5-minute injection with a wearable device? Does a pharmaceutical company want to invest in a bespoke drug reservoir/fluid path system that can only be injected with the aid of a bespoke device? How much added value, convenience or differentiation does the wearable device add to the therapy regime compared with the autoinjector?

These questions can only be answered by extensive research into the way new therapies are provided to patients and a thorough understanding of patient preferences. But, it is clear that the wearable injector market will grow significantly over the coming years and establish itself as a third device class to complement the already well developed markets for pens and autoinjectors.

WEARABLE INJECTOR NEEDS

Ideally, a wearable injector should be as easy to use as a disposable autoinjector (or easier) based on less frequent injections, which means it must incorporate the following key technical features:

- Prefilled and fully disposable to remove any need to assemble the drug reservoir and device
- Easy adherence to the skin during injection; and easy to remove after injection
- Automatic insertion and retraction of the needle at the start and end of the injection process.

In order to be truly versatile, the device also needs to be able to deal with the following aspects:

- Recognise that the device is ready to inject when attached to the skin
- Cover a range of fill volumes and viscosities and provide a reproducible injection time per drug
- Communicate via audio and visual signals clearly with the patient before, during and after the injection
- Ideally, have a wireless connection to allow patient monitoring.

All of these requirements mean that the wearable injector is a significantly more complex device than a disposable



Figure 2: YpsoDose®, the prefilled, preassembled, electromechanical wearable injector for injection volumes in the 2-5 mL range.

autoinjector but, in cost terms, this may well be compensated by the lower number of devices required compared with an equivalent therapy provided by an autoinjector.

YPSODOSE WEARABLE INJECTOR DEVELOPMENT

The development and manufacture of a wearable injector system brings with it a number of challenges to fulfil the device needs described above.

Ypsomed has a proven track record of working on complex injection devices with in-house engineering expertise, combined with a high level of technological integration for manufacturing pens, autoinjectors, pen needles, insulin pumps and infusion sets under clean and cleanroom conditions. All these competencies are key in developing the subsystems required by YpsoDose (Figure 2).

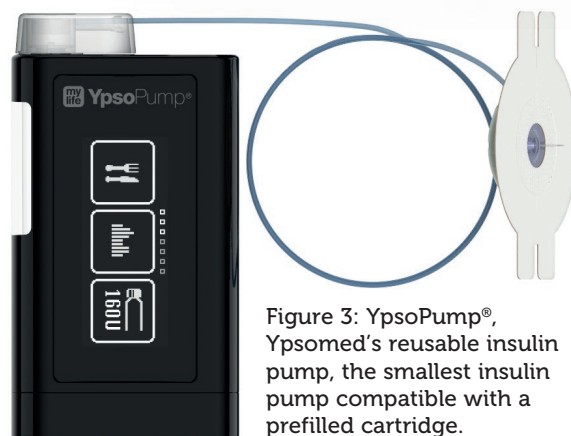


Figure 3: YpsoPump®, Ypsomed's reusable insulin pump, the smallest insulin pump compatible with a prefilled cartridge.

The subsystem development for YpsoDose focuses on the drug reservoir/ fluid path, needle mechanism, drive mechanism, adhesive patch and electronic interface. With such a complex project the close proximity of development and manufacturing within the company and access to an existing supplier network in the heart of Europe help to simplify the development and industrialisation process.

Ypsomed has changed the rules in the market and accelerated customer projects by developing platforms, by engineering them, by patent protecting them and – this is key – also industrialising them. YpsoDose is no exception and the device is now moving from innovation into the realisation phase based on the following device features:

- Conventional cartridge technology for the primary drug container
- Proprietary integrated sterile needle unit and needle mechanism to complete the fluid path and insert the needle
- Low noise proprietary electromechanical drive programmable to accommodate different injection flow rates
- Electronics to provide patient feedback and connectivity
- A technical design that allows the pharma company or contract filler to easily assemble the device subassemblies with the drug cartridge.

CUSTOM PRODUCT APPROACH AND THE PATIENT JOURNEY

Implementing the Ypsomed Custom Product platform approach for the YpsoDose wearable injector is a clear aim of the project. This involves significant investment in resources and infrastructure for fully automated manufacturing of the needle unit under cleanroom conditions and assembly of the device subassemblies. Streamlining the device technology and manufacturing processes is important in order to achieve a scalable and cost-efficient device. At the same time, customers demand the ability to customise the device for different drugs and patient groups. This is why Ypsomed is investing heavily in modular product design and human factors engineering for multiple user groups.

There is a parallel between YpsoDose and the significant development and manufacturing investments that have been made for YpsoPump, Ypsomed's reusable insulin pump, the smallest insulin pump compatible with a prefilled cartridge (Figure 3). At half the size of existing pumps, with an intuitive icon-based touch screen, it is a prefilled solution that avoids cumbersome manual filling of insulin. This pump, weighing only 83 g, includes sophisticated electronics and has an integrated Bluetooth connection module.

For YpsoDose, the journey is at the realisation phase and the results of the most recent design studies will be presented at

the forthcoming PDA *Universe of Prefilled Syringes & Injection Devices* conference in Huntington Beach, CA, US, October 17-18, 2016. The dialogue with pharma customers is now intensifying as YpsoDose moves through the realisation phase towards the clinical phase.

ABOUT YDS – YPSOMED DELIVERY SYSTEMS

Ypsomed is the leading independent developer and manufacturer of innovative autoinjector and pen injector systems for self-administration. The customisable product platforms cover autoinjectors for prefilled syringes in 1 mL and 2.25 mL format, disposable pens for 3 mL and 1.5 mL cartridges, re-usable pens that include automated injection mechanisms and easy-to-use injection devices for drugs in dual-chamber cartridges such as lyophilised drugs. Unique click-on needles and infusion sets complement the broad self-injection systems product portfolio. Ypsomed provides its partners with excellent technological expertise and full regulatory

support for the device-relevant aspects of the registration process.

The injection systems are developed and manufactured in Switzerland with strong in-house competencies covering concept and product development, tool-making, injection moulding and automated assembly. Ypsomed is ISO 13485 certified and all processes are run according to design control and current Good Manufacturing Practice (cGMP) guidelines with operational quality assurance (QA/QC) experts on-site at each location. Ypsomed's US

FDA-registered manufacturing facilities are successfully inspected on a regular basis by both pharma customers and regulatory agencies (including FDA) and supply devices for global markets including US, Europe, Japan and China. Ypsomed has more than 30 years' experience and well-established working relationships with numerous leading pharma and biotech companies. Ypsomed Delivery Systems continues to focus on the development and manufacture of next generation pen, autoinjector, wearable and connected injector technologies.

ABOUT THE AUTHOR

Ian Thompson has been with Ypsomed AG, formerly Disetronic AG, since 1995 in a number of roles in key account management and business development working with pharma companies to develop and bring to market innovative self-injection systems. He studied biochemistry and biotechnology in the UK from 1979-1983, working initially in commercial roles for fermentation technology. He has worked in medical device companies since moving to Switzerland in 1990. Since 2003 his main focus has been business development and new product innovation leading to the successful development and launch of a range of new pen and autoinjector Custom Products for Ypsomed Delivery Systems.

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**NEW**

The single-use, large volume wearable injector.

- Pre-filled and pre-assembled for easy patient training and use
- Attach, inject and dispose for simple and ergonomic handling
- Clearly communicates via audio and visual signals before, during and after injection
- Sterile ready-to-fill cartridge and needle unit for easy drug filling and final assembly
- Unique electromechanical drive system offers flexibility for a range of viscosities and fill volumes



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