2014 TO 2018: AN UPDATE ON THE STATE OF WEARABLE INJECTORS

Looking back on the developments in large volume injectors since his article in ONdrugDelivery's 2014 issue on wearable injectors, Paul Jansen, Professional Engineer, Board Member of both Haselmeier and Subcuject, reflects on the state of this technology space today, how it has progressed and the value it is likely to offer.

Four years ago, I had the privilege of writing the introduction to the first edition of ONdrugDelivery Magazine's "Wearable Injectors" issue. In preparing to write this introduction I went back and reread what I wrote in 2014. While much of it remains relevant and still stands, I did see that several changes have taken place. In this editorial I will share my views on those changes and trends.

It was my belief at the time, and it remains so today, that the adoption of wearable large volume injectors (LVIs) would accelerate in the coming years. What has surprised me, as I look back, is the glacial acceptance of the technology over the past four years. There are more products than ever to evaluate and to consider but relatively few actually approved and in use; a close look at the market shows that there are some approved applications for the delivery of insulin and a couple for biologics. Pharma and biotech companies appear to have maintained their traditional risk-averse stance and seem to be waiting to see large volume delivery become "real" before making their move. It seems that everyone wants to be second.

This is amidst a continued, and growing, requirement for subcutaneous delivery of larger volumes of drug product. Healthcare today is changing rapidly and there are several resulting key trends that are continuing to drive the market opportunities for LVIs. These trends are:

- The continued increase in the development of biologics
- Lifecycle management of older biologics products
- Cost containment pressure
- Reduced frequency of injection
- Data/connectivity being integrated into healthcare.

> "It was my belief at the time, and it remains so today, that the adoption of wearable on-body injectors or large volume injectors would accelerate in the coming years. What has surprised me, as I look back, is the glacial acceptance of the technology over the past four years."

In the past four years the number of injectable drugs approved and in development has grown. The number of products in development is two to three times higher than it was in 2014. There are currently more than 3000 injectable drugs in development. Of those, more than 2000 are biologics. Not only are there more products in development, but the biologics are becoming more complex and are increasing in size as bi-specific antibodies become more prevalent.

Biologics are viscous by their very nature, thus it is generally accepted that concentrating them to more than 150–200 mg/mL is difficult, if not impossible, without causing unwanted drug precipitation. There is also a trend towards fewer injections with weekly, bi-weekly and monthly applications being developed. The resulting math is simple. The required drug cannot be formulated to fit into a 1 mL prefilled syringe, nor into a 2.25 mL prefilled syringe. Furthermore, in those instances where the drug can be formulated into these volumes, it is typically too viscous to inject in a reasonable amount of time and simply will not meet patient usability requirements for the injection in either a safety syringe system or an autoinjector. Thus, LVIs come to the rescue. The 2–3 mL volume continues to be seen as a grey zone, with many companies trying to push the boundaries and find ways with innovative

Paul Jansen
Professional Engineer
T: +1 857 203 1740
E: paulejansen@gmail.com

Haselmeier
Board Member & Senior Advisor

www.haselmeier.com

Subcuject
Board Member

www.subcuject.com

"Companies are working to extend the life of their drug franchises, and as such are looking for new drug delivery systems to provide continued sales to compete with biosimilar products."

formulation solutions to allow them to adopt a prefilled syringe or autoinjector delivery system. However, should they not be successful an LVI can be used to meet the need.

Regardless of the volume, the design challenge for LVIs is making them size appropriate, convenient to wear, simple and intuitive to use and to make them operate free of noise and vibration. The volume ranges that will prevail are still not well defined, however the development pipelines continue to support the idea that a majority will be in the 3–5 mL range. Nonetheless, there are applications being looked at with volumes all the way up to 50 mL. The question I have with these very large volumes is how to attach and wear a 50 mL LVI. We will see how this works out as I am not sure I understand how one designs a system containing 50 mL of drug product that can be attached to the body long enough to deliver the entire volume of drug product. In the end, I foresee the market focusing on the 3–10 mL volume product.

Many very successful biologics have reached, or will soon reach, patent expiry. Companies are working to extend the life of their drug franchises, and as such are looking for new drug delivery systems to provide continued sales to compete with biosimilar products. As these drugs are older, they naturally use older drug delivery systems, developed some years ago. There have been a significant number of technology advancements since these systems were first designed. A wish to use modern technology that can be administered more easily by the patient naturally leads to LVIs. There are many opportunities for different form factors, volumes and improved patient convenience.

There continue to be developments of both prefilled and patient-filled LVI devices. The arguments for both are compelling but I believe that the convenience and safety aspects related to prefilled LVI devices will win out in most cases. There are of course exceptions, as demonstrated by those already approved devices, which are, in several instances, patient-filled devices.

There is a growing push to save cost and move treatment from hospitals and clinics into the home. Patients often travel long distances and spend several hours getting their treatment in a healthcare facility. There is also a burden for the healthcare professionals, who must prepare the medications properly and administer them correctly. Reformulating these intravenous (IV) drugs to be injected subcutaneously allows treatment to move into the home. The result is a lower cost for the healthcare institutions and much more convenience for patients. For example, oncology products, such as Herceptin (trastuzumab), are being reformulated from IV infusion delivery to subcutaneous delivery. These new formulations fit well in the LVI segment, based on their required volumes and delivery time. Patients have responded to this, as one would expect, with a resounding thumbs up.

The addition of digital health technologies and big data analytics will further provide patients, physicians and healthcare companies with the information to fine-tune individual therapies to optimise therapeutic outcomes. Another important benefit of connected devices is the ability to increase patient safety; medical errors are a leading cause of death and having timely data and feedback can help reduce those deaths. In the not too distant future, you can imagine a fully connected healthcare system capturing data that, in collaboration with artificial intelligence (AI) and machine learning, alongside clinical support decision algorithms, will result in improved patient outcomes. Luckily, the required technology can easily be incorporated into LVIs.

However, cost of the LVI devices is still a challenge for adoption in many therapeutic areas. The majority of the LVIs in development are electromechanical (60–70%), although there are new concepts emerging using purely mechanical or other advanced technologies (e.g. chemical, electrochemical) to power the LVI. Current electromechanical systems are quite pricey, so when purely mechanical LVIs, or those made with the other advanced technologies, make it to market they will have a significant cost advantage. Broader adoption of LVIs will require a step reduction in the cost of disposable devices or the use of reusable devices.

I do not believe that there will be widespread conversion to reusable devices given the downsides of more use-steps and increased risk of misuse. Furthermore, in order to really penetrate the market with connected LVIs, the cost of electronics and power will need to come down. I am anticipating that the next generations of sensors will come down in price, industry estimates are that from 2015 to 2020 the cost of sensors will decrease by 50%. Provided this reduction in cost is realised, sensors will become affordable for disposable LVIs and will be designed into the devices. Research is also underway to provide low cost power using technologies outside of batteries. Low power and sensor costs will allow cost competitive designs for disposable LVIs, which will facilitate market utilisation.

An important difference with LVI devices is that delivery is typically not rate dependent. The focus is on accurate delivery of total volume rather than accurate delivery time, the same being true for prefilled syringe and autoinjector systems. The primary packaging for some of these LVI technologies is being developed with novel materials and shapes, which provides significant form-factor flexibility and advantages. The disadvantage is the additional development work required by the pharma or biotech company to qualify these primary packaging containers. While this is a burden, more companies are biting the bullet and moving to rigid polymer containers, as well as flexible bags. This may be driven by the drug properties but, regardless of why it is happening, it is helping to drive further adoption of new primary packaging materials.

Regulatory requirements continue to evolve. The requirement of using "to be marketed" devices for Phase III clinical trials is still murky and not completely clear. The issuance of an ISO standard for LVIs ("on-body wearable injectors" in the ISO world) still appears to be some time away. It has taken longer than anticipated for the ISO experts to gain clarity on requirements. The US FDA has also taken the position in discussions around the ISO standard that LVIs will be subject to infusion pump tests. This means adherence to the infusion pump standard requirements is a must, although an exemption from tests is possible provided an explanation is given. There also continues to be a debate on the need for testing beyond bioequivalence testing when converting an existing drug to an LVI from an already approved drug delivery system. There may be situations where additional

testing is required for a conversion. However when the same formulation is moved from one device to another, the drug company should not require anything more than a bioequivalence test in their submission dossier. Anything beyond this would not add any value.

Most companies are looking for an LVI platform. The use of a platform LVI will reduce costs and reduce time to market. The platform route means that there is a need for only one LVI development, followed by specific and relatively minor variations for each new drug. That said, the platform needs to be flexible enough to meet the needs of the company's portfolio without major changes for each drug. In an attempt to gain a competitive advantage, companies continue to compete aggressively for access to technology that can provide a platform for many of the portfolio drugs that they have. This is not without risk, as there is a significant body of granted IP to be aware of. However, I have been impressed over the past four years with the ingenuity that has been shown in finding new ways to do the same thing. For example, I once thought that there were very few new ways to have a unique automatic needle cannula insertion device, yet I have recently seen several very nice designs. It seems that innovation can still solve any of the IP-related challenges that may come up.

In summary, while much of what I described in my 2014 article still stands (*ONdrugDelivery Magazine* Issue 51, July 2014, available online), and while adoption of LVIs is slower than I had anticipated, much has changed and the future for LVIs looks bright. As you read through all of the articles in this issue I am sure that this is the conclusion that you will also reach.

> "The platform route means that there is a need for only one LVI development, followed by specific and relatively minor variations for each new drug."

ABOUT THE AUTHOR

Paul Jansen is currently a board member and senior adviser with Haselmeier. He also sits on the board of Subcuject. He was formerly associate vice-president, medical device development, Sanofi. Mr Jansen is a professional engineer with more than 30 years of experience in medical devices. He completed his degree in mechanical engineering and has completed graduate work in biomedical engineering at the University of Toronto (Toronto, Canada).

Mr Jansen has extensive experience in the design, development, manufacturing and lifecycle management of medical devices. He has multiple patents to his name and has deep experience in the creation and management of IP portfolios. He has successfully led teams that have developed and launched several devices, including Lantus SoloStar®.