THE NEW EMERGING NEEDS DRIVING AUTOINJECTOR DEVELOPMENT

In this article, Iain Simpson, PhD, Director, Front-End Innovation, Phillips-Medisize, discusses the emerging needs to be considered when bringing new autoinjector drug-device combinations to market.

Although the first autoinjectors entered the market in the 1980s – for the delivery of epinephrine in the treatment of anaphylaxis – 2006 marked the start of a wider use of these devices in the management of chronic diseases, with the approval of three single-use devices in the US: SureClick for Enbrel (etanercept) (Pfizer) and Aranesp (darbepoetin alfa) (Amgen), and the Humira Pen (adalimumab) (Abbvie). Since then, more than 20 autoinjector-drug combinations have entered the market in the US and Europe, with many more in development.

From a patient perspective, the motivation in introducing these devices was to enable safe and effective administration of medication outside the clinic, either by patients or their caregivers. From a commercial perspective, the approach offered pharmaceutical companies an opportunity for product differentiation in competitive markets such as the treatment of autoimmune diseases and the possibility of achieving higher drug sales from improved medication adherence due to the convenience of self-administration.

Early autoinjector launches were for delivered volumes up to 1 mL. However, research suggests a preference by patients for less frequent dosing, which then requires higher doses for the same therapeutic effect. Consequently, autoinjectors that can deliver up to 2.25 mL have been developed and are starting to enter the market.[1]

Reviewing the devices that have been launched onto the market – and the published data relating to their usability[2,3] and user preference[4] – it can be concluded that the dominant design for autoinjectors has become that of a disposable, spring-triggered device, with manual needle insertion and removal, shield triggered activation and passive needle protection. Several commercially available devices conform to this design and are tending to dominate the market. There appears limited scope to further improve the usability and safety of these devices.

Although other devices offer other potential benefits such as automated needle insertion and retraction to improve comfort, the ability to provide higher injection forces to reduce injection time, and trade-offs around cost, size and complexity need to be considered, suggesting these may only address niche applications. In addition, there are some reusable mechanical autoinjectors on the market, which have seen limited uptake apart from in the treatment of multiple sclerosis. Research has shown that some user groups see these devices as easy to use,[5] but require

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more user steps and resetting each time. Potential benefits around reduced cost per injection and the flexibility of being able to use the prefilled syringe (PFS) alone need to be balanced by inferior ease of use and device reliability. Likewise, there are some reusable electronic autoinjectors on the market but their uptake has been limited, presumably due to issues around size and complexity compared with disposable devices, as well as cost.

Rather than considering drug-device combinations on a drug-by-drug basis, companies have started to look at platforms that can support multiple drugs. Although both 1 mL and 2.25 mL PFSs can be delivered using spring-based devices, the latter usually requires a more powerful spring and stronger device body to contain the spring in its compressed state prior to injection. To support this platform approach, mathematical models have been developed[6] to evaluate the trade-offs between spring force, needle size, injection volume and delivery time – and user studies conducted across broad patient populations to confirm platform suitability to different patient groups.[7] But this does not negate the need to change components and, as a result, platforms for 1 mL and 2.25 mL injections have tended to be distinct to allow usability and delivery parameters to be optimised for each case. Consideration has also been given to ensuring differentiation between devices developed from the same platform for different drug products.[8]

AUTOINJECTORS – EMERGING NEEDS

We see several emerging needs that need to be considered when bringing new autoinjector drug-device combinations to market.

Addressing Medication Non-Adherence

Although medication non-adherence has long been recognised as a complex and serious issue in healthcare[9] and a cause of lost revenue for pharma companies,[10] frustratingly little progress has been made in addressing the issue. The introduction of autoinjectors for self-administration improves convenience and allows patients to take better control of their treatment schedule, which should favour adherence.[11] However, treatment at home might adversely impact the training and support patients can get from healthcare professionals (HCPs) in a clinical setting, which could have a negative impact on adherence.

Pharma companies try to address this issue through activities such as patient support programmes, which can be effective,[12] but these are expensive to implement – limiting their applicability in mainstream healthcare. Connected drug delivery devices offer the potential of capturing medication data automatically and using it to support patients directly in medication management or enabling others, such as HCPs, to provide timely, contextual support based on reliable and quantitative data.

Back in 2006, there was little expectation of the rapid increase in smartphone device use and hence little need to consider connectivity for drug delivery devices. Since the launch of the first iPhone in 2007, smartphone penetration has grown rapidly – with estimates suggesting >80% uptake in many countries[13] – and low-power connectivity arrived via Bluetooth Low Energy in 2009. The opportunity to integrate drug delivery devices into digital health systems is now a reality.

Connectivity can be added to existing disposable autoinjectors either by integrating electronics into the device or by developing an add-on module that can be attached to a device prior to injection and then reused with a further device for each injection. Although these avenues are being progressed, they both present some disadvantages. The former raises concerns around environmental sustainability as the integrated electronics will only be used once, and there may only be a short opportunity to access the data after an injection before the device is disposed of. Add-on devices introduce additional user steps to attach the device to a disposable autoinjector before an injection and to remove it afterwards. There are also technical complications around the ability of the add-on device to reliably detect an injection event. Neither of these approaches is therefore optimal in introducing connectivity.

Improving the Ability to Leverage Device Technology Across Multiple Drug Products

As described above, disposable autoinjectors are being developed as platform devices by device companies and their pharma partners. But the need to match spring force to different drug properties and PFS components introduces complexity. A more straightforward means of configuring a platform to new drugs would be desirable.

Environmental Sustainability

Back in 2006, environmental sustainability was not a major area of concern for the pharma industry. The benefits of introducing more self-administration of medication and a focus on ease of use for patients outweighed the negative impact of single-use devices compared with alternatives. And when considering sustainability, the pharma industry had more urgent areas of focus around drug manufacture, such as reducing the use of solvents or eliminating greenhouse gases such as the propellants used in some inhalers.

However, the situation is changing, and many pharma companies assess the impact of drug developments on sustainability. Although the addition of electronics adds to the environmental impact of a device, this can be reduced by recycling and more than offset by

Intelligent, reusable drive unit

- Powerful motor to drive controlled injection of liquid drugs (low and high viscosity)
- Full dose delivery in 10 seconds (adjustable)
- Simple sleeve triggered operation
- Intuitive visual/audible User Interface (GUI screen in Advanced version)
- Rechargeable with three-year service life
- Built-in Bluetooth low energy (BTLE) Connectivity

Single-use disposable cassette

- 1 mL and 2.25 mL prefilled syringes with rigid needle shield (RNS)
- Standard subcutaneous delivery
- Full needle safety before/after injection
- Over 50% less waste and storage space
- Large inspection window
- Optional radio frequency identification (RFID)

Figure 1: Overview of the Phillips-Medisize smart autoinjector.

Smart Autoinjector
Basic device

- Both 1 mL and 2.25 mL staked needle PFS
- Sleeve-triggered, two step
- Manual needle insertion/retraction
- Needle safe, sleeve interlock
- Audio-visual user feedback
- Low-to-high viscosity
- Standard 10-second injection (programmable)
- Emptying (full dose delivered)
- User with moderate-to-severe dexterity impairments
- S3 safety/risk classification
- BTLE connectivity
- Optional RFID cassette reading
- Rechargeable battery, two-three-year life

Smart Autoinjector
Advanced device

- Both 1 mL and 2.25 mL staked needle PFS
- Sleeve-triggered, two step
- Manual needle insertion/retraction
- Needle safe, sleeve interlock
- ***GUI screen and buttons for user guidance and control***
- Low-to-high viscosity
- ***Injection time set/adjusted by user (within predefined limits)***
- ***Potential for partial dosing***
- User with moderate-to-severe dexterity impairments
- S3 safety/risk classification
- BTLE connectivity
- Optional RFID cassette reading
- ***Rechargeable battery, three(+)-year life***

Figure 2: Basic and advanced models of the Philips-Medisize smart autoinjector.

the benefits it brings through improved adherence and a reduction in the need to travel for healthcare consultations or hospitalisation.[14]

A NEW CONNECTED SMART AUTOINJECTOR

With the above points strongly in mind, Phillips-Medisize has been developing a new smart autoinjector that is small, intuitive and easy to use for patients, provides a powerful and flexible platform for pharma companies, reduces the waste generated by disposable devices and is ready for the connected world. As shown in Figure 1, it consists of a single-use disposable cassette that contains the PFS and provides needle safety, and an electronic reusable drive unit that contains all the electronics and a display.

There are two models: basic and advanced (Figure 2). The key differences between then are around user guidance and flexibility of control. The advanced model has a graphical user interface (GUI) to provide more detailed user guidance and feedback, and the ability to incorporate in customer variants controls such as adjustment of speed of injection and the possibility for partial dosing from the PFS.

The current cassette design accommodates ISO standard 1 mL PFSs with small, cut and round flanges as well as the 2.25 mL PFS with small round flanges. A second cassette design can accommodate the other 2.25 mL flange formats, using a slightly larger drive unit. Delivery parameters for a particular drug, volume and syringe format can then be optimised by adjusting the motor control algorithms.

An initial user study (14 participants: six injection naïve and eight experienced autoinjector users) found similar scores for ease of use from experienced participants compared with their existing autoinjector (on a scale of 1-10, 10 being the highest ease of use, they scored 8.6 compared with 8.7 for their existing device). Six of the eight (6/8) experienced users preferred the smart artificial intelligence (AI) device over their existing device and 5/8 wanted a connected smartphone app that would support them with medication management with features such as diaries and reminders. All six naive users thought an app would be useful, with smart reminders and the calendar history view most of interest. All participants were conscious of sustainability and wanted to reduce waste. On a scale of 1-10 (10 being most environmentally sustainable) the average rating for the basic smart AI device was 6.2 compared with 2.0 for their current disposable device.

Market research conducted with most of the top 10 biopharmaceutical companies confirmed a high level of awareness around the need for improved sustainability and connectivity. The research also confirmed the desirability of a platform that could accommodate both 1 mL and 2.25 mL syringes. There was very favourable feedback on the smart AI concepts presented – and recognition that the motor-controlled delivery offers benefits around adaptability, the ability to optimise delivery for higher viscosities and patient comfort. Although there was generally a preference for the basic device, the benefits of a GUI

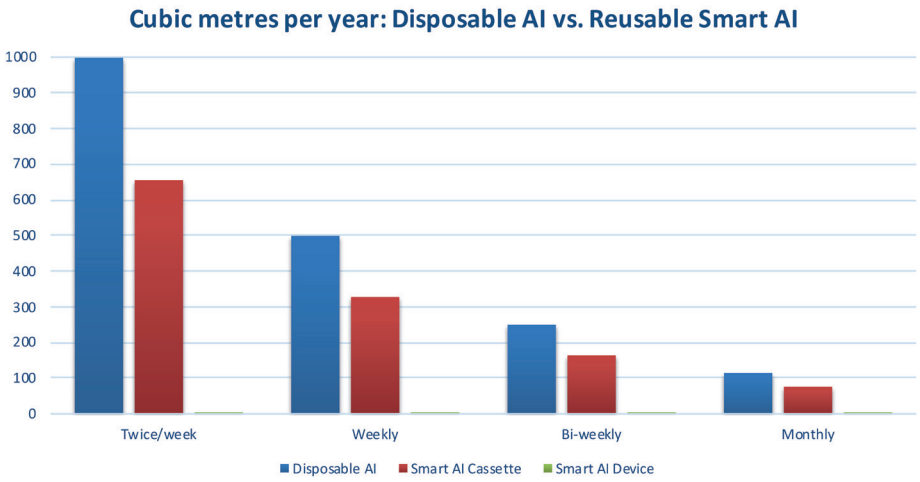

Figure 3: Waste generated by reusable smart AI devices compared with disposable autoinjectors (based on 150,000 patients per year and four years' device usage. Syringe and RNS not included for either device).

to support more complex use cases, such as a single dose involving multiple injections, was recognised.

Initial assessment of the environmental sustainability of smart autoinjectors compared with other autoinjectors has shown significant benefits when it comes to the impact of storage and shipping volume, and product waste on disposal. A full lifecycle assessment[15] – considering materials of construction, manufacture, distribution storage, use and disposal – is being developed. Figure 3 shows some early results on the wastage created by the smart autoinjector compared with disposable devices for a cohort of 150,000 patients over four years.

CONCLUSION

The current prevalence of single-use mechanical disposable devices has been built upon the need to address ease of use, convenience and safety of injection drug administration outside the clinic. Looking to the future, these needs will continue to be important in device development and selection. But they are becoming "hygiene factors" required by any self-injection device in the market and no longer differentiators that can create a source of competitive advantage for drug companies. Fortunately, new emerging needs create an opportunity to improve patient engagement in the management of disease in a more environmentally sustainable and cost-effective way that, in turn, creates new opportunities for competitive advantage for pharma companies willing to take on this challenge – as was the case back in the early 2000s when pioneering companies started to launch the current wave of disposable mechanical devices.

In conclusion, we believe that the requirements of new autoinjectors entering the market in the next 20 years will be based on four key aspects or "pillars":

1. Safety, convenience and ease of use, aligned with that already experienced with single-use disposable devices
2. The ability to configure device technology as a platform for use across multiple drugs and therapeutic areas with minimal redesign
3. Improved environmental sustainability
4. The use of connectivity to digitise medication events and provide additional off-device services that can improve patient engagement, monitoring and the gathering of more reliable real-word data around medication use.

In addressing the first of these pillars, it appears difficult to improve on existing disposable mechanical autoinjectors, although there are opportunities to make improvements in some areas – such as providing better feedback and reducing the force required to actuate the device and keep it in contact with the skin during injection. However, the development of reusable, electronic, connected devices offers distinct advantages when addressing the other three pillars. The main challenge in adopting this approach is then to ensure these new designs do not fall short in satisfying the first pillar.

Based on our experience in developing electronic autoinjectors over 10 or more years – and early market and user feedback on our new smart autoinjector platform – we are confident that we can address all four pillars and continue to play a leading role in supporting the self-injection market over the next 20 years.

ABOUT THE COMPANY

Phillips-Medisize is a provider of outsourced design, development and technology-driven manufacturing, with a primary focus in the medical device and diagnostics, drug delivery, primary pharmaceutical packaging and commercial markets. Phillips-Medisize operates on a partnering business model, and works with pharmaceutical, biopharmaceutical, consumable diagnostic and medical device companies with the purpose of increasing speed to market. It was the first company to deliver a US FDA-approved connected health system, consisting of a drug, delivery device and regulated digital service, to the market.

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Iain Simpson, PhD, is a Director of Front-End Innovation at Phillips-Medisize. He is part of a global team of engineers, designers, researchers and business analysts developing industry leading solutions for drug delivery, digital medicine and Connected Health systems. Dr Simpson has more than 25 years of experience in multi-disciplinary technology and product development including business development, project management and technology assessment in US and European markets, the last 15 years of which has been gained in the life sciences sector both in consultancy and industry, and with an increasing emphasis on the use of devices and digital technologies to create product differentiation, improve patient engagement and better measure clinical outcomes in real world settings. He has a degree in physics, a PhD in experimental solid-state physics both from UCL (London, UK) and also an MBE in Technology Management from the Open University (UK). He has published several papers, chaired sessions and presented at international conferences on drug delivery, digital biomarkers, healthcare technology and technology licensing.

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