MEDICAL TECHNOLOGIES

An SMC Ltd. Company

# USING POLYMERIC PDC TECHNOLOGY TO IMPROVE AUTO-INJECTOR DESIGN

**The limitations of using glass-based auto-injectors, such as contamination, and the need for delivering complex, viscous preparations, have led to a new approach that uses polymeric PDC technology instead. Jonathan Lawson, MSc, Senior Design Engineer, Jonathan Bradshaw, MSc, Device Development Engineer and Susie White, MEng, Mechanical Engineer, all of Oval Medical Technologies, look at what polymeric PDCs can offer in making auto-injectors truly patient-centric.**

Over the past 20 years, there has been a shift in pharmaceutical pipelines towards the development of biologics, which now make up around 70% of drugs currently in development.[1] However, although biologics offer better efficacy and safety, the glass-based auto-injector technology used to deliver these drugs has not significantly evolved since the 1950s.

Subcutaneous injection is the preferred route of administration for biologic drug delivery and so, with the need to reduce costs, auto-injectors have become increasingly important. Currently, single-use auto-injectors typically comprise a prefilled glass syringe, an injection mechanism for delivery of the drug and a needle safety mechanism for disposal of the device.

"Polymeric PDC technology offers a new approach that can resolve many known issues with glass, whilst unlocking opportunities for the delivery of biologies."

There are some advantages to using glass syringes as the primary drug container (PDC) within an auto-injector, including:

- Proven history of drug compatibility
- Regulatory acceptance
- Market familiarity
- Established manufacturing and filling processes.

However, there are known issues with glass syringes, some of which have led to auto-injector recalls:

- Lubricants risk contamination
- Tungsten contamination from glass
- Plunger stiction leading to delivery inconsistency, which can result in wet injections
- Risk of glass breakage
- Formulation viscosity and volume limitations
- Large manufacturing tolerances
- Complex supply chains reliant on specialist suppliers.

The most recent advances in biologics are now presenting new challenges to the design of delivery platforms. Innovative products such as long-acting injectables (LAIs) are being developed to provide slow-release capabilities. LAIs, as with other

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biologics, have a viscous formulation and complex fluid properties (e.g. suspensions and emulsions with non-Newtonian properties). The challenge is then to balance complex drug characteristics with delivered volume, whilst still ensuring a patient-centric approach. It is these requirements that are pushing the limits of current glass-based technology.

Polymeric PDC technology offers a new approach that can resolve many known issues with glass, whilst unlocking opportunities for the delivery of biologics. It is this approach to auto-injector design that allows Oval Medical to support a user-centric approach, unimpeded by the performance, integration capabilities and the limited design freedoms of a glass-based alternative.

## A USER-CENTRIC APPROACH

A user-centric approach to the medical device development process is key in ensuring the design of devices which promote safe, correct and effective use. The inclusion of human factors engineering from the outset of the development process allows for an understanding of user-group needs, their anticipated limitations and the environment in which the device will be used. Ultimately, the knowledge space that human factors engineering generates enables the minimisation of usage related risks, and avoids inadequate device design which could compromise the effectiveness of the device's user interface.

The differences between user populations can be vast. For example, patients with migraine may experience aura, causing visual impairment which hinders their ability to identify device features or text. Alternatively, patients suffering from anaphylaxis may require administration from a user with good vision, but who are naïve with respect to auto-injector use. These examples demonstrate that to create a well considered and intuitive device, it is essential to appreciate the various user-group dynamics and integrate them effectively into the design.

A truly user-centric approach must involve consideration of the device interface design. The constraints presented by glass PDC technology can limit the ability of a design to meet all the functionality requirements, which can compromise the user interface. Frequently, the use of a glass PDC leads to compromises in device size, form and/or simplified use steps, preventing a device from fully meeting the needs of its users.

Polymeric PDC technology (Figure 1) bypasses the constraints of glass-based PDC systems by facilitating an integrated approach to device design. Whilst the auto-injector industry has been limited by its reliance on glass-based technologies, polymeric PDCs allow design freedoms traditionally unattainable in many areas, e.g. within user interface design. The result is that a user interface can be fully tuned to the requirements of a wide range of user populations without the burden of potential glass breakage, dimensional variability and other known issues associated with glass.

Use of polymers provides increased geometric options combined with improved tolerance management unavailable with glass. The benefits of using polymer include:

- Delivery speed consistency, preventing wet injections even when injecting challenging formulations, e.g. non-Newtonian fluids
- Shorter injection times for viscous formulations, without the risk of glass breakage
- Needle depth consistency, reducing the risk of adverse events
- Improved user experience through smaller gauge needles.

PDC components can be moulded with features that directly interact with device mechanisms which can overcome issues such as device recoil, variable use forces and injection speed. Ultimately, this reduces the impact on the user, whilst ensuring all required user interface features are present without compromising overall device size or usability. Approaches to solving common user interface pitfalls through high risk, needleless systems or "power source" innovations can detract from fully user-centric devices. These pitfalls could be better avoided through the increased design freedoms offered by a polymeric PDC. This allows engineers the freedom to "design out" user interface weaknesses typically observed with glass-based PDC auto-injectors.

During the development of a combination device, two main streams of development occur; 1) the drug, and 2) the delivery device. It is imperative that any device development process places equal importance on the delivery requirements of the drug, as well as the requirements of the user interface.

For optimal device design and performance, the user interface should not be influenced by the forces required to deliver the drug and, similarly, the drug delivery mechanism should not be

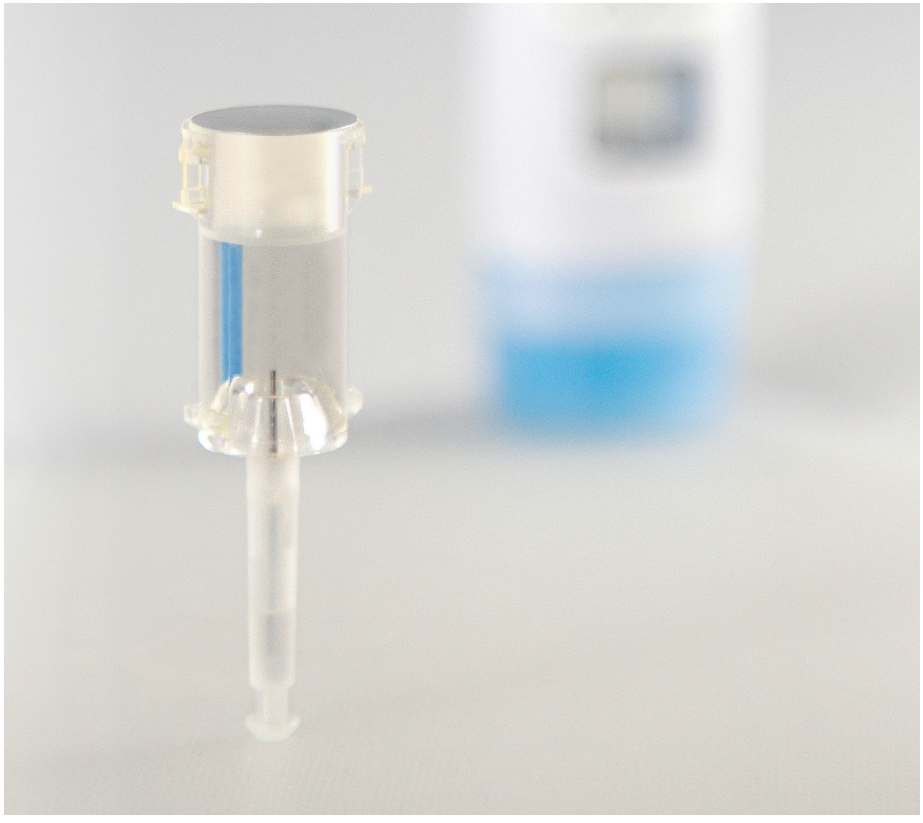

Figure 1: Oval's polymeric PDC technology.

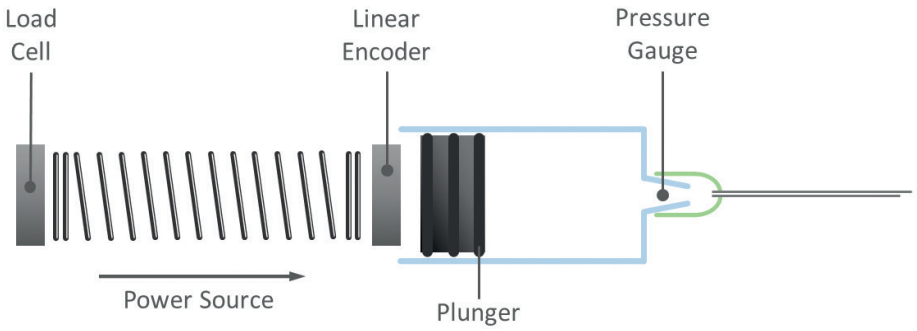


Figure 2: ICS Schematic.

influenced by any force applied through the user interface. However, in practice these forces often conflict: biologics may require high delivery forces, whereas specific user populations may require low operation forces from the user interface. Part of the challenge for engineers is to accept this conflict and design around it effectively.

It is possible to "decouple" the conflicting requirements between the user interface and drug delivery mechanism through use of a polymer PDC. To do this effectively, it is imperative that both the needs of the user and the delivery requirements of the drug are fully understood at an early stage in the design process.

## AN APPROACH TO COMPLEX FORMULATIONS

The characterisation of a drug is an important step towards designing a fully integrated device. Oval has developed an Injection Characterisation System (ICS) to thoroughly analyse a range of complex formulations and their properties, allowing an improved understanding of how they must be delivered. This knowledge facilitates designing the optimal auto-injector mechanism specification (e.g. needle bore, spring force and container type), and also identifies factors with the potential to affect the user.

The ICS includes sensing capabilities at key positions (Figure 2) to allow feedback on forces and pressures within an auto-injector system during drug delivery:

- A load cell reports on the amount of force produced by the chosen power source
- The pressure gauge detects the pressure within the drug container
- The linear encoder provides data on the location of the plunger which can then be extrapolated into delivery speed.

Figure 3 shows the outputs of these sensors which can then be used to inform the design of the delivery system. Observing the relationship between the internal pressure, $P$, and the speed of the plunger during delivery, $v$, reveals information about the formulation properties. By using the modified form of the Hagen-Poiseuille equation,[2] the viscosity of any formulation can be evaluated:

$$P = \frac{8L\mu Av}{\pi r^4}$$

$L$ – Needle length
$\mu$ – Viscosity
$A$ – Plunger surface area
$r$ – Internal needle radius

Testing the same formulation under different conditions (e.g. speed, needle gauge and temperature) allows for full characterisation of drug viscosity and the uniformity between conditions.

Many simple drug formulations are Newtonian (their viscosity will not change with shear force), however, complex formulations are becoming more common. These formulations may take the form of suspensions, emulsions or highly viscous fluids, often displaying many non-Newtonian characteristics, such as:

- shear thinning
- shear-thickening
- pseudo-plastic behaviour.

Comparison between the viscosity of the formulation and other characteristics will reveal any non-Newtonian behaviour, allowing it to then be modelled accurately.

The power law equation is the most common function used to model non-Newtonian fluids. It is assumed that rather than a direct correlation between shear stress, $\tau$, and shear rate, $\dot{\gamma}$, as in a Newtonian fluid, the shear stress is proportional to a power of the shear rate.[3]

| | |
|---|---|
| Newtonian fluid | $\tau=\mu\dot{\gamma}$ |
| Non-Newtonian fluid | $\tau=K\dot{\gamma}^n$ |

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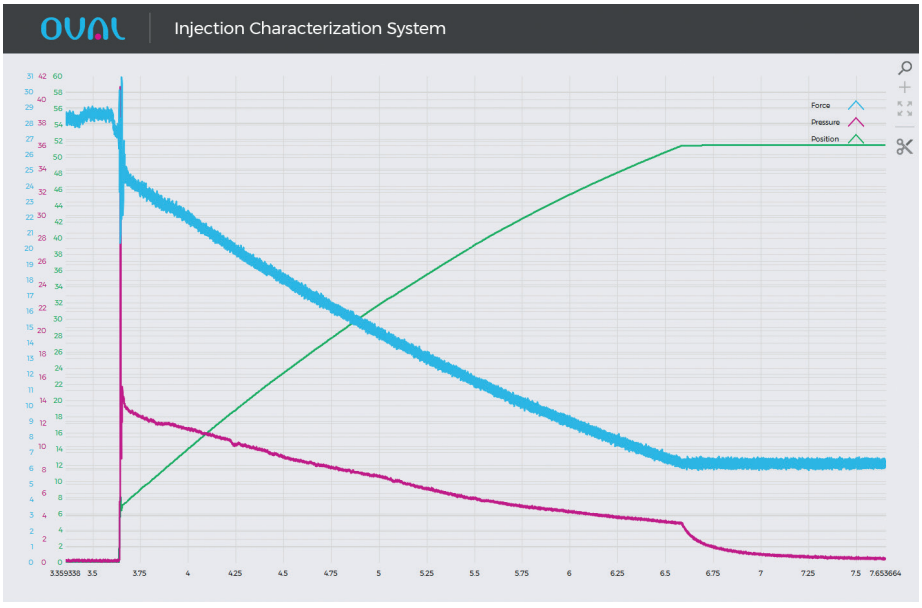


Figure 3: Output plots from the ICS during an injection. Plunger position in mm (green), delivery force in N (blue) and container pressure in bar (pink) against time in seconds.

Characterising formulations is a vital step towards developing an accurate numerical model for the behaviour of an auto-injector. It allows prediction of both delivery characteristics and the potential effects of external factors such as environmental conditions and device tolerances.

The culmination of this characterisation process is that the delivery mechanism can be optimised for each formulation through the appropriate specification of required functions and components, such as needle gauge and length, container dimensions and power source. Extensive knowledge of the drug delivery requirements allows for this aspect of the device to be decoupled from that of the user interface. This results in a fully integrated solution which has been developed with consideration to both the user and drug requirements, offering reduced risk, quicker development times and a competitive advantage over glass-based systems.

## COMBINING USER AND DRUG REQUIREMENTS

Oval's subcutaneous platform embodies this integrated philosophy to device design (Figure 4). Combining both user and drug requirements into its development, the platform provides a patient-centric device for delivery of Sumatriptan to migraine and cluster headache sufferers.

The cyclic olefin PDC provides the option to configure component geometry freely, whilst "designing in" strength to manage high viscosities (>100 cP). This permits the delivery of complex drug formulations alongside the inclusion of a full range of features (e.g. automatic needle insertion, end of delivery feedback and passive needle safety), within a simplified and compact form. The subcutaneous auto-injector platform actively decouples the drug delivery requirements from those of the user interface. The use of separate springs for needle insertion and for drug delivery reduces the risk of recoil and excessive force on the patient, whilst retaining the ability to deliver challenging formulations.


Figure 4: Sumalen Ovali, 6 mg/0.5 mL Sumatriptan single use auto-injector for the treatment of migraines and cluster headaches.

This integrated approach is intended to improve clinical outcomes through the greater management of key device aspects, such as needle depth. Oval has taken three steps to ensure that the Sumalen Ovali delivers into the correct tissue (i.e. subcutaneous):

- **Specify an appropriate needle depth:** Informed by "state of the art" population research (e.g. ultrasound studies), correct inserted needle depth is essential to avoid compromising drug pharmacokinetics.
- **Manufacture with controlled tolerances:** Enabled through the use of a moulded polymeric container which ensures needle depth and mechanism interface accuracy.
- **Reduce injection depth variability:** The device is designed to promote consistent tissue compression during use, reducing needle depth variation from user technique differences or high activation force requirements.

Overlaying the needle length for 30 Sumalen Ovali devices (pink) with the results of 30 established Sumatriptan reference products (grey), Figure 5 demonstrates the impact of needle depth on the risk of an intramuscular injection at the thigh. The tissue depth risk profile is derived from two ultrasound studies of the thigh in >400 adult subjects.[4,5]

In summary, the needle length of the Sumalen Ovali is better specified for the population, achieving tighter manufacturing tolerances than the glass-based reference products ($\sigma$ = 0.09 mm versus 0.20 mm). Tissue compression has the potential to further increase the risk of intramuscular (IM) injection. It should be noted that the IM risk estimates may be conservative, particularly for the reference product that incorporated a secondary activation button.

Oval's integrated device design philosophy has ensured that the subcutaneous platform has overcome many inherent issues seen in existing glass-based systems. Combined with their drug characterisation and user research capabilities, Oval is paving the way towards greater compatibility between auto-injectors and the delivery of biologics.

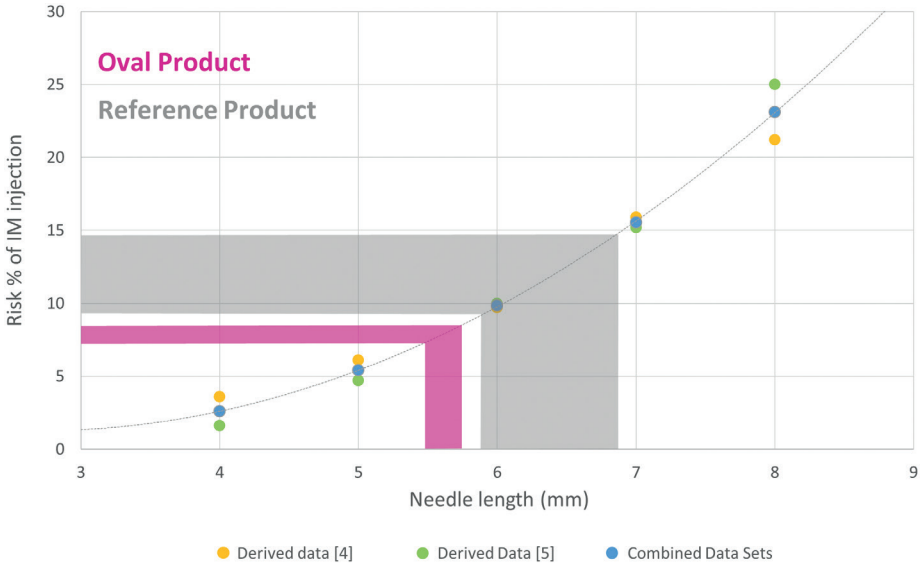


Figure 5: Injection depth versus risk of intramuscular injection at the anterolateral thigh.

## ABOUT THE COMPANY

Oval Medical technologies was founded in 2010 by Matthew Young for the development of new generation auto-injector platforms, intended to meet the needs of patients. Matthew had previously worked for a leading medical device design consultancy, as Head of Product Design. In this role he worked on eight auto-injector projects for pharmaceutical companies to resolve design issues that impacted product performance and patient safety.

While working on these projects Mr Young concluded that glass syringes – which were designed in the 1950s for use by a human hand – did not provide a good starting point for auto-injector design. He considered that, in order to design devices that are intuitive to use whilst giving optimal performance, including consistent delivery times, a new design of primary drug container would be required.

Oval was therefore set up to design auto-injectors that meet the needs of patients and a broad range of drugs, including biologics. Current Pharma pipelines include formulations that pose a number of challenges, including those that are fragile and easily degraded, viscous formulations (some of which exhibit non-Newtonian characteristics) and, increasingly, delivery volumes of up to 3 mL. Owning the primary drug container allows integrated devices to be designed. This design freedom enables novel mechanisms to be introduced, smaller devices to be developed and the use of polymeric materials, giving customers complete control over critical component tolerances and control over their supply chain.

The acquisition of Oval by SMC Ltd, a US-based medical device manufacturing company in 2016, has provided access to world-class device manufacturing capabilities in multiple locations in the US and India. Oval/SMC can now provide customers with a complete service, from customisation of subcutaneous and intramuscular platforms, to production of clinical trials devices and commercial scale manufacture. SMC can also offer integration of filled primary drug containers with secondary packaging and distribution if required.

## ABOUT THE AUTHORS

**Jonathan Bradshaw** is a Design Engineer with a background in industrial design and a Masters in Medical Device Engineering. Jonathan has experience in the design, development and commercialisation of fluidic dilution and dosing systems, cardiac catheterisation devices and more recently drug delivery technologies. Currently Jonathan works as a Device Development Engineer within Oval Medical Technologies where he focuses on furthering the development of their novel PDC and auto-injector technology to ensure their devices offer reliability and consistently high performance in combination with usability benefits.

**Jonathan Lawson** is a Design Engineer with 15 years' experience of the medical device industry, including the last five years working within the pharmaceutical industry on auto-injector technologies. Jonathan has developed an expert understanding of the medical device design process and has managed and delivered a range of novel development projects from artificial implants and surgical instrumentation through to drug delivery technology. Jonathan currently works within Oval Medical Technologies where his experience is helping to unlock the potential of their novel PDC technology through improved auto-injector designs. Specifically, Jonathan manages the corresponding design, test and risk management programme to ensure devices offer reliability and consistently high performance whilst introducing usability benefits.

**Susanna White** has worked as a Mechanical Engineer at Oval Medical Technologies for the past five years, where she is involved in the design and test programmes for their innovative polymeric PDC. Much of her work has focused on the study of highly viscous and non-Newtonian drug formulations – using numerical modelling techniques in combination with experimental investigation in order to achieve the most appropriate delivery system for challenging formulations. Susanna graduated from the University of Cambridge with a Masters in Engineering for the Life Sciences.

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