Battelle
The Business of Innovation

DECREASING RISK THROUGH TRUE INNOVATION: CROSS-DISCIPLINARY SOLUTIONS FOR DIFFICULT CHALLENGES IN DRUG DELIVERY

With protein-device combination products coming through development in increasing numbers, Battelle has developed a cross-disciplinary approach for de-risking device innovation, and overcoming the challenges for delivering viscous formulations. Here, Amy Heintz, PhD, Senior Research Scientist, and Reade Harpham, Manager of Human Centric Design, both of Battelle, provide examples of how this approach delivers results and can save pharma and biotech companies time and money. Battelle's emphasis on innovative device development, as exemplified by its alliance with Zogenix for the development of DosePro, is also highlighted here.

The lack of novel technologies in the delivery of highly viscous biologics and the costly development of new devices is stifling innovation in the drug delivery industry. The inevitable evolution of biologics, the high cost of device development and the fear of patient and physician rejection create risks that are inhibiting innovation by pharmaceutical and device companies. In today's cautious economic climate, pharmaceutical and medical device companies are leery of investing too much time and money in a product that requires a robust and costly development process if the outcome is unpredictable.

At Battelle, de-risking innovation through a controlled process that incorporates a cross-disciplinary approach to drug delivery enhances development and can potentially save pharmaceutical companies significant time and money.

PROTEIN-DEVICE COMBINATIONS & HEALTHCARE'S CHANGING NEEDS

While the 1980s and 1990s was the era of the small-molecule, blockbuster drug, we are now entering the era of the protein-device combination product. Therapeutic proteins can be designed with specificity that allows unprecedented ability to target disease mechanisms with fewer side effects. Furthermore, the complex and unique structure of proteins enables a broad range of patent protection.

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Biologics are predicted to generate 60% of biopharma growth this decade. There are more than 100 therapeutic proteins available for the treatment of diseases such as auto-immune disorders, cancer, infertility and osteoporosis. Of all the biologics, monoclonal antibodies are predicted to show the most growth.

Because of their large size and limited stability, proteins cannot be readily delivered by oral or transdermal delivery. Biologics are delivered by drug-device combinations like infusion pumps, injectors or syringes.

For patients suffering from chronic diseases that require regular treatment, the trend

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is towards self-administration. This trend is driven by patient preference, as well as reduction of costs associated with visits to healthcare facilities. Commercial injection devices are on the market for the treatment of diseases such as rheumatoid arthritis (RA), multiple sclerosis (MS) and Crohn's disease.

The spectrum of delivery devices for proteins spans from short to long delivery time and from small to large volume. Standard devices include syringes, pen injectors, auto-injectors and infusion pumps. Emerging devices such as patch pumps and needle-free injectors enable self-administration of high-dosage formulations that cannot easily be met with auto-injectors. Some of the key performance indicators for selection of an appropriate device include dose volume, drug viscosity, delivery time, injection site, injection depth, target population requirements and product cost target. In addition, the device cannot introduce any instability issues. For example, silicone and tungsten have been linked to protein aggregation.

The development of protein injection devices poses significant challenges – both technical and regulatory. Per ISO 62366, the US FDA now requires the application of usability engineering to medical devices. Pharmaceutical companies once focused only on obtaining clinical approval for a drug. Now, they are also responsible for minimizing the device's risk in regard to potential misuse, including documentation of the severity of failure and a focus on the users' perception, cognition and ability.

A SMARTER APPROACH – HUMAN CENTRIC DESIGN

In addition to integrated science, technology and engineering innovation, Battelle's Human Centric Design service features formative and summative usability studies that have determined the most common use errors for highly viscous therapies delivered via auto-injectors. These include inversion of the device, improper angle of insertion and incomplete dose due to failure to hold for the required amount of time. Compounding the issue, many of the patients suffering from chronic illnesses have impaired ability that creates unique usability challenges. While we know that physical strength increases during childhood and adolescence, it remains relatively constant over adulthood and then decreases with age.

However, the manner in which the behaviour changes for disabled or diseased populations is not well-characterised. We find that some diseases cause a general weakening, while others such as RA, make specific body movements, like pinching or twisting, more difficult. The limited strength and dexterity can cause significant user-related risks for injection devices. These issues must be addressed at the beginning of development activities in order to provide patients with safe and effective therapy.

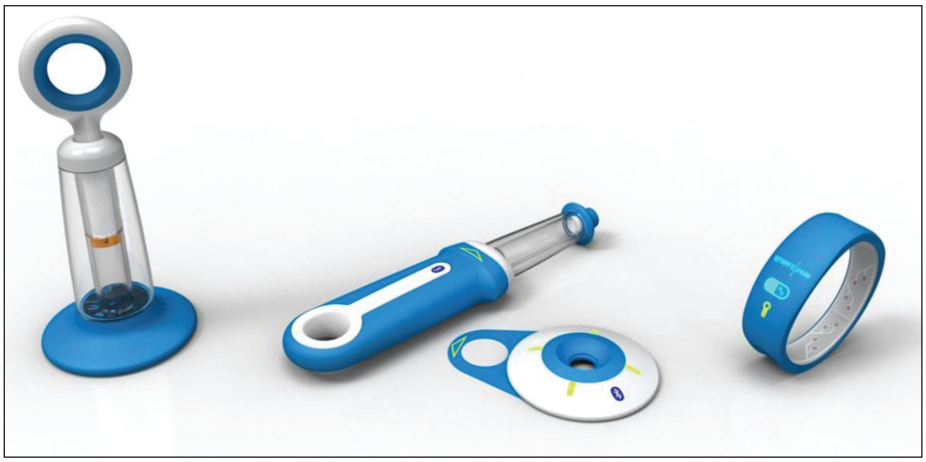

Figure 1: Syringe device enhancement that addresses stability and device feedback requirements.

Proper device design begins by integrating traceability to user needs at concept inception. Understanding the user population's unique characteristics is elemental to our design philosophy. This human centric design philosophy greatly accelerates the time it takes to bring safe and effective devices to market.

Therefore, Battelle is developing low-risk user interfaces for patients with RA and MS. The initial research phase used contextual research to understand user perception, cognition and abilities. Observation of patients performing hands-on activities provided an opportunity to understand participants' hand and finger capabilities and limitations. In addition, social media outlets including online patient forums and communities were leveraged to provide large amounts of information not only about specific issues or problems people encounter, but also potential aids and solutions as they share their experiences managing their health. The contextual research leads to the definition of high-level requirements in which traceability is integrated prior to design controls.

For example, patients with RA have physical limitations that require a device to maintain stability during injections. Cognition risks related to inadequate device feedback point to the need to gather obvious and accessible device feedback.

Quantitative anthropometric data can also be useful, but is not readily available for motions encountered in medical-device use such as auto-injectors or syringes for healthy adult populations or users with limited strength. To meet this need, Battelle has designed and built a set of ergonomic test fixtures to collect force and torque data for 20 different movements related to medical device use. This data can be used to develop appropriate and detailed design guidelines. While these design guidelines do not eliminate the need for formative user testing, they can provide early-stage recommendations for device use by intended users with physical limitations.

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The results of our research have led to product concepts that are now being tested in formative usability studies. For example, a simple device enhancement for a syringe (see Figure 1) addresses stability and device feedback requirements by including a wide base for stability and a plunger ring that provides obvious tactile and visual status indication. Formative testing of this concept and others will provide iterative testing to reduce risk and document mitigation strategies.

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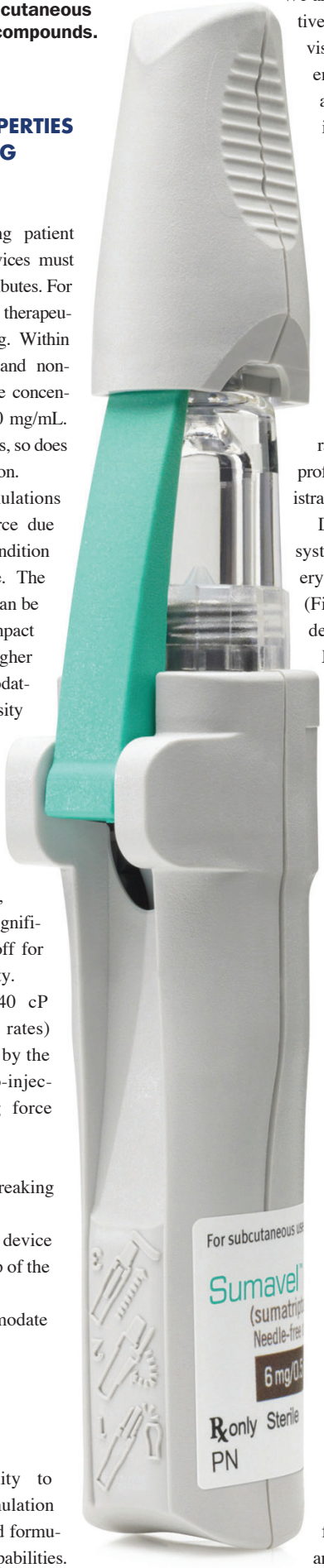
Figure 2: The DosePro™, Zogenix' novel injection system for subcutaneous delivery of therapeutic compounds.



FORMULATION PROPERTIES IMPOSE CONFLICTING DEMANDS

In addition to satisfying patient attributes, drug delivery devices must comply with formulation attributes. For instance, dosages for protein therapeutics range from 40-1000 mg. Within the limit of stable, active and non-aggregating formulations, the concentration can vary from 10-300 mg/mL. As the concentration increases, so does the viscosity of the formulation.

Higher viscosity formulations require higher injection force due to the no-slip boundary condition at the walls of the needle. The Hagen–Poiseuille equation can be used to approximate the impact of viscosity on injectors. Higher viscosity can be accommodated within a limited viscosity range by increasing the diameter of the needle or increasing the injection time. However, we find that these modifications generally oppose patient needs. For example, long injection times pose significant risk of premature lift-off for patients with limited dexterity.

Viscosities above 20-40 cP (measured at high shear rates) become difficult to deliver by the typical spring driven auto-injector. Increasing the spring force also increases:

- The risk of the syringe breaking during impact
- The risk of damage to the device during storage due to creep of the plastic parts
- The device size to accommodate the larger spring

A NEW WAY OF THINKING

Battelle has the ability to address design and formulation issues through our integrated formulation and engineering capabilities. We are actively researching alternative approaches to deliver high-viscosity formulations, including emerging devices, modifying auto-injector design and creating new formulations.

One solution to the challenges of drug delivery lies in emerging device technology. Delivery time increases with increasing viscosity due to viscous dissipation in the needle. Viscous dissipation can be substantially reduced by injection through an orifice rather than injection through a needle, using a rapid biphasic delivery pressure profile to achieve selective administration to subcutaneous tissue.

DosePro™ is a novel injection system for subcutaneous delivery of therapeutic compounds (Figure 2). The product was developed by Zogenix (San Diego, CA, US), and Battelle is seeking opportunities to advance the technology for the delivery of multiple biologics. In vitro studies have demonstrated DosePro's potential to deliver highly viscous formulations up to 2000 cP through an orifice in the device rather than a standard needle. In addition, the device provides almost instantaneous injection – less than 100 milliseconds – which may minimise premature injection for patients with limited dexterity (Figure 3). The DosePro™ is available as a 0.5 mL, and Battelle is seeking partners to design a 1.2-mL device that utilises standard filling.

Battelle's wide range of R&D capabilities in multiple industries also impacts the way we think about medical device development. For example, our experience in the oil and gas industry has inspired us to explore modifications to auto-injectors that enable delivery of viscous formulations by leveraging an approach frequently used to transport highly viscous oils through pipelines. By eliminating the no-slip boundary condition, the force can be substantially reduced. The approach is called core annular flow, in which a low-viscosity annulus, such as the formulation buffer, is used to lubricate a high-viscosity core, the protein formulation. A pressure reduction of 2- to 10-fold can be achieved with a protein core and buffer annulus depending on the fraction of annular fluid introduced and the viscosity ratio of the core/annulus. Device design incorporating core annular flow is in the early stages of development, and an early product concept and benchtop model is available.

Changes to formulation can also enable injection of viscous formulations. Suspension-based formulations are known to provide reduced viscosity relative to solution-based formulations of equivalent protein concentration. In a suspension, the protein particles are suspended in a non-solvent. This approach has been shown to work for crystalline monoclonal antibodies and milled proteins.

However, few processes exist that can be used to efficiently prepare protein suspensions with the appropriate particle characteristics, high activity and bioavailability. Battelle has developed an approach that generates highly active, dense, spheroid protein microparticles and differs from traditional protein microparticle preparations that inherently exhibit significant losses in biological activity from thermal, interfacial and shear stresses. In model proteins, 95% active protein was recovered. This approach should be useful for creating high-concentration suspensions suitable for use with auto-injectors.

SKIN CHARACTERISTICS

Finally, in addition to usability and formulation concerns, the skin characteristics of the patient population must also be considered. Effective delivery depends on the release of the drug to the proper tissue depth. During injection, the skin deflects (or "trampolines") as the needle enters, changing the depth of penetration. Traditional needle-syringe injection devices rely on the patient or caregiver to compensate by pushing the needle further into the skin.

By the nature of their design, auto-injectors remove the user from controlling the needle insertion depth. Skin trampolining can prevent the needle from reaching the intended depth, especially in patients with lax skin.

Battelle has created a Finite Element model to evaluate the effects of injection parameters and tissue characteristics on the amount of skin deflection during needle penetration. Ultimately, use of this model, combined with measurements from human subjects, will allow

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device developers to evaluate the ability of an autoinjector to reach the proper delivery depth for the intended patient population earlier in the device development cycle.

CONCLUSION

Transitioning protein formulations to injection devices requires the addressing of challenges associated with delivering high concentrations of sensitive, high-molecular-weight molecules in a manner that is easy, reliable and acceptable to the patient. Integrating traceability to user requirements at the inception of research is critical to designing marketable devices, particularly devices for use outside clinical settings.

The delivery of viscous protein formulations is a critical challenge. Battelle is taking a systems approach to addressing this challenge with a cross-disciplinary process that creates innovation from the intersection of our specialised science, engineering and technology capabilities. The collaboration of device design, formulation and usability considerations into our development process makes Battelle a unique partner in translating technology from the concept stage to commercial product and fulfills the distinct, dynamic and vital needs of the drug delivery market.

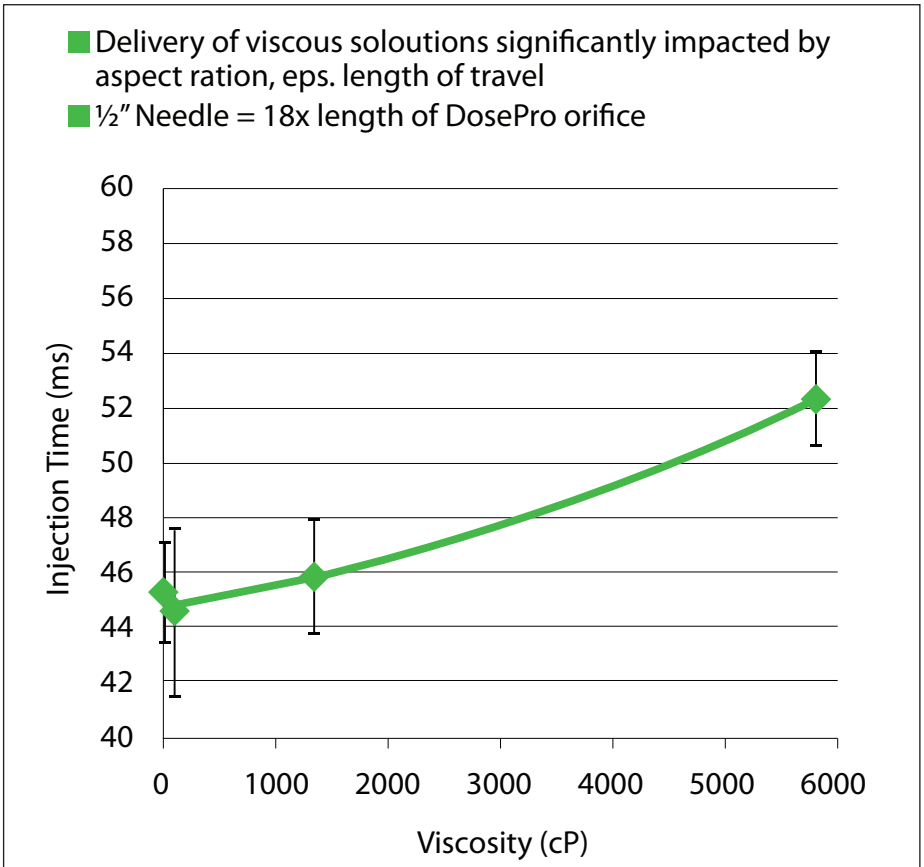

Figure 3: Rapid delivery of viscous formulation by DosePro™.

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