# INJECTABLE DELIVERY: DEVICES FOCUS

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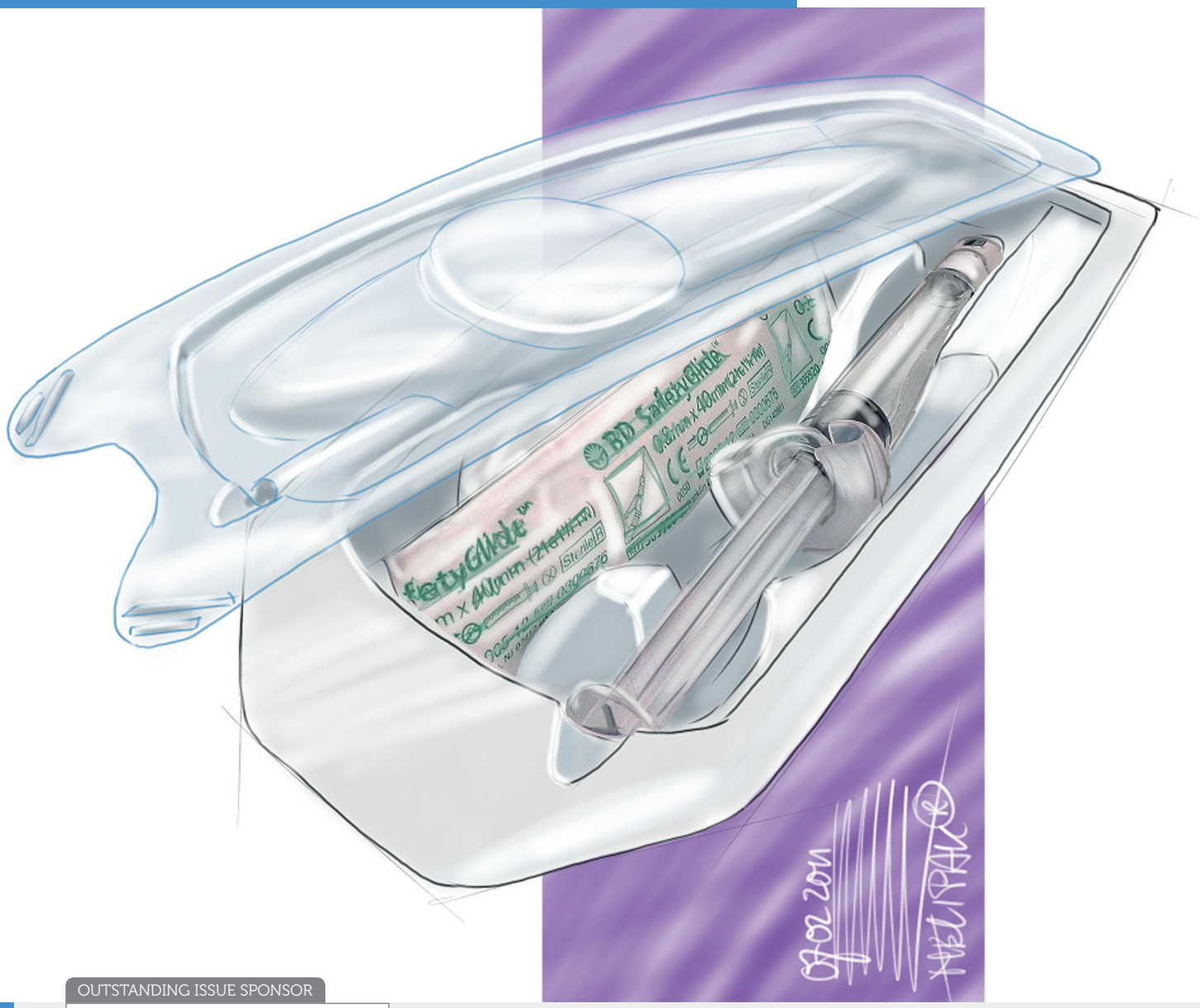

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## INJECTABLE DELIVERY: DEVICES FOCUS

This edition is one in the ONdrugDelivery series of publications from Frederick Furness Publishing. Each issue focuses on a specific topic within the field of drug delivery, and is supported by industry leaders in that field.

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Frederick Furness Publishing Ltd
The Candlemakers, West Street, Lewes,
East Sussex, BN7 2NZ, United Kingdom

ONdrugDelivery Magazine is published by Frederick Furness Publishing Ltd. Registered Office: The Candlemakers, West Street, Lewes, East Sussex, BN7 2NZ, United Kingdom.

Registered in England: No 8348388.
VAT Registration No: GB 153 0432 49.
ISSN 2049-145X print
ISSN 2049-1468 pdf



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# EMBRACING THE FUTURE: CONNECTED DRUG DELIVERY SOLUTIONS

SHL Group explore the opportunities that the advance of digital health can bring to pharma companies, using a connected device solution, which includes autoinjector Molly® C and the Recording Unit (RU), to illustrate how connectivity can improve adherence to medication, and ensure patients' lifestyle and quality of life is improved.

To be at the forefront of the healthcare industry, pharmaceutical, biotech, medical and manufacturing companies must take into account existing trends and needs. However, they must also be able to look into the future and anticipate the factors likely to change healthcare.

> "Importantly, connected delivery devices support adherence to medication. The growing prevalence of chronic diseases means that more people need to receive their medication on a regular basis."

One such factor is the advance of digital health. The use of wearable sensors, mHealth applications, telehealth, big data and other digital technologies will become even more widespread in the not-too-distant future. This shift is inherently connected with a change in lifestyle and attitudes. By 2020, there will be six billion smartphone users, so mobile technologies are likely to predominate over landlines or desktop computers.[1]

Improvements in global lifestyle and income will also bring about more awareness of personal health outcomes – leading patients to become even more discriminate consumers. At the same time, it is reported that healthcare costs are rising so fast that they might become unaffordable by mid-century,[2] leading payers increasingly to insist on value-based outcomes in the healthcare market. All of these changes are happening in the looming shadow of an ageing population and chronic disease epidemic.

What can be done to equip drug delivery devices for these new needs? What solution could accommodate higher lifestyle demands and cost reduction imperatives by supporting remote treatment, for example? To answer that, we need to look at the technology standing at the intersection of stakeholders' demands and technological supply – connectivity.

## CONNECTIVITY AND ADHERENCE

Connectivity is enabled by incorporating electronics and firmware into the device. A modified autoinjector, for example, can use wireless connection options to connect with users' mobile devices to transfer and store information about drug delivery. When information is saved to the application there are various possibilities for sharing it with different interested parties (Figure 1).

Use of the app, however, is not limited to just delivery data management. Additional in-app functions might include targeted information and training videos, contact with healthcare professionals, frequently

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asked questions, as well as automated reminders, and more.

Importantly, connected delivery devices support adherence to medication. The growing prevalence of chronic diseases means that more people need to receive their medication on a regular basis. Non-adherence creates unnecessary suffering for patients and avoidable costs for healthcare organisations and pharma companies.

Nevertheless, low adherence remains one of the biggest problems for chronic disease patients. Further, some new-generation biologics only need to be administered weekly, bi-weekly or monthly. The rarity of injections, being beneficial for patients in terms of quality of life, on the other hand, leads to problems in creating and maintaining a stable regimen.

Connectivity can solve these problems by helping patients and other stakeholders to keep track of injection data, and identifying patients who need additional support. Moreover, in-app training courses and notifications will educate and remind patients about the process, thus helping to avoid non-compliance due to forgetfulness and difficulty of administration.

## VALUE ADDED ON EVERY LEVEL

The availability of smart technology has led to a proliferation of connected devices. However, the purpose of medical devices is to satisfy the needs of stakeholders. That's why it is so important that connectivity should add value on every level. Patients could be the primary beneficiaries of connected devices. Improved adherence will certainly increase their wellbeing, but that's not the only benefit. Availability of instructions, reminders, records and advice at one's fingertips will make in-home care much more convenient, thus improving patients' lifestyle and quality of life.

In-home care will also reduce the burden of healthcare professionals. In addition, they will appreciate faster and easier monitoring and communication with patients that comes with connected devices.

The shift to value-based compensation means that payers are looking for cost-reducing innovations that will also permit monitoring of the outcomes. Connectivity allows just that by enabling patients to share the information with different interested parties. Consequently, payers will have the opportunity to monitor, assist and reward compliance.

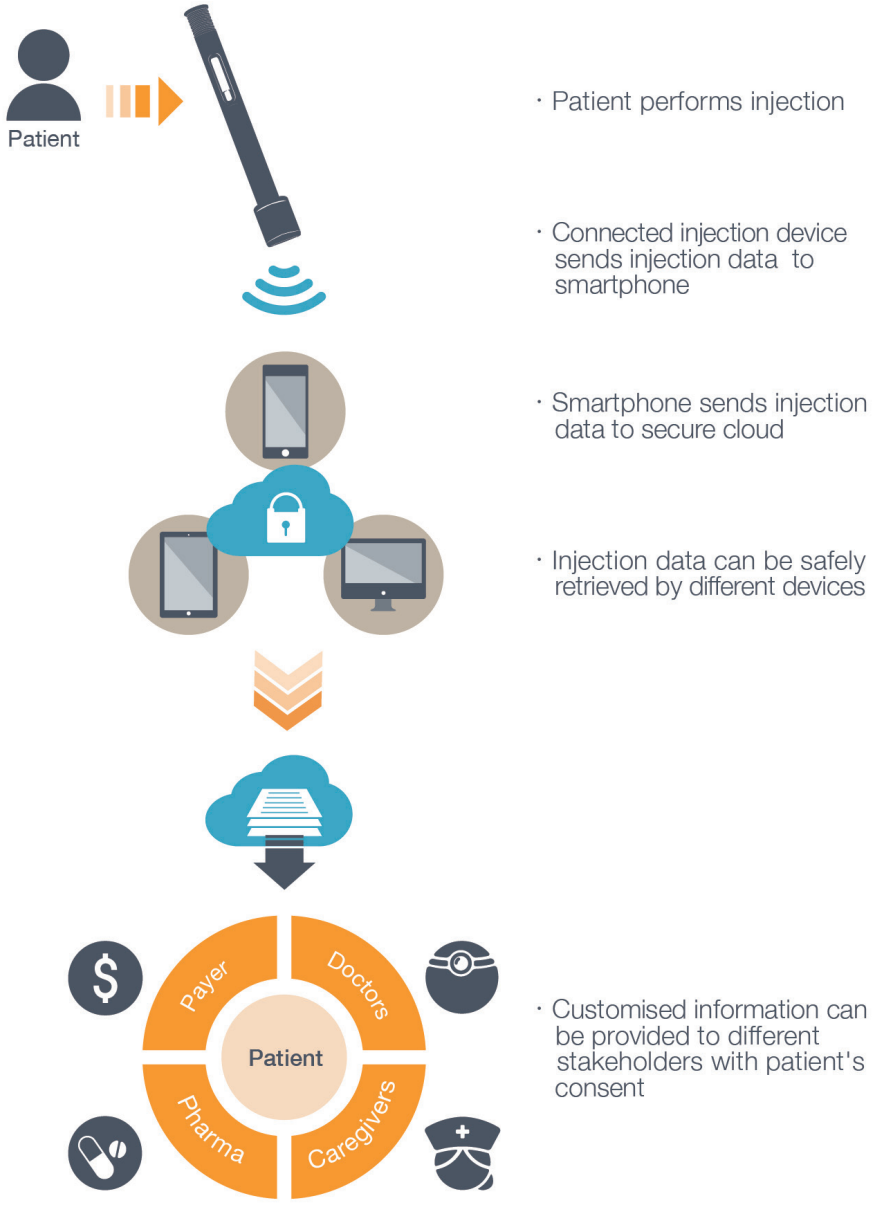


Figure 1: The concept of connectivity.

Finally, pharma companies will not only save money due to improved adherence by patients, but the brand differentiation that comes with connectivity will also be vital for drug lifecycle management. This will be because it can be used to ensure greater product acceptance and the ability to stand out in the sea of different drug options. Moreover, the availability of real-world data from patients could be put to a wide range of uses from clinical trials to development of new and better products.

## MOLLY® C AND MOLLY® RU

To demonstrate the opportunities opened up by connectivity, SHL introduced the Alubena® program dedicated to connected device solutions.

The concept of Molly® C and RU, developed under the auspices of Alubena®, shows the possibilities of a connected autoinjector. Molly® is a trusted and reliable device platform that has proven its efficiency, functionality and adaptability to different customer needs. The autoinjector itself is disposable, but the recording unit (RU) is reusable for two years without charging. It uses Bluetooth technology to transmit information to a user's mobile device (Figure 2).

The hybrid design combines the advantages of disposable autoinjector and reusable sensor and transmitter, giving remote recording capabilities in a very cost effective way. The RU and autoinjector are easily attached through proprietary interface. Distinctive audible and visual confirmation of the connection is given at every use (Figure 3). For the user, injection

is the same easy two-step operation as with Molly® RNS device; but he or she also receives RU's indication of the completion of the process and saving of the data (Figure 4).

Essentially, Molly® C and the RU concept incorporates compactness, robust design, user-friendly interface and the functionality of previous Molly® devices, while at the same time increasing the range of options for the patients, carers and other stakeholders. The simple inject-save-share process does not require any extra effort from the patient, yet it not only helps to improve adherence, but also ensures permanent access to injection history for further use.

## CONNECTIVITY AS CAPABILITY

Molly® C and RU is just one example of what the SHL Connectivity program – Alubena® – can offer. There are many further uses for connected devices that will differ from customer to customer.

Connectivity as capability could be used in supply-chain management, for example, by allowing tracking of the drug from production to end-user in order to verify quality and authenticity. Environmental recording solutions would ensure that the product has been handled within its allowed margins all the way down to the patient. Finally, connected delivery devices might further integrate into healthcare infrastructure by connecting and exchanging information with pharmacy networks and database-driven health records.

According to research, difficulty of administration process accounts for about 50% of non-adherence among chronic disease patients. Possibilities of in-app teaching through multi-lingual training method and graphic interface will give patients and carers learning opportunities they've never had before.

Finally, the advance of digital health means that there will be even further opportunities to integrate drug delivery devices into the broader healthcare network. Connectivity as a device capability will allow users to share their data instantly as well as connect with social networks, support groups and healthcare providers. Collection and analysis of big data will improve research and development, and lifecycle management for pharmaceutical companies, while permitting payers to monitor, analyse and motivate value-based outcomes. Integrated, connected solutions will bring about faster, better and more affordable healthcare.


Figure 2: Molly® C and the recording unit (RU).

Figure 3: RU connects to the mobile device, and provides audio and visual confirmation of the connection.

Figure 4: The injection process is the same easy two-step operation.

## PREPARING FOR THE FUTURE

The future of healthcare is digital. To avoid missing out on the new opportunities, pharmaceutical and biotech companies must prepare for the new era. Bearing in mind that adherence to medication will only grow in importance; adding connectivity, as a way to support it, is one of the most obvious choices. It is important to choose an experienced partner, because efficient partnership with the device manufacturer is essential to the success of the product.

SHL, being one of the leading advanced drug delivery device manufacturers in the world, has a unique insight into the needs of stakeholders and the core functions of devices that can accommodate those. Extensive market experience together with an innovative approach make SHL opportunely placed to develop robust solutions in the field of connectivity. We are always looking out for leading-edge technologies to incorporate into our devices. At the same time we think it's important not to be carried away by what contemporary technologies offer us and always keep in mind usability, efficiency and safety of the product.

In conclusion, developing a smart connected product in partnership with an experienced and trusted manufacturer is a timely and probably necessary step for pharma and biotechnology companies, and SHL is extremely well-suited to be such a partner.

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# APPLYING DEVICE DESIGN CONTROL CORE PROCESSES TO THE SELECTION OF AN OFF-THE-SHELF DRUG DELIVERY DEVICE

**In this article, Lilli Zakarija, President, EdgeOne Medical, examines the selection of off-the-shelf drug delivery devices by pharmaceutical and biologics companies, and shows how employing device design control processes can improve the outcome of the decision, helping to avoid costly, time-consuming mistakes and ensuring the best device is chosen.**

The selection of off-the-shelf (OTS) drug delivery devices is no small task for a drug/biologic development program. In the US market, a key benefit of selecting an OTS shelf delivery device (such as a pen/autoinjector or ambulatory pump) is that it has already been 510(k) cleared by the FDA. One would assume that FDA clearance implies a robust design verification package exists (including, amongst other things, human factors formative and summative studies and data per ISO 11608 standards for pen injectors).

> "It is important to keep in mind, the 510(k) review process is an evaluation of a comparison of a new product to one already cleared by the FDA. Unlike the NDA or BLA review process, the 510(k) process does not include a detailed review of all the design and manufacturing documentation that supports a device design."

Some companies that have minimal internal device expertise don't always realise that not all delivery devices are created equally and, by default, just because the device was cleared by the FDA doesn't mean the device design is adequate for their specific drug/biologic needs.

It is important to keep in mind, the 510(k) review process is an evaluation of a comparison of a new product to one already cleared by the FDA. Unlike the NDA or BLA review process, the 510(k) process does not include a detailed review of all the design and manufacturing documentation that supports a device design.

## LEVERAGE DEVICE DESIGN CONTROL CORE PROCESSES

When scanning the landscape of drug delivery devices, we see a wide range of options whose complexity is increasing as more of these devices incorporate embedded smart technology. While there are many delivery devices, what we can safely assume for each device is that it was designed with its own specific set of user needs and requirements. The output of those requirements and design efforts is the marketed design. As such, the requirements for a specific delivery device may not completely align with a drug/biologic company's needs. The best way to approach the process of selecting a delivery device is to apply some of the same design control principles for the combination product as was used in the development of the drug delivery device. Specifically:

1. Requirements: define your specific user needs and business requirements
2. Assessment: assess the array of available device options against requirements
3. Risk Analysis: for those requirements that are not met, conduct a risk analysis
4. Decision: select best delivery device for the drug/biologic.

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| Principle | Specific Steps | Tips |
|---|---|---|
| REQUIREMENTS:<br>Define your specific user needs and requirements | 1. Identify and list requirements-<br>Potential sources for critical requirements include: patient (user); dosage; manufacturing; safety; regulatory; and business<br>2. Rank and prioritise requirements | • Solicit input from cross-functional team as well as stakeholders<br>• A requirements list does not need to be exhaustive, but make sure everyone agrees on the most critical requirements |
| RISK MITIGATION:<br>For those requirements not met, conduct a risk analysis | 1. Source samples (whenever possible) and evaluate:<br>a. Bench top<br>b. Focus group / prelim human factors assessment<br>2. Document the output of assessment (e.g. spreadsheet) | • Make a quick note of reference that supports evidence identified or developed to support each requirement. This will come in handy later<br>• If the drug/biologic has unique properties (viscosity and density) don't forget to inquire with the device manufacturer about the range of liquids used to evaluate their device |
| ASSESSMENT:<br>Assess the candidate devices against requirements | 1. Explore risk mitigation strategies to increase submission clearance and/or commercial success of certain requirements<br>2. Assess risk mitigation strategies that support requirements and business objectives | • Keep track of mitigating strategies that need to be implemented into the formal project once design control is initiated |
| DECISION:<br>Select best device option | 1. Select the device that satisfies the majority of requirements | • Keep track of all information in a spread sheet and use this as a starting point for design control documentation |

Table 1: Simplified delivery device selection process.

Before diving into the details of this four-step process, consider the last time you had to make a big decision where you knew there were going to be trade-offs. Maybe it was the purchase of a new car or a new home. You write down your wish list (requirements), you look at your options and trial things out (assessment), you figure out what you may not get and how to adjust (risk analysis), and then you make your selection (decision).

The same selection principles we use for making these types of decisions apply directly to the selection process of OTS delivery devices, with the primary difference being a vernacular and a formal documentation process that is more commonly understood by device development team members than the drug/biologic development team.

## DEEPER DIVE ON CORE PROCESSES

The four-step process is further explained in Table 1, with detailed examples of types of things to consider in each step along with tips.

In order to provide tangible considerations for some of the steps in the process, following are some examples (or mini-case studies) of situations that different firms encountered.

**1. Requirements**

Often a single individual is tasked with the responsibility of identifying the delivery device options for a specific drug/biologic program. In one specific example, a drug company was working on the identification of a pen injector their drug. They assumed, since the pen injector was already 510(k) cleared, that they didn't need to do any other work/documentation for their files. Before the formal decision was made to select and incorporate the pen injector into the drug development program, a cross-functional team of individuals was deployed to audit and qualify the pen manufacturer.

> "The best way to approach the process of selecting a delivery device is to apply some of the same design control principles for the combination product as was used in the development of the drug delivery device."

The manufacturer passed the audit, but the team ultimately chose a different device because later in the drug development process, other critical device requirements were identified that ultimately disqualified the original injector pen manufacturer as a candidate. Had there been consideration of requirements beyond simply requiring 510(k) clearance, the drug manufacturer could have saved time and money to avoid the audit and qualification of a pen injector manufacturer they will never use.

**2. Assessment**

Another company was prepared to select a pen injector for their drug even though they had received some preliminary feedback that their patient population gave the particular injector low usability marks. The company wanted to select the device for the sole reason that the device had recently been cleared for use in the US market. The team believed that the recent FDA clearance decreased their time and risk to commercialisation. While this may be true, the firm didn't realise that they were going to need to generate their own human factors data (formative and summative) to support that this specific device met the requirements of their specific drug patient population. The drug company's preliminary feedback data already pointed to the fact that they would mostly likely have issues generating satisfactory summative studies with the targeted pen injector.

**3. Risk Analysis**

When issues are identified, risk mitigation discussions allow for brainstorming on how best to resolve those issues. A drug company was assessing two different designs for their own custom drug delivery device, and was seeking an external recommendation on

which device design to pursue given the unique risks inherent with each design. In order to develop the recommendation, the drug company was asked to provide their risk profile for that specific project. The response was: "We are willing to take high risk". The external recommendations were presented to the drug company keeping in mind the drug company's risk profile, but upon presentation of the recommendations, the drug company immediately said they were not willing to take on that much risk for the project.

This was not a surprise, and the next layer of recommendations was presented with a lower risk profile. Every organisation has a different (business) risk profile. As such, each company needs to determine what risk mitigating strategies may or may not be palatable for their own business.

**4. Decision**

There are many examples of OTS devices being selected for commercialisation, but the point to highlight in this step is not that the selection has been made. Rather, by making the selection and gaining business consensus to proceed with a particular device, this decision is the trigger for initiation of design controls to develop formal documentation that supports the device selection, along with formal qualification testing of the device for the specific drug or biologic. This is an important point, because despite all the interpretation and discussion about the recent FDA combination product regulations, one of the pain points that has surfaced in a recent survey of companies in the combination product space,[1] is that companies are still confused about how to handle development of combination products where one of the constituents is an OTS medical device.

This pain point is a broad statement. However, one of the myths consistently encountered is "OTS devices are already marketed and cleared medical devices by the FDA, therefore no further documentation is required". It's perceived as a simple "plug-and-play" scenario. Unfortunately, it isn't quite that simple. Combination product companies, per the new regulations, must follow design control processes even if the selected device is OTS.

"One of the myths consistently encountered is: 'OTS devices are already marketed and cleared medical devices by the FDA, therefore no further documentation is required'. It's perceived as a simple 'plug-and-play' scenario. Unfortunately, it isn't quite that simple."

## SMOOTHER TRANSITION INTO FORMAL DESIGN CONTROL

The obvious benefits of applying design control best practices to the selection of an OTS delivery device include:

- An integrated approach that seeks to incorporate critical cross-functional and stakeholder input from the beginning
- Early identification of potential risks
- Exploration of risk-mitigating strategies.

The additional benefit in following this process is that all the information and content generated directly feeds into the formal device design control documentation that commonly begins upon selection of the device. This simplifies the start of the device documentation and allows the team to continue to build on the information already generated, rather than starting from step one and rehashing information already sourced and reviewed.

Bridging the transition into formal device design controls is still a struggle for some companies, and this could be a simple method of aligning the team toward the desired goal of a qualified OTS device for their targeted drug or biologic.

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## ABOUT THE AUTHOR

Lilli Zakarija is co-founder and president of EdgeOne Medical, Inc, an ISO 13485-certified medical device testing firm and consultancy focused on supporting combination products through the device development (design control) process. Prior to founding EdgeOne Medical, Lilli developed and led the global device engineering function for Baxter's BioScience division (now Baxalta) in support of all their combination (biologic & device) products and single-use, disposable medical devices. Ms Zakarija has a BS in Biomedical Engineering and a Masters in Engineering Management from Northwestern University (Evanston, IL, US), and an Executive MBA from Kellogg School of Management (Evanston, IL, US).

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ON drugDELIVERY

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Medicom Innovation Partner

# ADVANTAGES OF USING AN ELECTRONIC INJECTOR FOR DUAL CHAMBER CARTRIDGES

**While dual chamber cartridge systems are becoming increasingly popular, patients can experience significant difficulties with them such as the length of the device and the force required to push the plunger. Bjarne Sørensen, Senior Business Development Manager at Medicom Innovation Partner explores the benefits offered by an alternative technology – the electronic injector – and how it can be used to incorporate likely future requirements such as connectivity and reduced packaging.**

Dual chamber cartridges (DCC), with separate chambers for the lyophilised product and the diluent, are becoming increasingly popular within the pharma industry and, compared with the traditional vial and syringe solution, potentially offer ease-of-use advantages for end users.

Reconstitution typically happens by pushing the plunger unidirectionally into the syringe, so that the diluent transfers to the lyophilised product via a bypass in the glass, and the drug reconstitutes ready for injection. Most DCC cartridges come without any separate device but, in some cases, a specific manual device handles the reconstitution process separately from the injection device.

## CHALLENGES OF DUAL CHAMBER CARTRIDGES

The preparation and injection process for DCCs can, under some circumstances, be a challenge for the end user:

- DCCs for high-volume applications tend to be quite long, given the sequential dual chambers, and can thus be a challenge to handle for patients with impaired dexterity, due to the overall length of the syringe and plunger.
- The viscosity of the drug can impose challenges because of the force required to push the plunger once the drug has been reconstituted.
- Limited solubility can impose certain time delays and mixing requirements before injection.
- The repeatability of reconstitution process is an issue – especially where the drug has a tendancy to foam, clump or where it may be damaged by over-enthusiastic agitation.
- Controlled orientation is required during the reconstitution – the needle must be pointing upwards.

## STRATEGY FOR DEVELOPMENT

Medicom Innovation Partner has an extensive background within advanced electronic injection systems and connected services, including new technologies and concepts for electronic injectors for DDCs. These innovative technologies are being embodied in products for Medicom's pharmaceutical customers.

> "An electronic injector offers significant enhancements to the user-friendliness of the whole drug administration process."

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It is important to consider the administration of the drug and the primary packaging very early in the drug development process. Medicom works with its customers on the long-term strategy for the drug and its delivery system, carrying out a 360-degree overview of the specific therapy to determine the optimum device strategy.

Ideally early enough in the lifecycle to influence and determine the optimum primary packaging, or with the already chosen primary packaging as a boundary condition. Part of our strategic review includes the consideration of electronic injectors for DCCs.

An electronic injector offers significant enhancements to the user-friendliness of the whole drug administration process.

## THE KEY COMPONENTS OF ELECTRONIC INJECTORS

The technologies typically used in the electronic injector are all tried, tested and proven elements, and configurable to the exact requirements of the therapy and each case.

**Motor-Driven Plunger:**

- The force needed by the patient is significantly reduced as operating the plunger simply requires the push of a button
- The device tightly controls speed of the plunger during reconstitution and injection. The speed can either be pre-determined by the device, or the user can be given control so that they can minimise any pain or discomfort
- The device can be set to deliver a full dose, or to deliver specific dose sizes as required
- Accommodation of large volume injections is straightforward
- A higher driving force is provided than can be reasonably expected from a patient so that administration of viscous drugs through narrow-gauge needles is possible
- The softly controlled start and stop of the plunger removes the typically sudden, jerky, noisy and uncomfortable release of forces from traditional mechanical injectors.

**Electronic Architecture:**

- There is seamless opportunity for advanced control options, connectivity options and interfaces
- Orientation sensing can be built in the device, enabling control over the reconstitution and priming process, for example and, if required, the injection process
- Additional time to ensure solubility can be implemented
- A specific dwell time after injection can be implemented
- Various options for reminders to take the dose are possible
- Connectivity options are available such as Low Power Bluetooth to smart phones
- Radio-frequency identification (RFID) tags or 2D barcodes can be read to avoid counterfeit and read exact drug data
- The lifetime of an electronic injector can be set – e.g. to three years – and then be recycled in a controlled process.

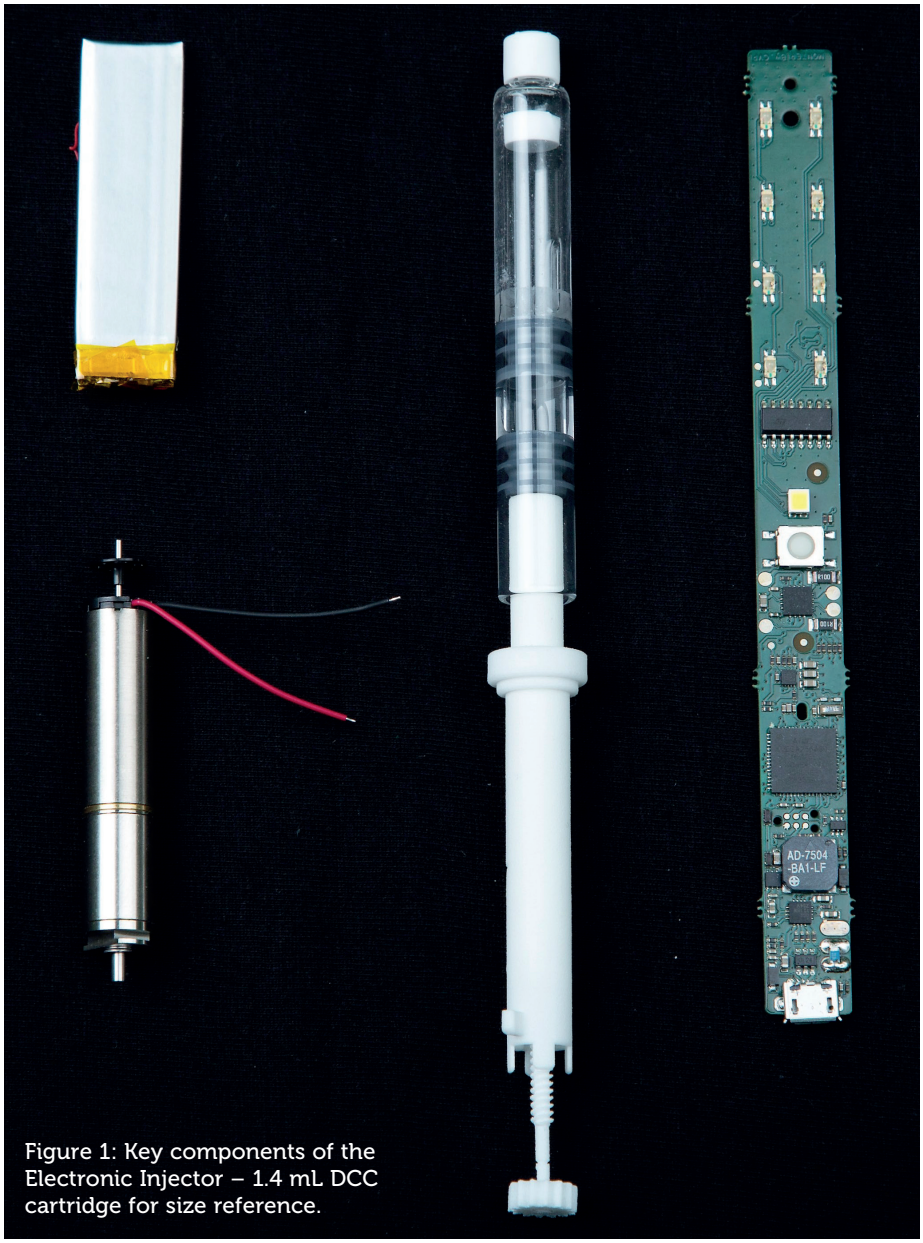



Figure 1: Key components of the Electronic Injector – 1.4 mL DCC cartridge for size reference.

**Main building blocks:**

The usual building blocks of an electronic injector include (Figure 1):

- A motor and spindle mechanism, which can drive the plunger forwards and backwards if necessary; the motor can be integrated with a small planetary gear
- A battery pack, which can enable a month of use between charging
- A control circuit with a small micro-processor that controls the overall functionality of the device and other peripheral elements like the connectivity interface
- A small display, if required by the functionality/therapy
- Buttons for controlling the device
- A motorised needle insertion, if required
- A hidden needle, with needle safety, if required

- Skin contact for automatic release of the injection
- A charging circuit – wired or wireless charging available, as required
- Provision to hold and exchange the cartridge, so that it can be changed effortlessly

> "For example, a bi-weekly injection over three years, with a disposable autoinjector, leads to 312 complete sets of plastic components, springs, packaging etc thrown away, versus only one electronic injection device – and this is just for one patient."

- Provision to mount the needle, e.g. needles from the comprehensive diabetes portfolio.

## FUTURE BENEFITS OF ELECTRONIC INJECTORS OVER OTHER TYPES

The flexible conceptual and technological opportunities of the electronic autoinjector provide significant opportunities for optimisations compared with traditional mechanical systems (Figure 2).

The built-in infrastructure and opportunities for connectivity, add a very interesting and future-orientated functionality to the electronic injector. By adding a Low Power Bluetooth interface in the injector, it is possible to communicate safely with a smartphone and, through an app developed and customised for the specific therapy, it is also possible to communicate with cloud storage and advanced data analytics. Such a system allows healthcare professionals, caregivers or other relevant stakeholders to access valid data of the drug usage, possibly also paired with behavioural data from the patients.

The electronic injector can uniquely convey exact and valid data about the drug administration, such as time of the injection, dose strength and volume, lot number etc, and it is now possible to create a coherent and consistent system approach to the drug delivery challenge, meeting the demands for game-changing innovation in the marketplace.

This is exactly the kind of functionality that will be hugely relevant, when the disruptive paradigm changes regarding demands for safe migration of treatment to home setting, outcome-driven drug pricing and demands for integration of drug delivery data with the health ecosystem, enter the marketplace in full force.

Another aspect of the electronic injector is that of waste management, which is of increasing importance throughout the industry and society. A reusable electronic

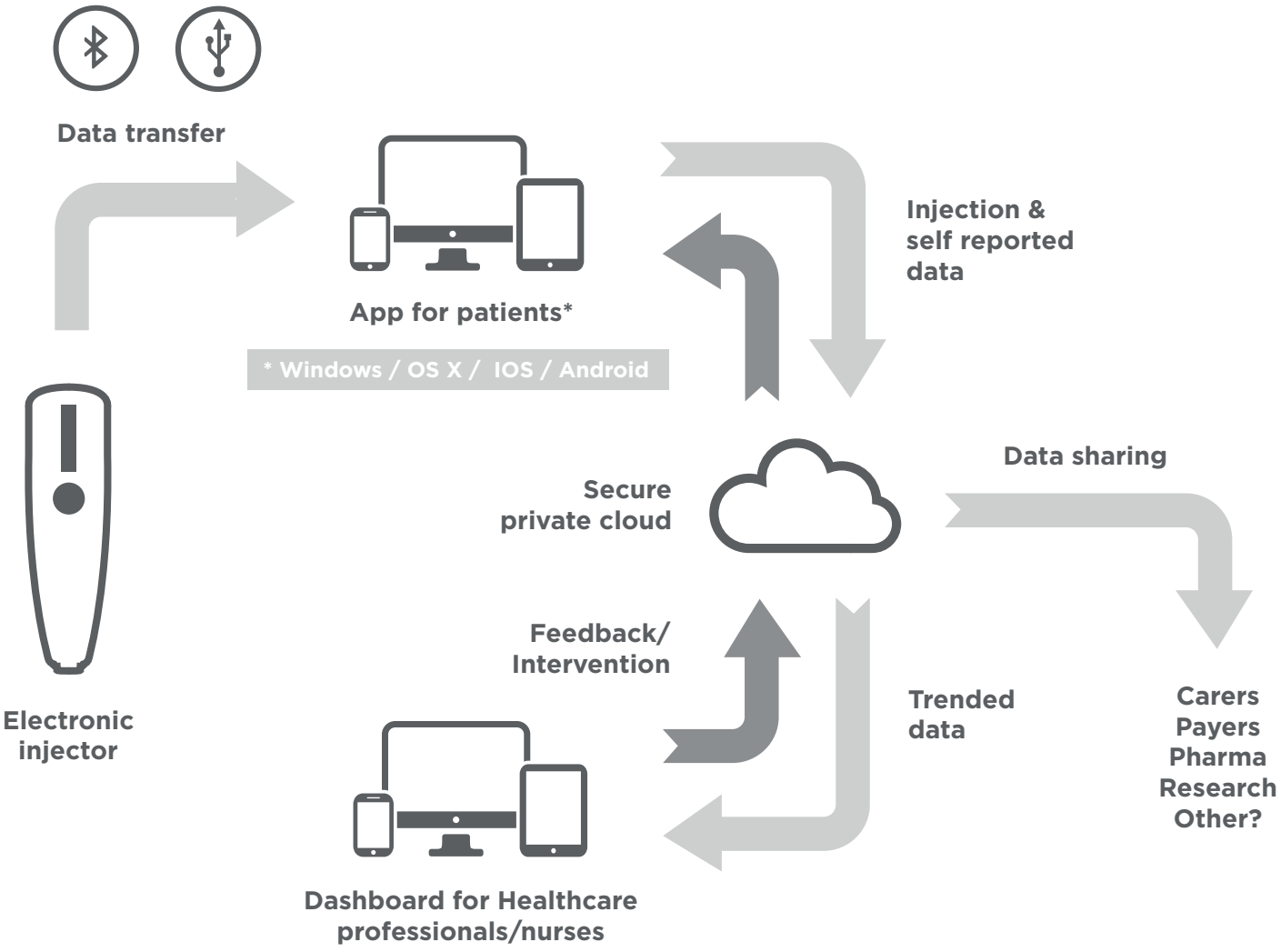
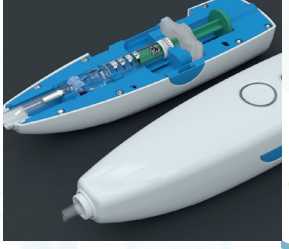
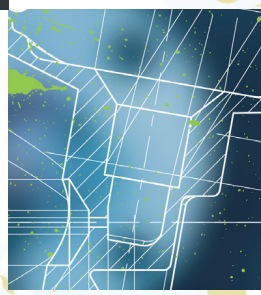


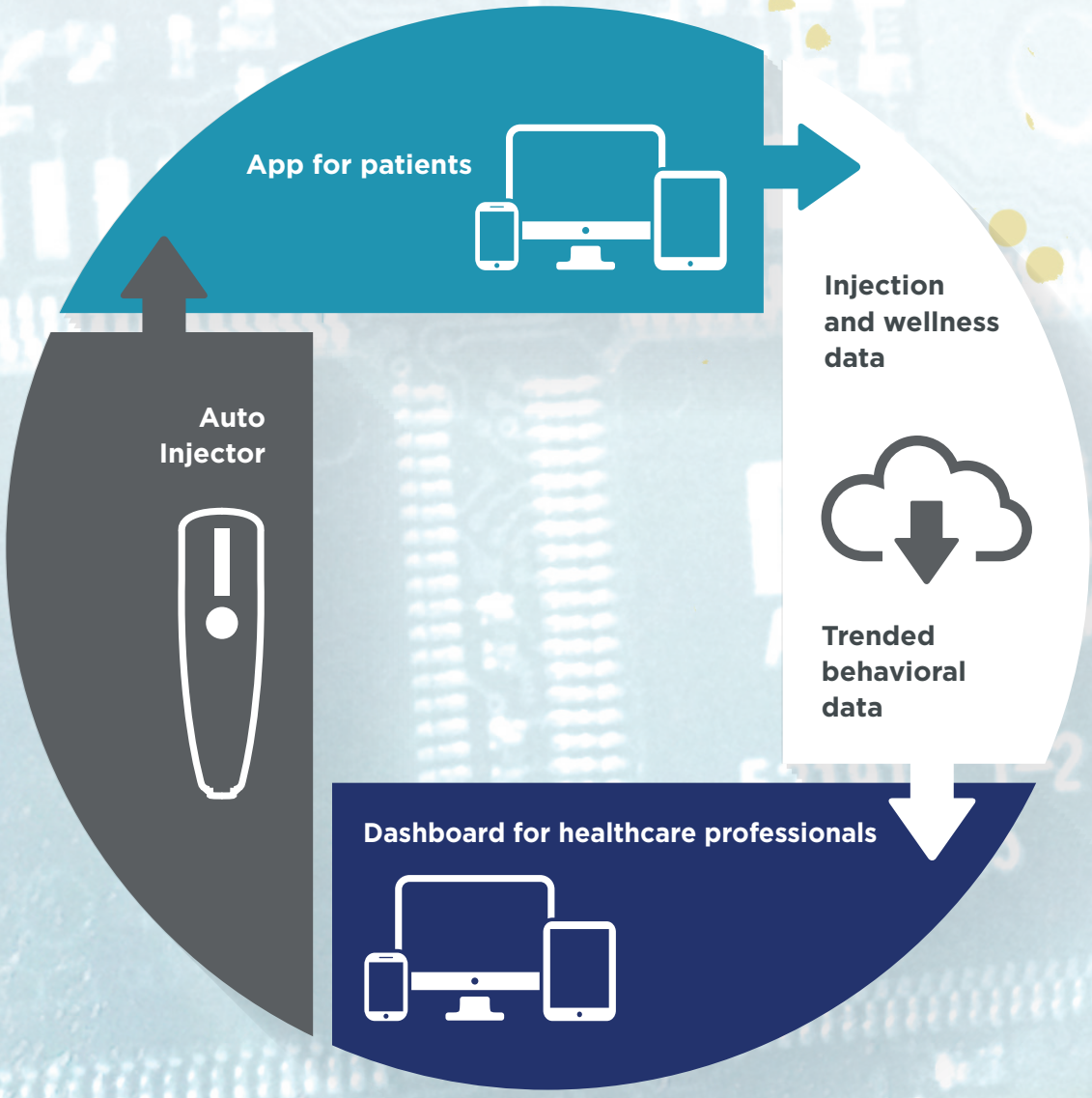

Figure 2: The complete connected system architecture.

# World leaders
## in patient centric drug delivery systems





**Devices**
**Connectivity**
**Connected Health Service Solutions**

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injector can significantly limit the waste generated by the administration of the therapy, as the only discarded part is the primary packaging.

For example, a bi-weekly injection over three years, with a disposable autoinjector, leads to 312 complete sets of plastic components, springs, packaging etc thrown away, *versus* only one electronic injection device – and this is just for one patient.

The necessary production volumes for an electronic injector are thus also significantly smaller compared with a disposable autoinjector, where expensive multi-cavity tooling and automated assembly lines are often required due to the high production volumes. The production set-up for an electronic injector is typically single cavity tooling and universal assembly methods and equipment, which result in a much lower investment for tooling and equipment.

The cost structure of the drug is positively influenced by reducing the costs of parts that will be thrown away for each injection, increasing the competitive edge of the drug and affecting the reimbursement aspects positively.

## CONCLUSION

Generally, it is widely recognised that user-centric devices and services:

- Improve efficacy and safety
- Reduce administration errors
- Improve patient & physician engagement and increases adherence
- Create brand loyalty, which leads to better patient and clinical retention
- Facilitate safe migration of treatment to home setting.

Medicom's view is that disruptive technologies change the pharmaceutical industry for the better, but it does require a mind-set that does not conform to pre-existing standards and norms, and they are not necessarily able to be valued by traditional quantitative market research.

In this article we have focused on the electronic injector for DCCs, but many of the unique advantages will also be beneficial for other primary packaging types, for which Medicom is also developing or manufacturing similar electronic injector solutions and complete connected systems.

## ABOUT MEDICOM

Medicom Innovation Partner was established as a technology venture in 1989 as part of Bang & Olufsen a/s. The company later became an independent company in the Bang & Olufsen group under the name of Bang & Olufsen Medicom a/s. In 2007 Bang & Olufsen Medicom a/s was part divested when Maj Invest Equity A/S acquired 65% of the shares. Today Medicom Innovation Partner is wholly owned by Maj Invest Equity and Medicom management.

Medicom is, by its size and 20+ years' track record, one of the most dominant players within our business focus of developing innovative drug delivery device and service solutions for high-value and differentiated drugs. Medicom holds a dedicated staff of more than 90 high-calibre innovation specialists, mechanical, hardware, software, quality assurance, regulatory and production engineers based in Struer, Denmark and Cambridge, UK.

The primary ambition of Medicom is to make sure that our innovation ability becomes a competitive strength for our customers.

CREDENCE MEDSYSTEMS

THE CREDENCE COMPANION
SAFETY SYRINGE SYSTEM

Innovation Without Change simplifies the commercialisation path for drug manufacturers while introducing critical innovation in the end device. The modular approach gives drug manufacturers the freedom to select existing syringe barrel, stopper and cap primary package components from preferred vendors, mitigating much of the development, regulatory and supply chain risk associated with combination product development.

The Companion needle and plunger rod are incorporated with the syringe barrel to provide a differentiated delivery device. Upon completion of the injection, the user receives audible, visual and tactile cues that the dose has been delivered and then the needle automatically retracts into the barrel of the syringe, rendering the syringe needle-free and preventing re-use (Figure 1).

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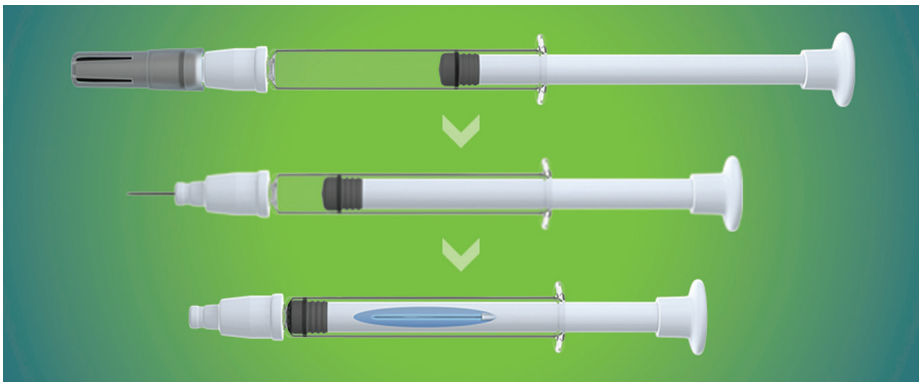


Figure 1: Needle automatically retracts, rendering the device needle-free, preventing re-use.

## A SIMPLIFIED PATH TO BEST-IN-CLASS DRUG DELIVERY

Benefits for the **Drug Manufacturer**

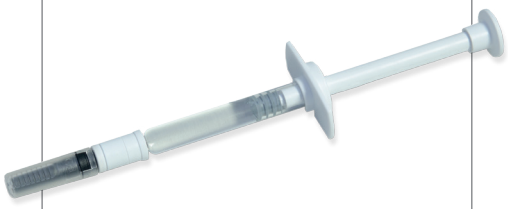
- Marketable Differentiation
- Uses Existing Syringe Components
- Simplified Commercialisation Path
- Reduced Supply Chain Risk
- Standard Filling & Assembly
- Glue-Free Design

Benefits for the **End-User**

- Passive Integrated Needlestick Safety
- Smart Syringe Reuse Prevention
- End-of-Dose Cues
- Glue-Free Staked & Luer Needles
- Allows Standard Syringe Procedures
- User Friendly Design

Credence shifts the paradigm for drug delivery device development.

## THE COMPANION PRODUCT FAMILY



**Companion Staked Needle Syringe**

When a pre-attached needle is preferred, the Companion Staked Needle Syringe allows the use of existing drug container components and provides integrated automatic needle retraction and reuse prevention.

**Companion Dual Chamber Reconstitution Safety Syringe**

The Dual Chamber Reconstitution Safety Syringe offers a pre-attached needle, the use of an existing syringe barrel and closure components, single-step reconstitution and injection, along with the Companion's passive needle safety and reuse prevention.

**Companion Luer Syringe**

Applications that require needle-choice flexibility or reconstitution call for the user to attach the needle. The Guide-On Needle Cover promotes a proper needle attachment and the Companion Luer Syringe provides the passive safety.

# PACKAGING FOR INJECTABLE DRUG DELIVERY DEVICES

In this piece, Seán Egan, Group Marketing Manager, and Angela Shotton, Business Development Manager, both of Nelipak Healthcare Packaging, describe how Nelipak's transit tray solutions are comfortably keeping pace with current and future trends in the pharma and biopharma industry, from greater use of robots and pick-and-place, to transportation requirements and stresses, clean-room and sterilisation specifications right through to the emergence of smart packaging and connected delivery devices that can increase adherence.

The past few years has seen the growth of injectable drug delivery in the pharmaceutical market with biologics now representing five out of the top ten drugs globally. Currently biologics sales account for approximately 20% of market share with high-single-digit growth expected through 2020.[1]

Growth in generics and biologics has resulted in the increased use of injectable drug device components including syringes, autoinjectors, insulin pens and wearable devices, with an estimated 30 billion units used annually.[2] This in turn has led to significant growth in the manufacturing of injection moulded drug delivery devices.

> "Greater use of robots and pick-and-place systems in manufacturing has led to a need for dimensionally stable transit trays to meet the demands posed by process optimisation."

While some pharmaceutical companies develop devices in-house, there is a trend toward specialist third-party contract manufacturers to meet increasing volumes and speed to market. Greater use of robots and pick-and-place systems in manufacturing has led to a need for dimensionally stable transit trays (Figure 1) to meet the demands posed by process optimisation. Empty trays that do not separate properly in the automation process and require manual intervention can result in extra costs, causing downtime and reduced run rates. Too much tolerance from tray to tray may lead to product misalignment causing potential product damage and disruption on the machine. As a result, there is greater risk involved if the tray is not properly designed due to a lack of understanding of the specific processes and how products interface with the equipment involved.

Additionally, components shipped between manufacturing locations for different assembly and fitting operations place transportation and storage demands on the part and the tray. Poor packaging density can reduce the autonomy of the machines, increasing both manual loading requirements and transportation and storage costs between the contract manufacturer and the filler. During transportation the tray must ensure those devices must be protected and remain correctly positioned in the tray. Functional features ensure product protection in transit. At the same time, trays are designed to nest inside each other reducing storage, space, labour and transport costs.

Nelipak Healthcare Packaging understands that it is crucial to develop the right transit tray solution that fits the device as well as the automation, transportation and user requirements identified in the overall

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Figure 1: Transit tray for automation line.

process. However, developing a solution often involves multiple parties – design authority, consultants, pharmaceutical company, device manufacturer and automation partners. In response, Nelipak has developed its Design Requirement Specification (DRS) process (Figure 2) to capture the requirements of the injection moulder, the automation provider, the packaging supplier and, if involved, the contract manufacturer, to specify the needs for both the process and the device before it is decided how the trays should be designed. This program draws on the company's unique project management experience gained from working with pharmaceutical and medical device OEMs on packaging, transit trays and automation systems across Europe and the Americas.

Starting with the initial technical project brief, Nelipak designers deliver digital sketches (Figures 3 & 4) to clarify aspects that are critical for the packaging, such as device orientation in the tray, critical areas of the device which require extra protection, or how the device will be handled. If, for

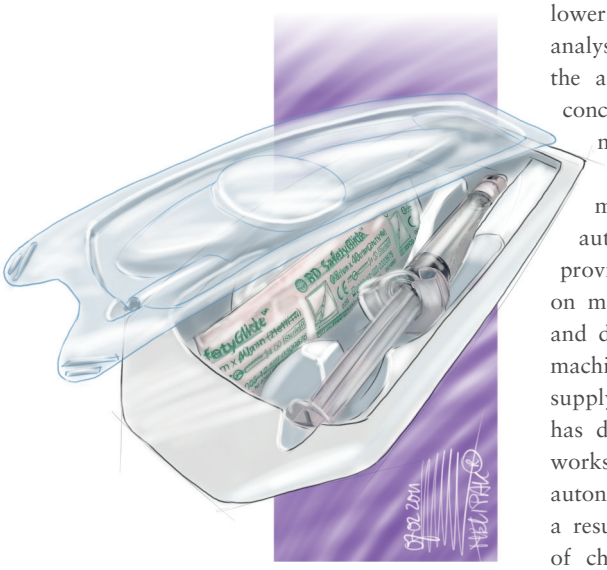

Figure 4: Nelipak concept sketch of a patient pack with syringe.

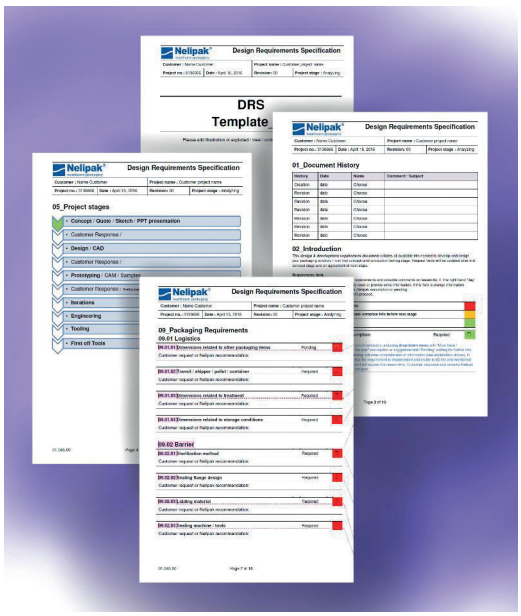


Figure 2: Nelipak design requirement specification.

example, the device will be picked up by grippers, the next question would be where and how much gripper access is required; this can result in an appropriate feature being built into the tray.

Agreement on design concept allows development of orientation and pallet load studies (Figure 5) to visualise quantities per tray, box and pallet to predict overall storage and shipping volumes. For example, a device placed upright in a tray may result in high density per tray during automation but a lower density per pallet in shipping. This analysis tool gives the wider project team the ability to review potential issues or concerns early on in the supply chain and make informed choices

Dedicated design and project management teams work closely with automation and filling companies to provide technical drawings, consultation on material specifications, tray tolerances and deliver prototype samples to support machine development, trials and ultimately supply. Through this process, Nelipak has developed an understanding of what works on their equipment to deliver greater autonomy and shorter lead times and, as a result, has become the solution partner of choice for many leading automation companies to deliver successful transit tray projects on time.

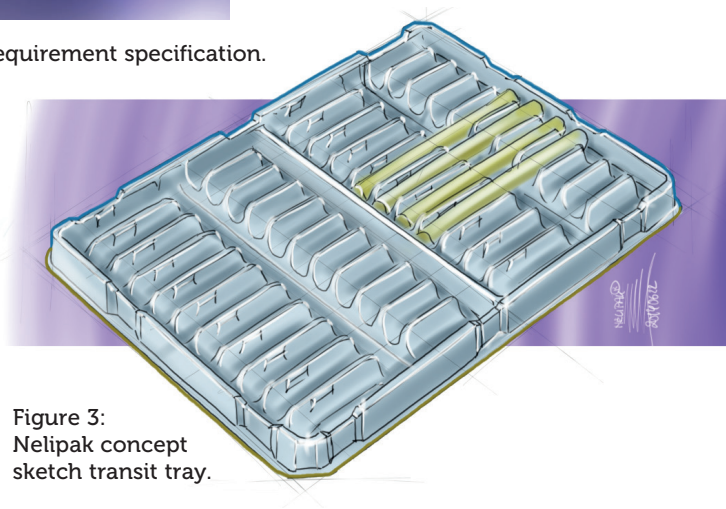

Figure 3: Nelipak concept sketch transit tray.

"Nelipak is one of the few thermoform packaging providers that has both the capacity and footprint to support global pharmaceutical manufacturing."

With the growth of the injectables market, a critical factor in the supply chain is the capacity to deliver an uninterrupted supply of components. Pharmaceutical companies build contingency into their processes to ensure they can continue to deliver product to market should one location go off-line and they expect the same back-up and support from their key suppliers. Nelipak is one of the few thermoform packaging providers that has both the capacity and footprint to support global pharmaceutical manufacturing. Five facilities in the Americas and Europe provide design, development and manufacturing in a variety of materials.

## FROM PRODUCTION TO PATIENT

Biologics, for instance, not only continue to disrupt the traditional drug market through platforms with better efficacy, but also with more effective delivery through new devices, enabling patients to manage their own treatment regimes. In

turn, this has allowed healthcare providers to move treatment from clinical settings to the home environment in order to reduce in-patient costs on hospital systems. While this move is welcomed by both clinicians and patients alike, it can provide a new set of challenges for pharmaceutical companies such as patient adherence / compliance. Medication non-adherence drives unnecessary medical spending when chronic conditions spiral out of control. The US healthcare system spends an estimated $290 billion (£199 billion) annually on "otherwise avoidable medical spending" related to non-adherence.[3]

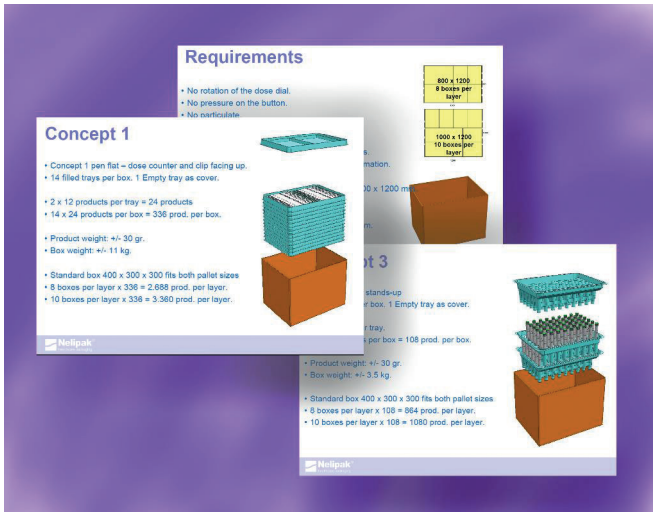


Figure 5: Nelipak part orientation packaging study.

Pharmaceutical companies are looking to address this through development of smart devices that can instruct proper use, report patient uptake, prompt reminders and monitor the patient's condition. Device developers also focus on human factors engineering in the development of devices to insure ease of handling and intuitive use by the patient – consider the elderly patient using an auto injector to treat their arthritic condition. This approach is more frequently being extended to final packaging. If the device is difficult to remove from the packaging it may affect the patient's ability to use the device and possibly their perception or acceptance of it.

Once the device has been filled, assembled and labelled, shipping packaging is required. This may simply consist of a shipper carton, clamshell, blister, thermoformed tray insert, pouch or a combination of any of the aforementioned. While some devices are hand-filled into packs, volumes generally dictate semi-automated or fully-automated processes in conjunction with automatic cartoning / IFU lines. As with transit tray automation, tolerances are critical for the smooth operation of high volume lines. In this instance, Nelipak employs the same DRS process in the development of thermoformed tray inserts used for transit trays to deliver solutions that work.

Material choice for packaging will depend on a number of factors such as barrier requirements, protection during transportation, storage requirements and how the packaging is to be accessed to use the device inside. For thermoformed tray inserts a variety of materials such as APET, PETG, High Impact Styrene (HIPS), Aclar® (Honeywell) and Eastalite™ (Eastman) are available for use. While most shipping packaging is considered secondary and therefore not required to be sterilised, these materials are cleanroom-compatible making them ideal for aseptic sealed packaging for drug products used within sterile clinical fields. When matched with Nelipak's automated tray heat sealers and lidding solutions, pharmaceutical companies have an end-to-end recyclable solution custom designed by a global provider around their delivery device needs and manufactured to ISO standards.

Nelipak has a track record in designing medical device packaging that protects product up to the point of use, is ergonomic and intuitive, and can be part of the procedure delivering benefits to the surgical team. This experience has been supplemented through studies carried out with healthcare professionals to understand their requirements and challenges. Building on its heritage of developing award-winning packaging for medical device OEMs, Nelipak is working with pharmaceutical industry partners to learn more about the diversity of the end user, the environment the packaging is used in and then, in turn, apply this knowledge to optimised packaging solutions. These can include intuitive packaging, which guides the user through the set up process, combination packs with all components required for administration or senior- friendly access.

## PACKAGING DEVELOPMENTS

As patients live with their medical conditions and self-administer medications, they demand more from their devices in keeping with their lifestyle. Increasingly, patients are also expecting more from the packaging their device comes in.

Packaging is evolving to meet the next generation challenges of drug delivery devices and user needs. From simply transporting and protecting to point of use, to being part of the procedure or home therapy, packaging continues to be an integral part of the solutions to address adherence and compliance issues.

Smart pill packs already monitor usage while packaging combined with new technology platforms inform patients when their next dosage is due and are capable of sending out reminders to the patient and/or caregivers if need be. Drugs sensitive to temperature and humidity can be monitored by smart sensors built into the packaging with data tracking. This intelligent packaging, such as SensePak, being developed by Nelipak and SHL Group (Figure 6), can also report on how the packaging and device were handled in transport, and when it was activated.

Smart pill packs already monitor usage while packaging combined with new technology platforms inform patients when their next dosage is due and are capable of sending out reminders to the patient and/or caregivers if need be."

While many autoinjectors discreetly fit in a jacket pocket or purse, devices with refill vials / ampoules require a number of components to be carried about. Packaging manufacturers need to take a variety of challenges in to account and develop solutions to meet these needs in order to deliver an overall better customer experience. For pharmaceutical companies, this also presents opportunities to use packaging that differentiates themselves to gain market share and build brand loyalty.

In the future, drug/device combinations may present new challenges in terms of


Figure 6: SensePak smart packaging under development with SHL Group. (Image courtesy SHL Group)

packaging such as material selection for drugs requiring additional barrier properties in order to maintain a controlled atmosphere within the package.

For instance, in oncology procedures patients undergoing surgery may receive drug therapy while in theatre. While the primary container – the syringe with the drug – is considered a sterile unit internally, the outer portion of the device is not. In this situation the drug delivery device needs to be packed in a secondary package which can be sealed and sterilised, maintaining a sterile device to the point of use when it is presented to the surgeon in the sterile surgical field. This places greater emphasis on the need for certified cleanroom-manufactured trays and lidding material used to seal the primary device. Nelipak meets this need through cleanroom-produced thermoformed packaging operating to ISO standards. In addition, the company has developed and supplies cleanroom-compatible heat tray sealers with the ability to log critical parameters during operation.

With the development of newer and smarter drug delivery devices, packaging manufacturers will face many challenges to reduce costs, improve compliance, provide tamper evidence, educate users and be sustainable. Nelipak, a leading provider of medical device and pharmaceutical packaging solutions, brings a deep technical understanding of supply chain requirements, particularly in regard to high speed automation for manufacturing and pack out operations for transit tray and patient packaging solutions to address these market needs.

## PACKAGING DEVELOPMENTS

1. *"The Global Use of Medicines: Outlook through 2017". Report by IMS Institute for Healthcare Informatics.*
2. *IMS and Tech Group Estimates from "Building for the Future". West Pharmaceutical Services Investor Day, March 10, 2016*
3. *"Estimated Annual Pharmaceutical Revenue Loss Due to Medication Non-Adherence." Capgemini Consulting and HealthPrize Report, 2012.*

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BD

Advancing the world of health

# BREAKING THE 1 ML BARRIER

This article, from Christian Herget, Worldwide Strategic Marketing Leader, Biotech, and Vincent Herin, R&D Staff Engineer, both of BD Medical-Pharmaceutical Systems, explores the evolution of innovative syringe-based combination products for the administration of biopharmaceutical drugs. Particular focus is placed on the increased interest in reducing the number of required injections in order to enhance patient safety and comfort. Often this can only be achieved by increasing the volume of each injection. However, to consider a subcutaneous injection of more than 1 mL as a possible design target, one has to establish the technical feasibility, safety and patient tolerability of larger-volume delivery options.

With more than 900 biologics under development,[1] biopharmaceuticals play a growing role in the treatment of a broad range of conditions. Their potential market is expected to reach US$278 billion (£190 billion) by 2020.[2] Due to their sensitive nature, biopharmaceuticals must be administered parenterally.[3]

Prefilled syringes (PFS) have emerged as one of the delivery systems of choice for biopharmaceuticals.[4] Unlike vials, which require a 20% overfill, PFS help reduce costs and drug wastage.[5] They contribute to improving dosing accuracy as well as patient convenience and safety, which results in enhanced patient quality of life.[5] However, the development of drug products, and in particular sensitive biologics[4] in PFS, creates a unique set of challenges (Figure 1). It is necessary to ensure the safety, efficacy, cost effectiveness and flawless operation of such syringe-based combination products.

One such challenge includes undesired container-drug interactions[6] which can cause drug degradation as well as protein or particulate aggregation of sensitive biologics.[4] To ensure a drug will not interact in unexpected ways with its primary container, a number of syringe attributes must be carefully assessed.

PFS for biologics like the BD Neopak™ (Figure 2) have been specifically optimised to minimise risks reducing tungsten level or improving the leachable and extractable profiles from the used elastomers and glue.[2] If not addressed, such factors can lead to development setbacks, unnecessarily high manufacturing costs and even failure of the combination products in the field.[4] This may jeopardise ambitious time-to-market goals, increase total cost of ownership, or lower patient and prescriber preferences – and, as a result, threaten the overall success of the project.

> "Conventional wisdom suggests that SC injections are limited to a maximum volume of 1 mL. However, there is a lack of evidence to fully support or contradict this belief.[9]"

To maximise chances of success, the development of syringe-based injectables should start with the definition of a target product profile. Leveraging the experience and expertise of container and device partners is also essential.

Based on experience gained during multiple co-development programs, BD has continuously worked to advance

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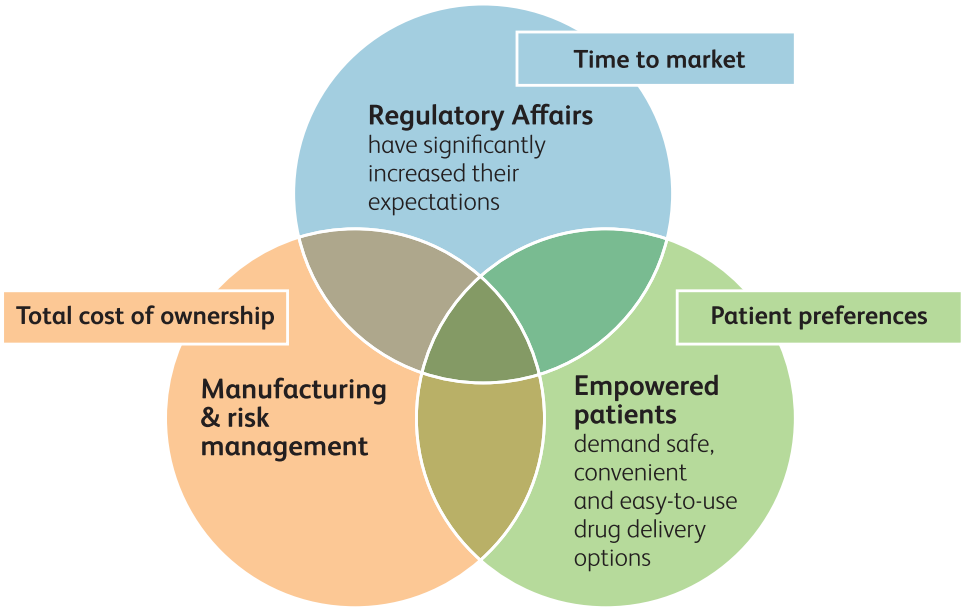



Figure 1: Challenges faced by pharmaceutical companies.

the design and performance of PFS for biopharmaceuticals to address these challenges.

With BD Neopak™, BD has followed a quality-by-design approach to create a new PFS that aims to achieve ppm quality levels. The product is manufactured using a fully indexed process. This eliminates glass-to-glass contact and produces fewer visual defects.[2] The result is lower rejection rates during visual inspection in the customers' production line and increased glass strength.[2] BD Neopak™ features reduced silicone levels while maintaining the low break-loose and gliding performance required for autoinjectors. By limiting dimensional tolerances and putting dead volume space under control, the BD Neopak™ glass prefillable syringe reduces drug wastage and overfilling, thus lowering the total cost of ownership.

## CHALLENGES OF LARGE-VOLUME HIGH-VISCOSITY INJECTABLES

Medical device companies are faced with new challenges. Throughout the pharmaceutical industry, the emerging trend is to reduce the number of injected doses. The primary causes of this trend include the desire to reduce the frequency of injections.[7] Various solutions have been explored to achieve this goal. For example, it is possible to optimise the pharmacokinetic properties of a drug by increasing the concentration or PEGylation of the API to create a longer acting drug. However, this approach does not always yield the desired result and eventually leads to the need for increased injection volumes.[8]

Conventional wisdom suggests that SC injections are limited to a maximum volume of 1 mL. However, there is a lack of evidence to fully support or contradict this belief.[9] If the clinical development of an injectable indicates that the target dose exceeds 1 mL and a syringe-based SC injection is the route of administration of choice, then a number of key questions must be answered. Before exploring the design of injectables with large volumes, we must analyse various factors such as technical feasibility, safety, tolerability and end user-related human factor aspects.

Figure 2: BD Neopak™ 2.25 mL glass prefillable syringe for large-volume injection.

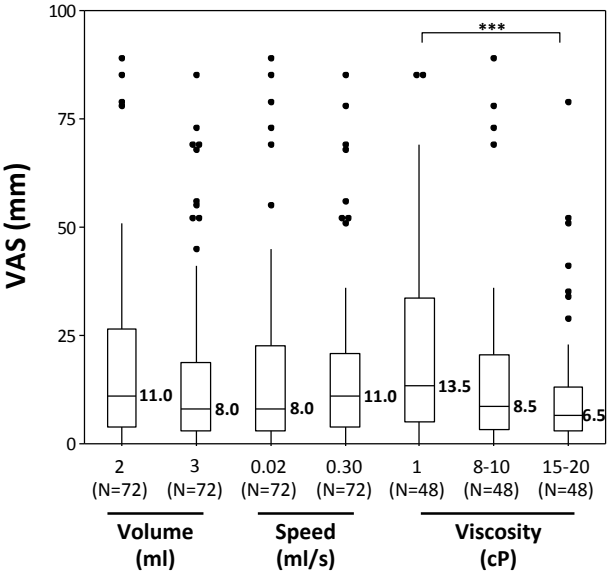
## FEASIBILITY, SAFETY AND TOLERABILITY OF LARGE-VOLUME INJECTIONS

Gathering robust clinical evidence on the feasibility, safety and tolerability of large-volume SC injections is a prerequisite for the development of any therapy that could use such injections. In partnership with a leading biopharmaceutical company, BD has performed a study to evaluate the impact of large-volume placebo injectables using a combination of various fluid viscosities and flow rates in order to analyse pain tolerability, feasibility and safety.[10]

In the single-centre, comparative, randomised, crossover Phase I study, 24 healthy adults each received six injections of either a 2 or 3 mL placebo solution in the abdomen area, with three fluid viscosities (1, 8-10, and 15-20 cP), and two injection flow rates (0.02 and 0.3 mL/s, the latter being comparable with the injection speed of autoinjectors).

> "In partnership with a leading biopharmaceutical company, BD has performed a study to evaluate the impact of large-volume placebo injectables using a combination of various fluid viscosities and flow rates in order to analyse pain tolerability, feasibility and safety.[10]"

During the study, various factors were evaluated to determine the feasibility, safety and tolerability of the injections. Pain was evaluated via a 100 mm visual analogue scale (VAS - 0 mm/no pain, 100 mm/extreme pain). The injected volume was calculated by subtracting the residual




Results grouped according to volume, flow speed and viscosity. A Visual Analogue Scale (VAS) was used to assess pain with a range of 0-mm/no pain to 100-mm/extreme pain. Medians are indicated. A significant difference was observed across the three levels of viscosity (*** p .0003) (1).10

Figure 3: Perceived: injection pain after 144 injections.

> The BD UltraSafe™ Plus Passive Needle Guard 2.25 mL not only delivers the intended safety function, but also extends available design space for combination products. Its user-friendly ergonomics enable the delivery of fluids with greater viscosity."

volume in the syringe. The local injection reaction was assessed by recording signs of bleeding, erythema, swelling and haematoma formation. Reactions were checked immediately and approximately 15±5 minutes after the injection. The location of injected fluid in body tissues was assessed by ultrasonography.

During the study, no severe reactions were recorded for local bleeding, erythema and haematoma. In two of the 144 injections (1.4%), swelling/induration was considered severe immediately after the injection but became moderate 15 minutes later; both cases were observed in the 3 mL group with a fast injection flow rate. The results (see Figure 3) indicated that relatively large-volume SC injections of viscous solutions can be performed in a safe manner.

Despite widespread belief that the upper limit for SC injections is approximately 1 mL, this exploratory study suggests that injections up to 3 mL in the abdomen area are in fact well tolerated regardless of injection flow rate and fluid viscosity.

The study demonstrated that the volume of an injection did not have a statistically significant impact on perceived pain. Injections up to 3 mL were well tolerated when carried out with a flow rate typical for autoinjectors and with solutions of elevated viscosity (e.g. 15-20 cP).

## USABILITY OF CONTAINER-DEVICE COMBINATIONS FOR LARGER VOLUMES

After establishing that higher volumes than 1 mL can be safely injected subcutaneously and such injections are well tolerated by the patients, another key question to address is whether such injections can be properly performed by the end users.

To demonstrate that the BD Neopak™ 2.25 mL syringes can be used as intended by representative end users, a human factors study was carried out asking participants to inject solution of various viscosities using BD Neopak™ 2.25 mL alone, equipped with backstop or combined with BD UltraSafe™ Plus Passive Needle Guard 2.25 mL. This device was developed in parallel to BD Neopak™ 2.25 mL as a solution to comply with needle safety regulation. Apart from reducing the risk of needlestick injuries, these devices are strongly preferred by end users compared with naked syringes.[2]

Study results[2] highlight that BD Neopak™ 2.25 mL allows the injection of a solution with low viscosity (defined as 1cP in the study) with a success rate of 100%.

Injections of a solution with medium viscosity (defined as 10 cP in the study) with BD Neopak™ 2.25 mL alone were successfully achieved by the vast majority of participants. The success rate could be increased to 100% by using BD Neopak™ 2.25 mL equipped with a backstop or combined with BD UltraSafe™ Plus Passive Needle Guard 2.25 mL, enabling all participants to perform the injection properly.

Asked to inject a highly viscous solution (defined as 30 cP in the study), the vast majority of participants were able to perform the task successfully using BD Neopak™ 2.25 mL equipped with a backstop. By using BD Neopak™ 2.25 mL combined with BD UltraSafe™ Plus Passive Needle Guard 2.25 mL, all participants were able to complete the high viscosity injection.

This finding highlights that the BD UltraSafe™ Plus Passive Needle Guard 2.25 mL not only delivers the intended safety function, but also extends available design space for combination products. Its user-friendly ergonomics enable the delivery of fluids with greater viscosity.

By applying a system approach to the development of the primary container and secondary devices and accessories, BD assesses and maps the design space, helps to ensure container and device compatibility as well as system performance.

As a result, biopharmaceutical manufacturers benefit from lower risks in terms of setbacks or delays during combination product development.

## CONCLUSION

Combining PFS and secondary devices is an increasingly popular option to differentiate drugs with relatively similar patient outcomes. In this case, product differentiation is not solely based on the safety and efficacy of the drug but instead on the overall experience relating to the administration.[11]

Choosing the right partner for combination product development is critical to achieve favourable outcomes in terms of time to market, total cost of ownership, and patient or prescriber preferences. BD understands that meeting customers' complex and evolving needs requires extensive consultation throughout the entire process from development to commercialisation. To meet this demand, BD has developed its capacities to deliver support every step of the way.

Thanks to BD Neopak™ 2.25 mL and BD UltraSafe™ Plus Passive Needle Guard 2.25 mL, BD has developed an innovative solution to deliver large-volume, high-viscosity biopharmaceuticals. These products address the need to reduce the frequency of injections while enhancing the safety and comfort of chronic-disease patients.[12]



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PRODUCT PROFILE: **PREMIUMCOAT™**

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## THE ALTERNATIVE COATED STOPPER FOR SENSITIVE DRUGS

Biopharmaceuticals are very sensitive in nature and prone to interaction with the rubber of the stopper. The challenge, therefore, is to maintain the integrity of the container closure while minimising interaction between the formulation and the components of the elastomeric closure system. To meet this demand Aptar Stelmi developed the PremiumCoat™ range of elastomeric stoppers (Figure 1).

PremiumCoat™ is a novel range of elastomeric stoppers developed by Aptar Stelmi, launched in 2015 and designed for the protection of sensitive and high-value drugs, including biopharmaceuticals. Based on an approved, pure, state-of-the-art formulation, the surface of the elastomer is coated during manufacturing with a thin fluoropolymer film (Figure 2). This coating acts as an effective barrier to many of the extractables and leachables that can be released from the elastomer and contaminate the drug. As a result, compatibility of the drug and the closure is significantly superior with PremiumCoat™ stoppers.

> "PremiumCoat™ is a novel range of elastomeric stoppers developed by Aptar Stelmi, launched in 2015 and designed for the protection of sensitive and high-value drugs."

The first design to be released in 2015 was a 20 mm coated stopper. A PremiumCoat™ 13 mm coated stopper was introduced earlier this year widening our range of coated stoppers.

## PROVEN INNOVATOR

Our experience in elastomeric closures and container closure systems is supported by the capabilities of our

Figure 1: Vials with PremiumCoat™ stoppers: the alternative coated stoppers for sensitive drugs. (Image courtesy of Aptar Stelmi)

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Driven by quality, service and innovation for more than 50 years, Aptar Stelmi is a trusted partner of leading pharmaceutical and biopharmaceutical companies throughout the world.

We design and manufacture elastomeric closures: stoppers for vials; and prefilled syringe and cartridge components such as plungers, needle shields and tip caps for all parenteral applications.

Whether for vaccines, existing or new drugs, applications, or delivery systems, our committed teams of experts work closely with our customers around the world to deliver fully compliant premium quality products.

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We strive to provide the highest quality packaging components for injectable drugs. Our consistent quality, innovation and customer service are the cornerstone of the trusted partnerships we build with our customers.

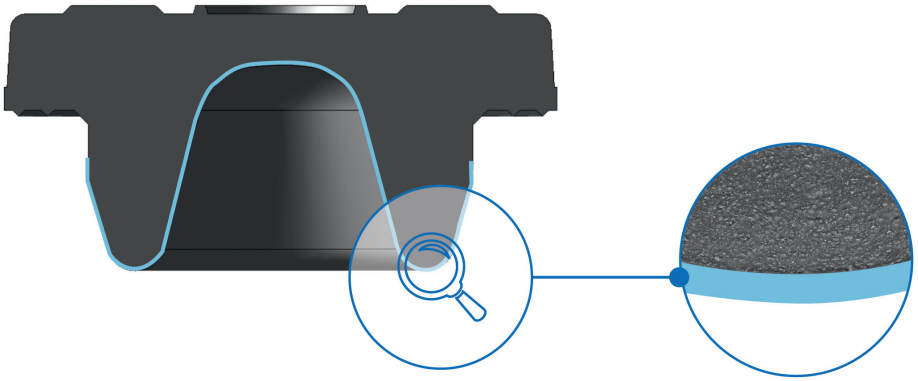

Figure 2: A barrier film covers the drug contact area. (Image courtesy of Aptar Stelmi)

## PREMIUM QUALITY SOLUTION PROVIDER

Our elastomeric closure solutions comply with the highest industry and regulatory standards. Our state-of-the-art cGMP-compliant manufacturing processes include automation, camera inspection and classified cleanrooms.

In addition, our team of experts, quality system and procedures support these production processes up to and including sterilisation – a premium quality environment for your drug products.

## ABOUT APTAR STELMI

Part of the Pharma division of AptarGroup, Aptar Stelmi is a trusted partner of leading pharmaceutical companies in the design and manufacturing of elastomeric closures for parenteral applications. Driven by quality, service, and innovation for more than 50 years, Aptar Stelmi products meet the evolving drug industry demands for cleanliness, efficiency and compliance. Our prefilled syringe components and stoppers for vials are used to multiple applications in more than 70 countries worldwide.

AptarGroup, Inc, (NYSE: ATR) is a leading global supplier of a broad range of innovative dispensing systems for the beauty, personal care, home care, prescription drug, consumer health care, injectables, food and beverage markets. AptarGroup is headquartered in Crystal Lake, IL, US, with manufacturing facilities in North America, Europe, Asia and Latin America.




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# AUTOINJECTORS: CREATING A DEVICE-COMPARABLE TRAINER TO ADDRESS INDUSTRY CHALLENGES

**Autoinjectors have become the main drug delivery devices of choice due to their ability to simplify the number of steps required for injection. However, many patients make mistakes using the devices such as not holding the device correctly or not keeping it in place for long enough. Mike Siemer, Director of Design and Engineering at Noble reports on the development of training devices that replicate the design and operation of the autoinjectors so patients can better understand how to use them.**

Since its inception for emergency medical use in the 1980s, the autoinjector has grown to be the predominate drug delivery device for single-use, fixed-dose self-administration of biologic and biosimilar drugs requiring less frequent administration regimens.[1]

> "While the number of biologic and biosimilar drug launches continues to rise in in the market, so does the use of autoinjectors as a preferred drug delivery device."

The autoinjector was developed to be a self-contained, easy-to-use injection device for clinical and home administration applications. It was designed to simplify administration by reducing the complexity of user steps required for injection, taking into account human-factors including psychological considerations as well as dexterity and mobility impairments. Other integrations included tactile feedback such as auditory and visual signals indicating the beginning and conclusion of administration.[1]

While the number of biologic and biosimilar drug launches continues to rise in in the market so does the use of autoinjectors as a preferred drug delivery device. The Pharmaceutical Research and Manufacturers of America (PhRMA) estimates more than 907 biologic medications and vaccines are currently in development across more than 100 disease states.[2] As more patients are being diagnosed with chronic conditions and being prescribed biologic and biosimilar medicaments delivered via autoinjector, training and education will remain essential success components for determining a patient's ability to adhere to therapy safely and effectively.

A study conducted by the University of Texas Medical Branch at Galveston (UTMB), found 84% of patients failed to demonstrate correct autoinjector administration technique, with more than half of users missing three or four steps. Common errors made by patients included failing to hold the device correctly, not choosing a suitable injection site and not pressing the device hard enough to trigger release of the drug. The study also found the most prevalent error to be the failure of 76% of patients to hold the device in place for the required amount of time to receive the full dose, sometimes referred to as a wet injection.[3]

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According to one of the authors of the 2015 UTMB study, *Misuse of medical devices: a persistent problem in self-management of asthma and allergic disease*, Dr Rana Bonds: "Despite the redesign of the autoinjector for easier use, most patients continued to make at least one mistake with the device. Most patients made multiple mistakes and would not have benefitted from self-administration of the potentially life-saving treatment if the need arose."[3,4]

Additional findings reveal other factors contributing to the inability of patients to correctly use autoinjectors. As part of being diagnosed and prescribed a drug delivery device, most patients receive training within a healthcare provider's (HCP's) office. Studies suggest 76% of HCPs fail to review device use with patients and 68% of HCPs fail to correctly demonstrate administration technique.[5]

Furthermore, for the 14% of providers who do demonstrate correct administration technique to a patient, other findings suggest 40-80% of medical information provided by HCPs to patients is forgotten immediately.[6]

## ADDRESSING USER CHALLENGES THROUGH A DEVICE-COMPARABLE AUTOINJECTOR TRAINER

To reduce user errors and anxiety, and to build patient confidence, medical device training tools have been developed to support patients in learning how to use their drug delivery devices properly.

In an excerpt from the UTMB study mentioned previously, researchers Bonds, Asawa and Ghazi state: "There is room for improvement in ensuring that patients are able to correctly self-administer medications. Repeated verbal instruction and, perhaps even more effective, repeated visual education, including demonstration using training devices, are highly recommended. Novel methods of providing this repetitive training for patients are needed."[3]

## EXTERNAL CHARACTERISTICS: DESIGN AND DEVELOPMENT

In order to set patient expectations and increase familiarity with a drug delivery device, device trainers must mimic the actual device in form and in operational and sequential function. The basic assembly of an autoinjector consists of a prefilled syringe integrated into a barrel housing with a viewing window, springs, activation button, locking safety mechanisms and needle shield.

When creating an accurate representation of a brand's commercial device, such as an autoinjector, designing an analogue device begins with matching the shape and design and external characteristics including barrel dimensions, viewing window, size and shape of actuation button, needle shield and end cap.

## INTERNAL MECHANISM: DESIGN AND DEVELOPMENT

Designing and developing an autoinjector trainer can be quite challenging with considerations that do not appear at the surface. The device needs to contain almost all of the elements of the brand device, and also include the ability to completely reset the mechanism back to the original state, while keeping the overall size as close to a 1:1 scale as possible. Not only


Figure 1: Example of a trainer exhibiting typical autoinjector characteristics including the ability for device customisation.

does the training device need to function within the operational requirements of the brand device, but it also needs to perform repeatedly for up to hundreds of cycles depending on the customer requirements.

Although a trainer may mirror an actual autoinjector's exterior, a trainer's internal components do not contain a needle-based prefilled syringe or the same internal mechanisms. Developing the internal mechanisms to represent an existing device's functionality, administration and sequencing attributes accurately, including plunger drop speed, breakout and glide forces, sound replication and actuation forces, requires engineers to modify the internal portion of the barrel housing design to accommodate a plunger.

Additional design considerations must be made for the inclusion of custom and/or proprietary technologies including activation, plunger-drop, reset and safety lock-out mechanisms, or battery-powered electronic smart technologies such as sensors, audio and visual feedback components, and error-correcting platforms.

During the design and development phase, human factors are also taken into consideration with regard to visual and/or auditory cues, which signal beginning and completion of administration – matching the actual device signals – and the Newtonian forces involved in unlock, actuation and reset mechanisms, which allow the trainer to be reusable for multiple training sessions.

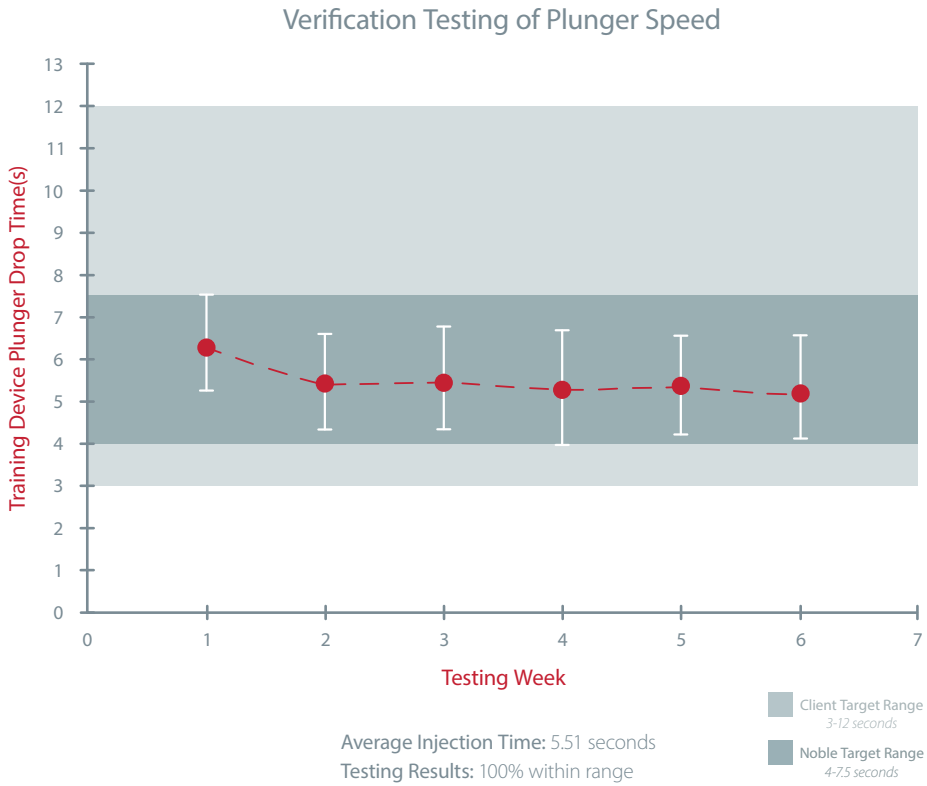


**Figure 2: Results showing the average training device plunger drop speed for 35 randomly sampled units tested over six consecutive weeks.**

The referenced UTMB study findings suggest most patients do not hold their autoinjector in place for the proper amount of time to receive the full dose, resulting in a "wet injection". Therefore, accurate simulation of plunger speed is very important to effective training.

Preparing patients' expectations for actual device usage and injection times – to prevent a "wet injection" and ensure the user receives the full dose – requires trainer characteristics to replicate a brand's formulation viscosity without actually containing any liquid. Based upon brand specs, autoinjector trainers are developed within a specified delivery time target range to duplicate plunger speed. Similar to the actual device, the training device allows a patient to experience the amount of time an injection takes realistically and enables patients to track the progress of the plunger through the end-of-dose indicator viewing window.

> "In the patient-centric era, companies providing reusable, device-comparable training products will be well positioned for competitive differentiation through improved patient satisfaction, adherence and outcomes."

To develop a training device which accurately represents the administration characteristics of an actual autoinjector, devices are designed to mimic viscosities and volumes, breakout and glide forces and plunger drop speed. Varying viscosities of biologic and biosimilar medications increase the complexities of incorporating a prefilled syringe into an autoinjector platform. Higher-viscosity formulations may require higher injection forces and longer injection times during administration.[7]

## VERIFICATION TESTING FOR ACCURACY AND CONSISTENCY

To ensure brand specifications are fulfilled, and an accurate representation of an autoinjector is produced, a systematic methodology process is followed to guarantee consistent optimised manufacturability. Noble conducts rigorous testing, based upon brand specifications and strict internal auditing criteria, spanning from prototype to mass production stage in order to ensure that finished products meet the quality standards necessary for effective training.

One of the keys to success is utilising optimised standard operating procedures (SOPs) and standard inspection procedures (SIPs) during the trainer assembly process throughout both pilot and full production runs, continuously improving critical variables. As sub-assemblies are constructed, various tests are integrated throughout the process to verify targets will be met at the end of the assembly line. For example, plunger speed is measured through semi-automated testing at three different levels throughout the assembly line. A large benefit of making a resettable, multi-use trainer as compared to a single-use device, is that 100% inspection of all defined operational parameters can be

# *Device training happens here.*

There's life beyond injections. Distractions, anxiety and using incorrect administration technique can all affect compliance. One study found 84% of patients failed to demonstrate correct autoinjector technique with 56% of users missing three or more steps.[1]

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Reference: 1. Bonds, R. S., Asawa, A., & Ghazi, A. I. (2015). Misuse of medical devices: a persistent problem in self-management of asthma and allergic disease. Annals of Allergy, Asthma & Immunology, 114(1), 74-76.e2. doi:10.1016/j.anai.2014.10.016

verified before the product is completed and okay-to-ship.

In addition to complete product inline verification, AQL sampling is also performed to test all required critical, major and minor parameters. For example, to validate the consistency in auto injection times of recently developed training devices, a random sample of 35 units was pulled directly from the final production line and was tested over a six-week period. All of the tests showed that the training devices, not only fell within target range of 3-12 seconds requested by the client, but also consistently remained within Noble's specified target range of 4-7.5 seconds and averaged approximately 5.51 seconds per week throughout injection time testing.

## CONCLUSION

As patients are becoming more active participants in their own healthcare, the number of patients required to self-administer injectable medications will continue to grow. For these patients, anxiety, confidence, familiarity with the injection device and understanding correct administration technique will be factors affecting adherence.

The development of training devices that replicate the design and operation of the brand device improves patients' ability to anticipate the steps needed to administer the drug, be more familiar with the ergonomics and device interaction, as well as anticipate a device's expected injection time.

By providing patients a better understanding of their device, with the ability to practise administration technique frequently, autoinjector trainers help promote positive onboarding experiences and empower patients to lead healthier lives. In the patient-centric era, companies providing reusable, device-comparable training products will be well positioned for competitive differentiation through improved patient satisfaction, adherence and outcomes.

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Nemera

# ASSESSING THE IMPACT ON DRUG DOSE DELIVERY OF A TWO-STEP AUTOINJECTOR

In this article, Isabelle Delcroix, Strategy Director, Nemera, introduces the company's two-step autoinjector platform, Safelia, which incorporates innovative, patented design features that enable it to deliver a both fluid and viscous formulations from standard glass prefilled syringes with benefits across the board from reducing the risk of syringe fracture to increasing patient comfort.

Injectable formulations are the fastest growing pharma segment. Biologics are increasingly used to treat a wide range of chronic diseases requiring frequent administration over a long period. Developing drug delivery devices able to administer the pipeline of biological molecules is a challenge as biotherapeutics tend to be more viscous, concentrated and administered in a larger volume. Considering patient adherence is an additional challenge. Less frequent injections, therefore larger volumes and more concentrated formulations, is a target for injection, devices which should also deliver with possibly less pain, less bruising and over a short delivery time.

> "By design the coupling inside the autoinjector is not made around syringe's flanges, a structural weak part of the syringe, but around the syringe shoulder. The spring release shock and the energy is absorbed by a rotating cam system and allows highly viscous injections as well as large-volume delivery."

Nemera's new generation of two-step autoinjectors, Safelia™ (Figure 1), has been designed to ease the patient self-injection experience and to deliver a variety of drug products in glass syringes. These range from more fluid formulations to the most challenging drugs such as viscous, sustained-released, concentrated formulations, products for subcutaneous and intramuscular injection, and including larger volumes.

The Safelia™ autoinjector:

- Administers a large range of formulations and injection volumes; the platform can adapt by design to handle both fluid and highly viscous formulations, taking care specifically of biologics, sustain-released formulations and sheer-sensitive molecules, of up to 2.25 mL injection volumes
- Improves the patient experience, with the possibility to reduce needle gauge, reduce injection time, and slow down the needle penetration inside the body tissues, and gives the possibility of a delayed retraction for viscous injections especially.

## DESIGN SPECIFICS

The specificities of Nemera's patented autoinjector design include the ability to handle high injection spring forces and deliver formulations in standard glass syringes. By design the coupling inside the autoinjector is not made around syringe's flanges, a structural weak part of the syringe, but around the syringe shoulder

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Figure 1: 1 mL and 2.25 mL versions of the Safelia™ autoinjector.

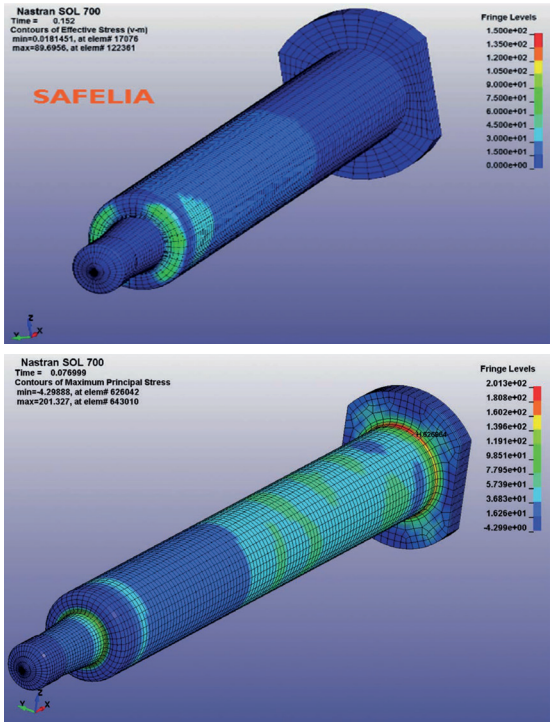



Figure 2: Comparative stress maps of the Safelia (top) and another marketed autoinjector (bottom).

> "The results obtained during this study showed that by design, syringe speed at needle insertion can be reduced, as can the stress on the glass syringe, reducing the risk of syringe breakage."

(Figure 2). The spring release shock and the energy is absorbed by a rotating cam system and allows highly viscous injections as well as large-volume delivery. Risks of breakage are therefore reduced by design during triggering of the autoinjector but also during transportation, drop and handling.

## THE SPRING FORCE & DRUG VISCOSITY PARADIGM

The mechanism of two-step autoinjectors, as their name indicates, involves two consecutive steps: cap removal and syringe emptying. Injecting a large volume (2 mL) of viscous formulations in a short time (10 seconds) using a thin needle requires greater force than smaller volumes over longer times. The consequence is that the higher the spring energy, the higher is the kinetic energy (E) delivered to the syringe at impact (just after needle insertion, and just before start of syringe emptying).

A high-energy spring will induce high syringe velocity during needle insertion. Thus, at the impact (just after needle insertion, and just before syringe emptying) the force on the syringe could lead to problems. Specifically, at impact, the syringe velocity reduction will produce high stress on specific syringe areas; resulting in syringe breakage in some cases.

Typically, using a spring force of 70 N could lead to 272 N applied on the glass syringe (air bubble is not considered in that calculation). This force can lead to glass syringe breakage.

Different methods can be used to reduce the risk of glass breakage:

- One way is to grip the syringe by the shoulders instead of the flanges as illustrated in Figure 4
- Another way is to use damping materials
- Finally another method is to reduce the impact force that can be transmitted to the syringe.

The Kinetic energy can be calculated as follows:

$$E = Fx - \frac{1}{2}Kx^2 = -\frac{1}{2}Mv^2$$

E = Kinetic Energy
x = Displacement of syringe from point of firing to completion of needle insertion
M = Mass of syringe assembly before impact with the case
V = Velocity of syringe assembly before impact with the case

The syringe speed can be calculated as follows:

$$V = \sqrt{2\frac{E}{M}}$$

The total force on the syringe can be estimated as follows:

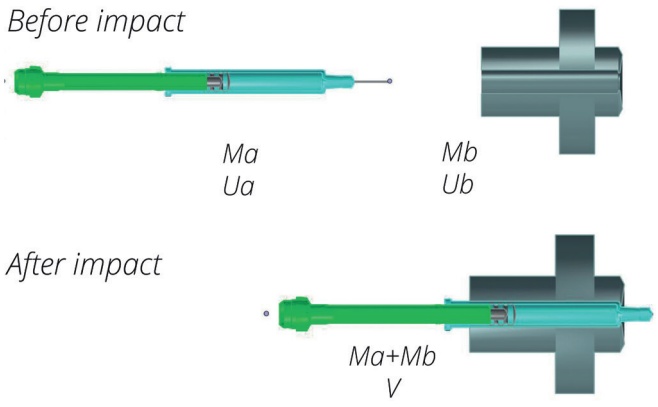



Figure 3: Calculation of total force on syringe resulting from a spring force of 70 N.

| | |
|---|---|
| x (m) | 0.009 |
| K (Nm) | 700 |
| F (N) | 70 |
| E (Nm) | 0.60 |
| Ma | 0.013 |
| Ua | 9.5 |
| Mb | 0.016 |
| Ub | 0 |
| Ma+Mb | 0.029 |
| V=Va=Vb | 4.32 |
| d (m) | 0.000341 |
| f (m/s2) | 39997 |
| $M_{syringe}$ (Kg) | 0.00519 |
| B (N) | 202 |
| Total force on syringe=B+F(N) | 272 |

Ma: Mass of syringe assembly before impact with the end stop
Mb: Mass of barrel before impact with the end stop
Ua: Velocity of syringe assembly before impact with the end stop
Ub: Velocity of case before impact with end stop
Va=Vb=V: Velocity of syringe assembly at end stop after impact
d: deceleration distance
B: brake force

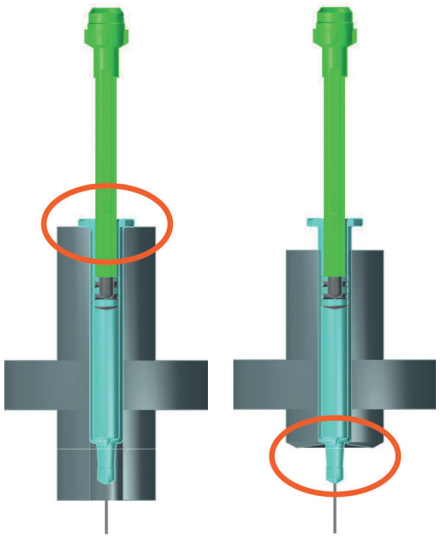


Figure 4: Gripping syringe on the shoulders (right) instead of the flange (left) reduces overall stress.

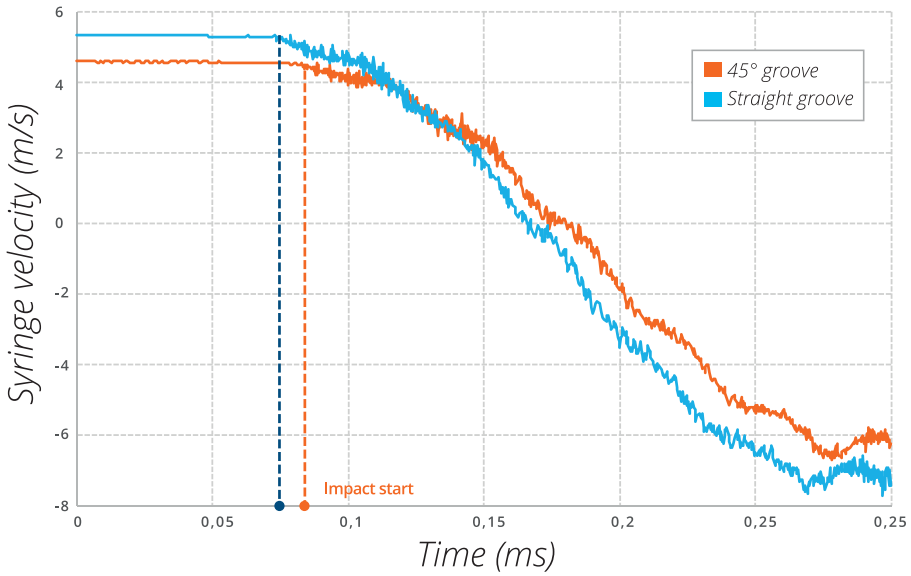



Figure 5: Syringe velocity (m/s) over time during simulation auto-injections using a 45° orientated cam and a straight cam design.

## STUDY REPORT: REDUCTION OF INSERTION SPEED

Nemera recently conducted a study to investigate glass syringe fracture risk in autoinjectors by lowering the impact force that can be transmitted to the syringe. Stress analysis was used to demonstrate the effect of lower impact force on syringe stress level.

### Method

Numerical simulation was performed using:

1. Adams™ 2014 Multibody Dynamics Simulation. This software simulates all parts, movements and speeds. The out put of this simulation provides a full model.
2. Finite element simulation with MSC Nastran™ 2014 Structural & Multidiscipline Simulation (Explicit transient).

This software simulates stresses between all parts at the calculated speed (Adams 2014).

Assumptions: deformable parts; transient dynamic simulation; and initial condition is the impact velocity given by the full model.

The study compared two models: one with a straight cam guiding the syringe needle insertion and the other a model with a 45° cam, guiding the syringe needle insertion.

All other conditions were constant including: spring force; formulation viscosity; syringe size; needle gauge and length.

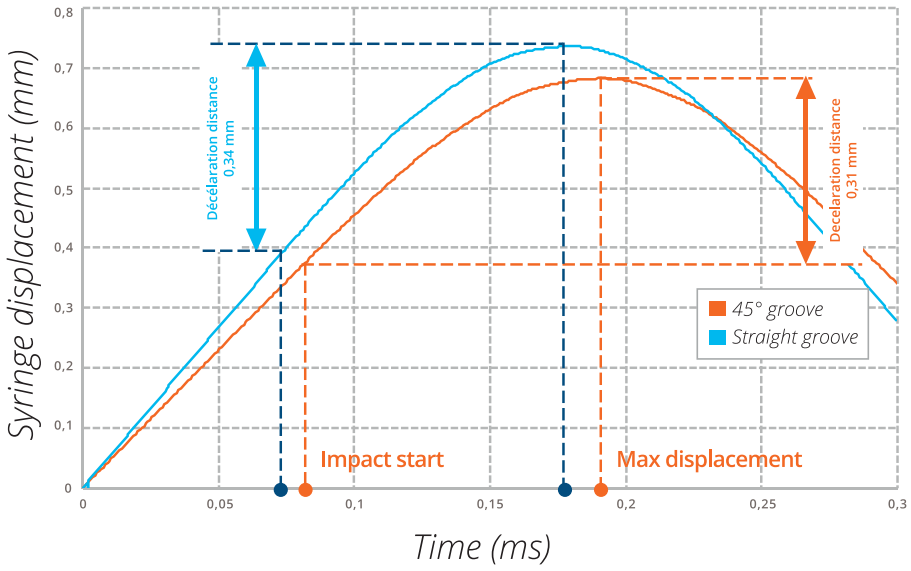



Figure 6: Syringe displacement distances (mm) over the course of the simulated autoinjection.

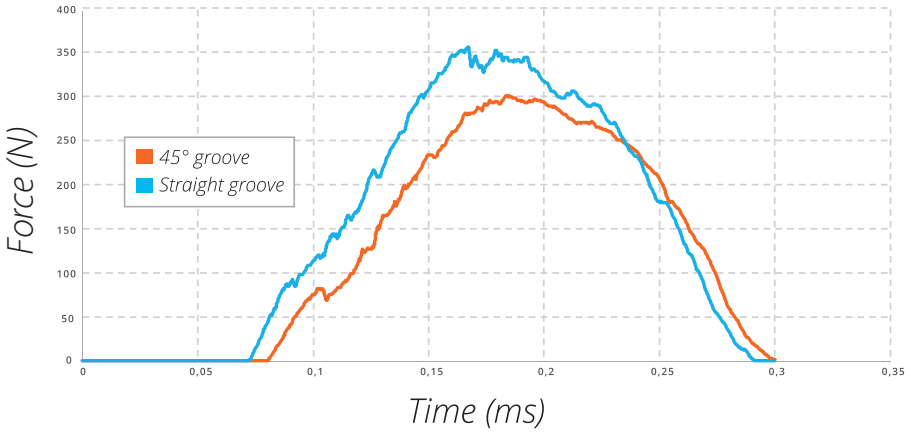



Figure 7: Shock force (N) on the syringe / syringe housing during the simulated autoinjection.

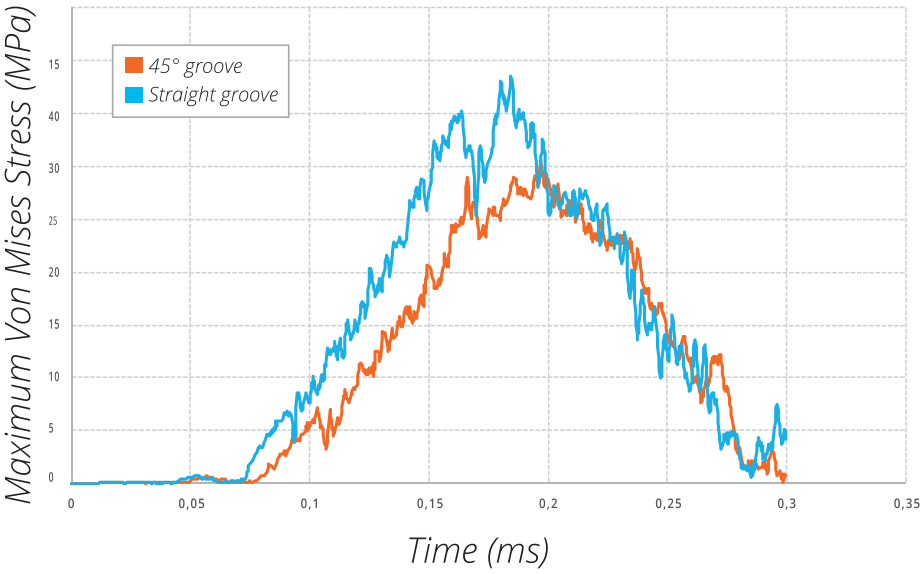



Figure 8: Maximum stress (MPa) on the syringe from the simulated autoinjection with 45° cam compared with straight cam.

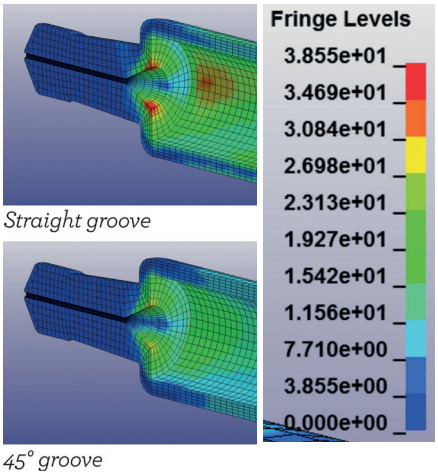



Figure 9: Simulated stress maps of the two autoinjector designs (top) straight cam and (bottom) 45° cam.

**Results**

As shown in Figure 5, the syringe speed was simulated during its shock with the device. Considering a spring 70 N, the maximum syringe speed was 5.4 m/s with the straight cam, and 4.6 m/s with the oriented cam. According to the configuration with the 45° cam, the syringe deceleration was smoother compared with the other configuration with a straight cam.

The deceleration distances can be estimated at 0.31 mm with the 45° cam compared with 0.34 mm with the straight cam (Figure 6). The distance leads to a reduced shock on the syringe.

The shock force on the syringe / syringe housing over the course of the auto-injection was simulated (Figure 7). As expected, maximum force on the syringe was lower (300 N) with the 45° orientated cam compared with the straight cam (350 N). Time to reach maximum force is also shorter with the straight cam. Similarly, as Figure 8 shows, the maximum stress on the syringe from the simulated auto-injection was lower with the 45° cam (30 MPa) compared with the straight cam (38 MPa).

Finally, the simulated stresses were mapped for each of the autoinjector designs, 45° cam and straight cam. Figure 9 shows that the highest stresses were all in the autoinjector shoulder, with higher stresses being generated from the simulated straight cam design, compared with lower streses from the 45° cam design.

**Study Conclusion**

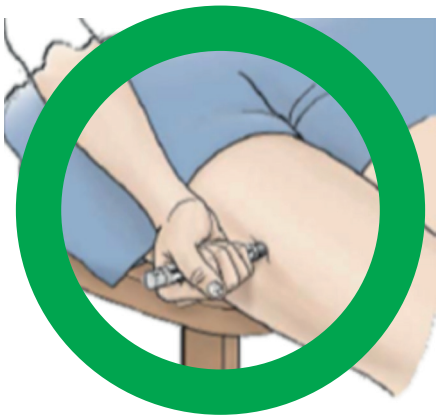
The tendency for larger injected volume with higher viscosity highlights the need to consider this risk at earliest stage in the development process. The results obtained during this study showed that by design, syringe speed at needle insertion can be reduced, as can the stress on the glass syringe, reducing the risk of syringe breakage.

## CONCLUSION

The Safelia™ autoinjector combines design elements (summarised in Table 1) such as gripping the syringe by the shoulder rather than the flange, and a slower insertion time achieved through 45° orientation of the cam, which provide significant benefits in terms of patient comfort and safety (Figure 10).

## Pain reduction

### Patient friendly



- No initial injection peak
- Constant delivery flow
- Adjustable needle insertion speed
- Needle insertion disconnected from injection
- Automatic needle retraction
- Possibility to have thinner needles

## Even viscous drugs, no breakage

### Syringe friendly

- Syringe is held encapsulated through the barrel
- Syringe front housing
- No stress on the syringe flange
- Possibility to inject very viscous drugs

Figure 10: Benefits of the system for patient comfort and safety.

Safelia™ is now ready to be customised to your formulation and delivery specifications.

## ABOUT NEMERA

Nemera has a well- know and established reputation in designing, developing and industrialising parenteral devices. As an example, every day over five million diabetics rely on devices manufactured by Nemera over our four manufacturing plants with harmonised high standard quality. Upstream of production of pens, autoinjectors, implanters, we rely on the expertise of our Innovation Centre at La Verpillière, near Lyon, France (Figure 11). Safelia™ development has benefited from the implication of creative design and human factor specialists, mechanical engineering, testing in our world-class laboratory, manufacturing and assembly knowledge and extensive mathematical modelling.

| Expected benefits | Standard AI | Safelia | Safelia Features |
|---|---|---|---|
| Creating possibilities for viscous injections with the same AI platform as for standard glass syringes | x | ✓ | Injects fluid and viscous drugs up to 1000 cP |
| Risk of syringe breakage eliminated Possibility of using all (or no) syringe flanges | x | ✓ | No stress on syringe flanges |
| Enables increased spring force and use of small gauge needles (less patient pain) without risk of glass breakage | x | ✓ | No stress on syringe flanges |
| Reduction of pain at needle insertion | x | ✓ | Adjust needle insertion speed |
| Reduction of pain during injection | x | ✓ | No initial injection peak |
| Drug is delivered at the right depth | x | ✓ | Needle insertion disconnected from injection |

Table 1: Summary of Safelia benefits and features compared with standard autoinjector.


Figure 11: Nemera's Innovation Centre at La Verpillière, near Lyon, France.

Nemera


# Safelia™

NEW GENERATION OF
2-STEPS AUTOINJECTOR
PLATFORM

parenteral

pulmonary

ophthalmic

dermal/
transdermal

nasal/
buccal/
auricular

## INNOVATIONS FOR INJECTION DEVICES




Nemera provides solutions for the pharmaceutical industry, including standard innovative products, development of custom devices and contract manufacturing.

we put patients first

**www.nemera.net** information@nemera.net Phone: +33 (0)4 74 94 06 54

WEIBEL CDS AG

safer, easier and faster drug delivery

# A CARTRIDGE-BASED DRUGDELIVERYSYSTEM FOR PUMP SYSTEMS

**Cartridge-based drug delivery systems are small and easy to use. As discussed in this article by Ludwig Weibel, Chief Executive Officer, and Hans Peter Manser, Business Director, of Weibel CDS, this system incorporates all the parts needed for a specific drug application into one product. This novel and innovative approach offers patients numerous advantages including saving time and a reduction in needlestick injuries.**

Currently, the most familiar use of pump systems is for insulin where such systems are widely accepted. Unfortunately, nearly all systems available today require patients to transfer the drug from a vial, for example, into the pump by using a syringe. Self-medication is heavily dependent on the ability of the patients to prepare and manipulate the injection device. This can be a major issue, especially for elderly patients.

> "Following our mission to support safer, easier and faster preparation and administration of drugs, all functions and parts needed for a specific drug application are integrated into one product."

Following our mission to support safer, easier and faster preparation and administration of drugs, we have integrated all functions and parts needed for a specific drug application into one product – a cartridge-based DrugDeliverySystem. The user only opens one package and the complete handling is done in a closed system in order to reduce contaminations, handling errors and needlestick injuries, combined by a reduction in the time taken to administer the drug.

This system is designed to accept standard 3 mL insulin cartridges. Barely larger than the cartridge itself (Figure 1), the system is extremely small yet still incorporates all functions including a needle insertion system, a unique pump system, a battery, a drive and an electronic control unit.

## AUTOMATIC NEEDLE INSERTION

After a purge function, the automatic needle insertion system is launched inserting the steel needle into the tissue. Immediately the steel needle is retracted leaving a soft cannula assuring the highest level of comfort to the patient (Figure 2). The mechanism is engineered to make it impossible to launch the mechanism twice, as the cannula is in a locked position.

## UNIQUE PUMP SYSTEM

Not requiring any type of plunger rod, the system is designed to suck out the drug instead of pushing it out. This requires a pump system that is extremely powerful in order to overcome the break-loose forces and allow the rubber stopper to slide smoothly.

Nevertheless, for basal and bolus

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Figure 1: Small yet incorporating all functions.

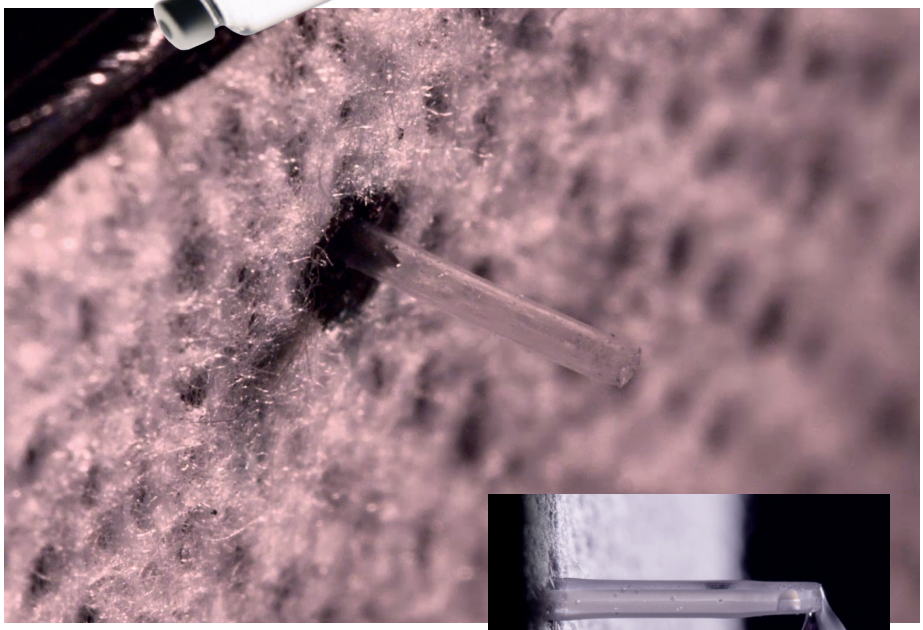

Figure 2: Automatic needle insertion system with soft cannula remaining in the body after insertion.

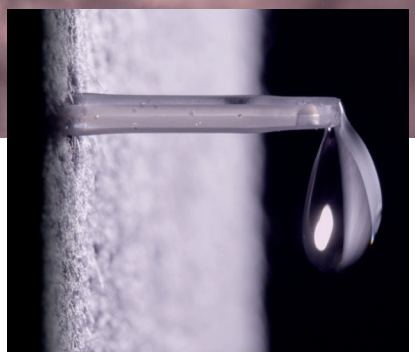

Figure 3: Accurate dosing assured by the unique pump system.

"The system offers pharma companies full flexibility in setting the doses as required up to a maximum dose."

injections, the pump is able to provide the required dose accurately (Figure 3).

The system offers pharma companies full flexibility in setting the doses as required, up to a maximum dose. There are no constraints such as stroke volume limiting individual doses.

## FREEDOM OF CHOICE

The cartridge may be pre-assembled by the pharmaceutical company using their specific cartridge which can hold less than 3 mL, or alternatively the patient can choose the insulin supplier by himself (Figure 4).

The device is patched to the body – often the abdomen – and may be operated via an external control unit allowing the patient to have some control.

## ELECTRONIC CONTROL UNIT

The software used to control the DrugDeliverySystem offers the highest degree of flexibility. Various levels of access guarantee its proper use. The pharma company can set the overall limits relative to the drug administered, doctors or healthcare personnel can define the patient's specific settings and the patient can, for example, set a bolus as required by his diet (Figure 5).

The external control unit may be combined with a glucose monitoring system.

## BATTERY

Once the cartridge is empty, the patient receives an alert requesting a change of the disposable part including a new, full cartridge. The battery of the reusable part can be reloaded. One battery load supports a minimum three to five-day operation of the device.

## ADVANTAGES

The advantage for the end user is a reduction in:

- Contamination
- Handling errors
- Needlestick injuries
- Time spent administering medication.

Pharma companies can differentiate themselves from competition. The final design is according to your specific needs from a functional as well as design perspective.

## PORTFOLIO

As well as this DrugDeliverySystem, Weibel CDS offers:

- DrugDeliverySystem large volume (LDV) based on our MiniBagSystem concept for micro-infusion of 30-50 mL.[1]
- DrugDeliverySystem 1 mL long syringe based. Automatic injection of 1 mL long syringes over a period or at a specified time.
- DrugDeliverySystem with automatic reconstitution functionality.
- Squeezer Test and Application System for stability testing of drugs in the MiniBagSystem.


Figure 4: Available for all 3 mL cartridges.

- The SuperCapSyringe® product family upgrades your vial practically to a prefilled syringe. Based on a modular design, the syringe is fully adaptable to your application needs. It is supplied in different sizes and with staked needles including a passive safety device.[2]
- The Reconstyringe® product family is first in offering a fully automated reconstitution of lyophilised drugs. The drug is contained in its original vial, the solvent in the MiniBagSystem. With a spring mechanism and holder plates the content of the MiniBagSystem is emptied into the vial. Like a Swiss watch, it runs through the full reconstitution cycle. Finally, the drug is drawn into the SuperCapSyringe® for injection.[2]


Figure 5: External Control Unit.

*International patents pending. SuperCapSyringe® & Reconstyringe® are registered trademarks of Weibel CDS AG.*

To watch the system in operation go to: http://www.weibelcds.com/wp-content/themes/cdsweibelag/videos/weibel_dds.ogv

## REFERENCES


1. *Weibel LD and Manser HP, "DrugDeliverySystems: Ready to Use for Highest Patient Comfort". ONdrugDelivery Magazine, 2015, Issue 58, pp 16-18.*
2. *Weibel LD and Manser HP, "Reconstyringe: Full Integration of all Functions & Parts, Fully Automated Reconstitution". ONdrugDelivery Magazine, 2015, Issue 55, pp 66-67.*

# DrugDeliverySystem
# Cartridge based

Designed to accept standard 3 ml insulin cartridges, yet barely larger than the cartridge itself, the system is extremely small and still incorporates all functions needed.

## safer, easier and faster drug delivery

*International patents pending*

WEIBEL CDS AG

safer, easier and faster drug delivery

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SENSILE MEDICAL

# EFFICIENT RESULTS FROM A PARTNERSHIP THAT WORKS – THE DRIVE UNIT OF THE PATCH PUMP

**Sensile Medical needed a better motor for a new micro-pump application, and they selected Buehler Motor (Nuremberg, Germany) as their partner. Here, Gerhard Mayer, PhD, Vice-President Business Development North America; and Sandra de Haan, Head of Business Development outside North America, both of Sensile Medical, describe how, together with their pharmaceutical partner scPharmaceuticals (Lexington, MA, US) and Buehler Motor, developed the drive mechanism for a new, soon-to-be launched patch pump.**

Sensile Medical has developed a novel micro pump which is the heart of the patch pump for scPharmaceuticals. This patch pump offers a wide range of advantages and is superior in many aspects over narrowly-defined drug delivery systems. The patch pump consists of two main components: an activator, which is reusable up to 300 times, and a single-use cartridge. In April 2016 scPharmaceuticals initiated clinical trials with the patch pump.

## BASIC DEVICE CONCEPT

For many applications, semi-disposable product concepts may be preferred. The overall objective for the development of the complete patch pump was to offer the most advanced features for safety and convenience, with the cost and utility of a disposable product.

The disposable part contains all components that come into contact with the drug or the patient: the core pumping mechanism, fluidic channels and patient interfacing elements like the needle and the adhesive. The reusable part of the patch pump includes electronics, sensors, drive unit, rechargeable battery and the simple user interface.

As a "patch pump", this drug delivery system is affixed to the patient with an adhesive. An integrated needle is deployed prior to the injection and retracts automatically after the injection.

> "The overall objective for the development of the complete patch pump was to offer the most advanced features for safety and convenience, with the cost and utility of a disposable product."

## ADVANTAGES OF THE PUMP SYSTEM

These pumps are increasingly being used to enable large-volume subcutaneous delivery of modern pharmaceutical and biotech products for self-administration by patients. Due to Sensile's SenseCore technology the products are highly cost-efficient, accurate and safe.

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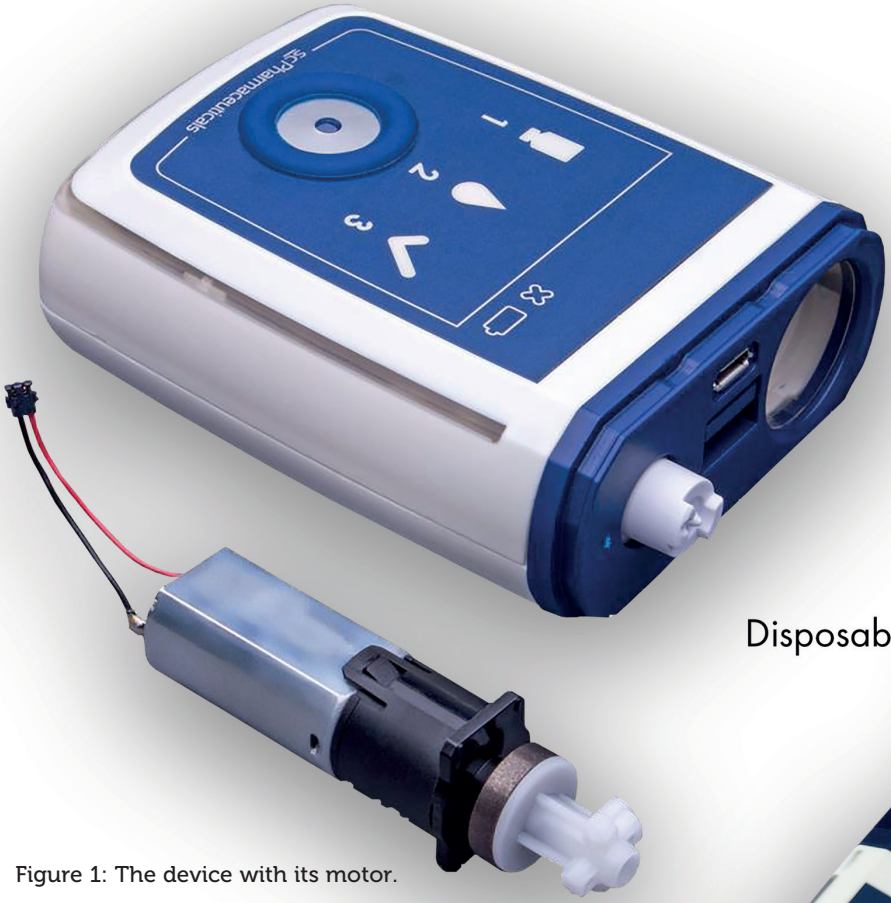


Figure 1: The device with its motor.

> "These easy-to-use, safe and discrete devices enable better therapies while improving the daily lives of patients."

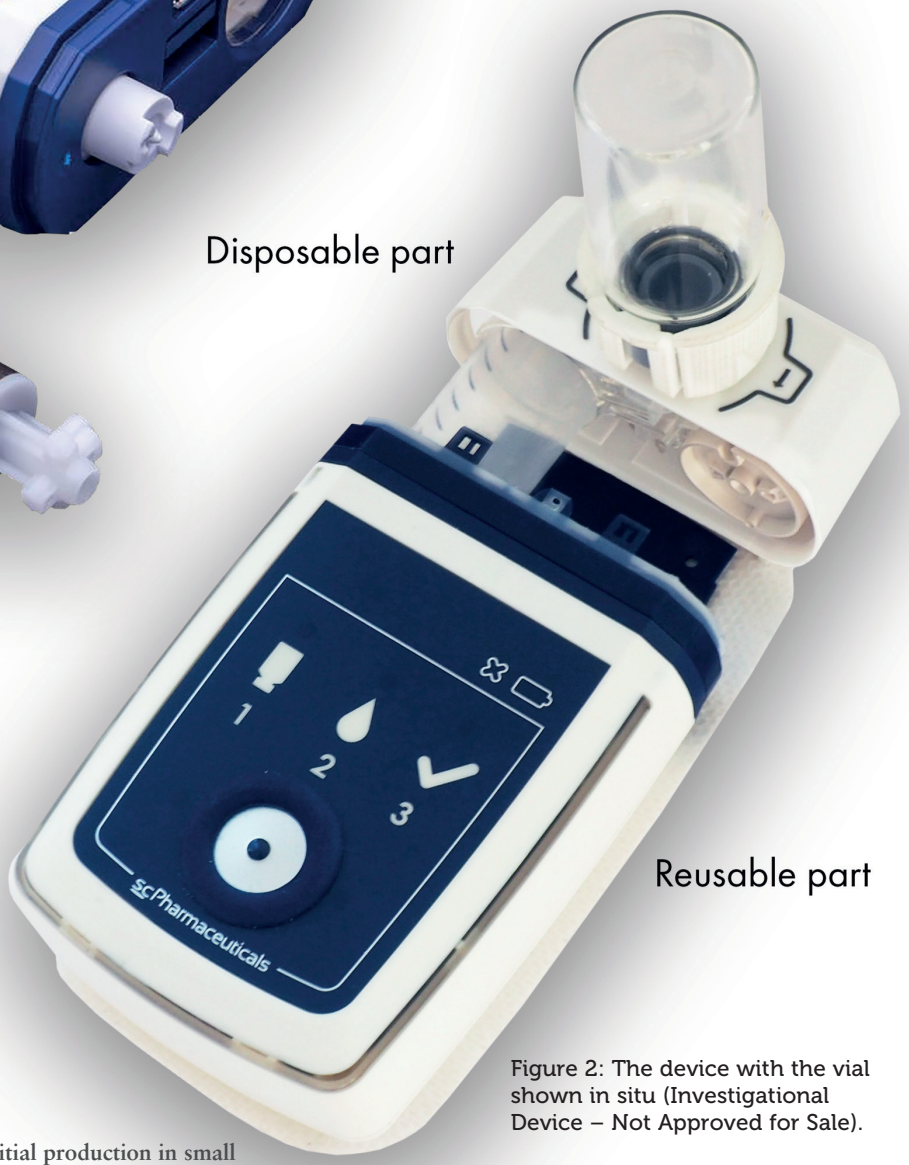


Figure 2: The device with the vial shown in situ (Investigational Device – Not Approved for Sale).

These easy-to-use, safe and discrete devices enable better therapies while improving the daily lives of patients. At the same time, by taking the therapy out of a clinical setting and allowing patients to self-administer their medication, healthcare costs are reduced significantly.

## CHOOSING THE RIGHT DRIVE UNIT

The project with scPharmaceuticals involved choosing a drive unit where key criteria included:

**1 Optimisation of sound and space**
Special care was given to minimise the noise levels of the planetary gear train, providing discretion for patients during use. Due to the small available space inside the reusable part of the device, an additional focus was also given to the size of the gear motor.

**2 Drive unit customisation**
The integration of the clutch into the motor unit allowed for power consumption optimisation. Additionally, the permanent axial load towards the gear motor had to be addressed.

**3 Fast prototype availability**
Time was short. A working prototype was urgently required.

**4 Initial production in small quantities but high quality**
ISO 13485 requires that production processes for the patch pump are mapped out. Despite small initial production levels, rapid transition to efficient, high-volume production was targeted.

## FINDING A PARTNER TO PROVIDE THE DRIVE MECHANISM

Sensile Medical chose Buehler Motor, a specialist in micro-drive mechanisms, to be the partner for scPharmaceuticals' pump.

Buehler Motor started with humble beginnings as a clock-making company more than 160 years ago in Germany's Black Forest. Since then, it has transitioned into an international supplier of high-tech drive solutions for automotive, healthcare and industrial applications. Innovation, change, new developments and continuous improvements have all made an impact on what the company can now deliver.

Buehler Motor can provide system solutions from a single source. Quick and flexible implementation of complete

Figure 3: The patch pump is affixed to the patient with an adhesive.

customer-specific solutions – from prototype to series production – is only possible in combination with Buehler's in-house system capability, in-house development competence, in-house production expertise and in-house quality commitment.

Development proficiency is the strong foundation upon which Buehler Motor is built. An extremely high process capability in developing motors and gearing, along with hardware and software, is one of Buehler's exceptional strengths. This expansive knowledge allows Buehler to provide a complete solution independently.

## THE INITIAL CHALLENGES

**1 Meeting industry standards**

Medical industry norms EN 60601-1 and EN ISO 13485 guide the development for the pump and motor. The final product had to meet stringent criteria for temperature, mechanical stress, as well as low noise levels. This included, not only the core motor, but also components such as the gear train, transmission and clutch.

**2 Creating the custom drive unit**

The drive mechanism has to perform three functions: transfer the medication from a vial to the internal pump reservoir, insert the needle into the subcutaneous tissue and deliver the medication. This drove the use of a Snap-Fit connection and a custom-designed clutch between the motor's core pumping components. The clutch and the output shaft of the gear were designed in a very smart way to decouple the planetary gear train from the permanent axial load, as well as reduce the short-term stress during drop off.

**3 Constructing the prototypes**

The prototypes required construction in a clean-room environment. The development of such a small, highly-precise drive mechanism required a unique solution for a lubricant-dosing system, while implementing the process within the confines of an existing production area.

**4 Production**

A small-scale production line, for clinical trial units, was set up at Buehler's headquarters and development centre in Nuremberg, Germany. A dedicated clean-room was constructed that mimicked the processes of the planned, future large-scale production in Mexico. The same team that developed and implemented the prototype production in Germany also led the efforts to build the production line in Mexico.

## CONCLUSION

The partnership between Buehler Motor and Sensile Medical worked well. Employees from both companies established an efficient team to implement a good solution to meet scPharmaceuticals' specific needs. Highly-efficient communication between all involved parties was key for the successful development in a very short time frame.

## ABOUT SENSILE MEDICAL

Sensile Medical is a leading company in the area of advanced micro pump technology developing a broad range of customer-specific delivery and dosing solutions. Sensile Medical is a full-service provider of pump-based drug delivery solutions, with in-house specialists for engineering, electro mechanics, software development and more. Our partners include well-known pharmaceutical companies and research organisations.

# We are Swiss pioneers in Large Volume Injector Devices

## Offering a clever platform for unique devices


## BUILDING BRIDGES FROM DRUGS TO PATIENTS.

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Designed and Engineered in Switzerland

SENSILE MEDICAL

# COMPANY PROFILE: HASELMEIER

HASELMEIER
Drug Delivery. Tailormade.

## User Focus

At Haselmeier, our mission is to create products enabling a convenient and comfortable experience. This is why patient feedback is integrated early in our device designs. Early concepts are prototyped for testing and Human Factors studies to capture the handling needs and skills of potential users. This knowledge is integrated into the device design to provide successful administration of the drug product and a positive user experience.

Haselmeier offers a range of early-stage activities:

- Think-tank discussions and paper concepts
- Detailed product concepts and industrial designs
- Detailed user handling review and risk-analysis
- Prototyping of initial concepts up to functional devices
- User focus groups and human factors studies for concept and prototype evaluations
- Detailed user requirements and product design specifications based on selected concept.

## Bridge to Market

Successful development and industrialisation of drug delivery devices is dependent upon the understanding and execution of today's technical, regulatory and operational requirements. At Haselmeier we provide integrated design, development and industrialisation services to help you bridge your serial product into the market. Our qualified design control process, certified quality system, regulatory expertise, solid network of partners and strong manufacturing operations are all designed to achieve your expectations. Together we enable a smooth market introduction for your commercial drug delivery device.

Haselmeier's commercial development and industrialisation services include:

- Concept transfer into detailed User Requirements and Product Design Specifications
- A certified Design Control Process and Quality System
- Design verification, product and process validation processes
- Regulatory expertise to support your approval strategy
- Controlled design-to-manufacturing transfer, verification and validation.

## Manufacturing & LifeCycle Partner

We understand that each customer has individual and specific requirements for their product. Regardless of your requirements, Haselmeier applies the highest quality standard for manufacturing your drug delivery device to ensure a reliable and reproducible manufacturing and quality process. We work continuously with our customers to identify product improvements at all stages of the product's lifecycle to provide a safe and state-of-the art drug delivery device.

Haselmeier provides flexible, reliable, manufacturing and lifecycle management:

- Certified and modern production facilities and manufacturing processes
- Qualified and well trained personnel
- A strong network of sub-suppliers and manufacturing partners
- Continuous Engineering and product improvement programme
- Innovation meetings to identify next product generation.

> "Successful development and industrialisation of drug delivery devices is dependent upon the understanding and execution of today's technical, regulatory and operational requirements."

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# Working together to inspire your patients

At Haselmeier we work in close cooperation with our pharmaceutical partners to create and deliver the safest and easiest to use injection devices for their patients.

Our proven device platforms, world leading engineering and global manufacturing capabilities combined with an intense focus on patients provides our partners with a total product solution that helps improve patients' lives.

Experience **User Focus, Bridge to Market** and **Manufacturing & LifeCycle Partner** here:


HASELMEIER

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# COMPANY PROFILE: HASELMEIER

## PLATFORM & PRODUCTS

The Haselmeier Axis-D Pen System is a disposable, variable-dose injection device designed for the use with a 3 mL cartridge (Figure 1). The elegant and compact Axis-D Pen System is available as a high quality plastic version.

- No or minimal priming
- Accurate dose reading with sliding window
- No rotating outer components
- Protected dose scale.

The Haselmeier i-pen (Figure 2) is a reusable, variable dose injection device for use with a standard 3 mL cartridge. The i-pen features an elegant non-medical design which is the result of extensive research and patient testing.

- Dose adjustment from 0.01 mL to 0.6 mL per injection
- Compact size enables easy handling and portability
- Large, easy-to-read dose indicator
- All metal outer body.

The i-pen² (Figure 3) is a reusable, variable-dose injection device for use with a standard 3 mL cartridge. The i-pen² was specifically created to provide a high-quality pen at economic cost.

- Dose adjustment from 0.01 mL to 0.6 mL per injection
- Compact size enables easy handling and portability
- Large, easy-to-read dose indicator
- All plastic components.

The Softpen (Figure 4) is a fully automatic, reusable injection device featuring Haselmeier's patented hidden needle design. Upon depressing the clip on the pen, the needle automatically enters the subcutaneous tissue followed by delivery of the solution.

- Fully automatic needle insertion and injection
- Needle is hidden prior to and during injection
- Multiple injections from single 3 mL cartridge.


Figure 1: The Axis-D Pen System – disposable, variable-dose injection device designed for the use with a 3 mL cartridge.


Figure 2: The i-pen – reusable, variable-dose injection device for use with a standard 3 mL cartridge.

"We understand that each customer has individual and specific requirements for their product."


Figure 3: The i-pen² is a reusable, variable-dose injection device for use with a standard 3 mL cartridge.


Figure 4: The Softpen – a fully automatic, reusable injection device featuring Haselmeier's patented hidden needle design.

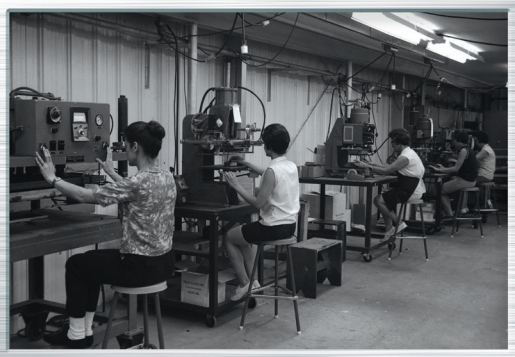
Figure 5: The Penlet is a fully automatic, fixed-dose injection device.

The Haselmeier disposable Penlet (Figure 5) is a fully automatic, fixed dose injection device designed for use with a standard 3 mL cartridge. Upon depressing the clip on the pen, the needle automatically enters the subcutaneous tissue, which is followed by delivery of the solution.

- Ready for use by the patient and no dose adjustment required
- Fully automatic needle insertion and injection
- Needle is hidden prior to and during injection.

# At Phillips-Medisize We're All About Process

This



Not This

We know process is the absolute key to assuring that we deliver upon our customers' expectations, **the first time and every time**. That's why our people are all about process. In fact, our process requirements apply not only to manufacturing and quality SOPs, but also to our customer facing operations such as Program Management and Design and Development engagements, ensuring our customers benefit from a repeatable and scalable model.

So, when you work with Phillips-Medisize, you can be certain we'll exceed your highest expectations **the first time and every time**.

Phillips Medisize

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# INJECTING HUMAN FACTORS ENGINEERING/USABILITY ENGINEERING INTO INJECTABLE DEVICE DESIGN

In this, the fourth in a series of articles covering quality system requirements for medical devices used to deliver drugs and biologics and combination/borderline products, Marc Egeth, PhD, Director of Research; Patricia McGahern, Associate; and Sarah Johnstone, Research Associate, all of Core Human Factors, discuss use errors associated with marketed and in-development injection systems.

In the US, any medical product that contains a medical device is subject to FDA Quality System Regulation (QSR) 21CFR820. The design control requirements of the QSR (21CFR820.30) require that the design of a medical device be validated (i.e. ensure that devices conform to defined user needs and intended users). Human factors engineering / usability engineering (HFE/UE) is a methodology used to assure that the ultimate design of a medical device is "safe and effective for the intended users, uses and use environments".[1]

> "While effectively addressing some of the use errors associated with disposable syringes, the use of prefilled injectors presents a new set of use errors."

A component of HFE/UE is human factors (HF) testing in which representative users are observed interacting with developmental products to learn about use errors that could occur in real life.

Initially, formative HF testing is conducted to observe use errors and identify their root causes. Representative users interact with one or more aspects of the user interface, which includes the device itself, instructions for use (IFU), packaging, and intended training. Mitigations, based on the root causes of use errors identified during HF evaluations, are implemented during medical device design development to redesign the user interface to assure safety and usability.

A goal of HFE/UE is to have minimised use errors by the end of the iterative design development process. The final HF evaluation, known as the human factors validation (also known as a summative human factors evaluation), is used to demonstrate the validity of the device design. A HFE/UE report contains a summary of the HFE/UE process used to develop a medical device design and is an essential part of the design history file, required by FDA.

In the simplest case of an injection system, a disposable syringe may be used to deliver the wrong dose or the wrong drug unintentionally. To minimise these use errors and improve injection convenience, a variety of prefilled injection systems are available for professional and self-administration, including prefilled syringes, autoinjectors, injection pens and jet injectors. However, while effectively addressing some of the use errors associated with disposable syringes, the use of prefilled injectors presents a new set of use errors.

Prefilled drug delivery devices and kits that combine a drug product and a medical device, which are combination products, are subject to combination product good manufacturing practices (GMP) codified in 21CFR4, and by extension are subject to the QSR, and are therefore required to have validated designs. This article describes some of the challenges manufacturers have encountered in the process of validating the design of injection devices.

## USE ERRORS SEEN IN HUMAN FACTORS TESTING

In a study conducted at Core Human Factors, only 2/31 (6%) participants succeed in delivering a full dose from a

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currently-marketed rescue injection kit that included a prefilled diluent syringe.[2] Some participants injected the diluent only, not realising they needed to reconstitute the drug powder in the vial that was included in the kit. This included participants who had previously received training, and those who had the IFU available. Had the diluent syringe not come prefilled, it is unlikely that participants would have injected with an empty syringe, rather the fluid visible in the syringe provided a misleading cue that the syringe was ready for injection into the body. In the same study, other participants bent the needle attempting to insert the needle through the vial cap, not realising that the vial needed to be uncapped before use. Because there was only one needle included, the entire system was then unusable and there was no way for users to recover.

Some manufacturers produce syringes that include unit markings on their barrel that are specific for a particular drug and that are intended to simplify drug administration. However, users may not realise that the graduation markings on the syringe barrel are specific to that drug. This can lead to drug overdoses. With insulin for example, users may draw highly potent U-500 insulin into a syringe with markings intended for use with U-100 insulin.[3] This can lead to a five-fold overdose of insulin because if filled to the "50 units" line on the syringe, there would actually be 250 units of insulin in the syringe. Similarly, users believing they are using syringes with scales printed for insulin units have given ten-fold overdoses of insulin when they accidentally used similarly-packaged and -coloured syringes for the diagnostic tuberculin[4] (see Figure 1).

The insulin syringe confusion was caused by two products that were in some ways too similar to each other. At the same time, if a new technology is too different, users might not know how to use it or might not be confident in its use. For example, in our usability labs at Core, we have seen that using a prefilled autoinjector can lead to overdoses when users are unsure if the first dose was successfully injected and thus repeat the injection. What a user expects a device to do is intimately linked to how the user will interact with the device. When user expectations do not match the reality of the device design, use errors may occur.

Novel device mechanisms implemented to improve the safety and usability of the injection experience can introduce a completely different set of use errors. Issues seen with early device designs include the following:

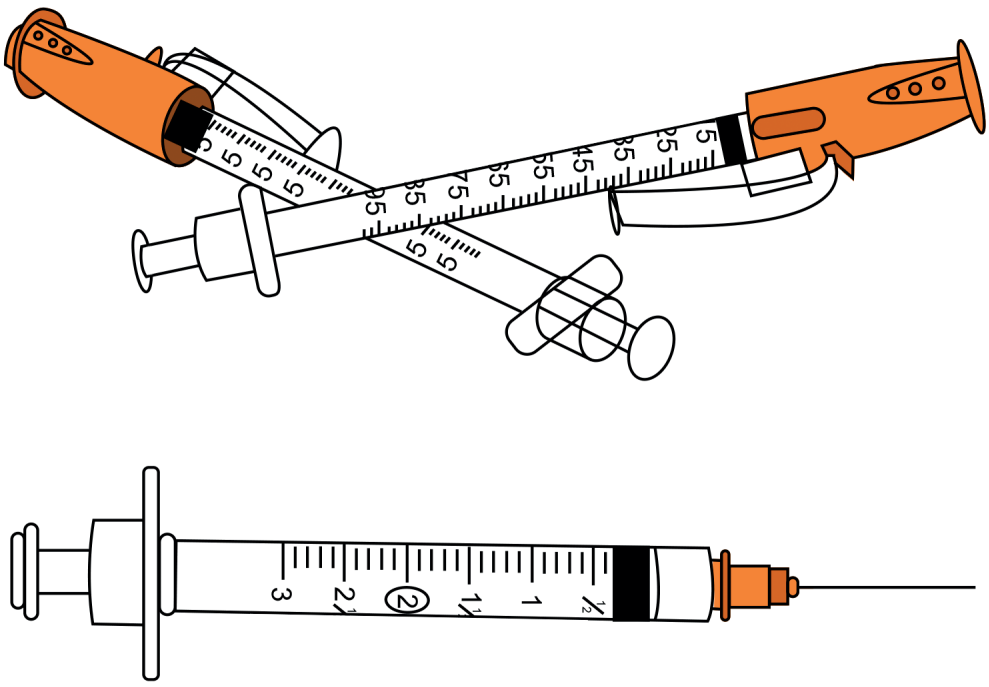

Figure 1: U-100 insulin-specific syringes (top), and generic syringe with 25-gauge needle for e.g. tuberculin (bottom). (Images created by Amanda Shames, BFA)

> "Explaining how products work in the IFU can mitigate some usability issues. However, some users have poor literacy, some do not bother reading the instructions, and others forget what they read after a short period of time. Some users only look at the pictures, others only read the words."

- Auto-injectors do not make the expected "click" sound leading to uncertainty over injection success
- Auto-injectors "click" twice, leading users to assume mistakenly the first click signalled that the injection was complete
- Labelling text too small, leading participant to not notice crucial warnings
- Printed dosing scale does not match user needs for dosing, users are not used to new units of measure, or users need gradations for dosing smaller than are marked and have difficulty with fractional doses
- Users confuse training devices for injection devices
- Users are not sure how hard to press injection device buttons, leading to wasted medication, by pressing too hard too early
- Users are not sure which end of an autoinjector has the needle, leading to injections into thumbs when trying to push a button on the opposite end
- Tactile or auditory feedback from the device is too strong leading users to be startled and drop the device.

## INSTRUCTIONS FOR USE

Explaining how products work in the IFU can mitigate some usability issues. However, some users have poor literacy, some do not bother reading the instructions, and others forget what they read after a short period of time. Some users only look at the pictures, others only read the words. Because of this, IFU are considered the least effective strategy for mitigating use errors. Nevertheless, IFU are an important part of the user interface. As part of the user interface, IFU must be validated.

Consider the figures and instructions shown in Figure 2, which are based on actual product figures and instructions (note that each has been re-drawn to avoid disclosing the particular product depicted).

Which side should be twisted according to Figure 2a, and which way? Unintentionally, the arrow is an ambiguous optical illusion. Is the light grey part in front of the black part so the twist is away from the reader, or is the black part in front so the twist is towards the reader? Does it matter, or is it just a minor inconvenience to twist the wrong way at first? Some devices can have internal mechanisms that can be disrupted if turned in the wrong direction, such that afterwards, re-screwing in the correct direction does not undo the damage. This can lead to incorrect dosing completely undetected by the users.

Figure 2b does not show Step "1" (number one, the first). This is step "I" (not the roman numeral but the letter, the ninth), which happened to be placed on the upper-left corner of page two, the backside of the instructions. Some participants in human factors evaluations start on the second page, thinking Step "I" was Step "1", and proceed to inject, thereby skipping key preparation steps A-H. This is the kind of usability issue that can be hard to detect without user testing. A graphic designer looking at images on a computer screen might not realise that down the line the size of the printed page could push this particular step to the start of the next page and appear as a "1" – when working with an alphabet, it might be hard for a graphic designer to see the "I" as anything but a letter. A key benefit of including user testing in the design process is detecting use errors that would otherwise be hard for designers to predict. Applying BF Skinner's maxim on the role of test subjects in experiments, "the rat is always right," designers need to address the use errors that participants encounter, however improbable they might seem a priori, because they point to real ways in which real people might hurt themselves in real life.

The part of the body is also unclear in Figure 2b. We have seen ambiguous

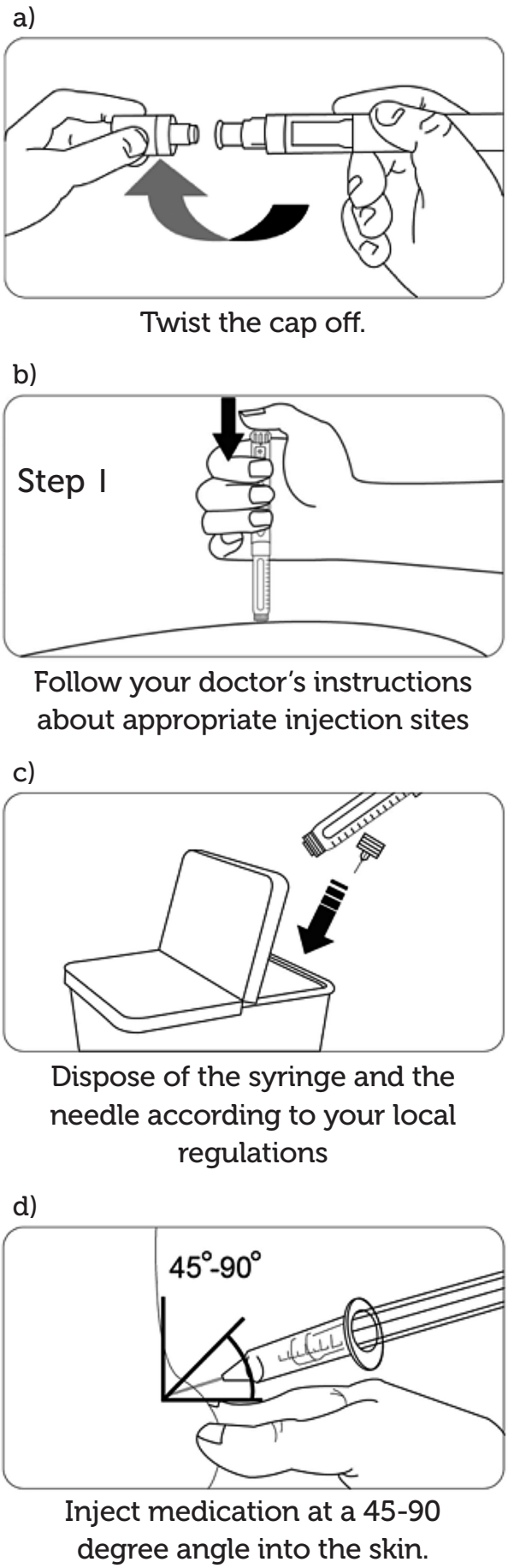


Figure 2: Example figures and instructions based on actual product figures and instructions. (Images created by Amanda Shames, BFA)

illustrations lead participants to inject in locations not intended by the manufacturer.

In Figure 2c, some participants in user testing assumed the black and white line drawing was a standard trash can, whereas the intention of the diagram was to depict a sharps container.

It can be hard for some users to grasp what Figure 2d is trying to convey. The graphic of the angle is superimposed on skin, but it is not lined up with the skin because the skin is pinched. The syringe looks like it is going in to something at greater than a 45° angle because of the orientation of the bold lines. However, looking closely at the fainter lines, the syringe truly is going into the skin at a 45° angle relative to the surface of the skin.

## SUMMARY AND CONCLUSION

The HFE/UE process aids medical device developers in improving their designs to meet the needs of users better and to satisfy crucial design control requirements. The method of observing representative users handle prototype products under conditions simulating real-life conditions has the proven ability to predict real-life user difficulties. The process is iterative and focused on the user perspective, such that every aspect of the user interface is tested and validated for safety and usability by the people who would use the device in their daily lives.

It is a common result in HFE/UE testing that designs that seem reasonable to engineers and designers (like a superimposed diagram explaining what angles are) turn out to have flaws that are first exposed only upon user testing. Indeed, it is for finding these "surprise" issues that FDA requires HFE/UE testing to support submissions. HFE/UE encourages early user testing of prototype devices, so manufacturers know early on in product development the sort of errors users are prone to experience. In this way, design safeguards can be introduced in advance of validation testing.

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## ABOUT THE AUTHORS


**Marc Egeth** received a PhD in experimental psychology from the University of Pennsylvania (Philadelphia, PA, US) in 2007. His academic publications cover evolution, perception and attention, child development, cognitive neuroimaging (EEG, MEG, fMRI), consciousness, experimental philosophy, medical hypotheses, and human factors in healthcare. Marc's experience in quantitative and qualitative methods includes neuroimaging, eye tracking, ethnographic research, audience/visitor studies, and moderating usability studies. His medical device research and design experience includes iPhone / Android apps, instructional material, and work/office environments including shared healthcare spaces.

**Sarah Johnstone** holds an MA in Experimental Psychology from the University of Pennsylvania. In her graduate work she received formal training in human perception, language processing, and decision making; her research focused on why people misunderstand or misperceive certain kinds of written, spoken, and visual information, and how they recover from those mistakes. Previously she studied linguistics and sociology, and has experience interviewing diverse groups of people, putting them at ease, and encouraging them to speak and act naturally. She is passionate about discovering what makes an instruction or interface ambiguous, and applying that data to design improvements.

**Patricia McGahern** holds an MSE in Bioengineering from the University of Pennsylvania. While at the University of Pennsylvania she was involved in neuroscience research on epilepsy and completed her Master's thesis on a project related to this research. She has a passion and fascination with medical devices, and joined Core Human Factors, Inc. to be a part of the medical device field.

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