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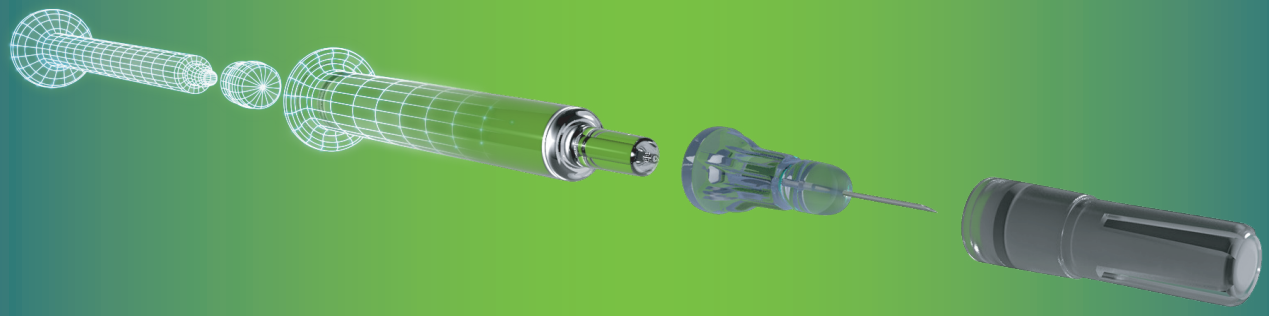

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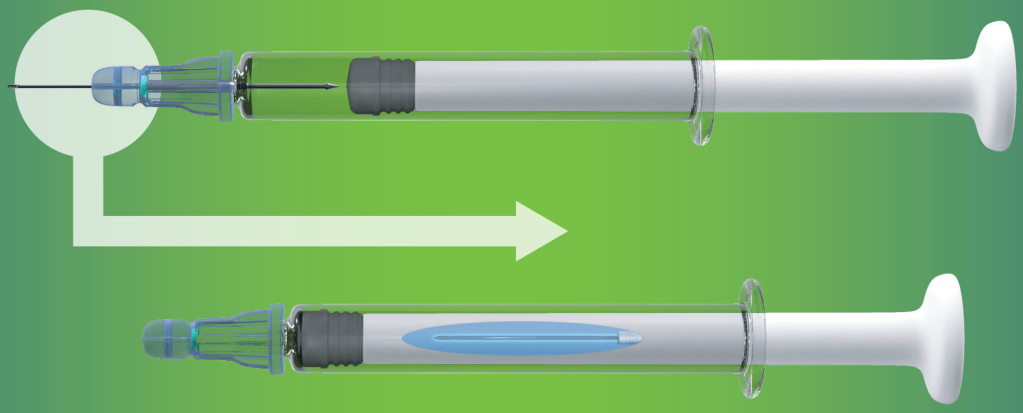

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ONdrugDelivery Issue N° 86, May 14th, 2018

INJECTABLE DRUG DELIVERY: DEVICES FOCUS

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Electronic subscription is always completely **free**.
Print subscription costs **£99/year + postage**.

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The Candlemakers, West Street, Lewes,
East Sussex, BN7 2NZ, United Kingdom

ONdrugDelivery Magazine is published by Frederick Furness Publishing Ltd.

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

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FINAL ASSEMBLY, LABELLING & PACKAGING: AN INTEGRATED SOLUTION FOR A FRUSTRATION FREE LAST MILE

For the development of combination products, pharma and biotech companies have the option to establish an assembly and packaging infrastructure internally or to outsource to a contract manufacturing organisation. In this article, one such organisation, SHL, explains what the benefits are of using a manufacturing partner and outlines what it can offer in terms of an integrated process.

For a pharma or biotech company working with a drug delivery device partner, the decision on final assembly, labelling and packaging is most often the final checkpoint in the development process for a combination product (Figure 1).

Well in advance of this checkpoint, the pharma/biotech company must make an informed decision regarding the device's final assembly: to either establish assembly and packaging infrastructure internally or partner with a contract manufacturing organisation (CMO).

Building internal infrastructure is a decision that is likely to involve input from a large cross-functional team across an organisation, with considerations such as:

- What is the overall cost of such internal infrastructure (e.g. capital expense, staffing requirements)?
- How does building this internal infrastructure align with the long-term commercial strategy of the company and the product?
- How long will this high quality and regulatory compliant infrastructure take to implement?
- What is the risk mitigation strategy if things do not go as planned?
- Are semi-automated equipment and processes acceptable or are more complex automated solutions required based on the forecasted demand?

Development Checkpoints for a Combination Product

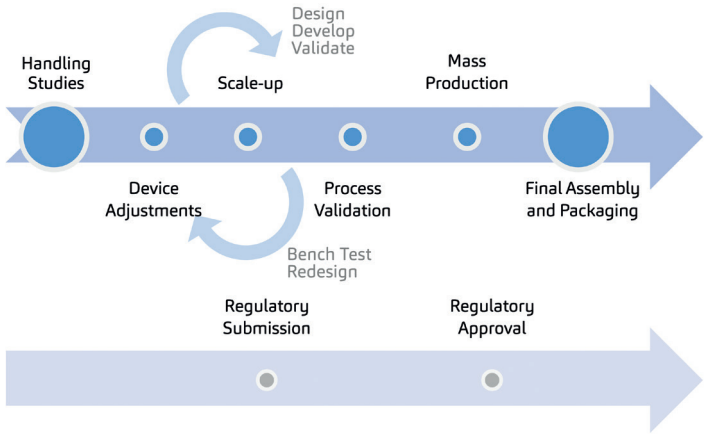

Figure 1: An overview of the stages of device development.

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Figure 2: SHL offers a range of drug delivery systems, giving customers the flexibility to accommodate changing market trends.

Lastly, it is important to consider whether the infrastructure can be leveraged across multiple products, keeping in mind that many devices differ in shape, size and industrial design. The company's infrastructure for final assembly should be future-proof: scalable to accommodate multiple products as well as changes to device volume over time – in both the best and worst case scenarios.

OUTSOURCING ASSEMBLY, LABELLING AND PACKAGING

After years of working with clients and understanding their needs, SHL Group has developed a simple solution that eliminates the frustrations commonly encountered in the final mile of the development process. SHL, a leader in device design and manufacturing, has heavily invested in recent years in establishing a contract manufacturing service offering final assembly, labelling and packaging for SHL-designed devices (Figure 2). With the addition of this business unit, SHL is able to offer a full turnkey solution that starts from device development and continues through to the commercial launch of a finished product, decreasing timelines to the clinic and/or commercial market for patients in need. Using our mature device platforms and infrastructure, SHL's quick-to-clinic or quick-to-market development process can take a partner from device development to clinic/commercial supply in under 15 months.

> "SHL Group has developed a simple solution that eliminates the frustrations commonly encountered in the final mile of the development process."

CONTRACT MANUFACTURING FACILITY

SHL's contract manufacturing facility for final assembly, labelling and packaging is based in Deerfield Beach, FL, US. This 45,000 square-foot (4,200 m^2), regulatory-approved facility houses specialised equipment and processes to support both low- and high-volume production requirements. Most of its device assembly and test equipment was designed and built by SHL's in-house automation team, resulting in total integration between the device and equipment developers. Additionally, SHL has invested in universal equipment designed to be flexible, providing a wide range of capabilities that include:

- final assembly
- bulk packing
- labelling
- packaging/kitting
- serialisation.

The required specialist skills are immediately available on-site to manage, drive and complete the project in scope. SHL's engineers are hand-picked from the pharma, biotech and medical device industries, offering a unique understanding of clients' needs. Located near multiple international airports, the world-class facility has an optimised materials flow process. Starting with the receipt of inbound goods to storage in refrigerated/ambient warehouses, the process also includes final assembly, labelling and packaging, and concludes with shipping of the finished product to our partners or a preferred distribution centre.

FROM DESIGN TO FINAL ASSEMBLY

Once a client has contracted us to design, develop and assemble its autoinjector, our final assembly team integrates with the device's project team to ensure knowledge transfer from development into commercialisation – building specific assembly equipment and processes needed per the device's characteristics. SHL's product engineers and programme managers are dedicated to creating a true supply chain alliance, providing design and tech transfer services to create a seamless commercialisation programme, while regulatory experts prepare a technical dossier that provides supporting documentation for our partners' filings. Our quality management system was specifically developed with SHL's processes, resources and needs in mind to make sure they satisfy all necessary regulatory requirements.

SHL is able to reduce lead time for equipment design and procurement by developing the client's device and the required assembly equipment in parallel. This means that in the initial stage of the device's development, SHL's in-house

design engineers are engaged with the equipment engineers to provide guidance on assembly and testing, ensuring that the final assembly process effectively aligns with the device; initiating these work streams in parallel inherently reduces lead times (Figure 3).

PROCESS DEVELOPMENT SERVICES

In addition to assembly, labelling and packaging services, SHL also offers a suite of process development services, consisting of manufacturing sciences, analytical sciences, statistics and project management.

- Manufacturing sciences are responsible for equipment commissioning and manufacturing process design. This group will partner with SHL's engineering team, automation team and the client to design an optimal and compliant manufacturing process and control strategy.
- Analytical sciences are responsible for design, development, validation and transfer of test equipment and test methods. This group is also responsible for managing a number of development studies, including syringe characterisation, feasibility testing, transportation studies and ageing studies, eliminating the need for clients to manage multiple suppliers.
- Statistical services assures optimal control strategy with high statistical confidence, eliminating waste.
- Project management provides the design and tech transfer plan, establishes and tracks completion of milestones and directly partners with clients during this process.

Given the complex regulatory requirements for stability testing of combination products, SHL conducts full stability programmes at its Deerfield Beach site for its clients. This includes creation of the compliant clinical and follow-on stability protocols, creation of stability stocks and functional testing of the devices at each stability time point. At completion of the study, a report with stability trending per FDA guidance is delivered to the client.

As the developer of the device, SHL is in the unique position to provide insight that cannot be done by outside sources. SHL performs rigorous internal analysis to determine the tests that should be performed for each process, writes the test methods, instructions, plans, protocols and reports in-house and performs test method validation prior to design verification. This provides time savings to clients and simplifies development by keeping all operations under one roof.

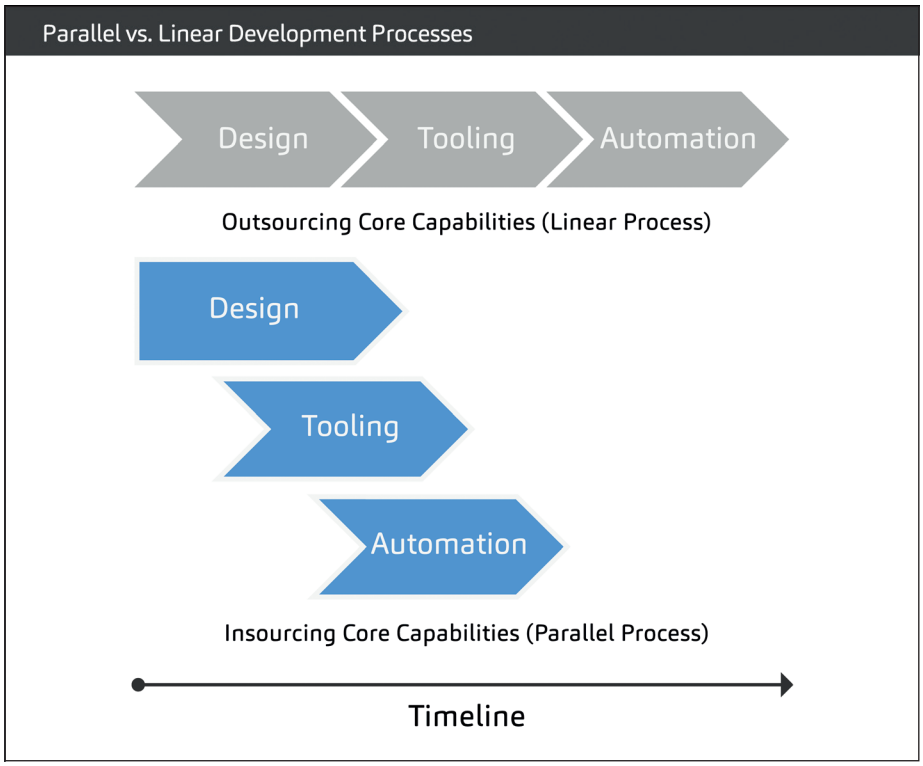

Figure 3: Running processes in parallel saves time and mitigates risk for clients.

SUMMARY

SHL's contract manufacturing service provides a full turnkey solution from device design to final assembly, labelling and packaging, reducing time to clinic/market and, most importantly, to those patients in need. Choosing SHL as a CMO partner provides a number of benefits, including:

- World-class assembly, labelling and packaging operations
- Programme/project management expertise with a proven tech transfer process
- Regulatory submission support
- Extensive combination product testing
- Combination product stability programmes
- Faster time to clinic, market and patients.

SHL Group's contract manufacturing services streamline our partners' operations, accelerating the commercialisation of critical medicinal products.

ABOUT THE COMPANY

SHL is a world-leading solution provider in the design, development and manufacturing of advanced drug delivery devices such as autoinjectors and pen injectors. With locations in Taiwan, Sweden and the US, experienced engineers and designers develop product enhancements and breakthrough drug delivery solutions for pharma and biotech clients globally. Significant investment in R&D has enhanced our broad pipeline of next-generation drug delivery systems. These innovative devices include a range of disposable and reusable injectors with fixed or variable dosing and the ability to accommodate high viscosities. With over 3,700 staff worldwide, the organisation consists of three distinct group companies:

- SHL Medical designs, develops and manufactures advanced drug delivery devices, as well as provides final assembly, labelling and packaging services for leading pharmaceutical and biotech companies across the globe.
- SHL Healthcare develops and manufactures equipment solutions for home, hospital and long term care use.
- SHL Technologies provides contract manufacturing and engineering services for the production of complex medtech and industrial products.

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PHARMA PARTNERING **CONSIDERATIONS** FOR INJECTION DEVICE COMPONENTS

In the modern world of injectable drugs, one of the major considerations for pharma is choosing partner companies for the development and manufacture of the injection device components. Here, Adam Shain, Director, Global Business Development, Injectables, Aptar Pharma, discusses several of the considerations that go into ensuring that the best possible partner is selected.

The needs of customers within the injectables sector are forever evolving and, as a result, the number of suppliers has increased in tandem, covering a broad range of specialities and portfolios. As the spectrum of choice grows, so does the opportunity to make a selection unwisely. With the modern paradigm of partnering between pharmaceutical companies and suppliers, selecting a partner is a critical decision. So, how can pharma ensure that they make the best possible choice? This article outlines many of the aspects that ought to be considered, such that the resulting partnership will be symbiotic, mutually beneficial and ultimately deliver superior outcomes.

> "Potential injectable device component partners should recognise that pharma and biotech customers are facing many complex challenges, from increased regulatory requirements to the needs of their own internal development programmes, which often involve extremely sensitive drug formulations."

There are, of course, myriad factors to consider. However, an initial list of potential partners can be refined with some simple considerations:

- A partner's capacity to scale manufacturing with demand, whilst maintaining production consistency.
- A partner's quality assurance methodology – particularly in light of the increasing demands surrounding the reduction of particulates.
- A partner's business continuity planning and ability to ensure a secured supply in the face of a quality or manufacturing failure.

Potential injectable device component partners should recognise that pharma and biotech customers are facing many complex challenges, from increased regulatory requirements to the needs of their own internal development programmes, which often involve extremely sensitive drug formulations. These challenges are new and therefore often need new thinking, new insight and new R&D solutions to meet them. Such fresh thinking requires a partner that is prepared to accept new challenges and work together to bring a product to life.

QUALITY ASSURANCE

Above all else, it is essential that the components of an injectable drug delivery device are of the required quality standard (Figure 1). As such, a potential partner must deliver said standard of manufacturing and cleanliness in components, even as the demand for higher quality standards grows. They should be able to demonstrate compliance to quality standards including ISO certifications, such as ISO 15378:2011. It is worth considering how open a potential partner is to inspection, from regulatory bodies and clients alike, and what methodology they use internally for validating their quality assurance systems.

CONSISTENCY OF SUPPLY

The nature of partnering means that often a pharma company selects only a single supplier. In this circumstance it is an

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Figure 1: The primary consideration of any partner should be their ability to ensure the necessary quality requirements are met.

Figure 2: Components that are ready to use without the need to sterilise are becoming a new standard.

absolute imperative that the partner can guarantee the security of supply – can they consistently deliver? Considerations here include how a single source partner would manage upward and downward variations in demand and the potential use of mirrored production sites.

STERILISATION OF COMPONENTS

The progression of manufacturing standards amongst injectables component suppliers in recent years has seen them match those required of laboratories and regulatory agencies to the point where products can be offered that simply need sterilising before use. However, as standards continue to increase, a demand has risen for components that are ready for use directly upon arrival (Figure 2). Such components greatly simplify use, as they are directly introduced into restricted access barrier systems (RABS) or isolators, bypassing the need for sterilisation beforehand and guaranteeing cleanliness. Before choosing such a product however, it is necessary to consider its compatibility with the overall process, e.g. is the product steam or gamma irradiated?

STABILITY AND COMPATIBILITY STUDIES

Regulatory and Pharmacopeial requirements continue to evolve, requiring companies to focus more on the product lifecycle. As such, it is of noteworthy benefit if a partner is able to demonstrate an understanding of this ever-changing regulatory environment and ability to provide guidance in their specialist areas. One of the most beneficial aspects a device or component partner can advise on is stability and compatibility, in particular extractables, preferably providing a full report identifying potential compounds that may migrate into the formulation from its container (Figure 3). A primary container will often have multiple materials in contact

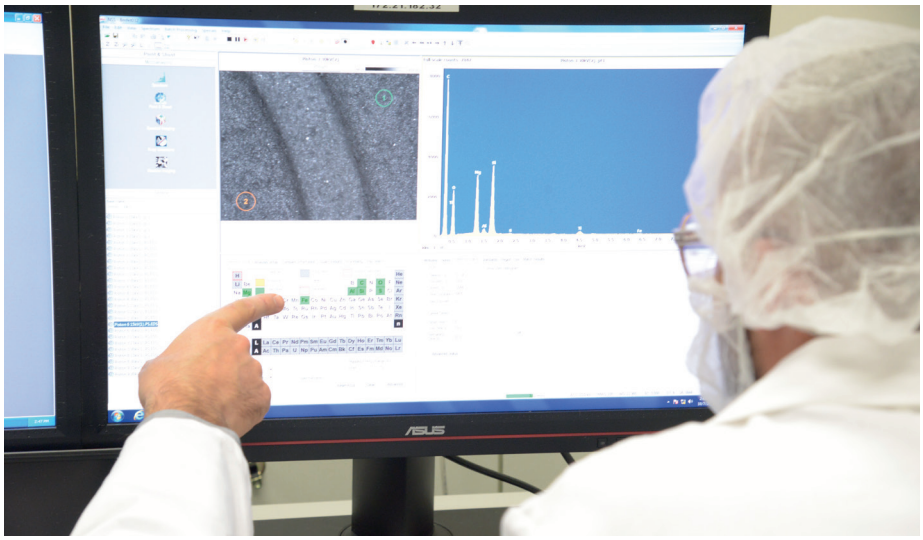

Figure 3: Extractables reports are highly beneficial when assessing primary container components.

with the drug product, most commonly a glass vial or syringe and a plastic stopper, each of which will have extractables and leachables profiles that will need to be assessed. Further to this, it is worth considering if a potential partner is able to provide a toxicological assessment as well.

TIME-TO-MARKET

If quality is the primary priority, time-to-market comes a very close second. When considering potential partners in this regard, as before with extractables, it is a significant benefit if they have a thorough understanding of the regulatory environment. It is desirable for a partner to have a proven track record of swift regulatory approvals derived from this understanding, as it will demonstrate that the partnership will likely accelerate that all-important time-to-market. To achieve this a potential partner needs both expertise in device development and a deep understanding of formulation science, combining them to develop devices and components that satisfy the requirements of the regulators and the drug itself.

TECHNICAL AND SCIENTIFIC RESOURCES

The quality of technical, scientific and R&D support a partner is able to provide is another aspect to consider, particularly with regard to the stability and continuous improvement of an injectable device. The things to look at here include the potential partner's existing portfolio of products, any patents they may have, their process development methods and history, the capability and credentials of their development team and their in-house laboratories and facilities. With an eye to the last, in particular it is important to note their scientific and technical specialities (e.g. analytical chemistry, microbiology, product engineering, materials science) and the standards and best practices for which they have accreditations.

Figure 4: Automated production reduces human contact and therefore the risk posed to highly sensitive molecules.

> "The last consideration to touch upon is that it is preferable to select a partner with similar company values and ethos. Though an intangible aspect, compatibility in this regard is a boon to a working relationship."

BIOLOGICS AND SENSITIVE MOLECULES

With the recent rise of biologics, the average new drug formulation is notably more sensitive than in previous generations. As such, when working with these complex proteins, the interaction of the drug with its primary container is a critical concern. Here, in addition to extractables, the device components must be assessed to ensure that they are inert with respect to the drug they are intended to contain. So, returning to the matter at hand, selection of a component partner with a specialism in this area, particularly when dealing with plastic or silicone, can make the development process much easier.

Secondary to this, but still worth considering with sensitive molecules, it is worth considering the degree to which the manufacture of these components is automated, including the charging and discharging of moulds and trimming

BOX 1: PARTNERING CONSIDERATIONS – QUICK CHECKLIST

1. Capacity to scale manufacture
2. Quality assurance methodology
   - Internal validation methods
3. Business continuity planning
   - Ability to deal with quality/manufacturing failure
4. Quality inspections
   - Regularity of regulator inspections
   - Openness to client inspection
5. Consistency of supply
6. Sterilisation of components
7. Stability and compatibility studies
   - Understanding of the regulatory environment
   - Extractables & leachables testing
8. Ability to reduce time-to-market
9. Technical and scientific resources
   - Existing product portfolio
   - Team and in-house laboratories/facilities
   - Scientific/technical specialism
10. Ability to deal with sensitive molecules
    - Automation of manufacturing process
11. Ethos compatibility

of components. By reducing human contact, manufacturing partners can mitigate against risks of errors or entrance of particulates into their facility, thus reducing the risk to the drug. However, when considering automated manufacturing it is important to go back to the previous consideration of quality assurance and note the methodology, for example in-line vision inspection (Figure 4).

ETHOS COMPATIBILITY

The last consideration to touch upon is that it is preferable to select a partner with similar company values and ethos. Though an intangible aspect, compatibility in this regard is a boon to a working relationship, and with the depth and length of relationship expected from a good partnership as discussed here, such a boon will pay dividends. Specifics to consider are their engagement with the healthcare trends of the moment, their attitude towards innovation and disruptive technologies, their communicativeness and responsiveness to feedback, and how they approach the challenges of development.

CONCLUSION

Pharmaceutical and biotech customers are facing many complex challenges today, including increased regulatory requirements and the need to deliver extremely sensitive drug formulations via the injectable route. These challenges require fresh thinking. Discovering a partner with the right balance of scale and care, one with the same values, the same commitment to quality, and a clear partnership approach gives you the best of all worlds – flexibility of scale, consistency of supply, speed-to-market, innovative thinking, and a commitment to meet tomorrow's injectables challenges today – together.

ABOUT THE COMPANY

Aptar Pharma provides innovative drug delivery systems, components and services to pharmaceutical, consumer healthcare and biotech customers worldwide, spanning a wide range of routes of administration, including nasal, pulmonary, ophthalmic, dermal and injectable. Aptar Pharma's mission is to provide complete solution services built around its drug delivery systems and to create stage-specific development packages designed to proactively address regulatory needs and accelerate approval. Overall, six billion components and systems are produced annually across 12 manufacturing sites and are accessed by 1.6 billion patients, and over US$50 billion worth of pharmaceutical products depend on Aptar Pharma's systems. Aptar Pharma is part of AptarGroup, Inc (NYSE:ATR).

ABOUT THE AUTHOR

Adam Shain is the Global Business Development Director for Aptar Pharma's injectables division and is responsible for driving the new business agenda, with a particular focus on reinforcing the division's innovation proposition. Mr Shain previously worked for Promius Pharma, a subsidiary of Dr Reddy's Laboratories, where he was instrumental in the development, commercialisation and launch of many of its branded products. Prior to his position at Dr Reddy's, Adam held various commercial roles within Aptar Pharma.

CONNECTED, NEEDLE-FREE DRUG DELIVERY: IMPROVE OUTCOMES WITH A NEXT GENERATION DEVICE

The healthcare industry is seeing an ever growing trend towards patients self-administering their therapies at home. Barbara Taylor, Senior Director, Marketing, Portal Instruments, discusses this trend and how Portal is making a bold step towards this goal with its novel needle-free injection device.

INTRODUCTION

When examining today's healthcare market, some clear trends become apparent:

- People are living longer, as such more people are living with chronic diseases (149 million Americans in 2015).[1]
- There have been tremendous advancements in treatments available for chronic diseases, especially with monoclonal antibodies (mAbs). However, despite their therapeutic value, compliance is as low as 50% (Figure 1).[2]
- This has put a toll on healthcare systems worldwide and requires rethinking how patients are treated and the overall population approach to healthcare.

One result of these trends is a push to move treatment to the home setting by empowering patients to take control of their health and treatments, with less direct supervision. With this in mind, the challenge for the pharmaceutical and drug delivery industry is to think beyond just the pill (or the injection) itself and to design the therapy to fit into patients' lives with minimum possible disruption. Treatment decisions should take into consideration a patient's lifestyle, anxieties, obstacles to taking the medication and necessary support, as well as what happens before and after the treatment administration. Patients should be provided with the tools and support needed to be better empowered to take control of their health.

With an understanding of the needs for home treatments, Portal is developing a needle-free drug delivery platform technology to transform the administration of medicines and improve the patient experience for chronic diseases (Figure 2). Portal's needle-free injector enables the administration of biologic drugs without the anxiety induced by needles. The Portal platform is also cloud-connected and provides reminders and real-time tracking of injections to

> "According to a survey conducted in 2012, 20% of RA sufferers report that they would not consider using a medication that required self-injection."

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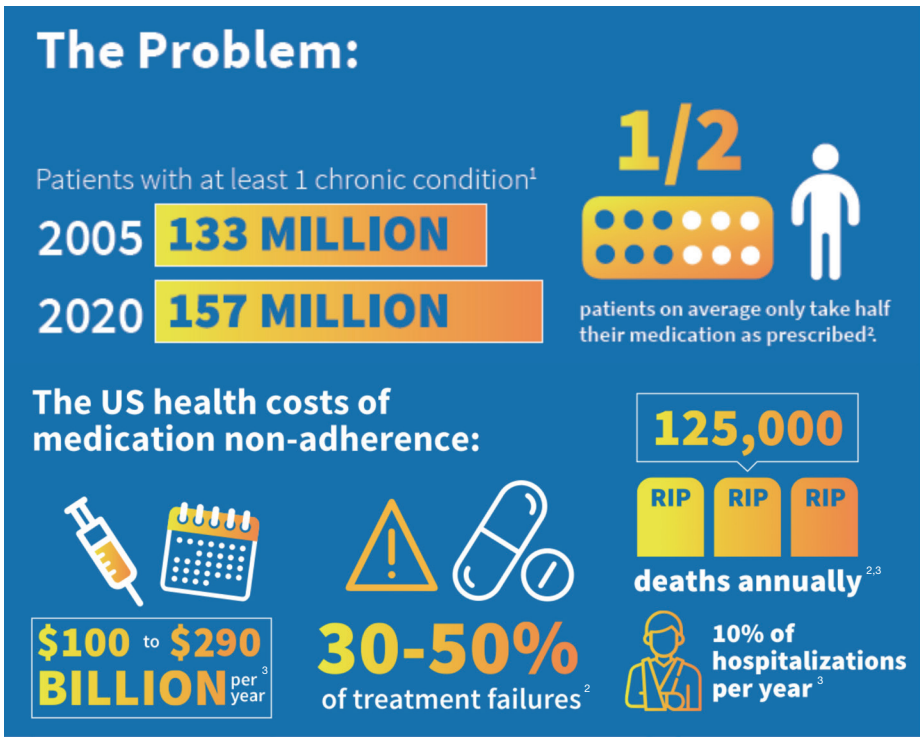

Figure 1: Despite the therapeutic value of modern medicine, adherence is low (50%), which puts a heavy burden on healthcare systems.[1-3]

Figure 2: Portal Instruments' needle-free, digitally controlled injector, represents the next generation of needle-free drug delivery platforms.

> "Algorithms in the device's software enable the injections to be specifically tuned, both in terms of injection depth within tissue and precisely controlling the release of medication during the injection process – fast at first and then slow."

improve adherence and communication between the patient and care teams – all with the aim to improve therapeutic outcomes.

UNDERSTANDING THE PATIENT EXPERIENCE

Many patients exhibit anxiety when it comes to the subject of needles. It is important to understand that this needle anxiety goes beyond physical pain; some patients dislike the stigma associated with needle usage, whilst others are afraid of not being able to properly self-administer injections. This fear of needles can interfere with administration and ultimately patient compliance. There are other circumstances that discourage patients from bringing needle-based devices into their homes, one example being parents with young children, who may fear that children will hurt themselves should they stumble across or decide to play with the device. According to a survey conducted in 2012, 20% of RA sufferers report that they would not consider using a medication that required self-injection.[4]

Alternative devices, utilising needle-free technology, could bypass such fear. Portal Instruments has developed one such device, a needle-free injector based in jet-injector technology. Uniquely, Portal's next-generation needle-free injector uses a computer-controlled linear actuator to pressurise the medication and inject it in a very fine liquid stream, roughly equivalent in diameter to a strand of hair. The entire injection takes place in less than half a second. The algorithms in the device's software enable the injections to be specifically tuned, both in terms of injection depth within tissue and precisely controlling the release of medication during the injection process – fast at first and then slow.

"A key problem with the historic approach is that the stored energy is the same fixed amount for every patient, despite differences in skin types and patient profiles, resulting in an injection depth that is difficult to regulate."

THE HISTORIC NEEDLE-FREE PROBLEM

Needle-free drug delivery devices are nothing new, examples have been around since the 1960s, but their widespread adoption has been hampered because, to date, such devices have been unable to overcome key issues, including:

- Being able to deliver only a limited volume of medication.[5]
- A limited ability to control injection depth.[5,6]
- Loud and painful during injection.[6]

The reason prior attempts at designing needle-free injectors have struggled is that they have been limited by relying largely on either mechanical or gas-based approaches to generate the high pressures required to expel the fluid at sufficient speed to pierce the skin and thus achieve a successful subcutaneous injection. Stored energy systems, such as a high-powered spring or compressed gas cartridges (e.g. air, CO_2, N_2), work by generating a sudden burst of energy (and often an accompanying loud bang) when that spring releases or the CO_2 cartridge explodes, driving the injection with the necessary force and pressure.

A key problem with this historic approach is that the stored energy is the same fixed amount for every patient, despite differences in skin types and patient profiles, resulting in an injection depth that is difficult to regulate. Stored energy systems lack the ability to control the injection (i.e. the fluid stream) in real time, meaning that once the mechanism of action is activated, there is no possibility of further modifications to the injection. Portal refers to this as an "open-loop system". This issue becomes very significant when attempting to deliver larger volumes, 1 mL for example, often needed for viscous biologics, to the subcutaneous space in a needle-free fashion.

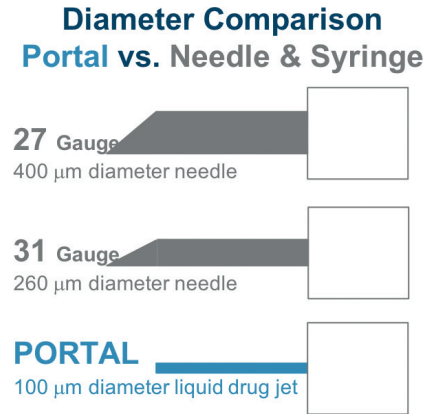

Figure 3: Comparison of standard needle gauges with the Portal device's liquid jet.

An additional problem is that, just as this energy is released quickly, it dissipates quickly - meaning only a limited volume of medication can be delivered at a time. With the spring-based approach, the spring is used to generate the necessary energy to force the fluid out of an orifice at high speed (>150 m/s). Since the spring has an energy profile that decays over the course of the injection, the fluid velocity will also decay over time. A similar decaying velocity profile is also characteristic for gas-based injectors. Thus, the highest velocity of fluid expulsion occurs at the onset of the injection, followed by a decrease to smaller and smaller velocities. When considering a 1 mL injection of a viscous biologic, this profile may be insufficient to achieve a successful subcutaneous injection. Furthermore, for every doubling of dosage volume, a fourfold increase in power is required, resulting in more force (and therefore theoretically more discomfort) on the patient.

PORTAL'S SOLUTION

To solve these problems, Portal Instruments, is developing a needle-free injector with a computer-controlled motor and with an internal feedback control system, similar to a car's cruise control. This "closed-loop" control system senses pressure and adjusts the jet speed to appropriately deliver the drug.

The Portal needle-free jet-injector platform consists of an electromagnetic actuator controlled by a computer that generates a jet of liquid with a diameter

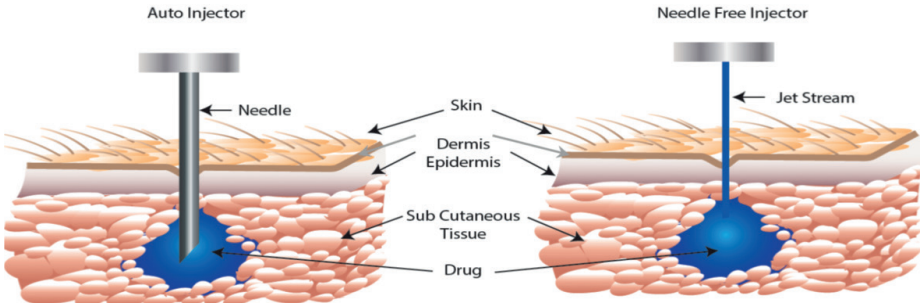

Figure 4: Comparison of injection by a standard autoinjector and Portal's jet-injection device.

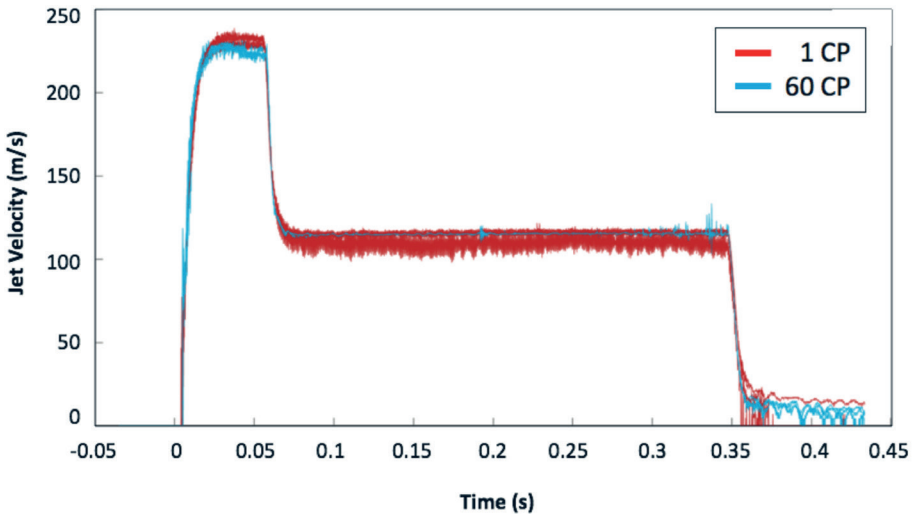

Figure 5: The velocity curve of the Portal injection over time: a fast penetration with a controlled, slower delivery phase, consistent across a range of viscosities.

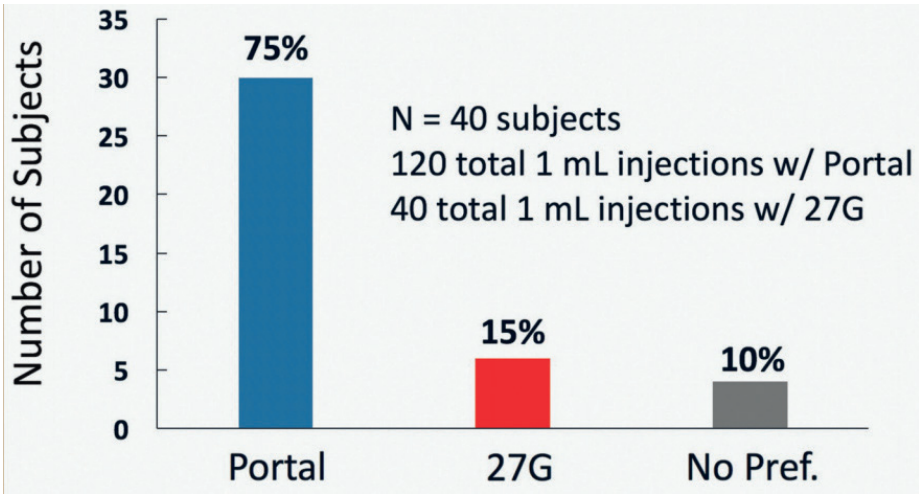

Figure 6: Subject preference for the Portal Handheld Device versus 27G needle and syringe.

of 100 µm, about a quarter of a 27 gauge hypodermic needle, approximately the diameter of a human hair (Figure 3). It is this jet of liquid, which contains the drug of interest, that pierces the skin to reach the desired subcutaneous space, without the intervention of any physical component to puncture the skin (Figure 4).

The actuator enables precise control of the speed of the pressurised jet of liquid, thus resulting in accurate targeting of the desired subcutaneous space with the exact amount of drug needed. In contrast to historic devices, the velocity profile of Portal's device is much more controlled, with an initial fast penetration phase followed by a consistent, slower delivery phase (Figure 5). The high adaptability of the system further allows the jet-injection device to accommodate the delivery of low to very high viscosities and drug concentrations without any changes to the device. The design of the device currently supports the subcutaneous administration of up to 1 mL of drug preparation in less than a second.

"Portal's unique technology allows full control of the jet via a computer-controlled feedback mechanism, thus decreasing sensation when compared with needle and syringe," said Patrick Anquetil, CEO of Portal Instruments.

Furthermore, the jet-injection device is relatively quiet, fast and the software automatically adapts injection parameters to suit not only the viscosity, but also the temperature of the medication. The pain of traditional needle-free injectors has also been addressed; studies have shown that patients perceive less pain using, and demonstrate an overall preference for, Portal's needle-free injector compared with needle-based injections (Figure 6).[8]

The other advantage with Portal's innovative injector is that Portal has developed a primary container that is compatible with standard pharmaceutical fill/finish lines. This reduces any additional capital expenditure for manufacturing on the pharmaceutical line. And the patient receives their medication dose pre-packaged in the cartridge, ready to be used; there is no need for the patient to have to transfer medication from a syringe to the injector.

Portal's development process is based on a design, build, test and iterate model throughout which Portal places a heavy emphasis on patient input and expertise of healthcare providers. Portal has run rigorous human factors studies including contextual inquiries, formative and other

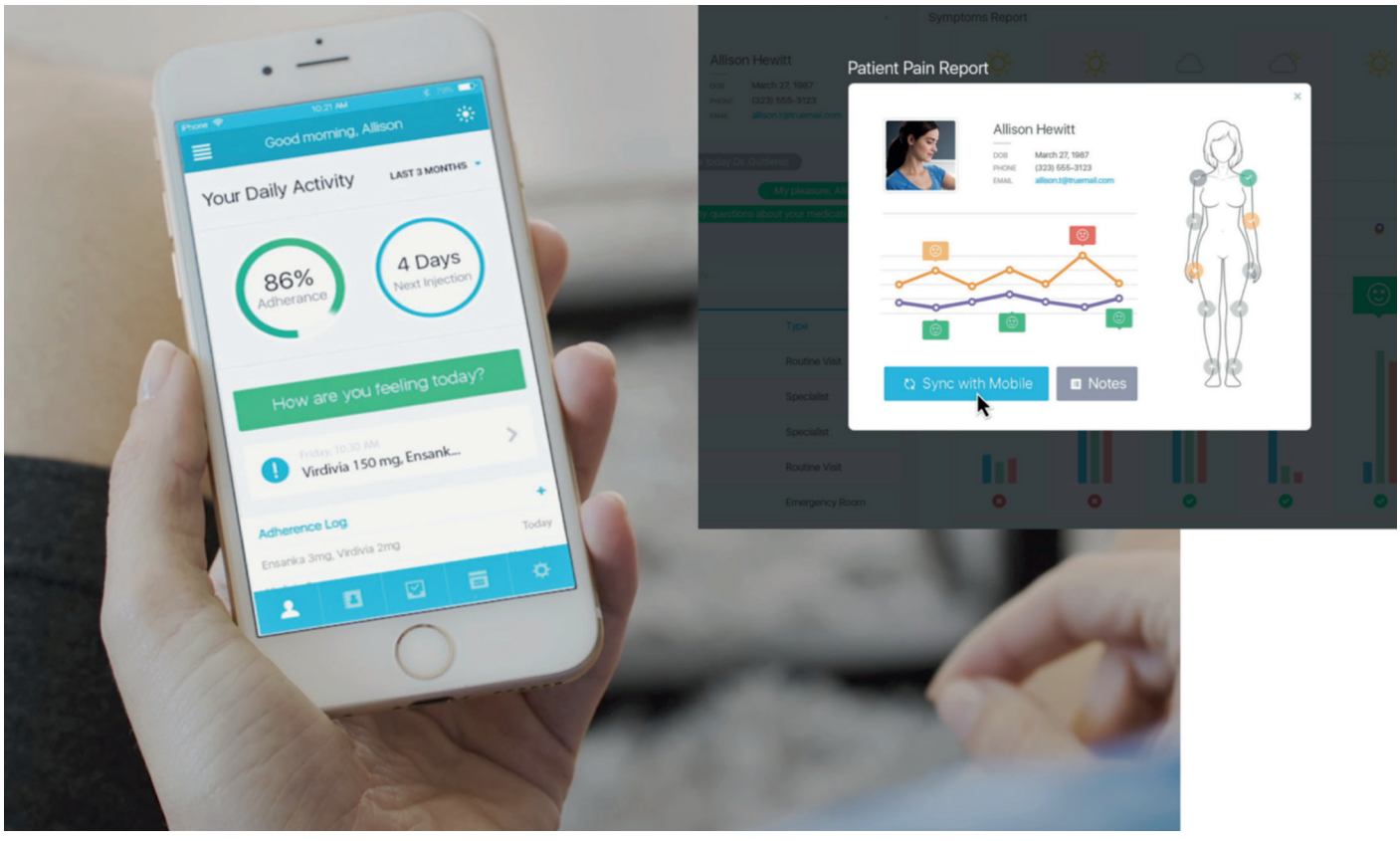

Figure 7: Portal's digital ecosystem, designed around the patient with the goal to improve outcomes.

heuristic evaluations. In-depth interviews with patient groups revealed challenges and needs and provided valuable insight about how the design of the device could affect the experience of their prescribed therapy and overall adoption of their treatment as an integrated part of their lifestyles.

DIGITAL TOOLS FOR IMPROVED EXPERIENCES & OUTCOMES

Digital tools and accompanying services are another way to build a positive patient experience and enable the patient to take control of their health and medication. When properly designed around the patient, such tools can assist with educating a patient as to the proper usage of their device, reminding them to take their medication at the correct times and logging treatments and symptoms – all important aspects of managing a chronic disease.

In a similar vein, Portal is looking to ensure their digital tools can assist communication with physicians by providing injection and symptom data (Figure 7). With clear, accurate data recorded over time, physicians can review patients' therapeutic results and make more informed decisions about further treatment.

Additionally, when digital tools are integrated with the drug delivery device, information can be gathered in near real-time. At the aggregate level, this data can lead to identification of trends with regard to adherence obstacles, patient behaviours and possibly correlated lifestyle data. This data can, in turn, be used to enhance the patient experience with the goal of improving adherence and therapeutic outcomes.

If trends continue, nearly 50% of the population will have a chronic disease by 2030.[1] However, with novel therapeutics, patient-centred treatments which take the patient's lifestyle into account and digital tools to aid in treatment support and decision making, progress is being made towards a healthcare system in which patients are empowered to take control of their health and therapy.

PARTNERSHIPS

Portal is looking to develop strong partnerships with all major biologics players seeking to gain an edge by offering their therapeutics fully integrated with a digital, patient-centred delivery system.

ABOUT THE COMPANY

Portal Instruments is a clinical-stage medical device company, developing a next generation needle-free drug injection platform to transform the drug delivery experience for patients suffering from chronic diseases such as ulcerative colitis, multiple sclerosis, rheumatoid arthritis and psoriasis.

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*Kojic, N., Goyal, P., Lou, C.H. et al. *AAPS PharmSciTech* (2017) 18: 2965. https://doi.org/10.1208/s12249-017-0779-0

** The Portal device can deliver 1ml of drug in 1/3 of a second per Portal internal studies

THE FUTURE OF DRUG DELIVERY

With an eye on the current trends and range of innovations in the sector, particularly data and connectivity technology, Uri Baruch, Head of Drug Delivery, Cambridge Design Partnership, looks back on how far injectable drug delivery has come in the past thirty years, and forward to what the future may hold.

Cast your mind back 20-30 years and an autoinjector would have been a rare sight – a real novel approach to drug delivery. It was the time when these devices started to come onto the market due to conditions which allowed for, or even demanded, patients to self-inject a drug as part of a specific treatment regimen. Most people were uneasy about using syringes and needles, and unfamiliar with them unless they were suffering from diabetes. And even diabetes patients had to cope without the sophisticated next-generation insulin pens we now take for granted.

> "Patients are becoming more informed "consumers" and demanding autoinjectors in preference to prefilled syringes and exposed needles."

Autoinjectors were originally developed for the military – for the rapid administration of nerve gas antidotes. The first EpiPen was invented in the mid-1970s and took its design cues from these military requirements, eventually being introduced into the general patient market in the 1980s. But patients would, of course, first need to be fully diagnosed, a process that often took weeks. A blood sample or biopsy would usually need to be sent away for analysis as only a handful of leading hospitals had the in-house facilities to enable a complete and timely diagnosis.

Fast forward to today and self-injection is commonplace in managing chronic diseases. Patients are becoming more informed "consumers" and demanding autoinjectors in preference to prefilled syringes and exposed needles. Therapies are also becoming more complex and can be targeted to specific indications rather than whole diseases. This in turn leads to much more targeted diagnostic tests and treatment delivery solutions, as well as new disease management tools.

Advancements in multiple areas are pushing the boundaries of what we deem possible today, all whilst developments in material science, electronics and software are happening at an ever faster pace and making inroads into pharmacotherapy. This is opening up vast new opportunities in healthcare management. We can track and monitor our activities and the "state" of our bodies more closely and frequently than ever before. But we are currently unsure of what to do with the sea of data we can collect – and what it actually means. Are we being enabled? Or will we drown if we do not carefully address why we are obtaining this data and how we can "translate" it into actionable information?

What does the future hold if we fast forward another 30 years?

A VISION OF THE FUTURE

Even with today's understanding we could imagine a future where, when feeling ill, you would have an instant video chat with a doctor located anywhere in the world who has access to all your medical records. You would take readings of simple metrics such as temperature and blood pressure using a bespoke "tricorder" unit which could measure everything in real time and upload the data to your health records. The online physician could then consult an artificial intelligence software package to diagnose your specific symptoms and perhaps prescribe further tests which could be delivered to your door in a matter of hours or minutes using an Amazon-style drone service – anything from an ECG monitor to full blood-works could be delivered to your door and the data streamed instantly to your physician to help them make a diagnosis and prescribe treatment.

However, this is a reactive system where we are waiting for external indicators to signal that something has gone wrong before we take any action or even consult a physician. If we look at the total cost of

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healthcare, as well as the cost of treatment, we have to include the impact on the patient themselves – their quality of life, for example, the number of work days missed and any support that may be required long term as a result of a debilitating condition. It soon becomes clear that a reactive healthcare system is far less cost effective in the long run. In the same way that you would rather not wait for your car's timing belt to snap before fixing it, to avoid expensive collateral engine damage, we should not have to wait for symptoms to be apparent before taking any action with our health. It would be far better to diagnose and treat any issue before it becomes a much bigger problem.

Envisage a fully integrated healthcare system, combining constant monitoring and instant diagnostics to provide a full picture of any healthcare issues and person-specific attributes. Your DNA could be sequenced to understand specific indicators suggesting you are more likely to suffer from certain health issues which could be specifically monitored for. Once any disease or first indicative symptom is detected, it could be analysed to understand its genetic make-up and then a targeted therapy could be specifically manufactured and delivered to you either in hospital or at home. This would mean very low-volume drug manufacturing and administration – potentially even just a single dose.

The same monitoring and diagnostic systems could continuously monitor your health and wellbeing. Further to this, it could potentially also regulate your diet to ensure your body has all the nutrients and vitamins it needs, without needing to overdose just in case of a specific deficiency. It could also monitor chronic conditions where regular therapy is required – using a combination of physical attribute monitoring as well as diagnostics, not only monitoring how well the therapy is working to treat the condition but also how your overall wellbeing is affected. Slow release/ultra-long-acting formulations would be able to stay in the body for extended periods (think weeks, not days) and continuously release drugs at therapeutic levels, with the release being triggered by disease indicators within the body; it would be effectively a self-regulating therapeutic system.

CAN IT BE DONE?

This may seem far-fetched at the moment, instant diagnostics, person-specific medication with low-volume manufacturing and at-home delivery, but the building blocks for these ideas are already in the works today. But how will these things connect? Do we have the understanding and tools to realise them? Is the desire there from patients?

There are already huge advances in diagnostics – from faster, more accurate tests at the point of care to personal diagnostic tools, such as a breath analyser to detect several different diseases, as well as continuous monitoring and analysis of several key physiological indicators. As costs and "time to result" are reduced, these diagnostic tools will become much more commonplace. Considered alongside an ever-reducing cost and time requirement to sequence an individual's DNA, coupled with the understanding we are currently gaining about the meaning and impact of different genetic markers, and the possibility arises that we may soon see these tools being implemented as standard care for all patients.

The thinking around disease management and the approach to identifying a treatment/cure are being challenged today with initiatives such as the approved CAR-T therapy from Novartis and Roche's innovative Personalised Healthcare, which uses liquid biopsy to identify specific biomarkers that shed light on the molecular root cause of a disease and then developing patient (group) specific therapies. Add a greater understanding of these biomarkers and continued iteration of the process and you can see how, in the near future, we will be seeing personalised medicine as the norm.

The drive to patient-specific therapy, as enabled by diagnostics, is putting pressure on manufacturing methods to enable these advances, current high-volume bulk manufacturing is no longer appropriate as each patient may need a personalised version of the same therapy. We are seeing existing pharma and large contract manufacturing organisations exploring new manufacturing methods which will enable this change – looking to take in-lab "development" processes and industrialise them into a personalised low-volume, low-cost manufacturing method.

"With low-volume manufacturing and personalised delivery, a certain kind of device will be needed."

"The thinking around disease management and the approach to identifying a treatment/cure are being challenged today with initiatives such as the approved CAR-T therapy from Novartis and Roche's innovative Personalised Healthcare."

Combine all these current developments and you can start to see how we are enabling this vision of tomorrow. So how can we make use of this vision of the future to inform our activities today? Let's look at the challenges/issues still to be addressed.

THE CHALLENGES AHEAD

With low-volume manufacturing and personalised delivery, a certain kind of device will be needed. The physical qualities of any given therapy will vary and be highly dependent on person-specific attributes, as well as the disease, and may even need to change as part of the course of treatment. This is compounded when this variation is not just indication dependent but also patient specific, and will thus require a new family of devices to be developed that can be as flexible and programmable as the therapy itself – as these devices will have to contend with (in the case of injection) volume, viscosity, needle depth and many other variables which may be wildly different from patient to patient, even within the same disease space.

The building blocks to address these challenges may already exist, but we are yet to put them together and see whether they will address all the issues. We need to come up with a long-term strategy to develop the devices that will one day be used to deliver these therapies. I'm not suggesting we aim for our vision of 2050 – but we should look to see which halfway points we can target to further our understanding, and so be ready for the next challenges that will surely arise.

/H&B/'S FOUR-STEP-TECHNOLOGY: STATE-OF-THE-ART IN AUTOMATIC REUSABLE INJECTION SYSTEMS

Ensuring medical devices are easy to use and completely safe are key drivers in developing innovative solutions. In this article, Tobias Morlok, Head of Development – Medical Devices, at /H&B/ Electronic, outlines how the company's Four-Step-Technology approach ensures that devices are totally safe to use by protecting against inappropriate use in several ways and at four key stages: needle insertion, injection of the medication, dwell time and needle withdrawal.

The market for medical supplies faces constant challenges such as coping with new developments in pharmaceuticals but also meeting increasing customer expectations.

To meet these challenges, companies need a thorough understanding of current needs, but also of upcoming requirements and future growth opportunities, as developing new features or entirely new instruments cannot be done in the short-term. Therefore it is paramount to listen to clients, watch market developments carefully and act pre-emptively.

It is also a great advantage when engineering competence, innovative technologies, technical knowledge and, last but not least, extensive manufacturing experience all come together under one roof. That combination – together with short paths and straightforward communication – guarantees close co-operation and turns out reliable product solutions.

The result has been the development of various innovative injection systems over the last 20 years with patented solutions for single-use, reusable and electromechanical devices. One such system is the Four-Step-Technology.

> "Our primary goal is to provide easy-to-use devices for patients, including those with disabilities or who are under stress, and to make those devices absolutely safe to use."

THE FOUR-STEP-TECHNOLOGY

The driver of innovation and evolution of our devices has always been safety concerns as well as meeting customers' and patients' needs. Our primary goal is to provide easy-to-use devices for patients, including those with disabilities or who are under stress, and to make those devices absolutely safe to use. This is the key to our success as well as our motivation to keep on improving.

To meet these values in a practical setting, any device must be able to be protected against inappropriate use. Our unique Four-Step-Technology aims to ensure

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this by focusing on safety at four key steps:

- Insertion
- Injection
- Dwell time
- Needle withdrawal.

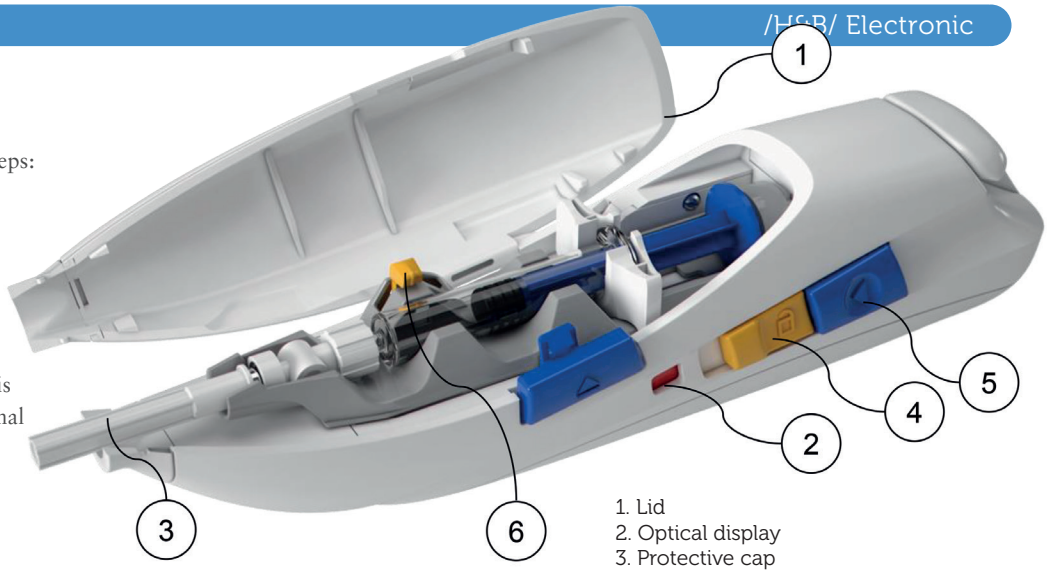
If one of the preparation steps is executed incompletely or incorrectly the final activation of the device will be prevented.

EXAMPLE OF THE FOUR-STEP-TECHNOLOGY IN PRACTICE

To illustrate how the four-step-technology works, we will use the example of BETACOMFORT®, a device which has been adapted by /H&B/ for Bayer AG to meet the needs of multiple sclerosis patients (Figure 1).

BETACOMFORT® provides application assistance that enables patients to inject medication on their own, subcutaneously at home. Since market entry, almost 300,000 autoinjectors for the treatment of multiple sclerosis have been sold and they are used in 56 countries worldwide.

Using Four-Step-Technology, the device is protected against inappropriate use in several ways (Figure 2).



1. Lid
2. Optical display
3. Protective cap
4. Safety catch
5. Start button
6. Lever for adjusting the insertion depth

Figure 1: Reusable autoinjector for prefilled syringes.

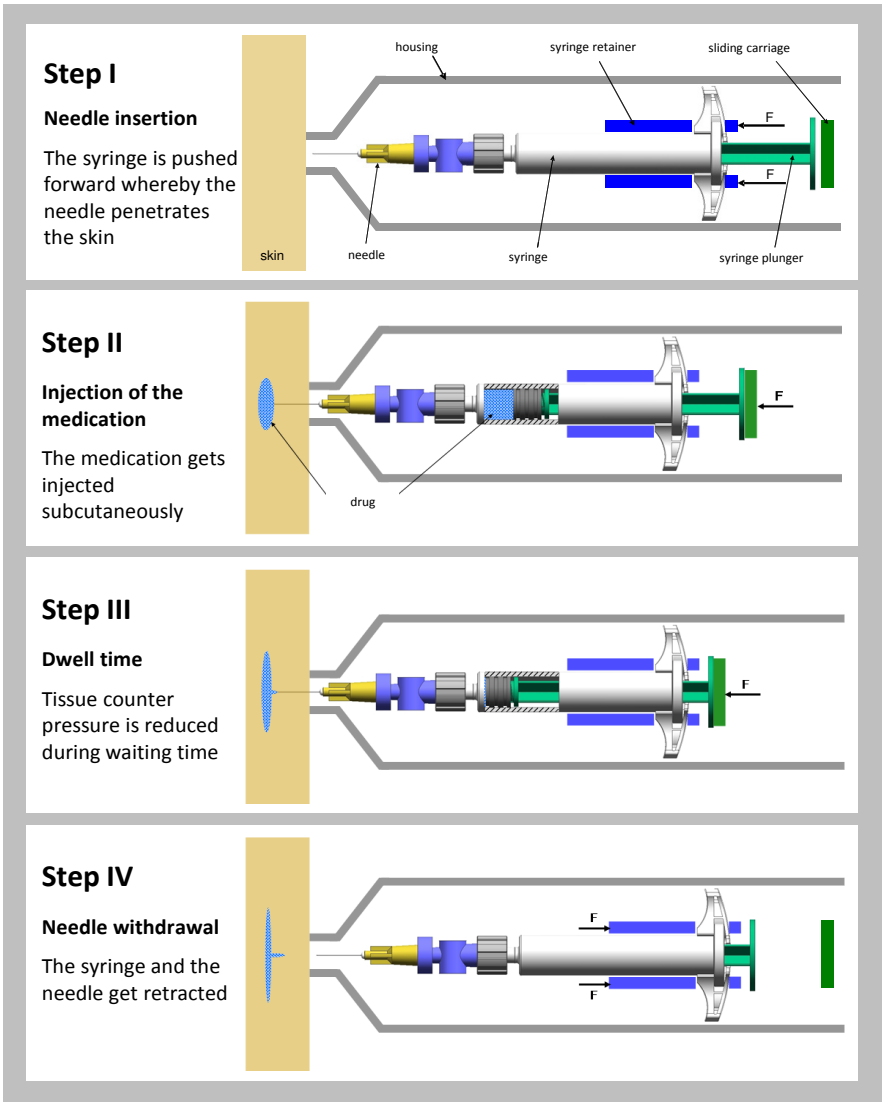


Figure 2: Illustration of the Four-Step-Technology

To start with, BETACOMFORT® is equipped with a mechanical locking lid which allows a simple syringe insertion. Just in case the syringe is not inserted correctly the lid can't be closed. Thus an injection with an inaccurately inserted syringe is prevented. After closing the lid completely and manually loading the mechanism, a green indicator in the optical display shows the device is ready to use.

STEP 1: Needle Insertion

After removing the protective cap, pushing the safety catch in the direction of the injection, positioning the device on the desired injection area and pushing the start button, the syringe is pushed forwards so that the needle penetrates the skin. Here another special feature comes into play: the insertion depth is adjustable beforehand depending on the tissue where the medication is being applied.

STEP 2: Injection of Medication

The medication is injected subcutaneously only after the needle has been completely inserted. The speed of injection can be adapted depending on the medication, tissue or patient's needs.

STEP 3: Dwell Time

During this period of waiting, tissue counter pressure is reduced. This reduced pressure prevents a reflux of the medication through the puncture and therefore reduces skin irritations significantly.[1,2]

STEP 4: Needle Withdrawal

The syringe and the needle are withdrawn automatically. The visual indicator in the optical display has now turned red and an additional acoustic signal indicates the end of the injection process.

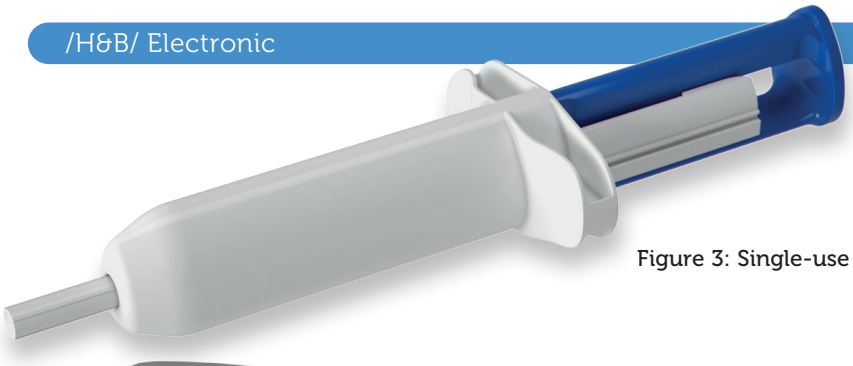


Figure 3: Single-use injector.

Figure 4: Electromechanical autoinjector for prefilled syringes.

EXAMPLE OF THE FOUR-STEP-TECHNOLOGY IN PRACTICE

Various groups of devices have been developed by /H&B/ over the last few years, which make use of the Four-Step-Technology.

It is important to highlight that this technology is available to its full extent in all devices described below – even in the single-use injection systems – giving it a major advantage over other systems in the market.

Group A: Single-Use Injection Systems

- Single-use injector (Figure 3) – injection device with prefilled syringe and single- or dual-chamber cartridge for single-use injection. The injection is performed manually or by pressing a release element (start button) performed by spring tension.
- Application: e.g. as single-use injector for subcutaneous or intramuscular self injection.

Group B: Reusable Injection Systems

- Reusable injector (Figure 1) – injection device with inserted syringe. The injection is performed by pressing a release element by spring tension or manually. Manual resetting of the mechanism.
- Application: e.g. as autoinjector for subcutaneous or intramuscular self injection.

Group C: Electromechanical Injection Systems

- Reusable injector (Figure 4) – electrically driven injection device with inserted syringe. The injection is performed by pressing a release element. Automatic resetting of the mechanism after the injection. Communication with other devices and datalogging is possible.
- Application: e.g. as autoinjector for subcutaneous or intramuscular self injection with datalogging for therapy monitoring.

Any of the above-mentioned devices can be used with syringes and single-chamber cartridges but can also be adapted to use with dual-chamber cartridges. In addition, the design and features of any device can be adapted to the specific needs of the customer.

ADVANTAGES

The main advantages of the Four-Step-Technology are:

- The injection is completely separated from the penetration of the needle.
- The entire injection needle is capsuled before and after the injection and is at no point visible to the patient (hindering needle phobia and providing total safety).
- It can improve patient confidence during injection and reduce any potential barriers to continuing treatment.
- As the speed of injection and the insertion depth are variable, the injection process can be adapted to safety and effectiveness requirements of the medication.
- The withdrawal of the needle occurs automatically. This is convenient for the user as injuries and pain are excluded[3] – especially when the device is withdrawn at an angle.
- Both previous points make all kinds of tissues – especially abdominal regions – easily accessible for an injection.
- A reflux of the injection through the puncture is prevented as the dwell time leads to a reduced counter pressure in the tissue. That leads to significantly less skin irritation.[1,2] And – on top of that – the dwell time is variable and adaptable to customers' needs.
- It can easily be adapted to different cartridges and volumes.
- The user does not need to take any extra steps to shield the needle after use. This reduces the risks associated with needle re-use and the risk of needlestick injuries, and provides additional protection for patients and healthcare professionals.

All these devices (like the BETACOMFORT® device) are ideal for self-injection by any patient at home.

FUTURE PROSPECTS

The medical devices market provides constant challenges. /H&B/ is well prepared and eager to tackle these new prospects, further developing existing devices and also creating new products. Our efforts are focused on expanding new services and generating sustainable, lasting results to improve the experience of patients. In addition it will be a major improvement to provide connectivity for single-use injection systems as well as mechanical injection systems.

CONCLUSION

With safety becoming ever more important in healthcare, medical device manufactures are exploring new ways to protect end-users and healthcare professionals. The requirement to achieve a market-ready device in an efficient and timely manner has encouraged medical device manufacturers to evolve quickly. In an increasingly competitive landscape, the output achieved must not only meet the desired device specifications and market regulations, but also the end-user requirements.

With our portfolio of devices and the Four-Step-Technology, /H&B/ already

offers an ideal range of products, bringing together product design and manufacturing engineering to create an injection system that will help improve lives, reduce healthcare costs and deliver treatments more efficiently.

ABOUT THE COMPANY

Established in 1984, /H&B/ Electronic soon became a reliable and important supplier for key players in the automotive and industrial electronics sector, developing and manufacturing high-precision mechanical components, connectors, sensors, housings and electromechanical systems. In 1998, /H&B/ made the step into medical engineering. Providing solutions and developments in medical devices using hybrid components made of metal and polymers made /H&B/ a trusted partner in more than 50 countries worldwide, especially in the field of injection systems for multiple sclerosis.

Today, /H&B/ has built a reputation for ultraprecise products, providing product development from the initial concept to maturity, planning of all project phases, simulations, part design and tools as well as customer-specific, cost-optimised and certified manufacturing. For many years, the company has implemented – besides the standard certifications – the EN ISO 13485 and the EU Directive 93/42 EEC Annex II.

/H&B/ is situated at the north rim of the Black Forest region in southern Germany. Its 13,500 m² production and development site houses more than 350 employees.

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ABOUT THE AUTHOR

Tobias Morlok is Head of Development for Medical Devices and has worked for /H&B/ since 2009. He started working for the company during his dual course of study specialising in construction and development. He also studied innovations and technology management and holds a Masters degree in Mechanical Engineering. Today his focus is on developing new products in medical engineering and he is responsible for IP management as well as the expansion of the the company's medical sector.

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Economy Spring

THE SECRET TO A SINGLE AUTOINJECTOR DESIGN FOR MULTIPLE MEDICATIONS

The autoinjector market is booming and is predicted to continue doing so for some time to come. In order to capitalise on this, pharma companies are looking to use their autoinjectors for multiple medications. David Philbrick, Business Development Manager, Economy Spring (MW Industries), presents the case for bringing on metal component manufacturers in the initial design phase to make the most out of the crucial expertise they can offer.

This article is based on an MW Industries white paper: "Designing Auto-Injectors for Multiple Drug Viscosities".

The global injectable drug delivery market and, more specifically, the autoinjector market is booming. That growth is predicted to continue throughout the coming decade. According to a June 2016 report by Roots Analysis, the global autoinjector market is predicted to grow at a rate of more than 8% per year for the next 10 years. Mordor Intelligence estimated the global injectable drug delivery market to be US$40 billion (£29 billion) in 2016. The market is expected to experience a $CAGR_{2016\text{-}2021}$ of about 18.1% and so reach around $93 billion by the end of 2021.

These predictions are borne out in the real world as evidenced by increases in production at Economy Spring, a metal spring supplier and a division of MW Industries. Specifically, in 2016, Economy Spring produced 40-60 million springs across all of the drug delivery systems it supplies (including autoinjector devices), whereas the company is now producing 250-300 million springs.

With such a huge market in play, taking into account the range of physical properties exhibited by drugs and biologics being administered via autoinjectors, it is crucial for pharma and biopharma industry original equipment manufacturers (OEMs) to optimise device designs to be as adaptable, and thereby as cost-effective,

> "Proper design of the plastic housing and specification of the material and size of the springs are essential for any single-drug autoinjector, but those tasks become even more vital and complex if an OEM wants to repurpose that same device for multiple drugs and biologics with varying formulation characteristics, particularly viscosity."

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Figure 1: Recent history has seen an inexorable trend towards at-home self-administration of injectable drugs for patients with chronic conditions.

as possible. And that means bringing metal spring component manufacturers on board in the initial design phase.

HOW AN AUTOINJECTOR COMES TO MARKET

A major factor of the global injectable drug delivery market's predicted growth is the widespread increase in the self-administration of drug therapies, propelling the manufacture of autoinjectors like the EpiPen (Mylan, PA, US). The proliferation of this practice is due to the influence of health insurance and managed care companies, which aimed to reduce the number, and expense, of physician office visits by enabling patients to inject themselves with treatments for chronic conditions (Figure 1). While the medical community pushed back, the pharmaceutical and biopharmaceutical industry saw the writing on the wall.

Pharma and biopharma OEMs (e.g. AbbVie, UCB, Eli Lilly) began investing in the research and development of devices that could safely and effectively accommodate the self-injection of drugs and biologics. They enlisted and aligned world-class new product development firms (NPDs) and plastics and moulding contract manufacturing organisations (CMOs) to design and produce new autoinjectors. Soon, that practice became routine.

Typically, a pharma OEM would contract an NPD to create an autoinjector around a new drug or biologic it is bringing to the market. The NPD would then begin research to plan the device design. The OEM would also contract a CMO (e.g. Nemera, West) to mould the plastic components, specify and source the metal components, and send those to the OEM for final assembly, at which point the syringe is installed and the drug loaded. Alternatively, final assembly and drug-loading can take place at the CMO, provided it has the capability to maintain the drug in a stable, climate-controlled environment. However, due to their extreme sensitivity, biologics are nearly always loaded at the OEM. Once the NPD locks down a working design, the CMO typically manages manufacturing while the NPD shifts into a support and consulting role.

CREATING ONE DESIGN FOR MULTIPLE DRUGS AND BIOLOGICS

Proper design of the plastic housing and specification of the material and size of the springs are essential for any single-drug autoinjector, but those tasks become even more vital and complex if an OEM wants to repurpose that same device for multiple drugs and biologics with varying formulation characteristics, particularly viscosity. And that's where experienced metal component manufacturers are invaluable. The springs that control the introduction of the surgical sharp or syringe needle, the delivery rate or dosage of the drug, and the automatic retraction of the needle are the most critical metal components of any autoinjector.

In practice, several big pharma OEMs have successfully launched a new autoinjector for a specific drug. However, the attempt to repurpose that device to accommodate other injectables, particularly biologics, encountered problems largely due to differences in the viscosity of the different medications. Drugs with different viscosities require springs with different physical characteristics – composition, length and thickness – to create spring rates that provide enough power to push higher viscosity drugs and biologics through the syringe to the needle, in order to deliver precisely the correct amount of drug. This includes the specified length of time for the syringe to be fired and the timely retraction of the needle at the end of that time period. Without knowledge of this complex science of metal performance and how it translates into the successful and accurate delivery of injectables with dissimilar viscosities, pharma OEMs (and their NPDs and CMOs) inevitably struggle to repurpose existing autoinjector designs for different drugs.

> "Most autoinjectors contain a main spring and a return spring. With each application, a delicate dance occurs between the two. The rates of both springs work in concert to control the amount of medication delivered and the duration of the administration."

THE CRITICAL ROLE OF METAL SPRINGS

Autoinjectors come in many forms – pen-injectors (e.g. EpiPen), trigger-activated, twist-and-depress and more – but the majority require metal spring components designed to control the needle and achieve precise delivery of the drug.

Most autoinjectors contain a main spring and a return spring (Figure 2). With

Figure 2: Most autoinjectors are driven by a delicate balance between a main spring and a return spring.

"Given the vast number of autoinjectors projected to be produced in the future, the cost-savings that can be realised by using a single injector design with interchangeable springs is indeed remarkable. That given, the importance of having a collaborator that understands the material science of spring design at the initial design phase cannot be understated."

each application, a delicate dance occurs between the two. The rates of both springs work in concert to control the amount of medication delivered and the duration of the administration. When engaged, a main spring must provide the necessary force to depress the syringe plunger within a specified time frame and surmount the device assembly friction to properly deploy the needle into the skin. A return spring must be able to counterbalance the remaining force of the main spring to safely retract the needle at an exact time. Both must be designed so they don't damage the plastic parts that comprise the rest of the device. If the metal springs are not meticulously fabricated to accommodate the viscosity of the specific drug or biologic involved, as well as to work smoothly within the confines of the device's plastic components, then the medication simply cannot be self-administered accurately and safely.

When you understand the interplay between the metal springs in an autoinjector and the correlation of their characteristics to the viscosity of the drug or biologic being delivered, it becomes obvious that there's no such thing as a one-size-fits-all autoinjection device. But that doesn't mean that a pharma OEM with a variety of drugs eligible for self-administration needs to design a completely unique device for each medication.

In the circumstance of designing an autoinjector that will ultimately be used for multiple medications, the plastic housing and components of a device can be designed to accommodate springs with rates that vary by as much as 30-40%. Simply put, an autoinjector can be designed so that the metal spring components are interchangeable. In such cases, OEMs need to be thinking from the get-go about these possibilities and need to get a qualified metal component manufacturer involved in the device design process as early as possible. Doing so can save millions of dollars in R&D and production costs.

INTERCHANGEABLE DESIGN

According to the US National Center for Biotechnology Information (NCBI), "Recent studies confirm that the incidence of anaphylaxis ... is increasing worldwide." The first line of defence for an anaphylactic reaction is the administration of epinephrine, often via an EpiPen. That rising need – combined with the growing trend to treat other common chronic conditions such as diabetes, rheumatoid arthritis and multiple sclerosis via injectable self-administration – translates to an escalating demand for autoinjection devices.

Given the vast number of autoinjectors projected to be produced in the future, the cost-savings that can be realised by using a single injector design with interchangeable springs is indeed remarkable. That given, the importance of having a collaborator that understands the material science of spring design at the initial design phase cannot be understated. That knowledge allows for:

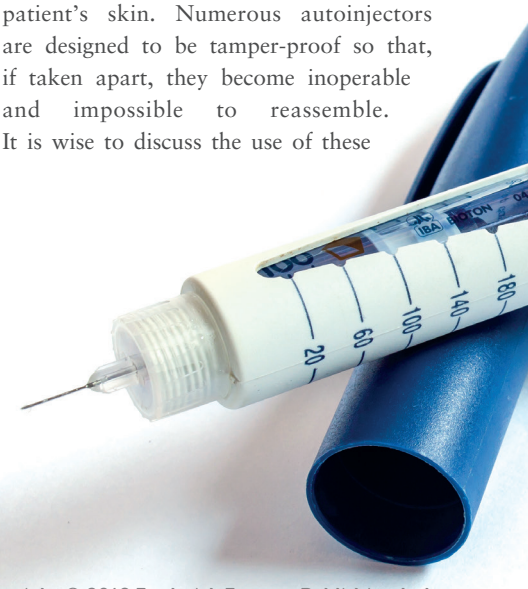
- Producing precision springs and other metal components that perform consistently from device to device without failure
- Specifying springs with metal characteristics that allow for the precise and accurate delivery of a drug or biologic of a given viscosity
- Understanding how springs with varying rates impact plastic housing and component design.

All of that (and so much more) requires years of specialised experience, investment and research, in an area of expertise not traditionally held by NPDs or plastics and moulding CMOs. Only an experienced, highly-qualified metal component manufacturer can offer that knowledge. It is incumbent upon pharma and biopharma OEMs to directly engage such firms at the onset of device design. As OEMs come to understand the importance of springs and other precision metal components in autoinjector design, the advantages of direct access to those fabricator-suppliers at the earliest stages of product development become clear.

Using an example from Economy Spring, the company was brought on board early to work with a high-profile pharma OEM, its NPD and moulding CMO on a device design project, now entering its final phase. With the metal spring manufacturer's help, the NPD conceived an autoinjector to use with two completely different drugs under the OEMs purview. Economy Spring fabricated and is now supplying two different main springs with distinct rates to the CMO to assemble into the same plastic device housing. The springs look exactly the same, so Economy Spring came up with a brilliantly straightforward solution to prevent mix-up during assembly: it delivers the springs to the CMO in different coloured trays. The CMO's automation system can then detect if the correct spring is being used simply by monitoring the tray colour on the line. This example clearly illustrates the importance of including the spring manufacturer in the initial design, resulting in substantial savings in time and money.

NOT ONLY SPRINGS

Autoinjectors often have other metal components, such as anti-fire mechanisms that prevent the device from accidentally triggering if dropped or prematurely activating during self-administration and harming the patient (Figure 3). Many autoinjectors must be cocked or twisted to release these safety components so the trigger is free to release. Others have a built-in tip that acts as a trigger so the device won't fire until a certain level of force is achieved by pushing it against the patient's skin. Numerous autoinjectors are designed to be tamper-proof so that, if taken apart, they become inoperable and impossible to reassemble. It is wise to discuss the use of these



types of components at the beginning of the design cycle so that the device can successfully accommodate all safety and performance requirements necessary.

CONCLUSION

The inclusion of the metal spring component manufacturer, along with the NPD and CMO, in the initial design phase of injectable drug delivery systems, particularly autoinjectors, represents a huge potential saving in time and money for pharmaceutical and biopharmaceutical industry OEMs. It's a methodology that is being repeated more often today and will continue to spread in step with the market boom.

ABOUT THE COMPANY

Economy Spring, a division of MW Industries, is a manufacturer of advanced medical device components, including highly-engineered, precision metal components and assemblies such as springs, surgical sharps, needles, laser machined tubing, staples, titanium clips and complex assemblies. The company deploys its end-to-end product lifecycle know-how and design expertise to shorten product development time and lower costs. Economy Spring's >40-years' track record helps deliver product reliability and performance in demanding surgical and drug delivery applications. The company is registered with the US FDA and has ISO9001 certified and ISO13485 compliant quality processes.

ABOUT THE AUTHOR

Dave Philbrick is Business Development Manager & Lead Product Engineer for Economy Spring, an MW Industries Company. For more than 38 years he has been involved in supporting new product development for medical instrumentation & drug delivery systems for Medical / Pharma OEM's. He is a specialist in metal component development, design and integration.

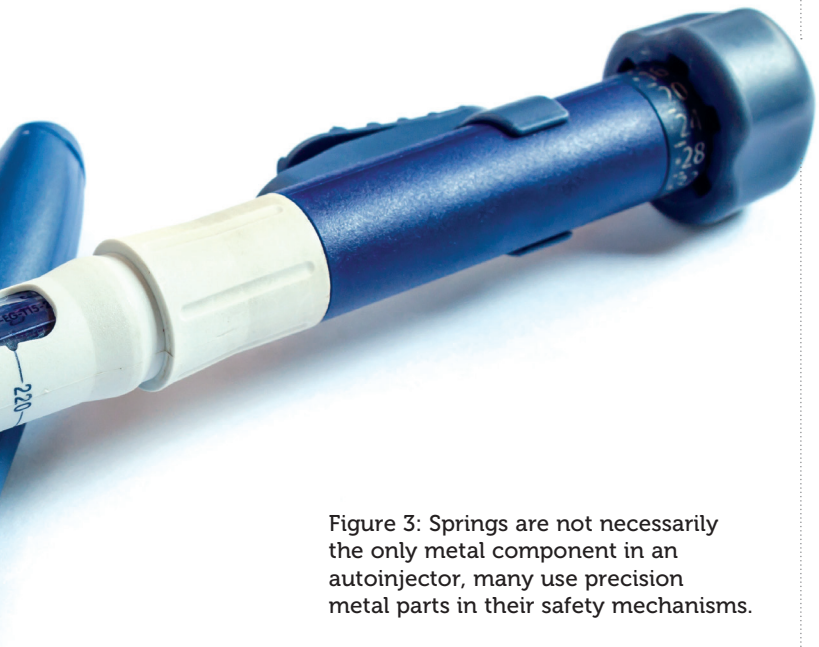


Figure 3: Springs are not necessarily the only metal component in an autoinjector, many use precision metal parts in their safety mechanisms.

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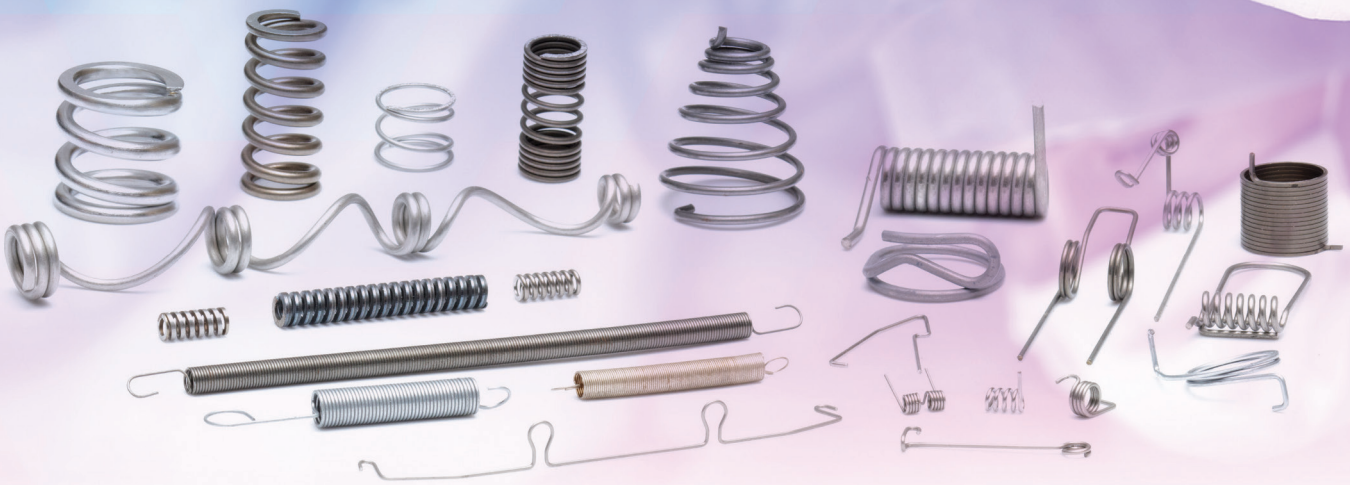

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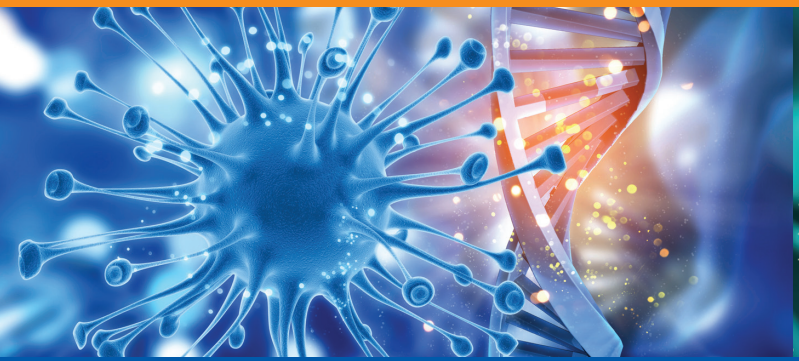

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INSERT. WEAR. INJECT. DISPOSABLE UNITS FOR WEARABLE DRUG DELIVERY DEVICES

Mobile drug delivery pumps can significantly improve patients' quality of life, however they require highly advanced disposable components to ensure that patients receive the exact dose required. Here, Claudia Fink, Senior Product Manager Marketing & Sales at Raumedic AG, reviews how the components are produced and which secondary processing techniques are required. She then looks at how partnering with Sensile Medical has helped with the development of the disposable units for a modern drug delivery system.

Worn discreetly on the body, mobile drug delivery pumps are simplifying the lives of many patients who need regular medication. With the help of a patch, they can simply affix the pump to their skin. The medication can then be administered regardless of time or place, without the need to travel frequently to hospital, which significantly improves their quality of life.

The core elements of such wearable drug delivery devices are a reusable electronic activator and a pump module for one-time use. To create these customised disposable units, Raumedic has used its expertise to produce high-precision moulded parts and micro-tubing (via extrusion processes) from a number of different medical-grade plastics.

PRODUCING THE THERMOPLASTIC AND SILICONE COMPONENTS

The fluidic outlet alone – comprised of four components – requires extensive knowledge to make, both in terms of production systems and secondary processing (Figure 1). The transparent slider and the tube clamp are injection moulded, whereas the tubing is produced in a coextrusion process. The manufacturer-specific Rauinert technology almost completely eliminates the possibility of interactions between the pharmaceutical and the material as the two thermoplastics are coextruded in a single step. The outer layer, made of polyurethane (PUR), ensures that the tubing can be optimally glued and sterilised. The inner layer is made of polyethylene (PE), which is an inert material that is very medication compatible. It is imperative that any materials used in pharmaceutical applications that come into direct contact with drugs are very carefully selected.

When patients self-medicate at home, they must be able to expect that the pharmaceutical will be delivered in the exact dosage. Therefore, the reservoir requires a syringe plunger with execellent sliding properties. To ensure that this component

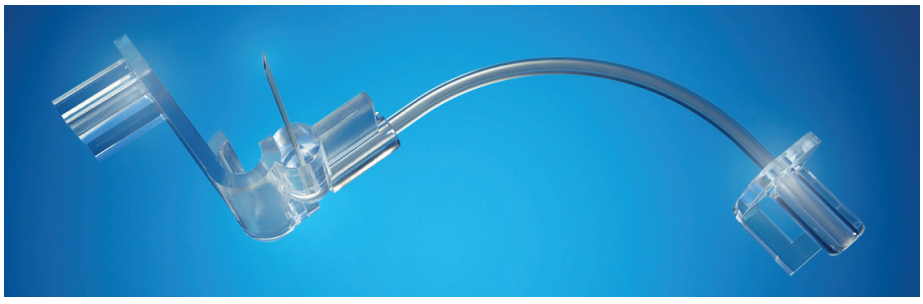

Figure 1: As a component group of wearable patch pumps, the fluidic outlet is primarily responsible for the subcutaneous injection.

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slides smoothly through the syringe barrel with little effort, medical-grade silicone is shaped into the desired form during an injection-moulding process. The syringe plunger, as well as all other required plastic elements, is produced under clean-room conditions on the basis of ISO Class 7.

SECONDARY PROCESSING

The secondary processing of individual components plays an important role, too: the micro-tubing and tube clamp are glued together with the help of UV bonding. To minimise the pain felt by the patient during a subcutaneous injection, the hypodermic needle must be siliconised. The medication reservoir receives similar treatment, but always with one principle in mind: the process should only use as much silicone oil as required for an even application. In addition, the desired graduated scale is stamped onto the reservoir, made of polypropylene (PP), in a pad-printing process. The serial number and instructions about the correct placement of the vial adaptor on the pump housing must be abrasion-resistant so a laser-marking process is used for these labels (Figure 2).

"Our polymer and secondary processing go hand in hand," said Thorsten Kellner, the senior engineer responsible for injection and dosing systems at Raumedic. He added that this relationship was a key consideration for business partners in the medical and pharmaceutical industry, "When all fundamental production and assembly steps are done under one roof, our customers have fewer external contact points, something that gives them greater process security."

WORKING WITH A PARTNER COMPANY TO DEVELOP DISPOSABLE UNITS

Since 2014, Raumedic has been working with the Swiss pump manufacturer Sensile Medical on the development and production of disposable units for modern drug delivery systems. Derek Brandt, CEO at Sensile Medical, summed up the partnership, "We needed a strong manufacturer who could turn our SenseCore micro-pump technology into a cutting-edge drug delivery device. We found in Raumedic a partner that could meet all of our requirements: a single point of contact for all necessary production steps, proven expertise in a range of manufacturing technologies and an understanding of the special needs of the pharmaceutical industry."

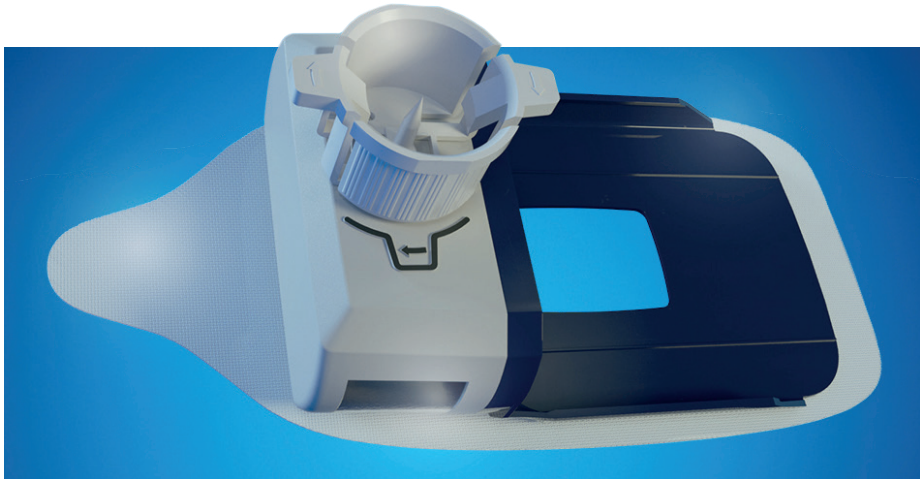

Figure 2: Manufacturers of state-of-the-art medication pumps require the broadest range of production and secondary-processing techniques, including two-component injection moulding and laser marking.

Many challenges had to be overcome in this multi-year project. "The end product consists of many components, some of which are complex, and they have to function on a system level," said Mr Kellner, "One of the most work-intensive steps we faced was developing an optimal design in terms of feasibility." One other wide-ranging task was the design validation that was done as part of a clinical trial.

In addition, leak-tightness, flow and 100%-inline function tests were conducted for the individual component groups. Finally, the finished product was packed in blisters and sterilised in accordance with customer requirements.

CONCLUSION

"We are certain that compact drug delivery devices still have a lot of untapped potential," Mr Kellner said in describing the company's view of the future. The constant stream of new products being developed by the pharmaceutical industry will ensure that the number of approved drugs for self-medication purposes will continue to rise. "And the application fields for large-volume wearable injectors in the home-care area are becoming broader and broader," he added.

ABOUT THE COMPANY

Human health is at the core of Raumedic Group's business. The company, which has a global workforce of 700 people, specialises in processing medical-grade thermoplastic polymers and silicones at five production sites in Germany and the US. As a partner of the international medical technology and pharmaceutical industry, the polymer specialist develops and produces customised components for customers, including tubing, catheters and moulded parts as well as complex groups of components and systems for diagnostic and therapeutic uses. With 70 years of experience in the areas of extrusion, injection moulding and assembly, the company turns customer ideas into mature products. The foundation of this work is formed by a quality management system based on ISO 13485 and clean room manufacturing on an area of 10,000 m^2 based on ISO 14644 (Class 7).

ABOUT THE AUTHOR

Claudia Fink has been working at Raumedic since February 2011. At the headquarters in Helmbrechts, Germany, she is responsible for the strategic orientation of the Injection/Dosing product segment in the Systems Business Unit. In this position, she works closely with sales and application technology. As Senior Product Manager, she primarily handles commercial and operational tasks. Participating in trade fairs, meeting clients and constant market monitoring are also included. Claudia Fink was involved in all critical steps of the development project with Sensile Medical: from drafting the offer through coordinating the production of samples to order processing, the Product Manager assisted in all core processes. Before joining the company, Claudia Fink studied Business Spanish and lived in Spain for a year.

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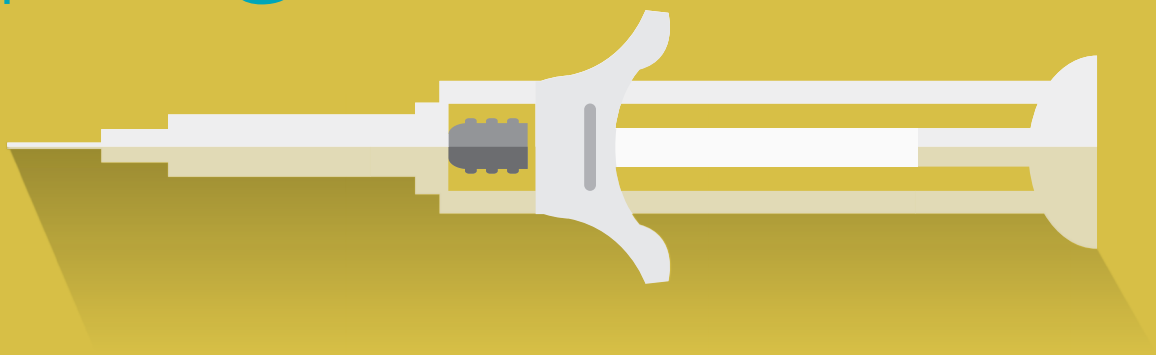

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AUTOINJECTOR TRAINER INNOVATIONS TO ENHANCE THE PATIENT EXPERIENCE

In an increasingly crowded marketplace, the availability of realistic trainers can serve as a key differentiator that can set a pharmaceutical company ahead of its competitors. Noble has designed an agitator needle simulation tip to replicate the forces and feel of the needles that are used in manual insertion. Joe Reynolds, Research Manager, looks at the benefits offered by the simulation tip – which can be incorporated into several types of autoinjector trainers – and reviews the development process.

With competition among drug manufacturers steadily increasing, each company faces the challenge of effectively differentiating itself from its competitors. A smart solution could lie in adopting patient-centric strategies that can make a course of treatment less daunting for those who are prescribed a specific medication.

One area where this is particularly important is the administration of biologic drugs, as many patients have to use self-injection devices and may not feel comfortable with them or well-versed in their proper use. Studies have indicated that needle anxiety can play a significant role when patients are prescribed a medication that involves self-injection.[1] Other studies suggest that, without proper training during the first 30 to 90 days of treatment, patients are more likely to drop off from therapy or use their devices improperly, thus receiving less than a complete dose.[2] To offer a truly patient-centric experience, it is important for drug manufacturers to ask what methods can be employed to rectify these problems.

THE AGITATOR NEEDLE SIMULATION TIP

One solution comes from the world of technology and engineering. Recent advances have made it possible to incorporate various special features into autoinjector training devices that can help patients achieve increased confidence and proficiency, giving them a solid grounding in self-injection before they begin using their actual autoinjector on a regular basis.

One recent feature-based innovation in autoinjector trainer design – known as the agitator needle simulation tip (Figure 1) – was introduced into the commercial market by Noble® in November 2017 and serves as a good case study on how autoinjector trainers can be made more realistic while providing multiple benefits for users.

USING AGITATOR SIMULATION TIPS IN TRAINING DEVICES

The agitator needle simulation tip feature can be incorporated into trainers that mirror the operation of manual autoinjectors, in which the patient applies pressure to insert the needle.

> "...a trainer with an agitator needle simulation tip allows patients to experience the sensation of what it would be like to use an actual prescription autoinjector on their own body as closely as possible..."

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Figure 1: Noble's Agitator needle tip simulator replicates the force and feel of needle insertion.

Prior to the advent of commercially available autoinjector trainers, the onboarding process for self-injection patients relied on other methods, such as practising an injection on an orange. In contrast, a trainer with an agitator needle simulation tip allows patients to, as closely as possible, experience the sensation of what it would be like to use an actual prescription autoinjector on their own body by replicating the four phases of needle insertion into the skin:

- Deformation
- Puncture
- Insertion
- Extraction.[3]

Patient Benefits

There are three distinct benefits to the use of agitator needle simulation tips:

- Users have a better understanding of what to expect when injecting
- Patients gain confidence that they can self-inject correctly
- Needle anxiety is reduced.

Figure 2: Noble's simulation technologies can be incorporated in multiple platforms.

The use of agitator needle simulation tips as a feature in autoinjector trainers can help relieve patient anxiety by replicating the actual sensation of needle insertion. In many cases, patients discover that the sensation of the needle is less painful than they had initially feared. This is significant because the perceived pain that is often associated with needle use can lead to a tendency among some patients to remove the needle almost immediately following insertion. This could result in them not receiving the full dose of medication.

Practising with a trainer that incorporates an agitator needle simulation tip can also prepare patients to the point where they are more comfortable with the initial sensation of needle insertion and keeping a needle inserted for the entire interval as recommended by the Instructions for Use (IFU).

Additionally, by training prior to an actual self-injection, the user gains familiarity with the IFU and how the device functions, which can help lower the risk of errors, such as needlestick injuries or wet injection.

Use with Other Self-Injection Devices

The use of agitator needle simulation tips is not exclusive to autoinjector trainers for a particular drug class or patient population. In fact, Noble conceptualised and developed agitator needle simulation tips to be compatible with a wide range of trainers that mirror the variety of commercially available autoinjectors, prefilled syringes and potentially other kinds of self-injection device as well.

Additional Components

Agitator needle simulation tips are just one of several "device-agnostic" features that can be easily incorporated into a wide variety of trainers, depending on a drug manufacturer's specific needs. Aside from the agitator needle simulation tips, a range of other preconfigured components can allow additional features to be integrated into autoinjector trainers – such as plunger speed simulation and actuation force simulation (Figure 2). These can further replicate the realistic experience of using the prescribed autoinjector.

WORKING WITH DRUG DELIVERY MANUFACTURERS

To date, Noble has forged industry collaborations with some of the world's leading drug delivery device manufacturers

> "Incorporating special features such as agitator needle simulation tips into autoinjector trainers can provide benefits not only to the patients for whom they are designed, but also to the pharmaceutical companies that choose to have them produced."

to ensure the highest quality trainers are produced. Many such companies have come to appreciate the importance of improved patient training and, in particular, the benefits of realistic training devices. Consequently, the demand for training devices within this market space is likely to continue to rise in the years to come.

A positive "word of mouth" reputation has been fuelled in part by feedback from those in the industry who have had the opportunity to see a trainer up close and observe first hand how Noble's agitator needle simulation tips and other features work, as well as from participants in various market research forums. Noble has the capability of working with a company at every stage – from establishing product requirements to concept development, prototyping and ultimately product manufacturing.

THE DEVELOPMENT PROCESS

Once a pharmaceutical company has opted to work with Noble to offer a training device in tandem with the release of a new self-injectable drug, the process of developing a realistic autoinjector trainer – one that integrates an agitator needle simulation tip or additional special features – begins. The Noble team collaborates closely with the company to develop the precise product requirements that will drive its design and concept development. Noble has vast in-house prototyping capabilities and will produce various high-quality, fully functioning prototypes for evaluation.

Some advanced training devices that have been developed by Noble incorporate electronics that allow for real-time feedback and instruction for patients who are self-injecting. Accordingly, these products require the use of printed circuit boards (PCBs) and other components that Noble can integrate as well. These capabilities are applied on a per-project basis when the pharmaceutical manufacturer has specifically requested such features.

Final product assembly of the trainers can be conducted either manually, semi-automatically or fully automatically, depending on the specific features of a product and the quantity of trainers required. Once again, product assembly protocols are determined on a per-project basis in advance by the requirements of the pharmaceutical manufacturer.

An integral element in the overall production process is printing and packaging. These initiatives are conceptualised early in the development process and produced in tandem with the production of the training device itself. For the most realistic experience by the patient, the trainer must resemble the prescribed autoinjector as closely as possible, so Noble works to replicate the colour and other features specified by the manufacturer for the exterior of the trainer. Similarly, Noble can produce packaging for the trainer that matches the packaging of the actual device to make the patient experience as realistic as possible.

Quality practices are incorporated into every stage of the development process of the autoinjector trainers, from initial conceptualisation through commercial production. Testing is conducted early in the development process to ensure that the trainer meets all of the requirements specified by the pharmaceutical manufacturer.

CONCLUSION

The technical advances that allow the production of realistic autoinjector trainers, and Noble's proven ability to work with leading drug delivery device manufacturers to ensure the highest-quality products, can serve as a win-win for drug companies, healthcare providers and patients alike. Incorporating special features, such as agitator needle simulation tips, into autoinjector trainers can provide benefits not only to the patients for whom they are designed, but also to the pharmaceutical companies that choose to have them produced.

ABOUT THE COMPANY

Noble® works closely with the world's leading pharmaceutical and biotechnology companies to develop autoinjector, prefilled syringe and respiratory device training solutions designed to provide positive patient onboarding experiences, reduce errors and improve patient outcomes. Cross-disciplinary designers and engineers provide fully customised solutions from the first concept sketch through production, in both regulated and non-regulated environments.

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ABOUT THE AUTHOR

Joe Reynolds is Research Manager at Noble, where he leverages his knowledge and experience to develop and implement strategies that improve the patient experience and maximise value for stakeholders. His experiences include commercial, managed care and product development initiatives with leading medical device, pharma and biopharma brands. Mr Reynolds holds a BS in Business Administration from the University of Central Florida, an MS in Marketing from the University of South Florida and an MS in Pharmacy and Master Certificate in Drug Regulatory Affairs from the University of Florida.

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**For manual insertion devices*

EXTRACTABLES AND LEACHABLES FOR INJECTION DEVICES

Mark Turner, Managing Director, Medical Engineering Technologies, explains the process involved in ensuring that pharmaceutical containers do not inadvertently transmit toxic substances, while maintaining the effectiveness of the active pharmaceutical ingredients (APIs).

Prefilled syringes, injector pens and cartridge pumps are convenient ways of self-administrating treatment, as well as being useful for carers, emergency situations and more general use. The range of treatments available in this format is large and growing. Just considering conditions or situations with the letter A, there is: antithrombosis (Enoxaparin), arthritis (Abatacept) and antiseptic (dental hypochlorite).

The containers in these devices may be produced from glass or plastic, and the delivery systems will most likely contain plastics and rubbers. In all cases they form primary pharmaceutical containers, for which it must be demonstrated that toxic substances are not administered to the patient. If they are to be used for intravascular injection, they are classified as "of highest concern" by the US FDA.[1]

According to the US Food, Drug and Cosmetic Act: "The reduction of substances migrating from the hardware into solution (or suspension) during production and what is often a three-year storage life is of primary importance for controlling toxicity and maintaining the effectiveness of APIs," and: "A drug is deemed to be adulterated if its container is composed, in whole or part, of any poisonous or deleterious substance which may render the contents injurious to health…"[2]

The toxicity concerns are to be expected, but there is also drug interaction to be considered particularly where the APIs are complex (for example, proteins such as insulin, and antibodies such as Adalimumab). Yet more complicated are disabled viruses in vaccines. In addition, all treatments, particularly those dependent on protein structure, can be vulnerable to degradation by migrating substances or contact with the container walls.

New materials and processes that minimise migration and maximise stability are being developed and marketed to address these concerns. These materials improve the situation, but the need for verification of safety and bioavailability (and efficacy) remains.

> "Once you know what you are looking for, and that you can find and quantify it, the analysis can begin."

THE VERIFICATION PROCESS

To ensure that materials of concern are found and quantified, an effective extractables and leachables analysis is required. Firstly, a thorough risk analysis to identify potential migrating species (chemicals that can transfer into the administered fluid) needs to be done of all the materials in the product and all the materials in contact with the product.

Once "potential migrants" have been identified, methods can be developed to search for them. These methods need to be validated using reference samples of the materials. Once you know what you are looking for, and that you can find and quantify it, the analysis can begin. Extraction media should be selected according to the potential migrating materials, component materials, drug materials, stability requirements and route of administration, with consideration also given to how to check for unexpected materials.

The resulting solutions – extractables and leachables (migrating materials) – are analysed using a wide variety of validated techniques. Most commonly, gas and liquid chromatography is used followed by mass spectroscopic analysis (for non-metallic materials), and atomic absorption (for metallic materials). Sample concentration may be required to achieve the required sensitivity.

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Once the potential problems have been highlighted, a systematic approach to identifying and quantifying what is truly a problem is required. One approach is given in the flowchart in Figure 1.

THE MATERIALS RISK ANALYSIS

There can be a large number of potential contaminants (suspected and unsuspected). In many cases, the API in liquid form could influence the amount of material migrating from the delivery system and container components and/or (especially in the case of proteins) the API may be altered by any leachates.

To complicate matters further, the interaction between all these different components can lead to secondary leachables (or reaction products).

The materials to consider in the risk analysis include processing chemicals and contact surfaces, as well as the delivery system components.

A (non-exhaustive) list might include the following:

From production:
- Cleaning materials
- Mould release or other processing materials and lubricants
- Contamination from nylon or stainless steel transport mechanisms and other processing metals
- Metals from other sources (notably tungsten for glass syringes)
- Residual solvents
- Airborne and environmental contaminants.

From the syringe components:
- Unreacted monomer
- Oligomers
- Solvent
- Initiators
- Accelerators
- Stabilisers
- Side reaction products
- Catalysts
- Vulcanising agents.

Within the formulation, some of the materials likely to be present are:
- API
- Excipients
- Buffers
- Lubricant
- Preservatives
- Solvent.

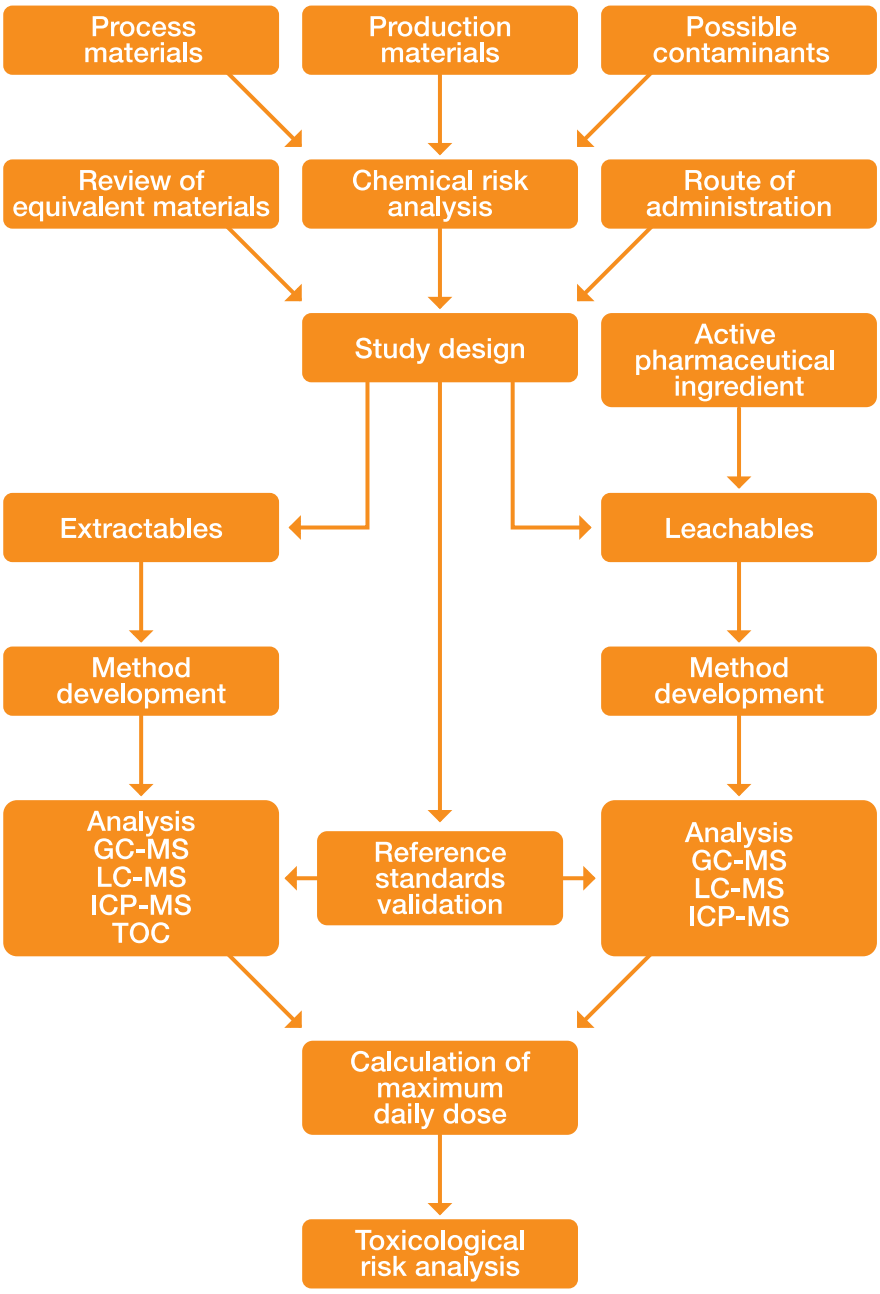

Figure 1: Using a flowchart to identify and quantify potential problems.

METHOD DEVELOPMENT

According to the flowchart (Figure 1), once the potential materials of interest are identified, a study is designed. This should take into account what information is already known about these materials (whether potential contaminants or system components). Information on the materials may be available publicly, and also from companies' internal knowledge.

This information is then used to implement the following stages of the study: analytical method development; analytical method validation; extraction, identification and quantification; and toxicological risk analysis (TRA).

> "The materials to consider in the risk analysis include processing chemicals and contact surfaces, as well as the delivery system components."

Analytical Method Development

Once the identity and nature of the possible migrating materials have been established, suitable solvents and analytical techniques can be proposed.

The analytical detection techniques

will involve chromatography in liquid and gas phases to separate chemicals for individual analysis. The separated chemicals will be examined by UV absorption, mass spectroscopy and a variety of other techniques. Each of these processes will have its own set of conditions and arrangements, which are selected according to the properties of the potential migrating materials to be investigated.

These processes must deliver sufficient sensitivity, and have the resolution (of material identification) required by the TRA.

Analytical Method Validation

Validation is achieved by the analysis of reference samples of known concentrations using the same methods and conditions that will be used for identification and quantification of the migrating substances. Once verified in this way, an analytical method can be used to quantify the materials extracted from the test sample.

Extraction

The first phase of the product analysis is the transfer (migration) of materials from the solid phase of the delivery device into a fluid system for analysis (and to simulate use).

Extractables are what is forced out of the container system and leachables are materials that are likely to migrate under normal conditions. Normal conditions for a prefilled syringe are usually two years' contact (often at 4°C).

Leaching studies are usually carried out using the API, in its normal presentation, as the leaching medium. The time duration and temperature that can be applied to obtain migrating leachables is limited due to the time available for experimentation and the danger of denaturing components. As a result, stronger solvents and higher temperatures are often used in extraction studies to access materials which migrate slowly. Consideration of the storage period may also necessitate the application of multiple leaching conditions (and periods, according to ICH guidelines – ICH Q1 R2).

Also, because of the different processing parameters and make-up (polarity, pH and viscosity) of different formulations, it is necessary to examine the leachables for each formulation in a delivery system design.

Extractable studies are usually repeated with solvents of several polarities (examples are water, ethanol/water mix, isopropyl alcohol and hexane) in exaggerated conditions. For short-term contact containers, elevated temperatures with agitation would be considered but for longer-term containers exhaustive extraction might be used.

> "It is not always obvious what surface area to solvent ratio to use for extraction. With leaching it is logical to use the container itself, preferably including the drug-contacting areas. For extracting, ISO 10993-12 gives some guidance."

It is not always obvious what surface area to solvent ratio to use for extraction. With leaching it is logical to use the container itself, preferably including the drug-contacting areas. For extracting, ISO 10993-12[3] gives some guidance.

In this standard, the volume of extraction medium is related to the surface area of the device. A further consideration is the need to obtain a sufficient concentration of any migrating species, in order to allow detection at the sensitivity required by the TRA (see note).

Identification and Quantification

The analytical methods are now validated and may be applied to the leachate and extractate solutions.

Unexpected materials will also be found in the analysis. These can sometimes be identified by the absorption spectra and fragmentation patterns (mass spectroscopy), but will need confirmation with reference materials. One of the more effective methods of identifying unknown materials is tandem time-of-flight mass spectrometry (MS/MS-TOF). This analysis is extremely sensitive (both in terms of concentration and in terms of molecular weight), which in turn gives more confidence in library identifications.

Toxicological Risk Analysis

Once all the data is gathered on what materials could (or would) migrate into the syringe content, the risk to patients can be assessed by calculating the possible quantities of materials reviewed. Typically, this will be the Product Quality Research Institute (PQRI, Washington DC, US) thresholds.

In terms of injection media contact time, injection devices can be broadly split into two categories. In one group the contact time is short, for example the drawing of an antibiotic into a syringe for immediate injection (whilst the syringe contact is short term, the contact time with the ampoule or vial is long term). Others have a long-term contact, such as that for solutions stored in prefilled syringes for several years or products used for chronic conditions. An example of chronic contact is an insulin pump which can be recharged. The contact time for each charge may be short, but the patient chronically receives repeated doses.

The toxicity of each migrating substance found should be assessed with regard to the nature of contact with the patient and the likelihood of migration.

Toxicity is often described as a safety concern threshold (SCT). Information on this can be found (amongst other places) through PQRI, which uses the Crammer Index to classify risks whilst employing a 10x overdose factor. This classification can be effected by using Toxtree software (IDEAconsult, Sofia, Bulgaria). A quantitative structure-activity relationship (QSAR) assessment may also be used to ascertain the risk level posed by a chemical.

There may also be a need for an efficacy risk analysis at this point, because solutes or particles in the dosage form may alter the effectiveness or availability of the treatment.

CONCLUSION

The key to a successful extractables and leachables study is a systematic approach. It is best to examine components and processes thoroughly and work out what could be present, then develop and qualify processes to detect these materials with the sensitivity that will be required in the TRA. Analysing extracts from appropriate solvents, quantifying known substances, and doing the detective work to quantify unknown substances is also important. Finally, know what you can potentially administer and assess its toxicity.

Note: ISO 10993-12 also allows an increase in temperature to accelerate the migration. Increased temperature will effect heat-labile APIs. This could interfere with bioequivalence studies or change the migration characteristics. This should be considered when analysing the results.

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ABOUT THE COMPANY

Medical Engineering Technologies (MET) has successfully delivered design validation testing to medical device and pharmaceutical companies in 20 countries across Africa, Asia, Australasia, Europe and the Americas. MET knowledgeably, reliably and effectively delivers medical device and packaging testing. Services include protocol development, laboratory testing and data analysis. The laboratory is equipped for performance testing, chemical analyses and sterile barrier verification and, with accreditation to ISO 17025, customers can have confidence in the quality and accuracy of the results.

ABOUT THE AUTHOR

Mark Turner is Managing Director of Medical Engineering Technologies, which provides a wide range of services to engineers and project managers in the medical device industry. Mr Turner founded MET in 1997 after 12 years of project management and device design with Smiths Medical. He has also worked as a perfusionist in the cardiac unit of Kings College Hospital (London, UK) providing experience of the application of medical devices first hand. He received a BSc in Chemistry (with Biochemistry) from the University of Wales in 1983 and has also studied astronomy, business administration, cosmology and opto-electronics.

ENABLE INJECTIONS AND FLEX SET AMBITIOUS PLANS FOR LARGE VOLUME DRUG DELIVERY

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The delivery of high volumes of biologics outside of the clinical setting remains a key challenge in the industry. Here, John Love, Vice-President of Product Development and Operations, Enable Injections, Mark Lee, PhD, Health Solutions Group Chief Technology Officer, Flex, and Amy Boyle, Vice-President of Marketing, Flex, discuss how the enFuse™ on-body injector, developed by Enable in partnership with Flex, may be the answer.

Enable Injection's enFuse™ drug delivery technology is set to redefine the standard of wearable injection devices (Figure 1). However, unlike many disruptive new medical device concepts, which often demand a change to practice, enFuse does not. It achieves great strides towards the goal of infrequent, large-volume injections of biologics, is easy to use and has wide-ranging benefits that are immediately evident. It can deliver large doses – up to 50 mL (Figure 2) – of the most viscous biologics subcutaneously, with no needle in sight and with minimal to no discomfort.

Figure 1: Enable's enFuse high-volume wearable injector technology.

> "According to Grand View Research, the drug-device combination market is expected to reach US$178 billion (£127 billion) by 2024. The research firm says it expects an "unprecedented adoption rate of these combination products" as a consequence of their many benefits."

enFuse allows health facilities to treat more patients who either choose or need treatment in the clinic, freeing up nursing time and increasing patient throughput and saves healthcare systems money whilst doing so. It allows pharmaceutical companies to decrease their drug development time and extend their commercialised products' lifecycles. It allows patients to potentially skip the infusion centre once therapy has been established and

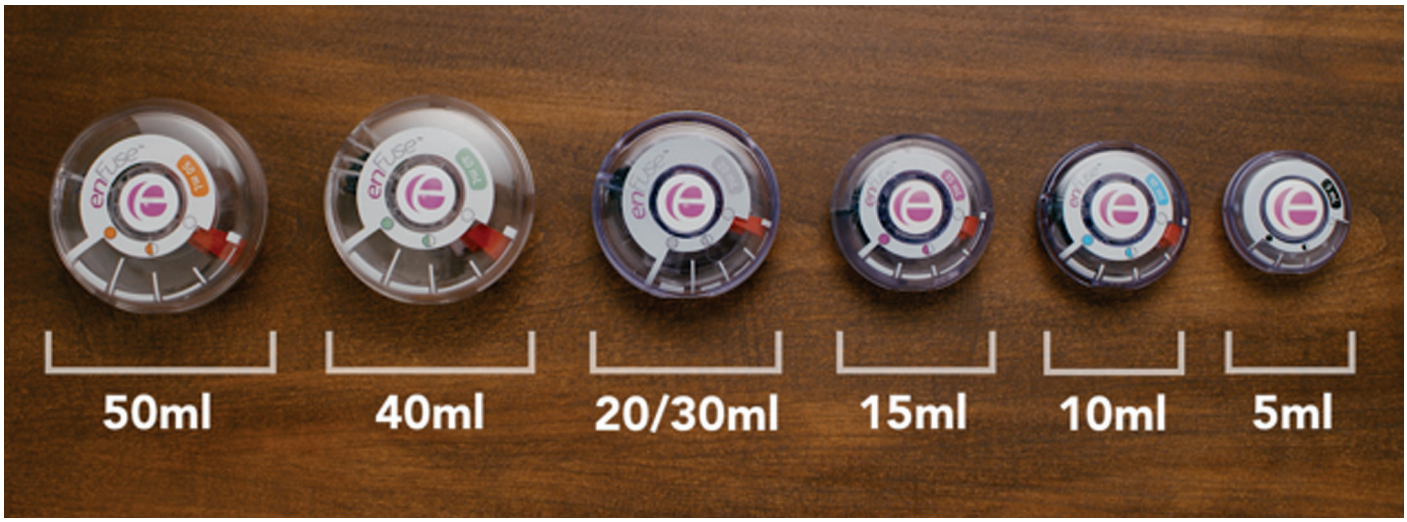

Figure 2: The enFuse platform handles dose volumes from 5 mL through to 50 mL.

self-administer their prescribed biologic at home or work, in a way that is easier, more comfortable and more convenient than intravenous (IV) administration and, most importantly, enFuse allows them to have agency over their own treatment and improve their quality of life.

Armed with the smallest, most advanced connected technology platform available for delivery of high-volume biologic drugs, Enable Injections is showing all the tell-tale signs of a startup that can meet the demands of the rapidly expanding industry for large-volume wearable injectors. Enable has an in-house manufacturing facility, as well a partnership with major international contract manufacturer Flex for the large orders anticipated, and a swiftly increasing number of development projects and feasibility studies.

enFuse is a technology that could result in better patient care in terms of improved compliance that will likely lead to better outcomes and enhanced patient satisfaction.

RISING DEMAND FOR COMBINATION PRODUCTS

A new, patient-centric way to administer the ever growing number of large-molecule biologics, as presented by enFuse, is sorely needed. Thus, combination products have been trending in the pharma market to catch up with this unmet need. According to Grand View Research, the drug-device combination market is expected to reach US$178 billion (£127 billion) by 2024. The research firm says it expects an "unprecedented adoption rate of these combination products" as a consequence of their many benefits.

> "When large volume production of enFuse units is required, it can be quickly integrated into any one of Flex's international production facilities with Class 8 cleanrooms."

THE ENABLE – FLEX PARTNERSHIP

Anticipating the high adoption rate of this new technology, Enable Injections sought out the world's largest medical device contract manufacturer, Flex. Flex's expertise in the miniaturisation of electromechanical pump systems, precision plastic moulding and connectivity technology supports present and future generations of the innovative enFuse delivery device platform, developed by Enable based on dozens of human factors studies for ease of use and patient comfort.

In particular, Flex's skill at miniaturisation ensures one of enFuse's major differentiators: its small size. The 10 mL device is about the size of an Oreo cookie, which makes the wearable large volume injector comfortable for any sized person to wear while carrying on with their day-to-day, no longer tethered to an IV at an infusion facility (Figure 3).

Flex's singular, rigorous quality system, conditioning know-how and large-scale manufacturing capabilities made the company an ideal partner to address manufacturing complexity and scalability. Their collaboration and joint engagement to establish material handling, pre-control of critical variable signals and manufacturing

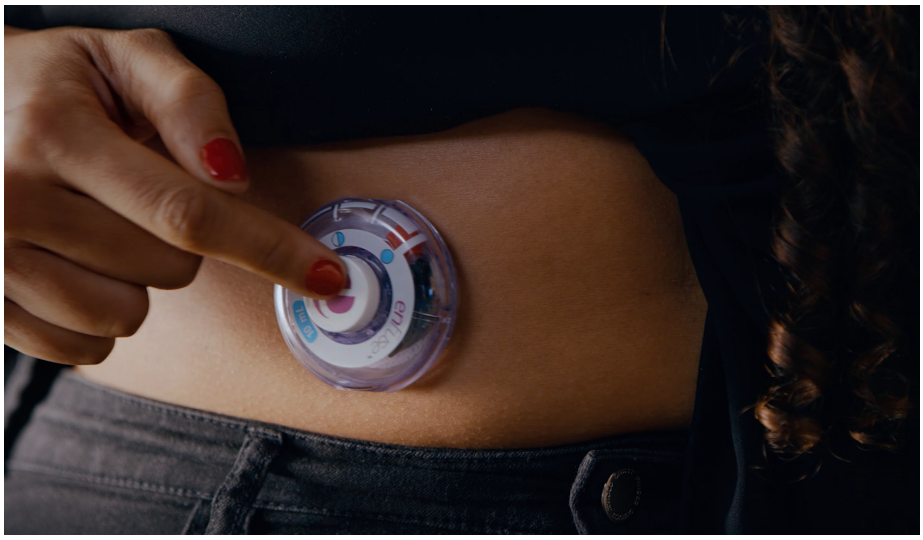

Figure 3: enFuse is small, convenient and comfortable.

requirements during the design phase set the stage for successful manufacturing from the very beginning. In addition, Flex has experience in combination on-body devices, ISO 11608 and regulatory requirements. Flex and Enable's partnership also helped to develop a competitive cost of goods across unique components, precision plastics, automated assembly and device packaging.

Through to this partnership, Enable's enFuse device boasts a full suite of digital health and connectivity capabilities, powered by Flex Digital Health's fully HIPPA compliant BrightInsight™ platform. These features provide avenues through which usage and compliance insights can be gleaned and patient's outcomes can be improved. This innovation expands market opportunities, allowing Enable's pharma partners to provide greater therapeutic value to their patients by facilitating a more outcomes-based approach to treatment decisions.

PROGRESS TOWARDS MARKET

After the companies collaborated on design, the work transitioned back to Enable in 2017 to prepare the versatile platform for clinical trials. As demand from pharma increases, Enable will provide clinical builds and initial production from its Cincinnati HQ and then transfer high volume production to Flex.

A Growing IP Portfolio

A series of granted patents and pending applications in the US, Europe and Asia-Pacific for Enable Injections' enFuse On-Body Delivery System technology solidifies the company's position as a leader in the large volume wearable drug delivery market. The most recently granted is a relatively rare utility patent issued by the US Patent and Trademark Office.

Development And Feasibility Studies

Enable has engaged with most pharma companies, from small start-ups to well-established global players. Extensive feasibility studies evaluating device performance and patient acceptance have been conducted, resulting in several development projects to date. Discussions are ongoing with current and future pharma partners to extend the collaboration to more products in the near future.

Ensuring Cost-Effectiveness

From the beginning, the development of enFuse focused on final product costs to maximise return on investment (ROI) for Enable's pharma partners. Utilising Flex's strength in global supply chain management and a continuous improvement mindset, the companies have developed a five-year strategy to ensure timely market entry of a product at a competitive price.

Built-In Technology Transfer

In drug development, time is always of the essence. As the patent life of newly discovered drugs continues to shrink, drug developers are forced to minimise drug development time. One bottleneck that often delays time to clinic is technology transfer. Manufacturing transfer expertise is essential to quickly ramp-up production for launch execution. In the event of earlier than expected regulatory approvals or accelerated adoption, special expertise and flexibility in production ramp-up speed is required.

The close collaboration between Enable and Flex ensures minimal production delays. When large volume production of enFuse units is required, it can be quickly integrated into any one of Flex's international production facilities with Class 8 cleanrooms. Technology transfer is built in for rapid response to pharma needs.

INTEGRATE DELIVERY EARLY IN DRUG DEVELOPMENT

The enFuse platform is available now for faster drug development and for investigational use. Nearly 60% of pharmaceutical combination product experts say that the time to add the delivery device constituent is in early stages of drug development. Introducing a delivery platform at the early clinical stage provides an opportunity to engage patient populations that much sooner, improving the product's ability to meet patient needs and thereby improving the likelihood that the outcomes align with the expectations of governments and payers. It also enables the pharmaceutical company to answer contextual questions regarding the patient sooner, and thus decrease cycle time for new product development.

"Nearly 60% of pharmaceutical combination product experts say that the time to add the delivery device constituent is in early stages of drug development."

An early start will also reward formulation teams. Today's more advanced technologies and wearable devices can reduce time to market by months or even years. They provide the means to more easily:

- Deliver drug product in high volumes
- Deliver much higher viscosities
- Address biologics' greater propensity to precipitate out of solution.

PATIENT TREATMENT EXPERIENCE

From the patient perspective, how a drug is delivered (method, frequency, device, etc) is often the defining element of the treatment experience. In today's clinical trials, the patient should always be at the centre. It's become much more important to have the treatment experienced by someone representative of the target patient population. Physiological data is of course gathered, but patients are now reporting back on how the treatment experience feels, how it could be made easier for them and what they liked and disliked about it.

In pharmaceutical company patient panels, enFuse was preferred to many other delivery methods, primarily due to its comfort and convenience.

LOOKING AHEAD

The result of the Enable – Flex partnership is an advanced, patient-centric biologics delivery platform that is an effective therapeutic solution to delivering high volume biologic drugs. The world's ageing population and rising incidence of chronic diseases has made the need for a product like enFuse inevitable. The need to reduce healthcare expenditures along with the increasing popularity of point-of-care treatments are also fundamental shifts underlying the rapid growth in the drug-device combination products market.

Looking forward to advances in on-body delivery device combination products, we can expect more connectivity to improve user experience, disease management, provider and caregiver interaction and communication with an electronic health record (EHR). Now and in the future, pharmaceutical companies can employ these innovative products with very low risk and cost of entry.

ABOUT THE COMPANIES

Enable Injections is a late-stage start-up company that has developed a disposable wearable injector to deliver high-volume, high-viscosity biological drug products (up to 50 mL) to the subcutaneous tissue. The system uses standard container closures (syringes or vials) and can automatically mix solutions or solubilise lyophilised product. Founded by medical device veterans the company has R&D, operations and manufacturing facilities in Cincinnati, OH, US.

Flex is the Sketch-to-Scale™ solutions provider that designs and builds Intelligent Products for a Connected World™. With approximately 200,000 professionals across 30 countries, Flex provides innovative design, engineering, manufacturing, real-time supply chain insight and logistics services to companies of all sizes in various industries and end-markets. Flex partners with a broad spectrum of healthcare OEMs to provide complete innovation, design, build, service and data solutions that make its customers more competitive in the areas of medical devices, drug delivery, diagnostics and medical equipment.

ABOUT THE AUTHORS

John Love is Vice-President of Product Development and Operations at Enable Injections. He has over 30 years of leadership, R&D and operations experience in the medical device industry. Prior to joining Enable Injections, he was VP of Operations at Triangle Manufacturing, directing a 240-person medical device CNC contract manufacturing facility. He has also held executive positions in R&D, engineering, operations, quality, regulatory and medical scientific affairs at Aesculap Implant Systems, Cordis Corporation, Novoste Corporation, Ethicon Endo Surgery and Baxter Laboratories.

Dr Mark Lee, PhD, is Chief Technology Officer at Flex's Health Solutions Group. His responsibilities cover human-factors-based user needs definition through innovation and design, ramp-up, full scale production, and supply chain management. Prior to Flex, Dr Lee was the Global Head of R&D for Johnson & Johnson, where he led research and development activities across the pharmaceutical, medical device and consumer health segments and identified new growth areas. Dr Lee has also held leadership roles in R&D with fortune 100 medical device companies including Baxter, GE medical and Amgen, where he developed the combination product design process for all of Amgen's pipeline molecules.

Amy Boyle is Vice-President of Marketing at Flex Health Solutions Group. She leads business development, promotional efforts, education and business growth strategy for all of Flex's health related business. Prior to joining Flex, Ms Boyle filled executive global marketing roles at Coloplast, IMRIS, St Jude Medical, and Medtronic. Over her career, she has launched well over 100 products and created and led associated market development and education initiatives.

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glass made of ideas

CREATING PREFILLABLE SYRINGES FOR THE BIOLOGICS MARKET

As pharmaceutical companies increasingly shift their focus towards biopharmaceuticals and large-molecule drugs, the need for syringes that can handle these sensitive and complex substances becomes more pressing. One such product, syriQ BioPure® is made of high-end materials and integrates seamlessly with autoinjectors to ensure patient convenience. In addition, the syringes link with an innovative filling platform that enables small batches and/or different containers to be filled on one line. Nicolas Eon, Global Product Manager, and Fabian Stöcker, Head of Global Strategy & Innovation, both of Schott Pharmaceutical Systems, explain more.

Over the last several years, the number of blockbuster drugs in the development pipeline has decreased. Drug companies have largely shifted their research interests towards biopharmaceuticals, protein-based therapies and other large-molecule drugs.

As sensitive and complex drugs are often highly viscous, it makes them more difficult to administer. Furthermore, biologic therapies face some constraints when it comes to drug storage, being prone to interactions with the packaging material. Those interactions can limit efficacy and purity, consequently requiring extensive risk analyses and staking tests before regulatory approval.

Figure 1: The new syriQ BioPure® syringe for biologics.

To tackle these constraints, Schott recently introduced prefillable glass syringes for the biologics market known as syriQ BioPure® (Figure 1). The syringes are designed to keep sensitive drugs stable during their shelf life and shorten time to market while making administration more convenient for patients. To do this, syriQ BioPure® syringes are manufactured under improved processes to lower tungsten and adhesive levels and to ensure a uniform silicone layer – all validated and documented under US FDA regulations.

USE OF HIGH-END MATERIALS

The syringes are made of highly inert Type I FIOLAX® borosilicate glass – the gold standard for packaging complex drug products. The suitability of this glass type for sensitive drugs is well researched and it has a strong track record.

In addition, the rubber plunger stoppers used in syriQ BioPure® syringes are made of the newest polymers to limit interaction with elastomer-coating compounds. The plungers and various closure systems, such as Aptar 4800, Aptar 4900, West 7025 and West 7028, are tailored for sensitive applications. More than 48 combinations have been validated. The use of high-end materials also gives syriQ BioPure® a

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superior extractables and leachables (E&L) profile. Lastly, the syringes are manufactured using a particularly thorough production method to limit the risk of adhesive residuals in the luer.

SEAMLESS AUTOINJECTOR INTEGRATION

The new glass syringes work with leading safety and autoinjector devices, thus meeting market demand for products that can be administered at home for patients' convenience. Seamless integration into these devices is achieved thanks to the syringe's high dimensional accuracy. Each single glass tube used for the manufacture of the syringes is closely inspected by lasers, cameras and infrared systems – a process which is known as Schott's big data perfeXion™. By collecting roughly 100,000 data tags per minute, the integrated IT system picks up imperfections with such precision that it can later identify the corresponding individual tubes, which can then be discarded.

ADDITIONAL DIMENSIONS

The syringes also have additional dimensions beyond ISO requirements, as well as new geometrical tolerances, which are achieved by cutting-edge forming technology and online inspection systems. This gives the device optimum compatibility, and leads to superior functionality for patients.

The syringes are documented according to the latest design-controlled guidelines (according to FDA 21CFR Part 820) to support the requirements for combination products. As all required documentation is fully available, this means there is a short time-to-market for the pharmaceutical industry.

THE IQ™ PLATFORM CONCEPT

The syringes are delivered in a standard sterilised nest and tub and can be filled on a wide variety of standard, ready-to-use (RTU) filling lines. They are part of Schott's new iQ™ platform, which is based on the proven nest-and-tub format of RTU syringes that has been used by the pharmaceutical industry for decades. The new platform builds on the advantages of RTU filling concepts by enabling pharma companies to fill small batches and/or different containers on one line (Figure 2).

Currently available solutions from packaging suppliers require drug manufacturers to fit the filling machines to the specific tub format, which means the machine needs to be optimised each time to fit the individual products and the same work has to be done multiple times.

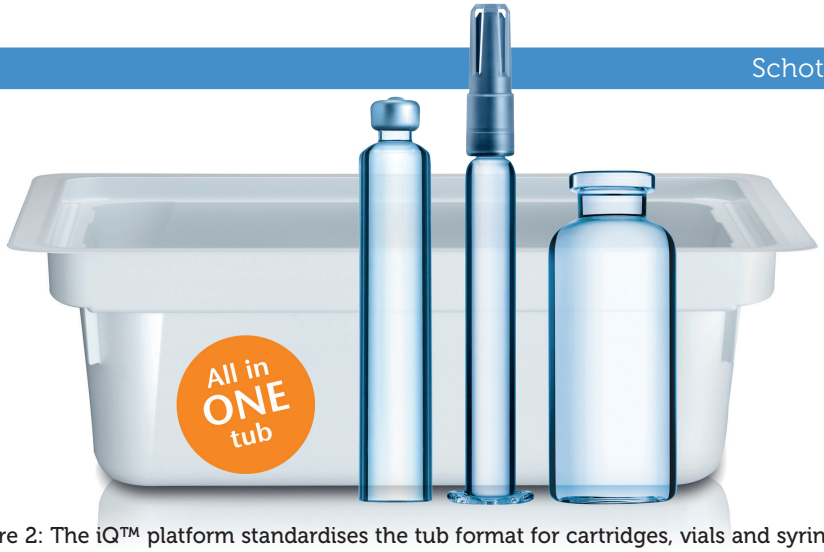

Figure 2: The iQ™ platform standardises the tub format for cartridges, vials and syringes.

Schott addresses this particular issue by standardising ready-to-use syringes, vials and cartridges within a single tub format to run on the same filling line. By standardising this part of the process, less changing of machine parts is necessary when switching from one container to another as the vials, syringes and cartridges all come in the same tub. Consequently, pharma manufacturers can fill various drug and container configurations on the same line with as little as 10–20 minutes of changeover time. They can also switch from one container to another, or one dosage to another, or to new drugs.

AIMS OF THE IQ™ PLATFORM

Maximise Flexibility

The platform was developed with the world's largest filling line and elastomer component suppliers to simplify the entire filling process and ensure pre-validated and flexible container/elastomer systems can be offered. This further reduces testing efforts, improves quality and accelerates time to market. It comes with a versatile container portfolio including Schott's syriQ® prefillable syringes and adaptiQ® ready-to-use vials, as well as the new cartriQ™ ready-to-use cartridges, which will be available soon. Moreover, iQ™ is compatible with over 30 machine platforms of all leading and also upcoming machine vendors.

Reduce Complexity

The platform enables pharma companies to reduce the total cost of ownership (TCO). A case study has shown that iQ™ decreases the need for format parts. Companies can thus reduce investments by up to 40%, clean room space by up to 60% and running costs by up to 40%. Additionally, when considering that nowadays drugs need to be manufactured in ever-smaller batches in shorter periods while adhering to higher quality standards, the iQ™ standardised tub format increases filling flexibility and greatly reduces complexity. Consequently, pharma companies can accelerate time-to-market and accommodate new drug development.

Enhance Patient Safety

With the highest industry-quality type I glass, FIOLAX®, and the nested configurations, the iQ™ platform eliminates glass-to-glass contact during filling, transport and storage. Thus, the risk of scratches and defects is decreased significantly, which ensures and improves patient safety. Moreover, the particle load is minimised in all of Schott's RTU containers. Therefore, the platform also provides a solution to various industry concerns, such as glass breakage and particle reduction.

CONCLUSION

By combining the advantages of Schott's new iQ™ platform and using the highest quality materials in the manufacturing process, syriQ BioPure® syringes are ideally positioned to handle the growing market in sensitive and complex pharmaceutical drugs. In addition, the syringes integrate seamlessly with autoinjectors through the use of Schott's big data perfeXion™, and time-to-market is reduced through documentation and use of the platform.

ABOUT THE COMPANY

Schott Pharmaceutical Systems is one of the world's leading suppliers of parenteral packaging for the pharmaceutical industry. More than 600 production lines in 13 countries worldwide produce more than 10 billion syringes, vials, ampoules, cartridges and special articles of tubing glass or polymer. The company has more than 130 years of outstanding materials and technology expertise.

SCHOTT Pharmaceutical Systems

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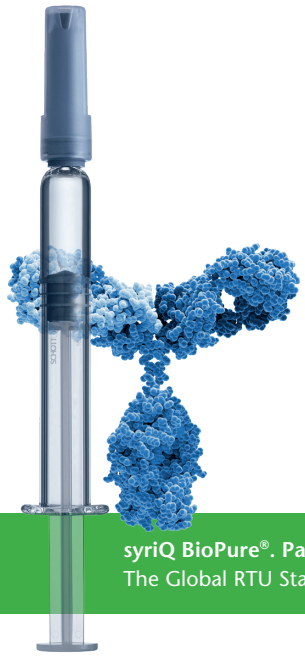

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PRODUCT REVIEW – SAFE'N'SOUND® & SAFELIA®

Séverine Duband, Nemera's Global Category Manager, Parenteral, provides a rundown of the features of Nemera's injectable device offering, the Safe'n'Sound® single-use safety device and the Safelia® two-step autoinjector.

SAFE'N'SOUND®

Safe'n'Sound® (Figure 1) is a single-use safety device to protect patients and healthcare professionals from accidental needlestick injuries. It is activated passively with one hand, suitable for low fill-volumes and higher viscosity formulations, robust against shocks and vibrations and compatible with all scales of assembly line, from manual to fully automated.

It is also compatible with both prefilled ISO standard glass syringes and PLAJEX plastic syringes, fitting 1 mL "long" and 2.25 mL long staked syringes with a maximum needle length of half an inch (12.7 mm).

Ergonomically designed, Safe'n'Sound® is intended for treatment-naive users, experienced users and healthcare professionals alike. It features a large thumb-pad for ease of use, clear visibility of the tip for easy inspection of the drug and a rounded shape for increased labelling surface.

Safe'n'Sound® is a highly customisable platform, able to respond to pharma and user needs. There are, for example, the options of an extended finger flange, coloured plunger rod, a "soft touch" thumb-pad and a one-handed, subcutaneous rigid needle shield (RNS) removal feature.

SAFELIA®

Nemera's two-step autoinjector, Safelia® (Figure 2), has been designed to respond to challenges posed by new formulations, while taking patient needs into consideration. A platform for 1 mL or 2.25 mL prefilled syringes, Safelia® features:

- A patented cam-based mechanism for delivering more viscous formulations through thinner needles.
- A disconnected needle insertion and injection system so that the right dose can be delivered at the right depth.

Figure 1: Nemera's Safe'n'Sound® single-use safety system.

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Figure 2: Nemera's Safelia® two-step autoinjector.

- Reduced risk of glass breakage due to forces being transmitted onto the syringe shoulder instead of the flange and reduced shock force and stress (thanks to a reduced needle insertion speed and increased needle deceleration distance).
- A tailored needle insertion and injection speed for each formulation.
- The ability to slow down the beginning and end of an injection.
- A hidden needle for increased safety.
- A simple two-step injection process for ease of use (Figure 3).

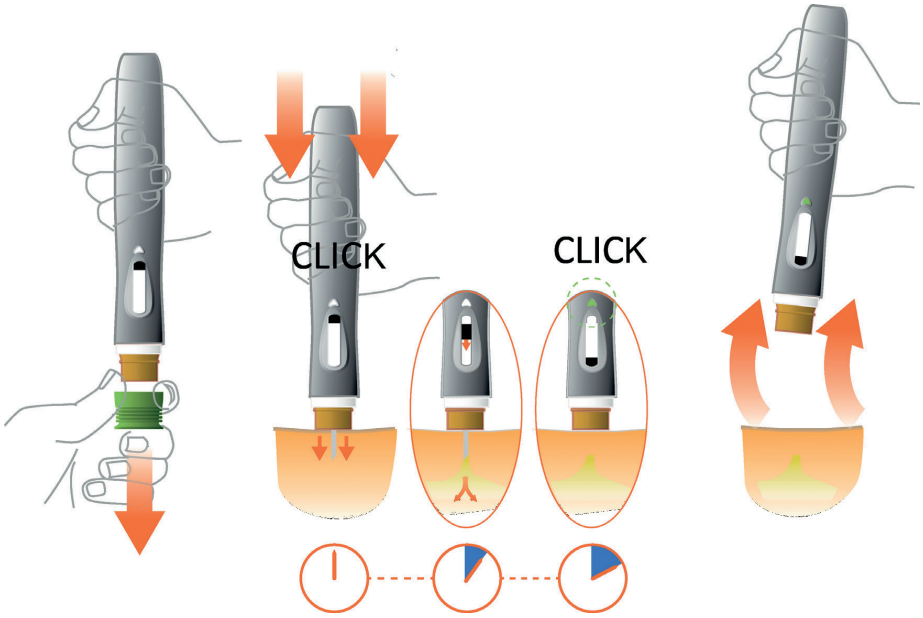

Figure 3: The two steps of using Safelia®.

CONCLUSION

Parenteral drug administration exposes patients and healthcare professionals to many hazards. To ensure adherence and users' safety, reliable and easy-to-use devices are needed. With decades of experience in developing and manufacturing some of the most complex and innovative parenteral drug delivery solutions, Nemera is the ideal partner for a successful product launch.

ABOUT THE COMPANY

Nemera is a world leader in the design, development and manufacture of drug delivery devices for the pharmaceutical, biotechnology & generics industries. Nemera's services and products cover several key delivery routes:

- Parenteral (autoinjectors, pens, safety devices & implanters)
- Ophthalmic (multi-dose, preservative-free eyedroppers)
- Nasal, buccal, auricular (pumps, valves and actuators for sprays)
- Inhalation (pMDIs, DPIs)
- Dermal and transdermal (airless & atmospheric dispensers).

Nemera always puts patients first, providing the most comprehensive range of devices in the industry, including innovative off-the-shelf systems, customised design development, and contract manufacturing.

ABOUT THE AUTHOR

Séverine Duband is Category Manager at Nemera in charge of the parenteral range of proprietary products including Safe'n'Sound®, the passive safety device platform for prefilled syringes. Ms Duband joined Nemera in 2018. She has ten years' marketing experience in fast-moving consumer goods with key competencies including strategic planning, NPD launches, project management, brand communication and team leadership in an international environment. Ms Duband has a Masters in Science in Business Marketing from EMLYON Business School, Lyon, France.

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MAKING SELF-ADMINISTRATION POSSIBLE FOR ALL PATIENTS

Medication non-adherence is well recognised as a major cause of poor patient outcomes. To address this problem, manufacturers of delivery systems are becoming more proactive in gaining patient feedback during design and development phases. At West, extensive human factors studies were carried out to help create the SelfDose™ patient-controlled injector, designed for patients who have dexterity problems. Carl Dabruzzi, Director, Product Management, Self-Injections Systems explains more.

The market demand for integrated delivery systems – which combine an injectable drug, its container and the system used to administer it – continues to grow due, in large part, to the popularity of self-administered therapies for rheumatoid arthritis (RA), diabetes and other chronic conditions. This shift is part of an even larger trend towards a more patient-centric approach in the manufacturing of integrated delivery systems. Because of this renewed focus on the patient, drug delivery system manufacturers are continually re-evaluating the processes by which they improve existing systems and how they develop new ones. As a result, delivery system manufacturers have become an invaluable partner to pharmaceutical companies.

Often, those left behind by these trends are patients with conditions that leave them with dexterity challenges, such as RA and multiple sclerosis. Despite any desire they may have to self-administer their treatments, they often cannot do so effectively due to their limited ability to use their hands and fingers. To empower them, West wanted to design a self-administration delivery system with these patients in mind, so it conceived the SelfDose™ patient-controlled injector (Figure 1).

THE RISE OF PATIENT INPUT

Everybody involved in manufacturing, packaging and delivering medication to patients wants to achieve optimal patient outcomes. However, if patients are uncomfortable with an injectable drug's delivery system, they are less likely to use it. This can lead to a natural drop in adherence levels, which can then have a negative impact on patient outcomes.

In fact, medication non-adherence is a leading cause of poor clinical outcomes and increased healthcare costs. According to Capgemini, the pharmaceutical industry's global revenue loss due to non-adherence to medication for chronic conditions is estimated to be $564 billion.[1]

To address the adherence issue, manufacturers of integrated delivery systems have become proactive in seeking out patient feedback during design and development phases to ensure that the final product is something that patients are comfortable using.

> "Simply designing a delivery system that patients "can" use is no longer sufficient. Delivery systems should be designed for affinity, and encourage patients to "want" to use them."

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Because of the demand for self-administered injectable medicines, patient feedback on how they interact with delivery systems is more important than ever. Drug manufacturers have often relied upon patient focus groups for insight into end-user considerations for self-injection systems. However, the narrow focus group setting doesn't provide a full picture of how patients use injection systems in multiple environments: at home, work and other settings.

Integrated drug delivery system development must take into account the fact that patients interact with the system differently at each stage of their journey and in the various environments they encounter each day. Human factors analysis and engineering and usability testing can provide a detailed understanding of patient behaviours, motivations and needs and how they change over time. This process uses in-depth statistical analysis, data aggregation and synthesis techniques to produce actionable opportunities for innovations and enhancements to self-injection system technology.

UNDERSTANDING PATIENT NEEDS

Environmental research is key to human factors engineering; observation and interviews provide the critical context needed to make a qualitative assessment of a patient's abilities and challenges. Observing patients as they go about their day – and considering all of the surrounding environmental factors, such as temperature, noise and lighting – can help researchers better understand how the patient will use a self-administration system.

In-person surveys, questionnaires, user-based performance testing and heuristic analysis also add to the base of human factors knowledge.

One-on-one usability testing enables contextual inquiry that is essential in effective human factors analysis. It helps better evaluate a patient's physical and cognitive abilities, state of being, knowledge of the disease state and experience with delivery systems. This type of testing also allows researchers to explore new product concepts while closely evaluating whether a delivery system is appropriate and effective for patients. The resulting data is valuable in confirming patient needs, desires and preferences.

Once all of the environmental and usability data has been collected, human factors experts can perform detailed analysis of patient habits, human error triggers and risk scenarios. From there, designers are able to make objective recommendations on self-injection system design and develop a product-adoption roadmap based on real-life experiences.

Figure 1: The SelfDose patient-controlled injection system.

Working with human factors engineering and research professionals, drug delivery system companies can learn more about how an evolving disease state can impact the system use in real-life situations. By employing a flexible set of design tools that will help refine and enhance the delivery system they can then help reduce user-based error and control or reduce current and future risks associated with system use. Such refinements can help to create a system that not only aids in the effective delivery of an injectable drug product, but that enhances the patient journey and potentially earns brand loyalty for the pharmaceutical manufacturer during the entire course of treatment.

By applying human factors principles and conducting extensive usability testing early in the design process, drug manufacturers and their delivery system partners can maximise the likelihood that the self-injection system user interface is safe and effective for use by the intended users in various environments.

BUILDING PATIENT FEEDBACK INTO DESIGN

Extensive human factors studies were performed with the SelfDose patient-controlled injector. Patients with mobility and dexterity challenges received special consideration during the research, design and development processes. Formative testing provided validation of the platform's design and informed enhancements to improve the patient experience.

Through this process, West identified that, most commonly, patients seek the following traits in a drug delivery system:

- **Ease of use**: Perhaps the most essential consideration is how the patient will use the drug delivery system. Even the most innovative drug can only provide the appropriate therapeutic benefit if it can be delivered effectively and the patient adheres to the necessary treatment regimen. Most patients are not trained medical practitioners, therefore, they need delivery systems to be simple and intuitive to use. Ensuring a self-injection system is easy to hold and deploy, as well as limiting the number of steps that a patient has to manage through administration, will greatly increase their satisfaction with the injection system and can help promote greater adherence.

- **Affinity-based design:** Simply designing a delivery system that patients "can" use is no longer sufficient. Delivery systems should be designed for affinity, and encourage patients to "want" to use them. This starts from a thorough understanding of patient needs, including the fact that these needs may change during their treatment journey. These same inputs also ensure that risks from user-based errors are identified early in the design and development process and provide critical user information to the development team for risk mitigation measures. The full development process should consider the effectiveness of the integrated delivery system constantly, and adjust as needed.

THE SELFDOSE INJECTOR

With these points in mind, both the shape and size of the SelfDose injector serve multiple purposes. First, they allow for worst-case patients with limited dexterity to be able to self-inject their treatments at home easily and safely, saving them from what can be difficult trips to a clinical setting. The design also makes the device not immediately look like an injector, which is helpful in regard to traditional attitudes and impressions that injectors can be scary, intimidating and "medical looking".

A human factors study with 66 participants, 33 of whom suffer from rheumatoid arthritis, looked at whether SelfDose was intuitive to use and found:

- Without instructions, 56% of participants used the SelfDose injection system properly, whereas only 3% used a traditional autoinjector properly.
- With instructions, 85% used the SelfDose injector system properly, whereas 64% used a traditional autoinjector properly.

Additionally, summative human factors testing of 45 subjects specifically addressed the potential challenges faced by those with limited dexterity. The testing yielded a 100% dosage delivery success rate, validating the SelfDose injector system's ease-of-use.

Another concern addressed by the SelfDose injector system's design is safety, specifically preventing potential needlestick injury. Its passive needle safety system helps to ease that concern through the following features:

- The 1 mL needle rests inside the device when not in use and includes a safety cap.
- When the patient is ready to administer a dose, the safety cap is removed, and a shallow ring protects against accidental contact during injection.
- After injection, the needle automatically retracts back into the device.

The SelfDose injector incorporates additional features to help ensure successful adherence:

- A window confirming drug delivery
- A colour indicator of completed injection
- An audible click confirming completed injection
- Patient control of administration speed, which can reduce pain.

Designed to be Customer-Centric

There is a growing need for novel drug delivery systems that accommodate new modes of administering injectable drugs of varying dosage and viscosity. This is especially the case with the rise of biologics, which are often injectable and may require the delivery of large volumes of a drug over a longer period of time.

West designed the SelfDose injector to be a platform system for pharmaceutical partners. Whereas many self-injectors need to enter new development phases if the dose volume changes – engineers may need to change parts such as the plunger rod or spring and then go through a design verification programme – with the SelfDose injector, a wide range of dose volumes and viscosities can be used without modifying the product.

CONCLUSION

The top consideration when developing any new drug has always been the patient, but patient centricity in injectable drug delivery has not been as pressing a concern until recently. The combination of increased self-administration, patient input and the almost limitless possibilities of new technology has given rise to injectable drug delivery systems like the SelfDose injector that are easier to use and can directly facilitate positive patient outcomes.

More than ever, patient input is shaping this trend and leading system manufacturers to more proactively explore new ways to deliver these critically important injectable medicines for chronic conditions. Additionally, the partnership between packaging and delivery system and drug manufacturers has strengthened, as delivery systems are designed and developed with an expertise that gives both patient use and drug efficacy equal priority.

SelfDose™ is a trademark of West Pharmaceutical Services, Inc. or its subsidiaries, in the US and other jurisdictions. West seeks partners for its SelfDose™ injector technology platform. This platform is intended to be used as an integrated system with drug filling and final assembly completed by the pharmaceutical/ biotechnology company.

ABOUT THE COMPANY

West Pharmaceutical Services, Inc, is a leading manufacturer of packaging components and delivery systems for injectable drugs and healthcare products. Working by the side of its customers from concept to patient, West creates products that promote the efficiency, reliability and safety of the world's pharmaceutical drug supply. West is headquartered in Exton, PA, US, and supports its customers from locations in North and South America, Europe, Asia and Australia. West's 2017 net sales of US$1.6 billion reflect the daily use of approximately 112 million of its components and devices, which are designed to improve the delivery of healthcare to patients around the world.

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ABOUT THE AUTHOR

Carl Dabruzzi has over 20 years of experience in the pharmaceutical and drug delivery industries. He joined West in 2017 as a Senior Manager in the Product Management organisation. Carl's primary responsibilities are to manage the development and commercialisation of West's portfolio of self-injection systems. The portfolio includes the SmartDose® platform of wearable on-body infusers and the SelfDose™ injector. Prior to joining West, Carl worked in the Pharmaceutical and Drug Delivery Systems divisions of 3M. Carl holds a BS in chemistry from the University of Wisconsin in River Falls, WI, US.

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