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ONdrugDelivery Issue N° 91, October 8th, 2018

PREFILLED SYRINGES & INJECTION DEVICES

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

EDITORIAL CALENDAR

Nov 2018	Pulmonary & Nasal Drug Delivery
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ONdrugDELIVERY

Front cover image, "Autoinjectors on an assembly line", supplied by PCI Pharma Services (see this issue, page 62). Reproduced with kind permission.

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Isn't our industry all about taking on challenges and pushing boundaries? Imagine just how dull life would be if we never tried to be better? Settling for the perceived standard is essentially settling for second best, and no-one can afford to do that.

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SIMPLE AND SECURE ADHERENCE MONITORING: YDS SMARTSERVICES™ FOR END-TO-END SMART DEVICE INTEGRATION

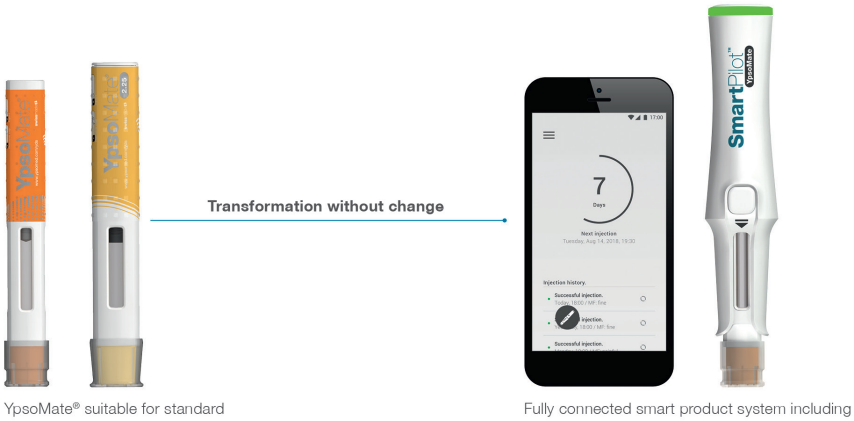
Whilst there is much discussion on how to apply connectivity and smart devices to therapies, there is far less dialogue concerning the challenges inherent to the digital architecture needed to make such innovations work in practice. Here, Andreas Schneider, Innovation & Business Development Manager, Ypsomed Delivery Systems, introduces YDS SmartServices™, Ypsomed's digital turnkey solution to effectively embed smart devices in a broader digital ecosystem.

INTRODUCTION

The self-injection industry is experiencing a transition from purely mechanical devices to digitally enhanced, connected smart drug delivery systems. Novel approaches to the self-management of diabetes highlight this emerging paradigm shift. For instance, smart self-injection pens may support patients with capturing information about dosage and timing of insulin administration. Mobile applications remind patients to monitor blood glucose levels regularly or assist in the calculation of prandial insulin doses.

CONNECTIVITY & SMARTPILOT™

Although diabetes management has a history of pioneering patient-centric drug delivery technologies, the concept of connected drug delivery has applications well beyond the administration of insulin. Other chronic disease states that similarly require repeated self-administration of drug products also benefit from novel connected technologies, for example SmartPilot™ for YpsoMate®, a reusable connected add-on module with built-in sensor technology and wireless communication capabilities for the two-step autoinjector YpsoMate® (Figure 1).



YpsoMate® suitable for standard 1 ml long and 2.25 ml pre-filled syringes

Fully connected smart product system including YpsoMate®, SmartPilot™ and mobile application

Figure 1: Illustrating the transition from mechanical self-injection devices to connected drug delivery systems, SmartPilot™ for YpsoMate® is a reusable smart add-on transforming the two-step autoinjector YpsoMate® into a smart product system.

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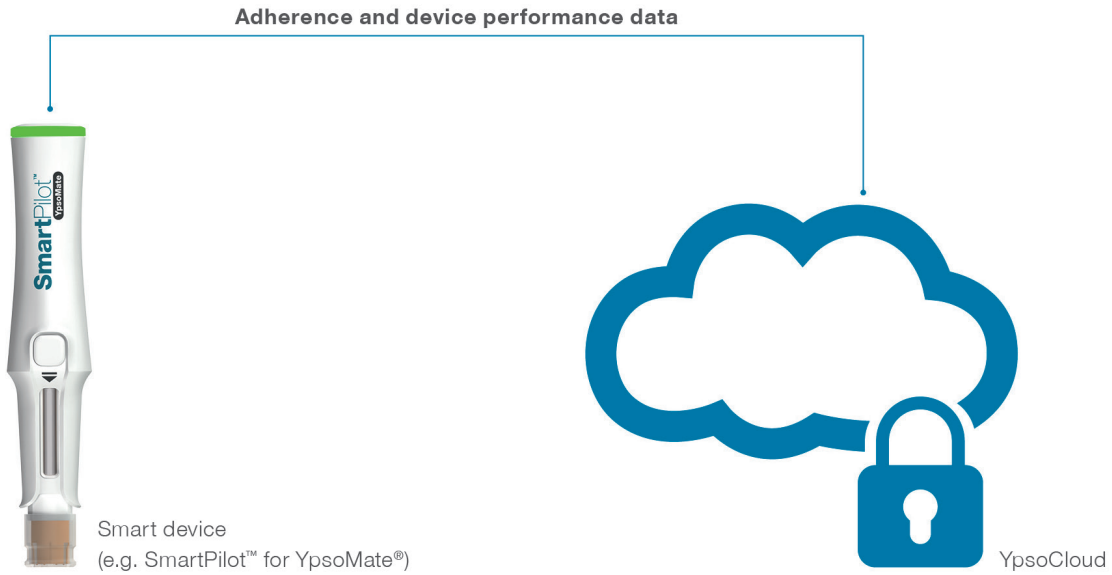
SmartPilot™ is used across molecular entities and disease areas both in clinical trials and as part of commercial product lifecycle management. The sensor concept has been developed so the standard proven autoinjector platform is compatible with SmartPilot™ without further modification.

The connected reusable add-on not only tracks injection date, time and success, but also provides advanced real-time guidance throughout the injection process. As such, it supports patients at each use step – including advice on the holding time – and confirms that the correct medication is being injected.

Streamlined connected device innovations, such as the SmartPilot™ for the YpsoMate® autoinjector, will provide innovative functionalities for patients, which digital health organisations can link with therapy-specific value propositions. While significant efforts are being made to link device functionality with disease-specific behavioural interventions or use cases, there still remains the key challenge of embedding connected devices into an end-to-end internet of things (IoT) ecosystem. This raises questions like:

- How to constantly monitor connected devices once launched across regions?
- How to control access to different smart devices?
- How to easily integrate smart devices with a therapy app?
- How to make therapy-relevant adherence and smart device performance data available?



Service 1: Ease-of-integration

Web-based application programming interface (API) as a standard interface for smart devices. The standard interface simplifies access to adherence and smart device performance data.

Service 2: Smart device life cycle management

Insights into and control of smart devices during clinical trials and commercial use. Ypsomed enables smart device life cycle management across disease areas.

Service 3: Securing device-to-cloud communication

Securing the communication from smart devices to cloud. YDS SmartServices™ provide true end-to-end security for the entire product system taking into account both device and cloud.

Figure 2: Overview of YDS SmartServices™, providing an end-to-end secured solution that integrates smart devices in order to simplify adherence monitoring.

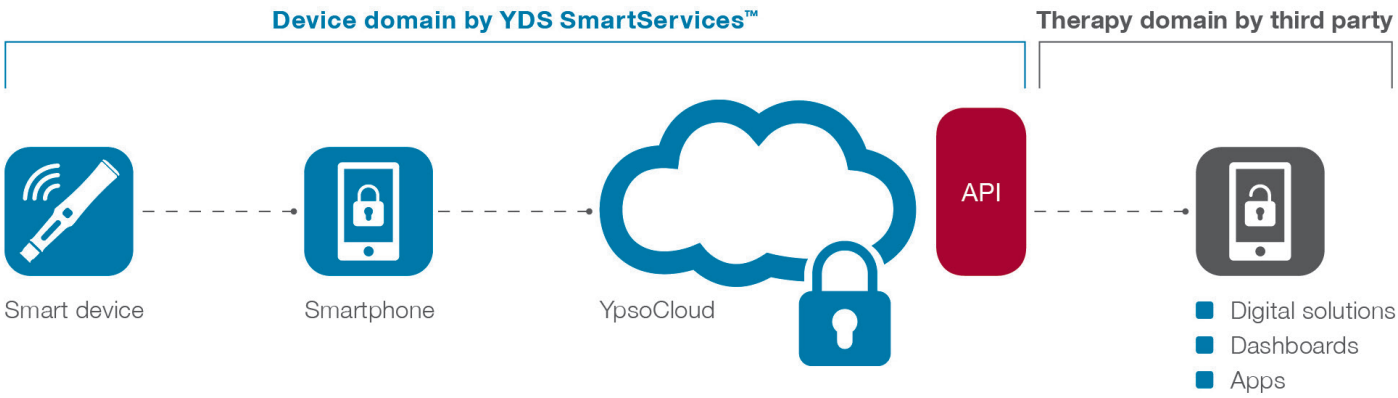


Figure 3: Service 1 – Introducing ease-of-integration across therapy-specific product systems. YDS SmartServices™ features a standardised web-based API to simplify reading and writing data to other third party services.

YDS SMARTSERVICES™

The pharmaceutical industry has been focusing extensively on the therapy and paying less attention to the device-oriented domain of connected drug delivery systems. This has resulted in a fragmented and distorted understanding of effectively embedding connected devices in a broader IoT ecosystem. Here we will present YDS SmartServices™: a turnkey digital solution that provides three key digital services to simplify adherence monitoring providing secure end-to-end smart device integration (Figure 2).

Firstly, YDS SmartServices™ simplifies access to adherence and smart device performance data, shifting the integration point to a standard web-based application-programming interface (API) as shown in Figure 3. Integration via web-based APIs reflects the emerging good practice for reading and writing data to services and third-party applications.

The web-based API connects the device domain with the therapy-oriented domain of connected drug delivery systems. Therapy-relevant adherence data that would normally be time consuming to obtain can instead be accessed easily. As such, the web-based API reflects the starting point for pharmaceutical partners to build therapy-specific mobile applications and to realise therapy-specific use cases and behavioural interventions in order to provide the most value to the targeted patient population.

Secondly, another device-oriented challenge is that the pharmaceutical industry has not systematically implemented therapy-agnostic digital lifecycle management services. It is the very connected nature of smart drug delivery devices that has a dramatic impact on launching, maintaining and retiring such devices during clinical trials or commercial use. Smart devices require constant monitoring once introduced across regions. Organisations must continually improve and collect data around smart device performance. YDS SmartServices™ offers a set of digital lifecycle management services in order to provide complete insights into and control of smart devices (Figure 4).

YDS SmartServices™ supports all five lifecycle management processes, independent of disease area:

1. **Plan:** Design and testing of end-to-end connectivity systems.
2. **Provide:** Effortless advanced onboarding and managed access to secure device usage data.
3. **Configure:** Effective implementation of network security.
4. **Monitoring:** Real-time analysis and interpretation of smart device performance.
5. **Retire:** Controlled end-of-life management of smart devices, e.g. after successful completion of a clinical trial.

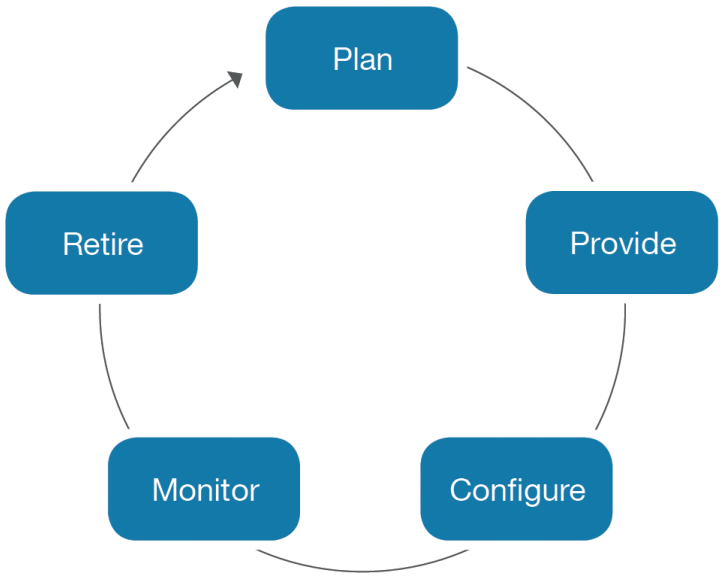


Figure 4: Service 2 – Smart device lifecycle management. YDS SmartServices™ provides digital lifecycle management services, thereby offering insights into and control of smart drug delivery systems during clinical trials and commercial use.

Thirdly, YDS SmartServices™ provides true end-to-end security for the entire product system, controlling both device and cloud (Figure 5). In so doing, the managed digital services not only meet the requirements concerning data privacy and security (e.g. HIPAA, GDPR, 21 CFR Part 11) but also act as differentiating factor to gain patient trust and motivate long-term usage of smart drug delivery systems.

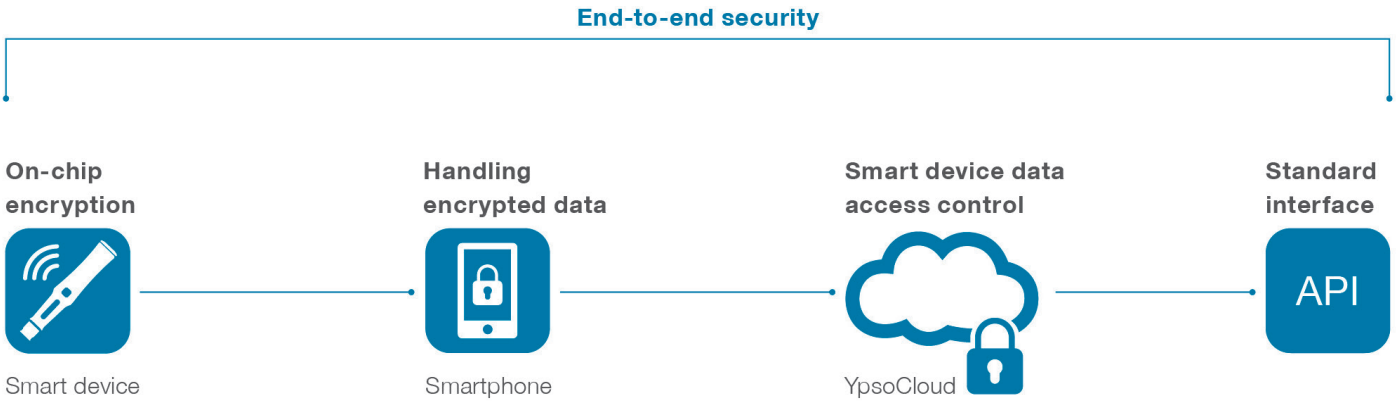


Figure 5: Service 3 – Securing device-to-cloud communication. YDS SmartServices™ implements security-by-design for the entire product system.

CONCLUSION

Soaring interest in smart drug delivery is urging the healthcare industry to fully understand the complexities related to embedding such connected smart devices into broader digital ecosystems. However, such device-domain challenges have received limited attention to date. The industry has been more concerned with the development of therapy-oriented use cases and linking device technology with disease-specific behavioural interventions.

This article calls for enlarging the scope from therapy-oriented to device-oriented challenges. Focusing on digital lifecycle management services, ease-of-integration and end-to-end security, YDS SmartServices™ addresses these often neglected device-oriented challenges independent of specific therapies. Leveraging Ypsomed's experience in and insights from the global marketing of a diabetes management IoT ecosystem, YDS SmartServices™ has established an industry-leading reference IoT architecture for embedding smart devices into digital ecosystems. In so doing, YDS SmartServices™ offers a new means to simplify and secure therapy-relevant adherence monitoring (Figure 6).

ABOUT THE COMPANY

Ypsomed is the leading independent developer and manufacturer of innovative self-injection and insulin pump systems for self-administration. Within the Delivery Systems business unit the customisable

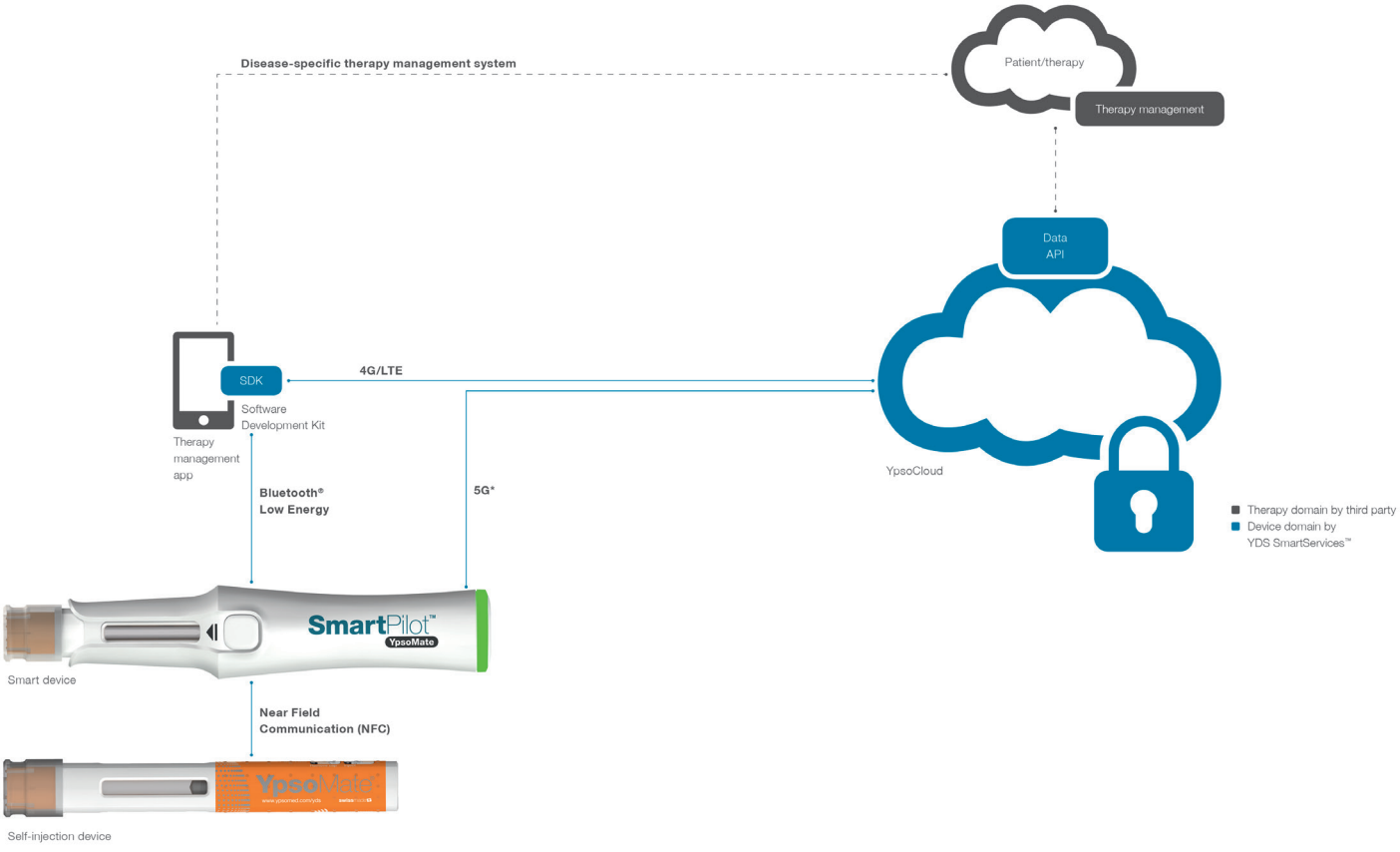


Figure 6: YDS SmartServices™ introduces an IoT architecture to provide secure end-to-end smart device integration and simplify access to therapy-relevant data.

product platforms cover autoinjectors for prefilled syringes in 1 mL and 2.25 mL format, disposable pens for 3 mL and 1.5 mL cartridges, reusable pens and easy-to-use injection devices for lyophilised drugs in dual-chamber cartridges. Unique click-on needles and infusion sets complete the broad self-injection systems product portfolio. The 3–10 mL YpsoDose patch injector draws on Ypsomed's depth of expertise in diabetes care with fully connected insulin pump systems. Ypsomed provides its partners with excellent technological expertise and full regulatory support for the device relevant aspects of the registration process.

The injection systems are developed and manufactured in Switzerland with strong in-house competencies covering concept and product development, tool-making, injection moulding and automated assembly. Ypsomed is ISO 13485 certified and all processes are run according to design control and cGMP guidelines with operational QA/QC experts on-site at each location. Ypsomed's US FDA-registered manufacturing facilities are regularly inspected by both pharma customers and regulatory agencies and supply devices for global markets including the US, Europe, Japan, China and India. Ypsomed has more than 30 years' experience and well-established working relationships with numerous leading pharma and biotech companies.

ABOUT THE AUTHOR

Andreas Schneider is Innovation & Business Development Manager with Ypsomed Delivery Systems. His responsibilities at Ypsomed include the definition and development of new platform devices with a particular emphasis on connected and smart device systems. As such, he has been actively involved in the design and development of SmartPilot for YpsoMate, a reusable connected add-on that transforms the proven two-step autoinjector into a connected system. Dr Schneider has published various articles and held presentations in the areas of innovation management and drug delivery. He received his PhD in Innovation Management and Organisation Sciences from ETH Zurich, Switzerland.

ON drugDELIVERY

2018/19 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
Nov 2018	Pulmonary & Nasal Drug Delivery	PASSED
Dec 2018	Connecting Drug Delivery	Nov 1st 2018
Jan 2019	Ophthalmic Drug Delivery	Dec 6th 2018
Feb 2019	Prefilled Syringes & Injection Devices	Jan 3rd 2019
Mar 2019	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Feb 7th 2019
Apr 2019	Pulmonary & Nasal Delivery	Mar 7th 2019
May 2019	Injectable Drug Delivery	Apr 4th 2019
Jun 2019	Connecting Drug Delivery	May 2nd 2019
Jul 2019	Novel Oral Delivery Systems	Jun 6th 2019
Aug 2019	Industrialising Drug Delivery Systems	Jul 4th 2019
Sep 2019	Wearable Injectors	Aug 1st 2019
Oct 2019	Prefilled Syringes & Injection Devices	Sep 5th 2019
Nov 2019	Pulmonary & Nasal Drug Delivery	Oct 3rd 2019
Dec 2019	Connecting Drug Delivery	Nov 7th 2019

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PERCEPTION, COGNITION, ACTION: APPLYING HUMAN FACTORS TO MEDICAL DEVICE DESIGN

In this article, Natalie Shortt, Human Factors Specialist, Medical Device Usability (MDU), covers the topic of the "Perception, Cognition, Action" model of risk assessment of medical devices, from both a proactive, early-stage design and a reactive, late-stage validation testing perspective.

PROACTIVE PCA MODEL

As with most facets of the medical device design process, human factors (HF) usability engineering starts with outlining the prospective risks associated with the device. When designing a prefilled syringe (PFS) or autoinjector (AI), they are likely going to be used by lay-users and therefore usability engineering will be a necessary part of the submission to regulators. There is a model – perhaps better described as a frame of mind – that will help any member of the design team to put themselves in the user's shoes from a HF perspective. This is PCA – Perception, Cognition, Action. But first, a little insight into the usability engineering risk process.

Risk, in relation to usability, covers the risk of a hazardous situation arising that exposes one or more people (users or otherwise) or the environment to sources of potential harm (a hazard) where hazard, hazardous situation and harm are defined as stated in ISO14971:2007.[1] These potential risks are collected into a risk assessment document called the "use-related risk assessment" (URRA). To populate the URRA, there are questions that should be answered first:

- Who are the intended users?
- What are the intended use environments?
- Are there any known use problems for this type of device?

All of this information helps to envision the scene when populating the URRA, meaning the risks considered come from a rational, justified place.

The URRA should be a living document that originates in the early stages of device development. This way the URRA can be utilised to inform designers of user interface design inputs that may reduce use-associated risk as far as reasonably possible, early in the process. This proactive approach means that, when it comes to validating the usability of the user interface, there are less likely to be inadequate risk mitigation. Inadequate risk mitigation by design usually leads to data that strongly suggests the need for better mitigation by design, which is more costly at the late design development stages than the early stages.

A URRA outlines potential use errors associated with using a device, but it is also necessary to explain the possible causes of each use error. These causes are used to outline and justify suggested risk mitigations. However, what is often seen is that the stated causes are either unrealistic (e.g. Use error: user holds syringe upside down. Cause: user is blind – it seems unlikely that they would ever be prescribed a self-injected medication in the first place) or under analysed (e.g. Use error: user does not remove cap. Cause: user does not read the instructions – too much assumption that problems can only arise from not reading the instructions). A probable cause of this is that the mentality of the author(s) is not

"The URRA should be a living document that originates in the early stages of device development. This way the URRA can be utilised to inform designers of user interface design inputs that may reduce use-associated risk as far as reasonably possible, early in the process."

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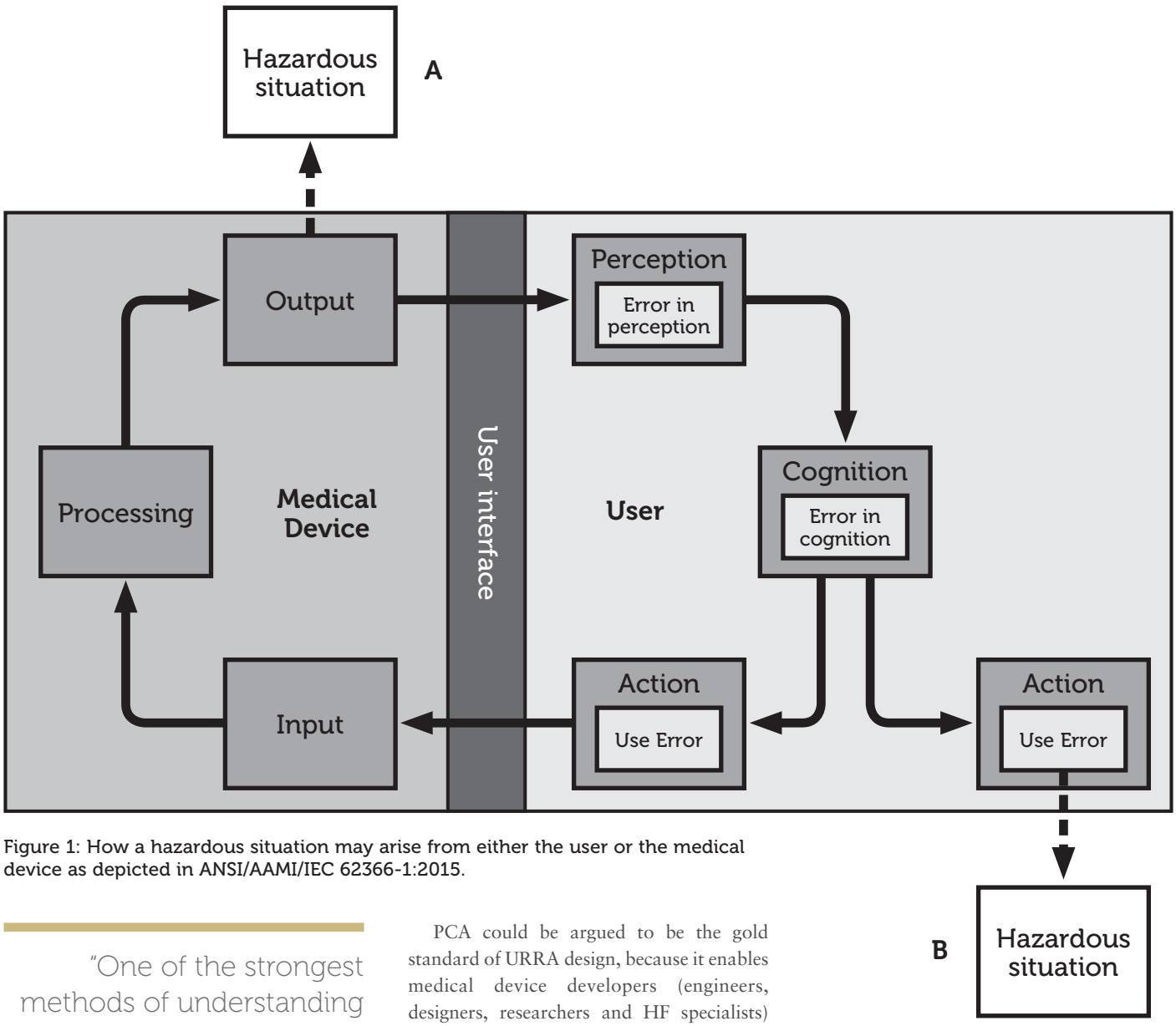

Figure 1: How a hazardous situation may arise from either the user or the medical device as depicted in ANSI/AAMI/IEC 62366-1:2015.

> "One of the strongest methods of understanding the causes of use errors is the Perception, Cognition, Action model, which serves as a lesson in empathy for the plight of the user."

coming from a place of empathy for the user and the situation they are in when using the device.

One of the strongest methods of understanding the causes of use errors is the Perception, Cognition, Action (PCA) model, which serves as a lesson in empathy for the plight of the user. It sheds light on things that seem obvious in hindsight but, at the design stage you only realise they have been missed when PCA is applied. For example, you have not included some form of alert to let users know the device is on.

PCA could be argued to be the gold standard of URRA design, because it enables medical device developers (engineers, designers, researchers and HF specialists) to consider justified, rational use errors and know more easily where to stop. This is a proactive use of the PCA model.

Perception

Perception is the first stage in the process of human interaction with a user interface. In Figure 1, there are two potential causes of a hazardous situation. "Hazardous situation A – caused by a response of the medical device" and "Hazardous situation B – caused by user action or lack of action".[2] Perception is considered a contributing factor to, or a cause of, a use error, but a use error does not happen during perception of the user interface.

There is no formal definition of Perception error in relation to usability engineering, however we at MDU define it as: "A failure to correctly perceive the output from the device interface."

An example would be for a participant to listen out for the second click that tells them their dose has been successfully administered, but the ambient noise is too great, such that they don't hear the click. The cause of error is that the user didn't hear the click, so the solution would be to increase the volume of the click to allow for the regular noise level in a home environment.

Thinking proactively when considering the intended users and use environments, if the intended users have reduced physical capabilities then there is likely to be greater risk that tasks cannot be completed as intended. If it is intended or most likely that the PFS or AI is used for self-administration at a user's home, then audible cues must meet ambient sound levels that are common in a home environment. Similarly,

if there are visual cues they must be visible at a light level that is common in a home environment.

Cognition

Once someone has perceived an output from the device interface, they need to consider what that output means. This is the second stage in the process of human interaction (Figure 1). Like perception, cognition is considered a contributing factor or a cause but not a juncture where the use error occurs.

There is no formal definition of a use error caused by cognition, however MDU defines it as: "The participant correctly perceives the output, but makes an incorrect or unexpected decision, or misinterprets the information in the instructional materials."

The distinction between perception and cognition can be blurred on occasion, but as long as the same rule is always applied when determining the root cause of a use error, it should be acceptable. In an instance where a participant sees the graphic indicating "20 seconds" on the instruction material for a PFS and assumes it to mean "wait 20 seconds after you have administered the dose" but it actually means "depressing the plunger should take around 20 seconds" this would be classed as a cognitive use error. They saw the information, but they understood it incorrectly and the action that manifested was counter to the intended use of the product.

In this instance it may be because the condition this hypothetical PFS is being used for is commonly treated with a medication delivered by an AI, therefore most potential users are used to using a product where you do need to wait for 20 seconds after actuating the device. A mitigation would be to draw more attention to the information or to present the information more explicitly in order to attempt to highlight to users that the correct procedure is different to what they are currently used to.

Action

Figure 1 describes how use errors can only manifest in actions or outputs, but this does not mean that use errors cannot also be caused by actions.

There is no formal definition of use error caused by action in relation to usability engineering, however MDU defines it as: "The participant knows what they intend to do, but perform an incorrect action or was unable to complete a correct action."

"When conducting formative or validation studies, the PCA model can be used in a post-test interview to understand use errors that have occurred in the main body of the test session."

An example of a use error caused by action follows: a PFS is intended for subcutaneous administration by a patient in their own home. The task analysis outlines that, to administer the dose, the user must depress the plunger. A use error may be that they can't depress the plunger. The cause? The plunger is too far away from the flange of the syringe, and the other hand is being used to pinch the skin. Action – the user physically cannot complete the task, despite knowing what they need to do. The recommendation? Ensure that the plunger is no farther away from the flange than the 5th percentile of capability for intended users.

In a home environment, it is a real possibility that a user may not have any friends or family who can help them, and they may have to miss a dose until someone has time to help them. It may be days or weeks, and efficacy of treatment may be reduced.

REACTIVE PCA MODEL

When conducting formative or validation studies, the PCA model can be used in a post-test interview to understand use errors that have occurred in the main body of the test session. A thorough post-test interview with a patient can unveil the root cause, which can be categorised as a difficulty with the perception, cognition or action of interacting with the user interface. When conducting test sessions, use errors must be analysed in a post-test interview. It is our experience that the root causes outlined in some reports can be too superficial – meaning the cause outlined for a use error can't be used to inform design inputs. If root causes of use errors can be categorised into perception, cognition or action then the moderator can judge at that point that the use error has been investigated enough.

The PCA model can then be used to write effective reports, it is a useful method for improving the readability of the causes of use errors. A readable results section will make it easier for the document author to then analyse the results and provide objective design outputs to contribute to design inputs for the next phase of design.

PFS and AI design usually requires some HF input because, increasingly, these devices are designed for the lay-user. Using the PCA model even gets easier with practice, and can help non-HF specialists become champions for their team within their companies.

ABOUT THE COMPANY

Medical Device Usability is one of the world's leading consultancies specialising in usability and human factors for medical devices. MDU provides consultancy for the usability engineering process, primarily conducting formative and summative human factors studies for global pharmaceutical, medical device and diagnostics clients.

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2. *"IEC 62366-1:2015, Medical devices – Part 1: Application of usability engineering to medical devices". International Electrotechnical Commission, 2015.*

ABOUT THE AUTHOR

Natalie Shortt graduated in 2014 from Loughborough University (UK) with a 2:1 in Ergonomics (Human Factors) and has worked at Medical Device Usability for three years. In recent years Ms Shortt has been a project lead consultant in advising clients on risk assessment methods and populating use-related risk assessment documentation.

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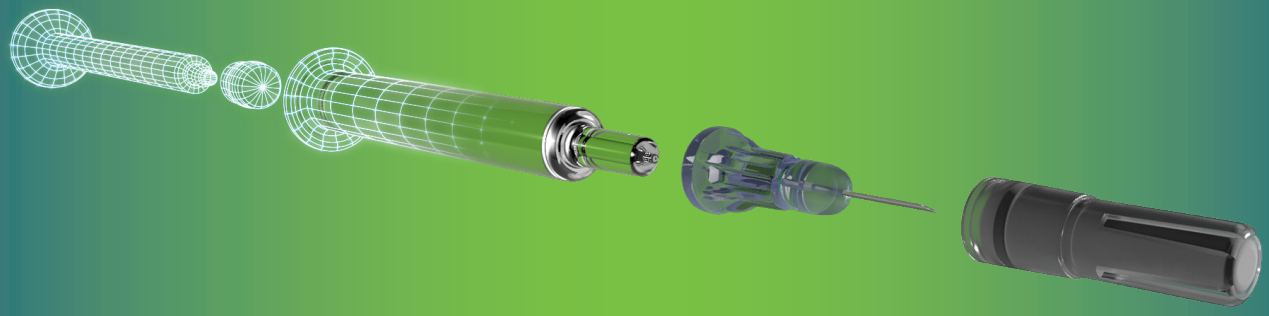

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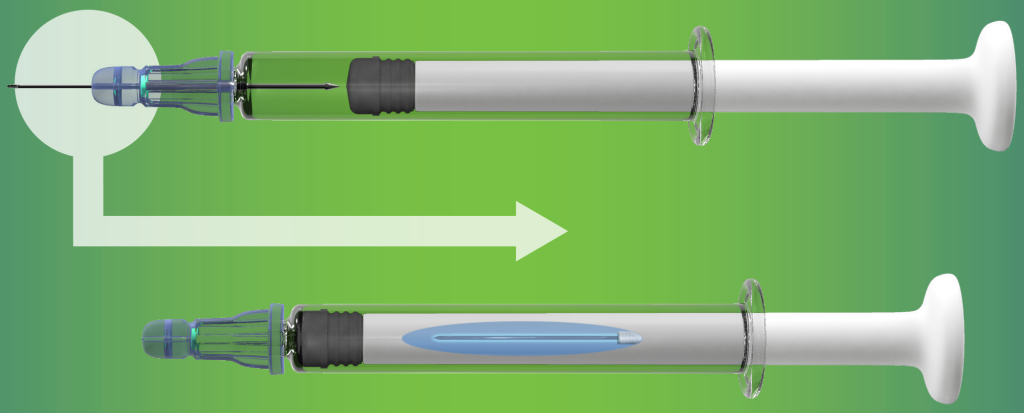

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COMBINING HUMAN NEEDS WITH HIGH VISCOSITY FORMULATIONS

In this article, Jonathan Bradshaw, Device Development Engineer, and Susie White, Mechanical Engineer, both of Oval Medical Technologies, discuss the requirements of designing an autoinjector capable of handling the high pressures necessary for the delivery of highly viscous drug formulations with minimal impact on the patient.

INTRODUCTION

> "When endeavouring to deliver HV formulations, there exists a delicate balance between the needs of the patient and those of the device mechanism."

Within the injectable drug landscape, the availability and usage of high viscosity (HV) drugs is growing, often driven by developments such as long-acting injectable (LAI) technologies. Currently, these products provide significant advantages in terms of more convenient dosage volumes for patients and healthcare professionals (HCPs). With a trend towards self-administration, LAIs allow for less frequent dosing thus promoting better patient compliance.[1]

Typically, LAI products consist of formulations that are highly viscous in nature (100–1000 cP), can present non-Newtonian and, in the case of suspensions, "clogging" characteristics. These characteristics are well beyond the normal limits of injection devices and techniques, presenting many challenges for subcutaneous (SC) and intramuscular (IM) drug delivery.

When endeavouring to deliver HV formulations, there exists a delicate balance between the needs of the patient and those of the device mechanism. From a device perspective, there are many ways in which HV delivery can be achieved, such as through larger needle diameters, longer delivery times and larger spring forces. However, all these approaches risk reducing patient acceptability due to an increase in pain, lack of usability and the resulting large, noisy devices.

To achieve HV delivery both acceptable to the patient and within the capability of the device mechanism, device developers can manipulate parameters such as injection speed, needle gauge or drug volume. Altering these parameters must be approached with caution however, as they can significantly affect bolus formation and therefore the desired pharmacokinetic profile.

Figure 1: ArQ™ Bios: Oval's high viscosity platform provides the ability to meet both patient and drug requirements.

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To maximise user benefit when delivering HV formulations, it is imperative that a "human" solution to autoinjector design is achieved. For certain patient populations this means smaller needle gauges and shorter delivery times are required, both of which can be facilitated using large, controlled forces. This results in a major challenge for devices due to the high internal pressure this generates.

Oval has managed to address this high internal pressure requirement within its HV delivery platform, ArQ™ Bios (Figure 1).

BALANCING THE VARIABLES

Generally, there are four key inputs that should be considered when developing an autoinjector mechanism capable of delivering high viscosity drugs:

1. Drug viscosity
2. Drug volume
3. Needle gauge
4. Delivery time.

These variables are key in determining the ability of the device to deliver highly viscous drugs and are crucial in defining the likely effect of the injection process on the user. When administering LAIs, it is imperative that these variables are tuned to produce consistent bolus characteristics. There is a potential for the surface area of the bolus formed on injection of LAIs to affect the pharmacokinetics of the drug. In such a case, consistent bolus formation is key in achieving the desired pharmacokinetic profile and therapeutic effect.[2]

When developing an autoinjector mechanism to achieve this, the main output from these variables for the design process is internal container pressure, which is produced by the power source acting on the plunger. Using a modified form of the Hagen-Poiseuille equation we can calculate the internal pressure necessary to deliver a given formulation:

$$P = \frac{128\mu LV}{\pi D^4 T}$$

P – Drug Pressure
L - Needle Length
μ - Viscosity
D - Internal Needle Diameter
T – Delivery Time
V – Volume

Modified Hagen-Poiseuille Equation.[3]

This internal pressure has a direct effect on the required strength of the primary drug container (PDC), and is therefore key within the device development process. When delivering a drug of a fixed viscosity, inputs can be manipulated to reduce the sensitivity of PDC design to internal pressure. However, altering user-perceivable inputs such as needle gauge, delivery time and volume should be approached with significant consideration to the user experience. When delivering highly viscous drugs, a simple approach would be to increase the needle diameter, thus reducing pressure. However, a larger needle would result in greater injection pain and negative visual perception by the patient. On the other hand, using a smaller needle would indeed reduce injection pain, but delivery time and risk of jetting would increase, again leading to a poor user experience.

It is possible to manipulate viscosity to aid delivery within patient-acceptable parameters, however with bolus formation key to ensuring drug metabolism, and therefore efficacy, this should also be approached with caution. Typically, formulation viscosities tend to be proportional to drug concentration, i.e. as viscosity decreases, volume must increase to achieve the same therapeutic effect, and vice versa.

THE IMPORTANCE OF DRUG CHARACTERISATION

LAI products are formulated to provide a specific therapeutic effect that is supported over monthly, bimonthly or, in some cases, three-monthly dosing regimens.[4] To achieve this, formulators can reduce the solubility of the LAI, facilitating a sustained and controlled release of drug over time. Currently there are three key approaches to developing slow release formulations:[2]

- Oil solutions
- Polymeric barriers
- Crystalline water-insoluble suspensions.

These approaches or "vehicles" are typically of high molecular weight, which in turn increases the viscosity of

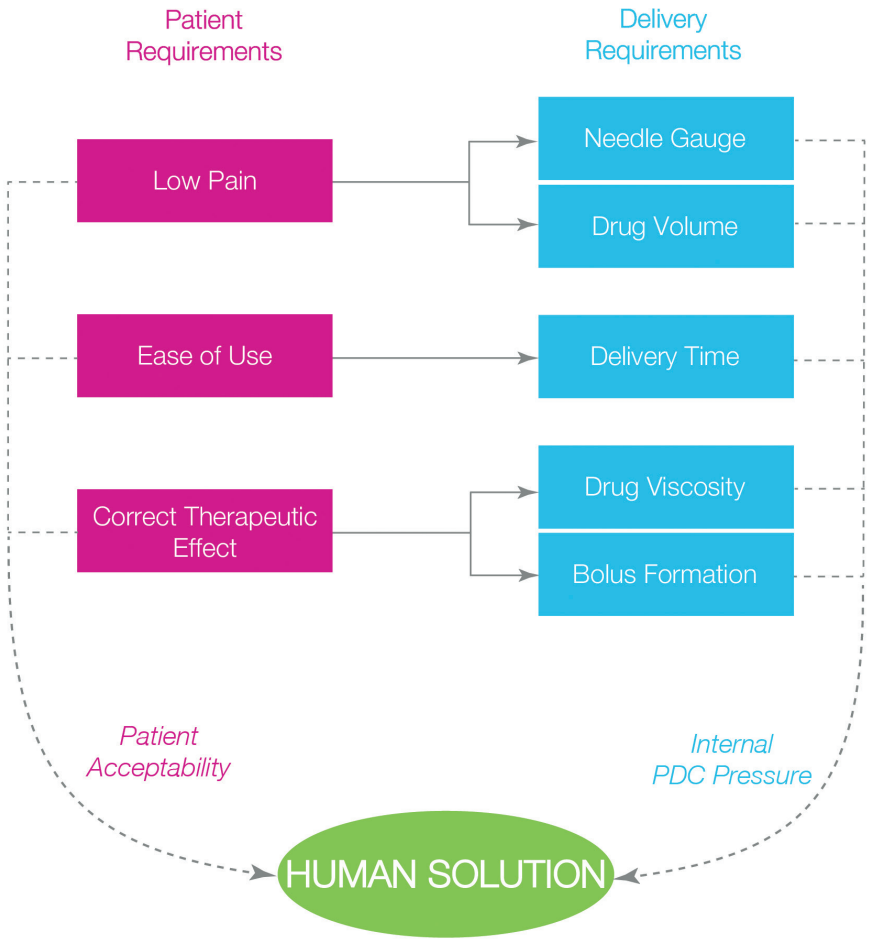

Figure 2: To maximise patient benefit, delivery variables must be influenced by a patient-orientated specification. This often results in increased pressure requirements for the PDC.

the entire formulation. This can lead to non-Newtonian behaviour and increased sensitivity to environmental conditions. Additionally, delivering these via autoinjector can be further complicated by other characteristics, such as clogging and settlement during storage in the case of suspensions. This puts great onus on the delivery mechanism to overcome or manage the delivery requirements of a formulation.

When developing an autoinjector mechanism that can deliver a drug in a time frame and manner acceptable to the patient, it is imperative to fully understand the flow characteristics of the formulation. Through implementing a full characterisation programme early within the device development process, any difficult or undesirable delivery characteristics will be quickly revealed. This allows developers the understanding necessary to manipulate delivery variables effectively, ultimately resulting in a device which is considerate of both patient and formulation requirements.

AN OPTIMAL DRUG DELIVERY SPECIFICATION FOR THE PATIENT

The requirements for HV delivery and patient acceptability can often conflict. However, achieving a suitable balance between the two provides the opportunity to create a truly "human solution" to HV delivery.

A range of factors can influence the acceptability of a device to a patient. As part of achieving a device which maximises patient acceptability, it is key to define a delivery specification which maximises benefit to the patient whilst also overcoming the challenging nature of the drug. The relationships between patient and drug requirements can be broadly defined as shown in Figure 2.

Typically, there are three key patient-perceivable inputs, needle gauge, delivery time and volume, which can be optimised to deliver highly viscous drugs in a manner deemed acceptable to patients:

- **Needle gauge**: The width of a needle can have an impact on the perceived pain of injection.[5,6] Generally, reducing needle size can reduce pain and increase patient acceptance, however needle selection is dependent on numerous factors such as formulation, administration route and intended patient population.[7] Often there exists a trade-off between minimising injection pain and overcoming common issues such as clogging or achieving the required needle strength. Ultimately, for IM injections, gauge choice is usually limited by needle strength, and those narrower than a 23G needle are infrequently used. If a SC route is required, then much narrower needles can be utilised (e.g. 25G), however here the drug flow requirements are more likely to be the limiting factor. It is important to balance adequate needle strength for application with pain perception and the required flow rate for highly viscous drugs.[6,8,9]
- **Delivery time**: With high viscosity drugs, flow rate and therefore delivery time is key in ensuring adequate depot/bolus formation.[8] Shorter injection times (<1 sec) can risk jetting and an undesirable bolus formation whereas longer injection times (>10 sec) can negatively impact patient acceptance. Although flow rate can have varying impact on perceived pain,[10,11] there are indications that longer injection times can prolong pain from needle insertion itself, thus reducing patient acceptance.[7,11,12] Ultimately a delivery time acceptable for both bolus formation and patient tolerability is desirable.
- **Volume**: Typically, LAIs range in volume from 1–3 mL, with lower volume injections being generally better tolerated in SC applications.[10,13,14] Interestingly there are indications that higher viscosity products can improve pain perception,[12] although this is likely dependant on other variables such as active ingredients, pH and temperature.

For highly viscous formulations, increasing the internal PDC pressure is of clear benefit to the patient (Figure 3).

To balance device, drug and patient requirements, Oval Medical Technologies has developed an ideal user-orientated specification which forms a lightweight framework for maximising patient acceptability of high viscosity autoinjectors:

- 3–5 second delivery time
- 23G needle (IM), 25G needle (SC)
- 3 mL maximum volume
- 1000cP maximum viscosity.

Using this specification, analysis has shown that a pressure of 100 bar would be required within the PDC for a 5 second delivery, however pressures of this magnitude are normally beyond the capability of most traditional glass containers. The ability to manage these pressures would create benefit to patients in addition to HCPs and formulators alike.

OPTIMISING PDC LOADING

Developing a PDC with the ability to withstand pressures of up to 100 bar poses huge design challenges for device developers, due to the risk that pressures of this magnitude have on effective and safe delivery. The loading of the PDC is a key factor to consider during development, although very high pressures are required to

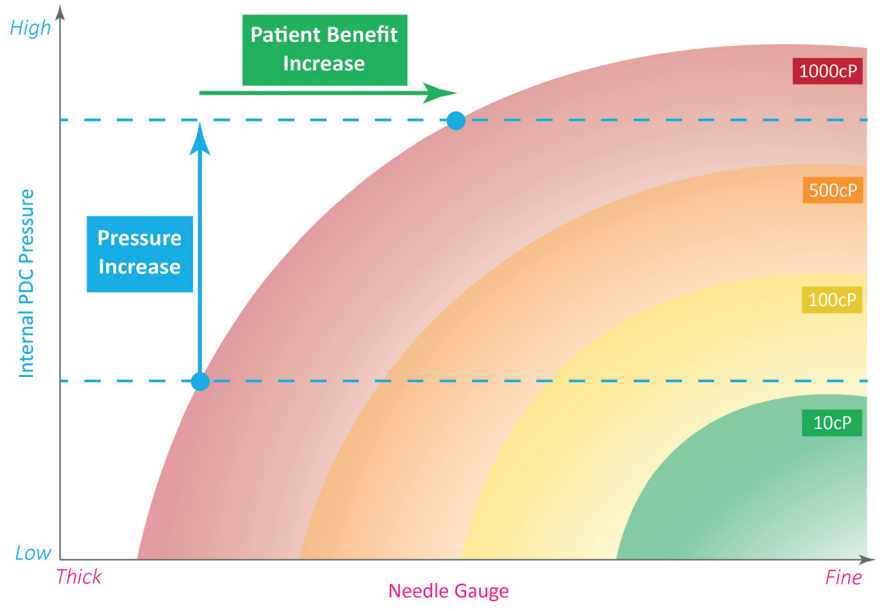

Figure 3: Increasing the pressure loading within the PDC allows for improved patient benefit through use of finer needle gauges at fixed viscosities.

deliver viscous products, developers must consider how the PDC is loaded within the device and whether stress is unnecessarily applied to the container.

A good example of this is the impact that can be exerted on a PDC at the start of delivery. Most autoinjectors are powered by springs held in a compressed state until the point of activation. At activation, the spring force is suddenly released which can cause serious problems for components which bear the brunt of this force – typically the PDC. This issue can be further compounded when manufacturing tolerances lead to excessive clearance between device components, allowing the spring to build up momentum. This momentum must then dissipate upon collision with the PDC, causing a brief but large spike in internal pressure, resulting in additional burden on an already highly stressed component.

It is important not to underestimate the benefits of reducing impact loads, indeed many materials respond differently to shock loading than they do to static loading. Dependent on material, many components will be capable of managing loads when applied progressively, yet when the same force is applied instantaneously there is little time for energy to dissipate and a brittle failure is more likely to occur. With some careful design consideration, it is possible to reduce this effect or eliminate it entirely.

When developing a high viscosity PDC, Oval has employed three strategies to manage the effect of impact loading on the PDC:

- **Damped power source:** Use of damping ensures that all components move at a controlled velocity, eliminating the impact that would be seen in a spring-driven device.
- **Impaction timing:** The second technique aims to prevent impaction on the PDC at the instant of delivery. Rather than releasing the energy in the power source at the point of activation, the power source is already engaged with delivery components. This provides greater control over component positions and loadings and therefore reduces risk of part failure due to impact.
- **Reduction of activation forces:** Keeping the device activation force low reduces the likelihood of the user exerting undue force onto the device, either by gripping it improperly or by applying it too forcefully onto the injection site. Typically, high pressure requirements necessitate the use of high activation forces. The ability to "decouple" these activation forces from pressure requirements allows minimal user input to deliver highly viscous formulations in a controlled manner.

CONTAINING HIGH PRESSURES

Once delivery variables have been altered to optimise PDC pressure, the next step is to ensure acceptable burst strength of the PDC. An obvious way to do this is through material selection. Glass, which is frequently used for drug containment, is a brittle material and therefore highly susceptible to damage, such as scratches, which can reduce fracture strength. Whilst it is not necessarily any stronger in principle, cyclo-olefin co-polymer (COC) is, in practice, far more robust. Comparatively, COC is a more ductile material than glass, allowing the PDC to deform, flex or fail plastically under high pressures. Glass, however, is susceptible to shatter under significant stress, making it a risky option for use with high viscosity formulations.[15]

The use of COC allows for greater design freedom in the development of PDCs, enabling integration of a wide range of features, which in turn increases the versatility of both components and the mechanism as a whole. The ability to adjust the shape, size and features of the drug container allows optimisation and a suitable safety factor for a 100 bar delivery pressure.

Finite element analysis (FEA) is an extremely powerful tool for assessing the capability of a container design prior

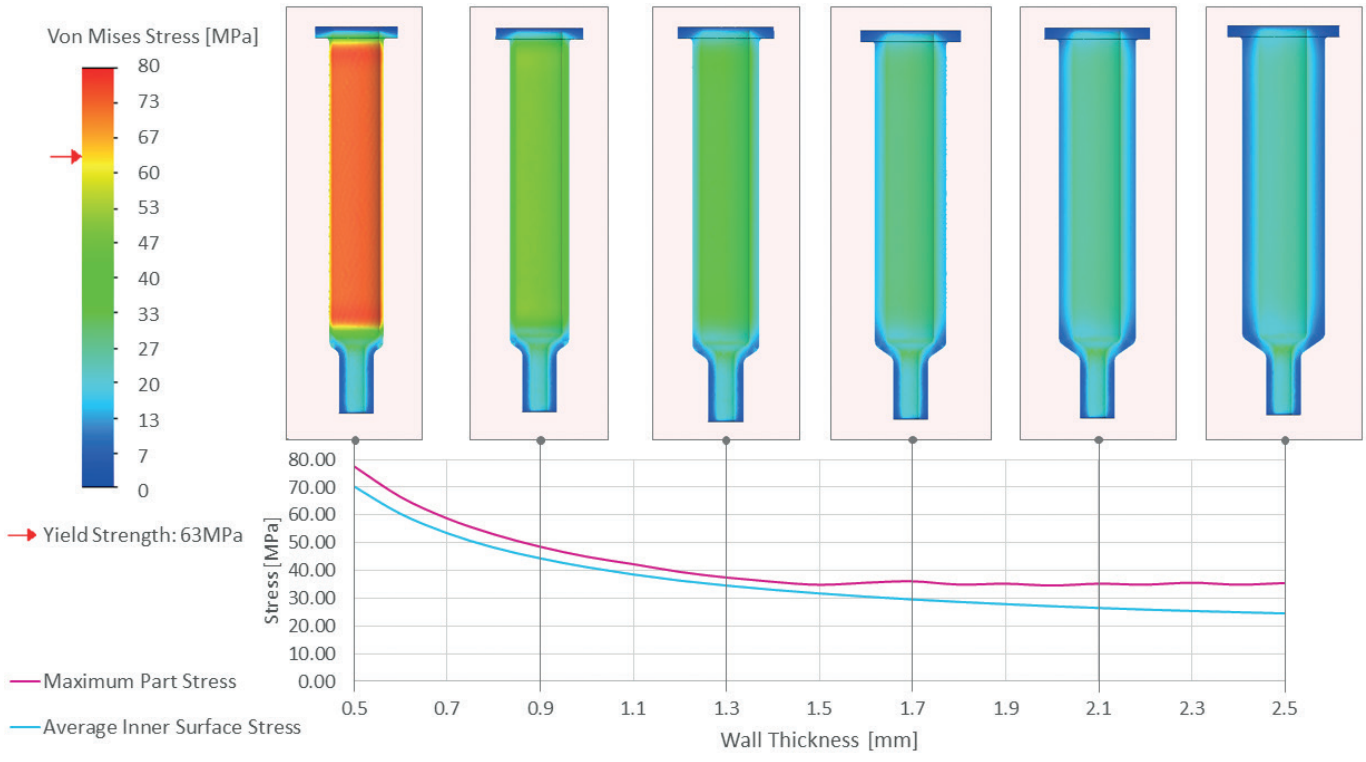

Figure 4: FEA analysis demonstrating wall thickness optimisation of a COC container at 100 bar pressure. Here, a wall thickness greater than 1.5 mm provides minimal benefit to stress reduction within the component.

to design freeze. Examining container design using FEA allows assessment of parameters (e.g. wall thickness or draft angle) which are likely to have the greatest impact on component stress. This understanding allows adjustment and trial of diverse geometries in order to reduce and optimise stress within the container (Figure 4).

ACHIEVING HIGH PRESSURES

Achieving high pressures within the PDC requires a plunger that will operate effectively at such pressures. The plunger must maintain a delicate balance between ensuring low friction within the container whilst preventing any drug backflow behind the seal when pressurised. The plunger should also provide a sterile barrier. This can present a challenge for plunger technologies.

A standard approach to plunger design is to use rubber. Rubber plungers seal effectively, but the friction force between the rubber and container can be notoriously difficult to manage. A range of surface finishes such as silicone oil or plasma treatment have been developed to manage this, with varying degrees of success.[16]

In high pressure environments, the breakout and glide force of rubber can be greatly exacerbated. Due to the compliant nature of rubber, when high pressure is applied the plunger can easily lose its shape, becoming highly compressed and thus producing a very high contact pressure with the glass. As the Poisson's ratio of rubber is very high, any axial force applied quickly becomes a localised radial force, which increases both breakout and glide force, in addition to the risk of container fracture.

To tackle this issue, Oval has developed a high-pressure cup seal design, which overcomes the friction challenges seen in traditional plungers. By decoupling the microbial and liquid seal barrier functions from one another, any conflicting requirements can now be managed separately. The design consists of a reinforced high-density polyethylene (HDPE) component, which provides the liquid seal. This provides a robust sealing surface with the stability to manage high pressures and sufficient lubricity to prevent excess glide forces. Container closure integrity (CCI) within the PDC itself is handled by a separate layer of aluminium foil, induction welded across the rear of the container, acting as a microbial barrier, and is a robust solution for high viscosity delivery. Figure 5 illustrates Oval's high viscosity platform PDC.

Figure 5: Oval's PDC technology optimised for high pressure, high viscosity delivery.

CONCLUSION

The tools and techniques used by Oval help to overcome many of the challenges presented by the delivery of highly viscous formulations. The combination of COC container technology with a thorough drug characterisation programme provides the ability to freely alter drug delivery variables. This allows the effective management of complex and conflicting delivery requirements, ensuring an ability to deliver high pressures in a safe and controllable manner. It is this approach which allows Oval the flexibility to achieve a truly "human" solution to autoinjector design and ensure increased acceptability and compliance for those patients using its devices.

ABOUT THE COMPANY

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

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

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ABOUT THE AUTHORS

Jonathan Bradshaw is a design engineer with a background in industrial design and a Master's in Medical Device Engineering. Mr Bradshaw has experience in the design, development and commercialisation of fluidic dilution and dosing systems, cardiac catheterisation devices and drug delivery technologies. Currently Mr Bradshaw works as a Device Development Engineer within Oval Medical Technologies where he focuses on furthering the development of the company's novel PDC and autoinjector technology to ensure its devices offer reliability and consistently high performance in combination with usability benefits.

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

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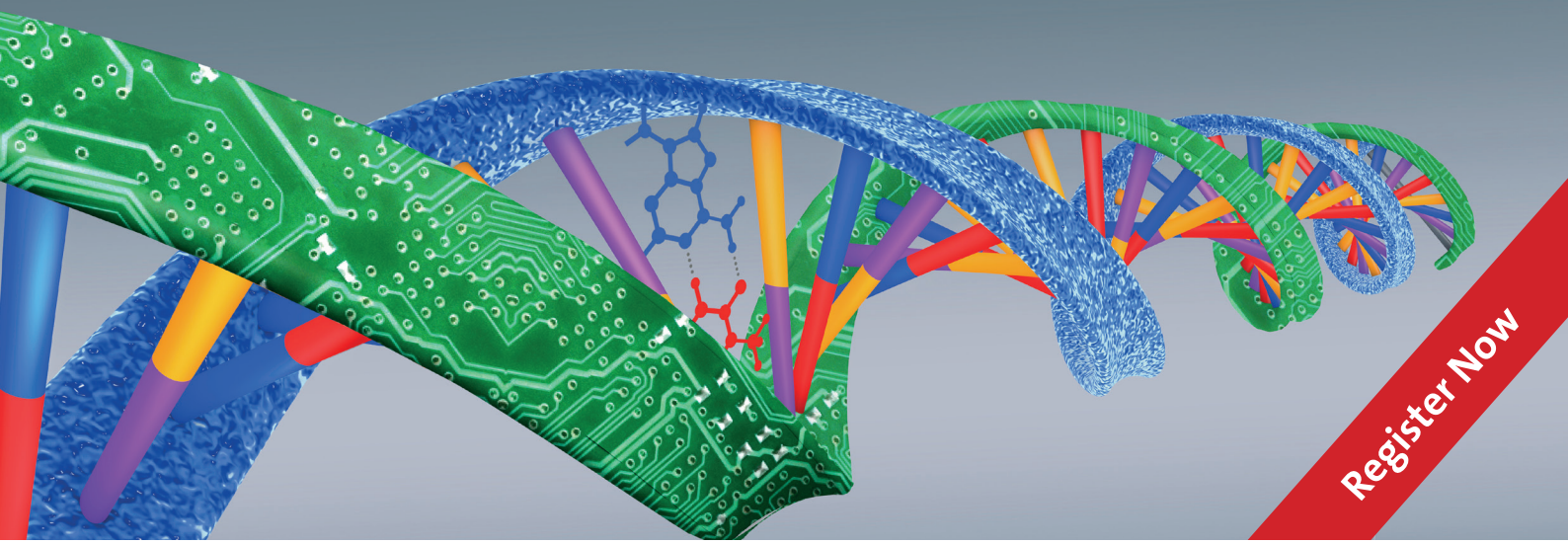

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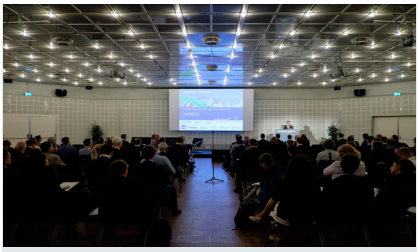

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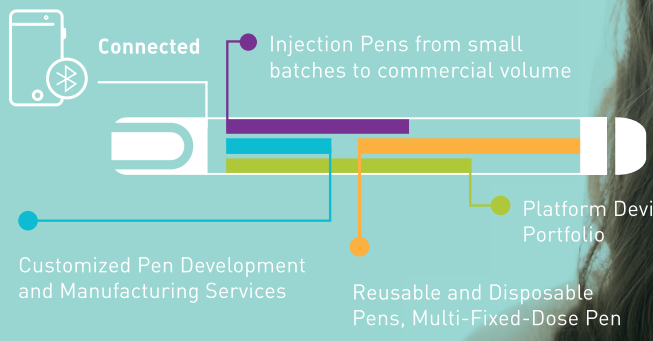

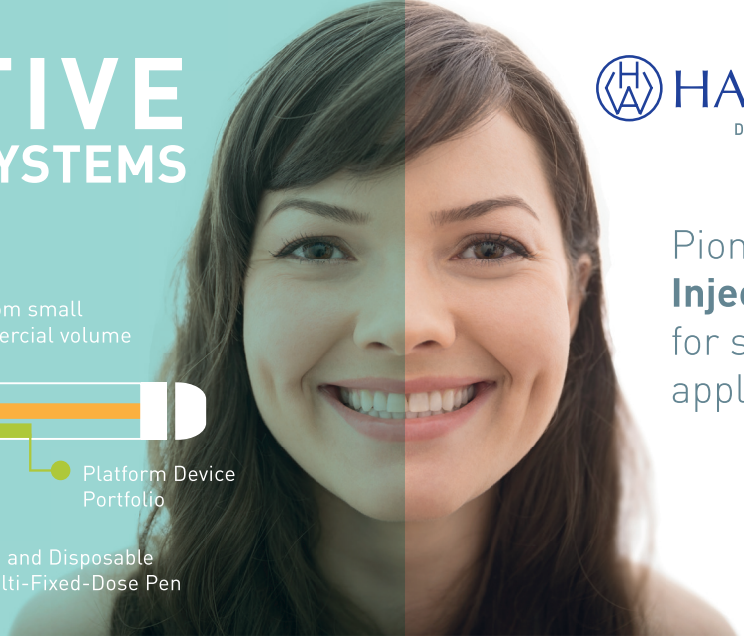

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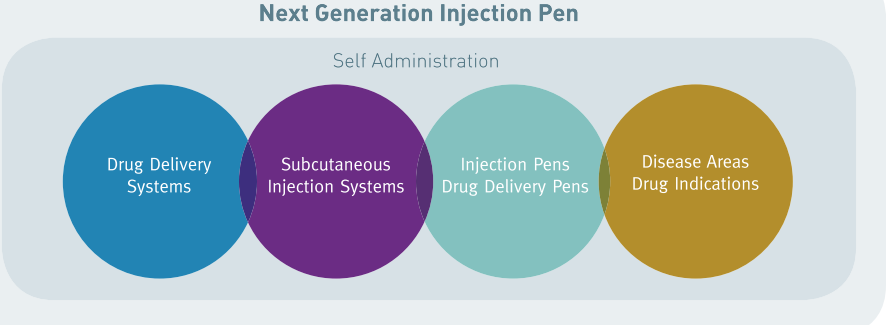

SHL GROUP

VOICE OF CUSTOMER RESEARCH – A CUSTOMER-CENTRIC APPROACH TO STRATEGY DEVELOPMENT

In this article, Michael McGowan, Global Director of Market Intelligence, SHL Group, discusses SHL's view on adapting to the shifts in market needs and stakeholder priorities in the pharma and biotech sectors, and details how SHL has implemented a "voice of customer" market research programme to ensure it provides the best possible service for its customers.

As many senior executives from medical device companies will probably confirm, there is a fairly high probability that at some point during the annual strategy review meeting, someone from the marketing department will show a bullet point stating "meet customer needs" or "satisfy customer requirements." Indeed, a dollar, pound or euro in the bank for each time I have heard this combination of words over the course of my career would certainly have made a significant contribution to my son's university tuition fees!

Most definitions of "marketing" generally refer to a business or management process that aims to identify and profitably satisfy the needs of target customers by means of a product or service. A part of Dr Philip Kotler's (Kotler Marketing Group, Washington DC, US) definition of marketing states that:

"Marketing is the science and art of exploring, creating and delivering value to satisfy the needs of a target market at a profit. Marketing identifies unfulfilled needs and desires. It defines, measures and quantifies the size of the identified market and the profit potential. It pinpoints which segments the company is capable of serving best and it designs and promotes the appropriate products and services."

Although the development of business strategy is generally an iterative process, building and refining on earlier strategic plans, having an in-depth understanding of customer needs and opinions is the base upon which companies construct (or reconstruct) long-term success. With almost three decades' experience working with many leading biotechnology and pharmaceutical companies across the globe, SHL Group has, since its establishment, been committed to understanding customer requirements, the foundation stone for strategy development, as well as delivering market-leading products that serve patients in need.

UNDERSTANDING MARKET TRENDS

The development and success of biological drugs to treat a range of chronic diseases have led to the rapid growth of injection devices for self-administration and advanced drug delivery systems. Having identified at a very early stage the macro market trends and the unsatisfied customer needs that accompany self-administration of injectable drugs, SHL has emerged as a world-leading solution provider in the design, development and manufacturing of advanced drug delivery systems, including compact disposable autoinjectors, reusable pen injectors and complex inhaler systems.

As the global prevalence of chronic diseases continues to increase through factors such as improved diagnostic capabilities, changes in lifestyle and ageing populations, the lifelong process of disease management will continue to move from the hospital and primary care setting into patients' homes. This trend brings with it

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some significant challenges with respect to monitoring, adherence and compliance. As such, new customer needs are constantly emerging. Moreover, the relative importance of key stakeholders is also changing over time, resulting in a constant churn in the hierarchy of needs to satisfy. It goes without saying, therefore, that a regular discussion with customers and other key stakeholders is critical to keeping your finger on the pulse of change.

IDENTIFYING CUSTOMER NEEDS

As a market leader in the design, development and manufacture of autoinjector systems, SHL has multiple touch-points with its pharmaceutical customers in the course of doing "regular business". Sales people call on contacts and functions within the customer organisations every day; project managers, programme managers and supply chain personnel communicate with their counterparts on a regular basis and quality and regulatory affairs frequently collaborate to co-ordinate audits and prepare product submissions.

With all these regular points of contact, it becomes easy to believe that you know the customer, that you understand what they need and what they think of you as a supplier. However, like running a marathon, the real challenge starts when you are well into the journey and the harder it becomes to make sense of even quite simple feedback or instructions.

With existing customers, it is easy to become focused on manufacturing, selling products and dealing with firefighting issues rather than keeping abreast of their present needs, opinions and level of commitment. To develop this kind of understanding and take a forward-looking view on the relationship with the customer requires a conscious and formalised process, which exists outside of the regular day-to-day contacts. It was with this approach in mind that SHL recently initiated a "voice of customer" programme with a number of its key customers.

CONDUCTING MARKET RESEARCH

Conducting market research as part of your business process is far from being a new idea. After all, most definitions of marketing mention the identification of customer needs as the starting point in the process of building a profitable business. In a technically challenging area such as

Figure 1: SHL's Needle Isolation Technology (NIT®) was developed to enhance the safety and usability of cartridge-based autoinjectors.

self-injection systems, the focus of market research has frequently been centred on the device itself.

Initially developed for use in emergency situations, autoinjectors were, by definition, operated by untrained users or by patients themselves. With the development of biological pharmaceuticals and the growth of self-administration in the home setting, the use of autoinjectors has expanded, leading to the needs of users becoming more diverse and condition-specific. Companies like SHL have traditionally focused most market research efforts on creating product solutions that improve devices for better usability (Figure 1). Human factors studies are now an essential requirement in any device development programme to gain insight into how the device satisfies the needs of the patients. Focus groups and product testing research have therefore been extensively deployed by the medical device industry for many years.

WHAT IS VOICE OF CUSTOMER?

Voice of customer (VoC) research is not a new concept, however, more companies are discovering the potential of the methodology to generate both qualitative and quantitative input to the strategic planning process. VoC research generates feedback by means of interviews with respondents who have been identified as key stakeholders, capable of providing relevant feedback according to the specific objectives of the research.

While VoC interviews follow a structure that has been designed to generate feedback on the specific objectives of the research, a skilled VoC interviewer will stay close to the designated interview structure but will also incorporate a level of agility that allows respondents to develop their feedback in spontaneous directions. It is often from these "excursions" that the most valuable feedback is generated. Once the interview phase has been completed, the results are analysed using a formalised approach to address customer needs, expectations, opinions, suggestions, new ideas, trends and so forth. The data generated is then organised into a hierarchy or prioritised action list depending on the specific objectives of the study.

Although the pharmaceutical industry has undergone a number of significant developments in recent years and the market for self-administration injection devices has evolved considerably since the early 2000s, it is probably no exaggeration to say that we are, at present, at a true inflection point. The opportunities presented by connected devices together with changing characteristics of new injectable drugs (volume, viscosity, injection frequency) all present significant new scope for product development. However, the economics of providing effective but expensive disease-modifying treatments to an increasing number of patients is placing national healthcare systems under mounting and unsustainable pressure. In the face of such potential for change, it should come as no surprise that SHL should be interested in performing a VoC research programme to better understand how our customers perceive the near and long-term trends and how they assess SHL's overall performance and capabilities.

IMPLEMENTING THE PROGRAMME

SHL's focus on every detail when creating self-administration systems for its pharmaceutical partners and their patients was one of the most important factors supporting our VoC programme. With so many internal stakeholders interested in obtaining customer feedback, there was a

temptation to fit too much into the scope. However, VoC programmes tend to be more successful when they are focused on relatively few objectives. In the VoC survey recently conducted by SHL, we decided to focus on three key areas that would help us to understand, and ultimately serve, our customers better:

- To establish a baseline understanding of our relationship with our customers and how they view SHL's strengths and areas for improvement.
- To gather our customers' thoughts on future trends impacting the healthcare and pharmaceutical industries.
- To gain deeper insight into the views of our customers regarding their requirements for future delivery devices.

The survey was performed across three continents with stakeholders from pharmaceutical companies of different sizes, structures, therapeutic focuses and maturities. While the scope of the programme was deliberately tightly focused, we targeted a wide geographic sample in order to capture regional, cultural and structural variances in the feedback. As the demands of the global healthcare industry evolve in different directions and at different rates, we are committed to understanding these differences and adjusting our offering according to these needs.

INTEGRATION WITH BUSINESS STRATEGIES

As a result of experience in a given market, it is to be hoped that most companies have a good idea or feeling about what they should be doing and the different opportunities they have to grow. Stand around the coffee machines in most companies and very quickly you will hear opinions on what the company should be doing, what it should not be doing, which products should be developed and which products should be dropped. However, such opinions often lack any validation and are often clouded by personal bias, incorrect assumptions, limited awareness and personal agendas.

To succeed and grow over the long term, the real challenge facing companies and their leadership teams is about addressing the right opportunities, making the right choices and selecting the best adjacent market segments to move into.

Figure 2: Strategy, organisation and operations need to be aligned to ensure successful execution of business strategy.

To help in this process, companies need to make evidence-based decisions, derived from key stakeholders. When supported by a good strategic planning process, VoC research can really help a company to make informed decisions that maximise the probability of sustained success.

VoC research can help to identify some fixes that are relatively quick and easy to put in place. However, more often than not, the outcomes from VoC research touch upon profound evolutions in the market that can significantly impact the fundamental activities of any company. The feedback is often complex to interpret and can require a long, and likely difficult, process to implement. As such, the recommendations from the customer feedback need to be totally integrated into the company strategy in order to ensure the opportunities are successfully addressed. Delivering on strategy is not simply a case of defining in words "what" the company is going to do, it requires operational and organisational changes that are aligned to support the strategic direction.[1] Such changes imply financial investment, carry greater risk and require commitment and conviction. For this reason, it is essential that VoC research is sponsored from the very highest management levels in the company (Figure 2).

ROLLING OUT THE FINDINGS

The recent VoC programme performed by SHL has enabled us to have a clearer understanding of how our customers see the future industry and device trends. As the findings are communicated and rolled out, the entire organisation has benefited from an increased awareness of how our customers view our working relationship and the overall performance of the company. This is helping to build customer focus and to create opportunities for cross-functional teams to work on improved processes and evolving customer requirements. The programme has also created new forums for dialogue and avenues of collaboration with customers who took part in the survey.

Placing the outcomes from its recent VoC programme at the heart of its strategic initiatives, SHL will continue to focus on meeting customer expectations to reinforce its market leading position in the design, development and manufacture of drug delivery systems. Using the feedback from the survey, SHL's aim is to create value for our customers by helping them to meet the needs of their patients and key stakeholders in the provision of healthcare for the years ahead.

ABOUT THE COMPANY

SHL is a world leader in the design, development and manufacturing of advanced drug delivery devices, such as autoinjectors and pen injectors. With locations in Taiwan, Sweden, Switzerland 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 the company's 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.

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ABOUT THE AUTHOR

Michael McGowan is Global Director of Market Intelligence at SHL Group, responsible for the research and analysis of market trends and business strategies. Mr McGowan has over 20 years of experience in the medical industry with a focus on the international sales and marketing management of injectables and drug delivery devices.

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PATIENT-CENTRIC REUSABLE INJECTED DELIVERY SOLUTIONS OFFER MULTIPLE BENEFITS

In this article, Bjørn Knud Andersen, Director, Front-End Innovation, and Head of Technology Accelerators and IPR, Phillips-Medisize, discusses the advantages of developing customised, reusable delivery devices in order to achieve patient-centricity.

Developments in consumer electronics and information technology are rapidly changing medical drug delivery. While manual delivery of self-administered injectables still predominates, the sector is now migrating toward more user-friendly, flexible solutions that better address patient and caregiver preferences and expectations.

Although manual delivery offers a high level of flexibility, it is often associated with being complicated and less intuitive, requiring more training for the caregiver and/or patient. In contrast, a conventional autoinjector can offer a much more intuitive injection process. However, this process is "locked" into the device structure and therefore cannot be altered without comprehensive design re-validation.

Finding a happy medium between these two options presents a challenge, not only for caregivers and patients, but perhaps most significantly for pharmaceutical companies. Too often, these companies struggle to solve the drug administration challenges of tomorrow and remain stuck with yesterday's technology solutions. For example, many innovative injectable therapies require individualised dosages, based on factors such as body weight or surface area. With a conventional autoinjector, such individualised dosing would likely require keeping multiple units in stock to respond to variability in the target patient population, thus dramatically increasing associated development, manufacturing and inventory expenses.

In addition, while the well known pen-injector provides a good solution for managing diabetes, it does not necessarily guarantee secure operation in other therapies. For example, people with diabetes are generally highly trained and skilled in administering selected doses of insulin. However, the inherent risk of patient-related variation due to user error might critically affect results with another medicine that has a narrower therapeutic window.

ADVANTAGES OF CUSTOM-DEVELOPED DRUG DELIVERY DEVICES

Instead of remaining within the constraints of existing generic delivery platforms and struggling with patients and regulators to establish safety and efficacy within specific therapies, drug developers may be wise to consider a custom device approach. In Phillips-Medisize's experience, custom device development provides enhanced value once patient needs move beyond the "press and fire" approach exemplified by a conventional mechanical autoinjector. More complex needs could include variable dose adjustment, lyophilised drug reconstitution or even features of dose reminding and other patient outcome measures possible when integrating with connected health services.

Developing device usability based on a patient-centric innovation process often leads to a system with significantly

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enhanced ease-of-use, where critical-to-therapy functions are deeply integrated into the device solution. Technically speaking, this naturally implies either advanced mechanical architectures or, more typically, leverage of electromechanical technology platforms customised for a specific drug preparation and its administration features, as well as user guidance and feedback.

Natural side effects of this approach include increased cost and pressure for reusability, in order to keep cost-per-injection reasonable. However, patients typically have strong preferences for the more user-friendly solutions offered by such devices and tend to embrace reusable devices from an environmental perspective. In addition, especially when frequent administration is required, there is a significant cost-per-injection incentive for companies and payers to pursue reusable devices (Figure 1).

Obviously, the price of a reusable electronic autoinjector varies with complexity and production volume. For example, assuming a price of approximately €150 (£134) results in a cost-per-injection below €1 over a four-year period of weekly administration. Products of this value constitute a market segment that includes a broad range of current biologic blockbusters.

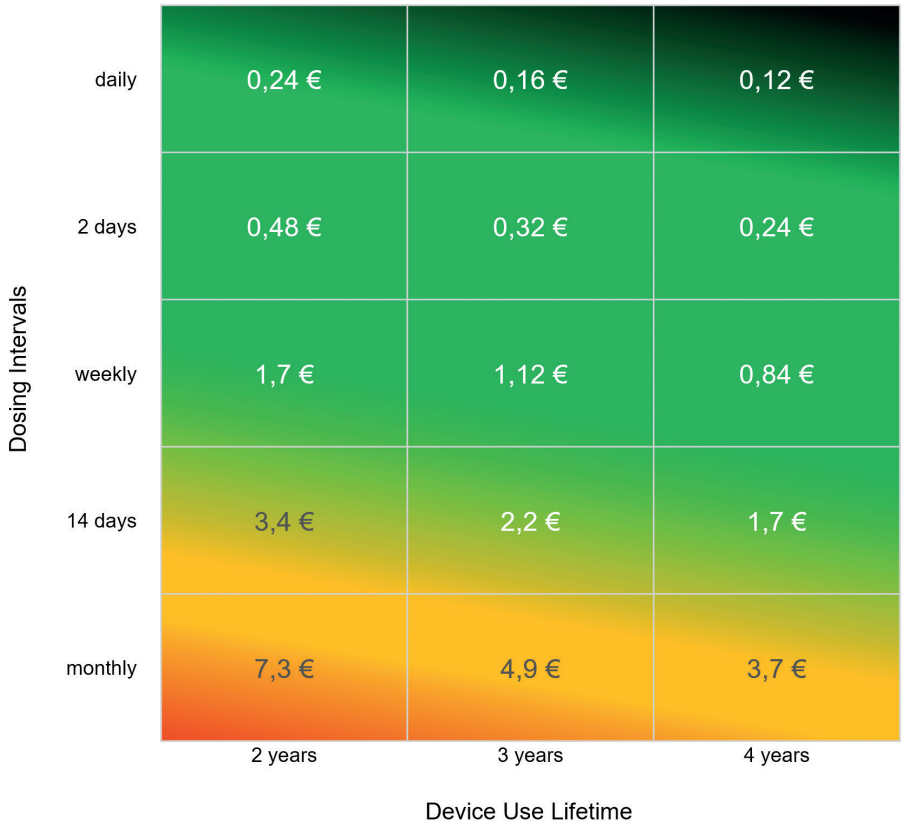

Figure 1: Device cost-per-injection examples with reusable drug delivery devices.

> "Substituting weekly disposable autoinjectors with one reusable device will, over four years, reduce production quantity requirements by a factor of more than 200."

REUSABLE PLATFORMS OFFER FLEXIBILITY

Custom device development is nothing new for bigger pharmaceutical companies servicing large therapeutic indications. Rather, it is a mandatory component of a competitive market strategy fuelled by sheer economies of scale, as well as by patient benefits. But the situation may differ substantially for smaller companies that service more specialised rare-disease indications with only few patients.

For such companies, even if applying a custom delivery device technology in a specialised segment potentially offers significant patient benefits, less competition typically means less imperative strategic incentives. Furthermore, a more specialised pharmaceutical company may often maintain a stricter focus on core drug-development disciplines and down-prioritise device technology and strategies. Relying on established technology suppliers to provide the necessary inspiration therefore often leads to single-use disposable autoinjectors as the device of choice.

In addition to being considered a nuisance to patients, a disposable device approach may carry critical consequences in terms of speed to market, thereby reducing company return on investment. For example, the time required to set up a high-volume manufacturing line, such as one that includes multi-cavity moulding tools and automated assembly stations, will be significant compared with production scaling for a reusable delivery device, due to the lower quantities of a reusable that will be needed. For instance, substituting weekly disposable autoinjectors with one reusable device will, over four years, reduce production quantity requirements by a factor of more than 200.

Obviously, the required development lead-time should also be considered. However, the reusable approach appears to offer advantages here as well. The application of software-controlled electromechanical systems allows for more design flexibility while fully respecting usability, risk and design robustness. Also, designs can be divided into functional modules which intuitively lend themselves to support new delivery device designs through alternative combinations and therapy-specific, user-related optimisation, thus avoiding the need for a total redesign between projects.

This is the concept behind Phillips-Medisize's Technology Accelerators, which enable extremely fast turn-around lead-time for innovation, feasibility and development processes, applying state-of-the-art technology solutions to produce optimised and individualised drug delivery device solutions. To illustrate this concept, the following example demonstrates alternative solutions to conventional mechanical autoinjectors.

PHILLIPS-MEDISIZE AUTOINJECTOR FOR PREFILLED SYRINGES

A mechanical autoinjector typically facilitates drug storage, administration and disposal. The administration is likely a straightforward "press and fire" handling

operation with simple acoustic signalling during injection. After use, the system is usually locked in a state where the needle is covered by a needle shield, which also clearly signals that the device has been used. In contrast, despite the potential benefits of reusable injection systems, they will not provide a pre-loaded dose of medicine. Instead, the patient must load the drug before administration and discard the used container afterward.

When injecting, patients will often be primarily concerned with possible pain, such as from the needlestick and drug contact, apart from speculation related to therapeutic effect and potential side effects. In Phillips-Medisize's experience with patients, adding a few minor user steps unrelated to those key concerns is typically completely acceptable. Therefore, loading and unloading a primary container is highly unlikely to pose an issue for the vast majority of patients offered a reusable autoinjector. Of course, it is important to simplify those specific user handling operations, as well as any other procedures, as much as possible.

A relevant example from the current Technology Accelerator portfolio applies a cassette concept to ensure easy loading and unloading, while providing full needle safety before and after the injection (Figure 2). The drug manufacturer installs the primary container, such as a 1 mL "long" prefilled syringe with a staked needle and needle cover, in the cassette. The cassette helps prevent needle stick injury after injection in addition to clearly signalling when it has been used by the patient, similar to a mechanical autoinjector. However, the amount and cost of material is significantly reduced. Loading the cassette through the front provides a compact, safe, effective system with minimal user interaction.

In another device, the same injector platform is customised to support delivery from a "naked" prefilled syringe, such as the same 1 mL one with a staked needle or a standard 2.25 ml syringe with an external needle attachment. Since these approaches avoid changes around the primary container entirely, they can offer an even faster track forward in support of potential clinical trial programmes.

Regardless of conceptual direction and application, the electronic reusable autoinjector platform will manage all relevant syringe movement handling (needle insertion and retraction, programmable to desired insertion depth) and patient-controlled drug injection (injection rate, pausing, etc). The motorised architecture inherently supports higher plunger forces, up to and beyond 100 N, potentially enabling significantly reduced needle diameter. For example, whilst ensuring that the pharmacological properties of the medicine remain unchanged, the increased plunger force capabilities may be capable of supporting a needle gauge reduction from 27G to 31G, potentially reducing pain related to needlesticks.

The durable electronic devices also contain multiple sensors and connectivity features, making it easy to store and transmit data to external applications, such as a connected health service system, further assisting patients, caregivers and healthcare professionals in improving therapeutic outcomes.

A PROMISING NEW OPPORTUNITY

Reusable electronic drug delivery devices have been around for many years, primarily in professional care segments. Historically, companies have had valid concerns about deploying such systems into patient self-administration settings. However, recent developments in electronics and information technology, along with emerging needs in the pharmaceutical industry, are driving change. Modern electronic reusable drug delivery systems offer a wealth of potential in terms of usability and flexibility, as well tangible cost-per-dose reductions, making them an obvious choice for patient-centric injected drug delivery solutions in global pharmaceutical markets.

ABOUT THE COMPANY

Phillips-Medisize, LLC, a Molex company, is an end-to-end provider of innovation, development, manufacturing and post-launch services to the pharmaceutical, diagnostics, medical device and speciality commercial markets. Post-launch services include a connected health app and data services. Backed by the combined global resources of Molex and its parent company Koch Industries, Phillips-Medisize's core advantage is the knowledge of its people to integrate design, moulding, electronics and automation, providing innovative high-quality manufacturing solutions.

Figure 2: Front-loaded autoinjector for prefilled syringes offering an optimal user experience.

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Bjørn Knud Andersen has been with Phillips-Medisize since 1997 and is part of the Front-end Innovation team responsible for innovation to translate pharmaceutical drug delivery needs into competitive patient-centric device solutions. As part of that role, he also heads activities related to developing the Phillips-Medisize Technology Accelerators. Mr Andersen is an industry expert with more than 20 years of experience within medical diagnostics, electronic drug delivery devices and connected health systems.

5 THINGS TO CONSIDER
WHEN MANUFACTURING CONNECTED DRUG DELIVERY DEVICES

The estimated number of connected drug delivery devices continues to increase and the impact of this trend could be significant, explains Phillips-Medisize

While digital connectivity or connected health can improve the coordination and delivery of patient care, original equipment managers need to keep these five things in mind when creating connected drug delivery devices:

1. **Development strategy and design consideration**
2. **Situation analysis and patient compliance**
3. **Connectivity ecosystem**
4. **Wireless subsystem**
5. **Security of device and information**

As the Internet of Things continues to become an integral part of people's lives, the opportunity to use it within drug delivery device applications remains promising. The manufacturers and device designers must identify, investigate and overcome these challenges so that the implementation of wireless and other related smart technologies can be achieved. When done successfully, connected systems enable the patient and caregivers to have a 360° view of both the patient and the disease – not only to manage adherence, but to improve results by understanding the effect of the regimen.

PREFILLED WEARABLE DRUG DELIVERY: HARNESSING TECHNOLOGY FOR PATIENT & PARTNER CENTRICITY

In this article, Mindy Katz, Director of Product at Sorrel Medical, describes in detail the company's journey from identifying a clear market need to development and commercialisation of Sorrel's prefilled and preloaded wearable injection device.

INTRODUCTION

For many medical device manufacturers, the development process is a delicate balance between the different needs of two distinct parties: the patient and the pharmaceutical partner. This is especially true when looking to design a device that is both cost effective and intuitive, easy to use and compliant with established pharma practices. To achieve this, technology must be harnessed accurately, with a profound understanding of what constitutes a truly patient- and partner-centric product.

This article outlines Sorrel Medical's insights on today's market needs and challenges, and points at how these are tackled by Sorrel's prefilled wearable drug delivery platform, bringing both patient-centric design and partner-focused strategy to the spotlight.

WEARABLE DRUG DELIVERY MARKET

Initially, wearable injectors may have been considered a fad, just a buzzword mentioned briefly in guessing what the future holds for drug delivery. Today however, the market indicates a great need for these wearable drug delivery devices. With the growth of biotech research and the increased number of biologics in pharmaceutical companies' pipelines, injectable medications expected to launch in the upcoming years have no solution for administration with today's commercially available hand-held injection devices. Moreover, pharma companies are putting more emphasis on devices, as a way of differentiating their product and providing their customers with a patient-

"Initially, wearable injectors may have been considered a fad, just a buzzword mentioned briefly in guessing what the future holds for drug delivery. Today however, the market indicates a great need for these wearable drug delivery devices."

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centric system. Accordingly, Sorrel sees an increased interest and great potential in the world of wearable drug delivery devices.

Over the years, several leading medical device companies have ventured into this field, coming from various industries and backgrounds, each with their own unique expertise and interpretation of the ideal wearable device. Nevertheless, only a few such products have been launched to date, and devices currently in development vary significantly in terms of user interface and technology.

While there are considerable barriers for entering this market, including complex technology, strict regulations, human factors and financial longevity, wearable drug delivery devices hold vast potential. The changes that this innovation brings to the healthcare market, in terms of enhanced user experience, administration of large volume and high viscosity medications, decreased dosing frequency, connectivity and more,[1] have set Sorrel on the path to perfecting a true platform solution.

SORREL'S BACKGROUND

Sorrel is a medical device company based in Israel, a hotbed of healthcare innovation.[2] It is one of three privately held companies in the world of drug delivery devices, including Q Core Medical, Avoset Health and Sorrel Medical, all operating under the Eitan Group. The joint experience amongst these three companies includes commercialisation of drug delivery devices across the continuum of care, multiple US FDA approvals, market presence in over 20 countries worldwide and a team of R&D innovators that are experts in parenteral drug delivery, flow control, human factors, software for medical devices, cybersecurity, and more.

After almost a decade on the market with the Sapphire infusion pump system, used in hospitals and healthcare facilities around the world, with over 15 million litres of medication already infused to patients, Sorrel is looking to the horizon to address the next big challenge in drug delivery. While researching the wearable drug delivery market, Sorrel has found the broad experience and multidisciplinary expertise accumulated across its R&D, regulatory, quality and manufacturing teams is an excellent fit to take on the challenges which lie ahead. With this, Sorrel turned to identifying the unique needs and challenges of the wearable drug delivery market.

IDENTIFYING KEY MARKET NEEDS AND CHALLENGES

As a first step, Sorrel characterised the two primary customers for its wearable platform. The end-user was anticipated to be a patient receiving injectable medication, most likely in the home environment without the presence of a healthcare professional. The partner would be a pharmaceutical or biotech company, partnering with Sorrel to bring a drug/biologic-device product to market together. Solving the challenges identified in the research and development process proved to be a delicate tango, which balanced between the distinct need sets of both of these customers, the patients and the partners.

Platform

Sorrel's goal was defined as designing, developing, and manufacturing a wearable drug delivery platform. The term "platform" carries significant weight, impacting design decisions throughout the development process. A device platform means a pre-determined strategy, applied from the initial design input stage to ensure that the device answers to the needs of multiple pharmaceutical partners across a variety of medications, indications and patient populations. A platform approach allows the device manufacturer and pharma partner to leverage marketed devices in terms of supply chain and regulatory approvals, requiring only slight customisation to adapt from one molecule to another.

Reliable, Controlled, Accurate Delivery

Based on Sorrel's experience in the world of infusion pumps, it identified its first challenge to be the development of a reliable, controlled and accurate delivery system. Reliability is the key, because, as a starting point, the system must deliver. Moreover, there is a wide variety of injectable medications out there, some requiring a controlled, variable and accurate dosing regimen, whereas others need a fast bolus injection. Led by the decision to take a platform approach, Sorrel wanted to ensure its technology held the capacity to adapt to the full range of medications.

By forgoing exotic technologies and selecting only proven, reliable components for its pumping mechanism, Sorrel was able to secure the reliability that it targeted. In addition, the electromechanical pumping

"Solving the challenges identified in the research and development process proved to be a delicate tango, which balanced between the distinct need sets of both of these customers, the patients and the partners."

Figure 1: Sorrel Medical's wearable drug delivery devices are available in 2, 3, 5, 10 and 20 mL versions (2, 3 and 10 mL shown here).

mechanism was designed to allow a 2 µL dose per step, at ±5% accuracy, giving the platform inherent accuracy and the crucial adaptability required for medications requiring lower rates and accurate deliveries, as well as those requiring bolus injections.

Primary Container Agnostic

Primary containers are a world of their own. A variety of parameters affect the choice of volume, material and manufacturer of a primary container for a specific medication, which is generally the choice of the pharmaceutical company. Formulation, chemical interactions, business partnerships and cost are all in the mix when it comes to choosing an ideal container closure system.[3] Accordingly, Sorrel's goal was to allow pharma partners the freedom to use a variety of drug reservoirs, and the technology was designed to have the flexibility needed to integrate the primary container of their choice. In addition, by being able to accommodate a broad range of volumes, the device platform can be easily customised to fit multiple products in a pharma partners' pipeline.

Decoupling the pumping mechanism from the primary container allowed for the flexibility that was required. Sorrel's platform can be customised to suit the different dimensions of any primary container, with only minor design changes. Currently, 2, 3, 5, 10 and 20 mL wearable injectors are available for customisation, all based on the same technology platform (the 2, 3, and 10 mL versions are shown in Figure 1).

Prefilled and Preloaded

For a self-administering patient, Sorrel wanted to ensure the best experience possible. A simple user interface offers a positive experience that reduces use errors, promoting adherence to therapy. Therefore, Sorrel decided to design a device that is intuitive and easy to use, with no compromises. Ideally, the drug-device system would come as one single unit, pre-loaded with a prefilled primary container (Figure 2). In this use case, the user would remove the device from its packaging, peel the adhesive liner, adhere to the body and initiate treatment. A critical challenge in the development of a prefilled and preloaded device is the process of integrating the aseptic drug filling process and the device assembly, in a way that ensures a disinfected fluid path, for a cost-effective device with no user intervention and minimal disruption to established pharma processes.

The industry's current standard practice, of manually swabbing the cartridge crimp with ethanol prior to loading into the wearable injector, does not allow for the preloaded solution that Sorrel desired, as it requires user intervention. On the other hand, creating a micro-organism-free fluid path for a preloaded solution necessitates alterations to be made to the established pharma processes, for accommodating proprietary cartridges that contain the entire fluid path, or loading the cartridge under aseptic conditions. The ideal solution that Sorrel envisioned could have the prefilled cartridge assembled into the device either at the pharma company, a contract manufacturer or at Sorrel's own facilities, with disinfection occurring at the point of care. The theoretical, ideal, solution would be a "Honey, We Shrunk Ourselves" scenario, in which someone may be placed inside the device, swabbing the cartridge septum prior to the engagement between the fluid path and cartridge. As Sorrel searched for an adequate technology that allowed this disinfection at point of care, it found UV technology to be ideal.

UV-C LED technology[4] enables a prefilled and preloaded device configuration, utilising standard cartridges, without disruption to existing drug filling lines. This method results in automatic, verified and controlled local disinfection at point of care. As with all components within the system, it is widely available, time- and scale-tested, and cost-effective. This is the ultimate prefilled solution, which permits Sorrel to deliver an ideal product configuration for the end-user, while also conforming to pharma practices, all in a cost-effective device. A scientific poster detailing experimental results of the UV technology will be presented at PDA's Universe of Pre-filled Syringes and Injection Devices, October 8-9, 2018 (Orlando, FL, US).

> "Sorrel has now completed the development of the technology platform on which the wearable devices are based, and is currently setting up manufacturing lines for its first product line."

Smart Sensing

Due to the nature of a patient's dependency on their wearable device, assuming they are prescribed self-administration at home without the aid of a healthcare professional, it is crucial that the device, via its technology, supports their user experience, notifies the patient of any issues, prompts desired actions and gives them the confidence they need to complete the treatment successfully. Sorrel achieved this with a blend of integrated sensors, as well as visual and audio indicators, clearly communicating the device status to the user. The sensors detect air and occlusion, and deliver alerts according to pre-defined parameters. A dedicated sensor ensures that the delivery will not initiate until the device has been firmly adhered to the skin. Additional sensors inside the device detect needle position, cartridge placement and run a range of internal system checks, ensuring that the device is functioning properly. It is not a trivial task to include smart sensing technology in a fully disposable and cost-effective device. In Sorrel's case, this is enabled by integrating sensors with smart algorithms, often using one sensor for more than one purpose.

Connectivity

Over the past several years, there has been significant focus on digital health and connectivity in medical devices. The power of connectivity can be harnessed in a variety of ways, primarily to promote patient engagement and adherence to therapy. Looking at the insulin delivery

Figure 2: Importance of a patient-centric, prefilled and preloaded device.

Figure 3: Bluetooth low energy and NFC connectivity.

market segment, it can be seen how connectivity has begun to sprout seeds that empower the diabetic patient population. While recognising the importance of connectivity, and the increased value it can bring to a drug delivery system, Sorrel believes that the connectivity conversation is one to be had with pharma partners, prior to the commercial release and per-patient population use case. Accordingly, Sorrel has both Bluetooth and near field communication (NFC) already integrated into its device, enabling connectivity in two widely accepted and secure routes of communication. For the purpose of clinical trials, Sorrel has developed a smartphone application that enables sharing of treatment reports during investigational use (Figure 3).

DEVELOPMENT METHODOLOGY AND PROGRESS

Sorrel is utilising a structured project management method built of phases and milestones, each with a set of predetermined requirements. Quality, regulations, operations and R&D all have responsibilities and sign-offs for each of the design stages, ensuring efficient co-operation across the board. In addition, Sorrel's pharma partners' participation has been built into this framework, ensuring that input is received and approval is given at relevant junctures throughout the development process. This operational methodology has been proven successful in the commercialisation of infusion pumps, and has been audited numerous times by regulatory authorities in Europe and the US. It also ensures full and automated traceability, starting from user needs, all the way to each device specification and every line of software code.

Sorrel has now completed the development of the technology platform on which the wearable devices are based (Table 1), and is currently setting up manufacturing lines for its first product line. The first configuration expected to be ready for clinical trial use is a 3 mL cartridge-based wearable injector that can be either preloaded or loaded by user, per the pharma partner's choice. The 3 mL device is expected to be ready for clinical trials in Q1 2019, post verification and validation. Working prototypes are available for feasibility testing.

Sorrel is actively pursuing partnerships with pharmaceutical companies, interested in bringing innovative drug-device combination products to market.

					
General Description	On body and fully disposable, delivering injectable medication to the subcutaneous tissue				
Duration of Use	Up to 3 days	Minutes - several hours			
Fill Form	Filled at point of care	Prefilled and preloaded			
Drug Reservoir	2 mL internal reservoir	3 mL cartridge	5 mL cartridge	10 mL cartridge	20 mL cartridge
Flow Range	0.01-60 mL/hr				
Connectivity	Bluetooth and NFC				
Indicators and Buttons	Audio and visual indicators, SW-controlled hard key for delivery initiation and/or bolus (optional)				
Viscosity	Up to 120 cP				
Customisability	Labelling, branding and software customisation available				

Table 1: Sorrel Medical's platform specification.

SUMMARY

With the wearable device market expected to provide a smart and straightforward drug delivery experience to patient populations worldwide, Sorrel is excited to be harnessing innovative technology that benefits both patients and pharma partners.

ABOUT THE COMPANY

Sorrel Medical is a medical device company focused on prefilled wearable injectors. Sorrel is one of three privately held companies operating under the Eitan Group, all in drug delivery devices, including Q Core Medical, Avoset Health and Sorrel Medical. Q Core Medical develops and manufactures the Sapphire infusion system, on the market in both hospital and homecare environments. Avoset Health is developing a connected homecare infusion pump, available for pharmaceutical companies in a dedicated application configuration. The joint experience shared amongst the Eitan Group's three companies, includes commercialisation of drug delivery products across the continuum of care, multiple US FDA approvals, market presence in over 20 countries worldwide, and a team of R&D innovators that are experts in parenteral drug delivery, accuracy, flow control, human factors, cybersecurity and more.

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ABOUT THE AUTHOR

Mindy Katz is the Director of Product at Sorrel Medical, responsible for product management, marketing and business development. Her involvement in the company's early days influenced Sorrel's decision to pursue the wearable drug delivery market, and she has been heading the product and business activities ever since.

Ms Katz previously served as Program Manager at Q Core Medical, where she worked across multidisciplinary teams to build structured and collaborative partnerships between companies in the world of drug delivery. She holds a BSc in Biomedical Engineering from the Technion - Israel Institute of Technology.

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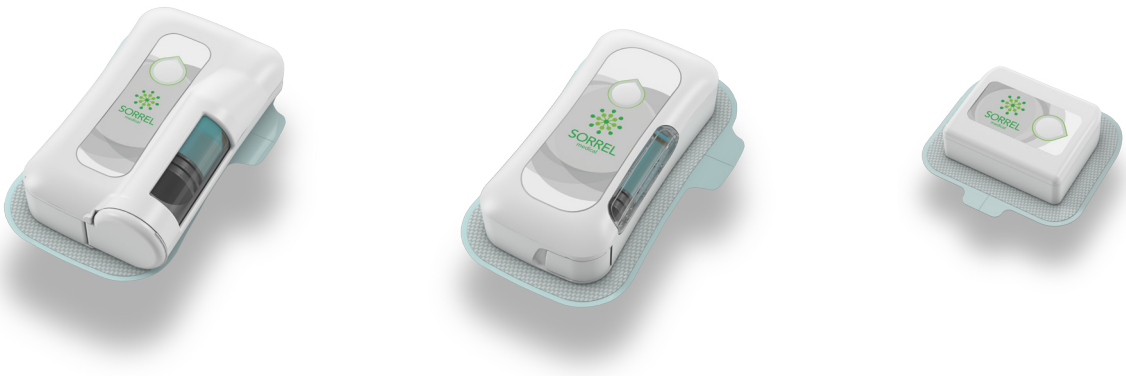

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MEDICAL ENGINEERING TECHNOLOGIES

GLOBAL EXCELLENCE IN DEVICE TESTING

THE NEED FOR A FULLY INFORMED LABORATORY IN COMBINATION DEVICE VALIDATION SERVICES

In this article, Mark Turner, President, Medical Engineering Technologies, runs through the advantages and processes of working with a high-quality preclinical device testing and validation partner when developing a novel combination product.

INTRODUCTION

Typically, pharmaceutical companies are confident that they understand the regulatory pathway for active pharmaceutical ingredients (APIs) and their own formulations. However, sometimes they are less confident about the requirements when these are coupled with a delivery system. A good preclinical partner/test facility, such as Medical Engineering Technologies (MET), can provide regulatory guidance and design validation testing (DVT) to help assist in getting a product to the marketplace.

> "A good preclinical partner/test facility, such as MET, can provide regulatory guidance and design validation testing to help assist in getting a product to the marketplace."

In some cases, the required testing is well defined (e.g. ISO 11608/ISO 11040 for pen injectors[1] (Figure 1) and prefilled syringes[2]), whilst with others it may not be so clear (e.g. hormone eluting rings and implants[3]). The process of addressing these requirements can be planned to ensure efficient project management and help reduce costs. When you work closely with your chosen preclinical partner/testing facility, they can help provide guidance on the test requirements and the sample requirements using acceptable quality limits (AQL) tables or test standards. Planning, in consultation with your chosen partner, should allow them to deliver testing efficiently and you to meet your deadlines.

DESIGN VALIDATION PLANNING

The prerequisites to developing a design validation programme are:

- Competitor submissions review
- Design inputs/targeted product performance
- European and/or US FDA Guidance review
- Risk analysis
- ISO/EN/ASTM/ICH/pharmacopeia standards review
- (If this is a first foray into combination devices) Gap analysis of the quality management system (QMS) and production processes and qualifications in place.

These processes can be conducted in-house or with a preclinical partner/test lab. A good knowledge of European and

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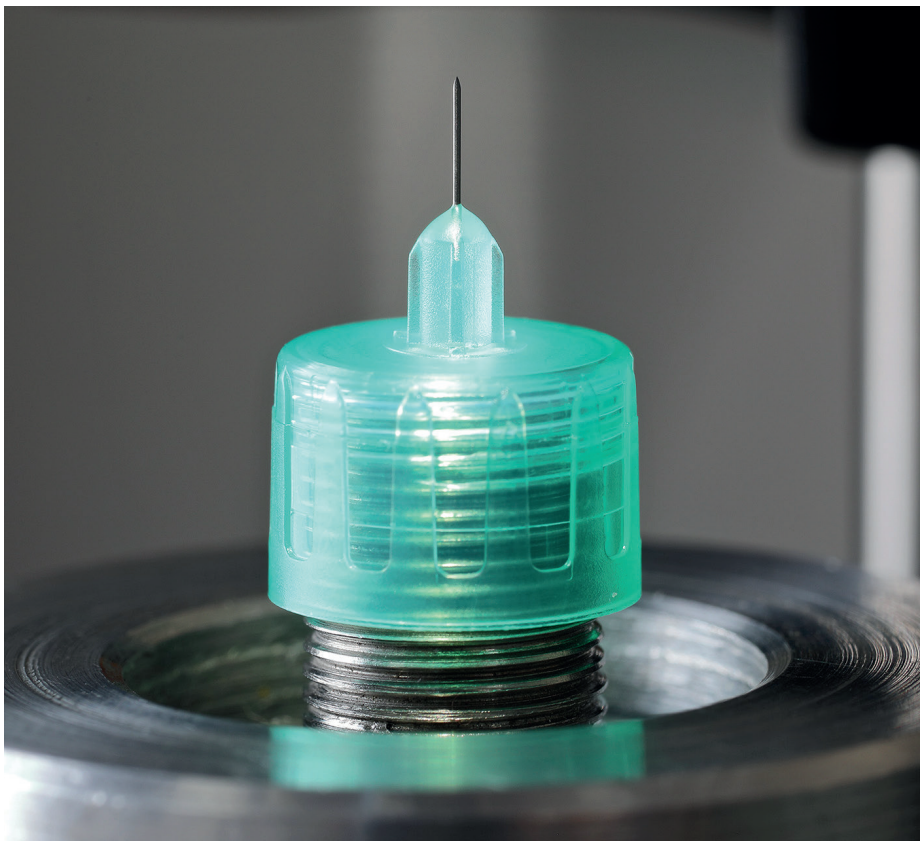

Figure 1: An injector pen needle undergoing testing.

"If a good product standard or European/FDA Guidance is in place, a lot of the required validation work may already be defined. Interpreting some standards can, however, be challenging."

FDA regulations will help to speed up this process. The European Directive, combined with ISO 13485, gives a lot of guidance in the general areas of design control and safety considerations.

If a good product standard or European/FDA Guidance is in place, a lot of the required validation work may already be defined. Interpreting some standards can, however, be challenging. Even with the defined requirements seen in some standards, carrying out the risk analysis can still be both very important and very helpful. If good guidance is not available, the risk analysis is crucial. This analysis aims not only to identify all the risks, but also to quantify them. It can then be used to ensure that all the necessary testing has been carried out, and also to reduce any superfluous testing. Similarly, if guidance is not available, the key performance requirements must be identified in a product review. This includes design inputs and a literature review, thereby saving time and money. MET has developed standard study plans for a large range of devices.

These reviews and risk analyses can be used to develop the test programme and design test protocols.

DEVELOPING A PROTOCOL

The testing regimes in a DVT programme could include:

- Assessment of hazards identified in the risk analysis
- Bioavailability studies
- Biocompatibility studies
- Drug/container interaction analysis
- Extractables and leachables studies
- Toxicological risk analysis
- Human factors studies
- Performance and dose accuracy assessments
- Reference listed drug (RLD) comparison
- Standard/FDA Guidance compliance testing.

"To help a project run smoothly, Gantt charts and a more descriptive plan may be helpful. This plan can include test costing, time requirements, sample numbers, production or sourcing delay and sample description."

Stability testing, following ICH (Q1A) guidelines, will also be required prior to launch. However, some stability testing will be required that will go beyond a product's launch. This repeat testing is likely to be carried out at intervals up to (and slightly beyond) the claimed acceptable storage period or shelf-life of a product. Evidence for product stability can be gathered using accelerated ageing (AA),[4] where raised temperatures are used to give real-time equivalence (RTE) for storage to the required ageing periods but less time is taken. The data provided by AA testing will require substantiation using data acquired from product that has been held at the normal storage temperature (real-time aged) for the actual ageing period. This can often be done after your product has been agreed for distribution.

To help a project run smoothly, Gantt charts and a more descriptive plan (provided by your partner laboratory) may be helpful. This plan can include test costing, time requirements, sample numbers, production or sourcing delay and sample description. Notes can then be added, explaining if a test is essential or just helpful. It can be shared between you and your testing facility, in order to ensure efficient communication of your requirements and required timelines.

MET testing plans shown in Tables 1, 2 and 3 use a transdermal patch as an example (though the same principles apply in injectable device testing) and give an idea of the types of testing, sample sizes and time requirements that would need to be considered. These tables are not comprehensive. Your chosen test facility can repeat this process for all the validation requirements identified in your reviews, giving you clear timelines and cost-effective plans.

Other considerations when looking at the timeline for the project, other than the longer-term stability testing, are factors that

CE ER Check List	Test	Detail	Sample Requirement	Sample Condition	Time Requirement
ISO 10993	Biocompatibility	Cytotoxicity	30	Final product Sterile	8 weeks
		Sensitisation			
		Irritation			
		Acute			
EMEA Guidance	Chemical Safety	Extractables and Leachables	25	Final product Sterile	12 weeks
		Drug compatibility	10		
		Toxicological Risk Analysis	Follows chemical analysis		3 weeks

Table 1: Biocompatibility and chemical safety tests.

CE ER Check List	Test	Detail	Sample Requirement	Sample Condition	Time Requirement
1,2 and 3 (4), 9.2	Laboratory Performance	Dermal adhesion	5	Final product Sterile	4 weeks
		Conformability	5		
USP 5/6		In-vitro dissolution	20		
EMEA Guidance					

Table 2: Bench tests.

CE ER Check List	Test	Detail	Sample Requirement	Sample Condition	Time Requirement
4 ISO 11607	Packaging	Transit simulation followed by pack strength and integrity	40	1 shipper carton	3 weeks
8.3 ISO 11607	Stability	Accelerated ageing followed by pack strength and integrity	40 per time period, plus 40 reference and 40 real time.	Final packs sterile (product not essential)	8 weeks per year

Table 3: Packaging tests.

may not at first be considered to require extended time. For example, if you intend to carry out predicate testing as part of the design process for your device, predicate or RLD products can be very difficult to obtain (particularly if several batches are required) and, in some cases, they can be very, very costly. Because of this, you need to be clear on what information is required and how many samples are required for statistically significant results.

DESIGN VALIDATION TESTING

The first step when your project is handed to your test facility will be a protocol document, usually developed by the test facility (in conjunction with you). This document will clearly indicate tests, sample allocation, acceptance criteria and reporting requirements. Once the protocol has been agreed and signed by both parties, the project moves to the DVT stage.

> "Some of the difficult questions relating to testing revolve around whether multiple batch testing is required and what kind of pre-conditioning is required."

The testing stage may be preceded by a gauge repeatability and reliability (GR&R) study to provide evidence that the test protocol is robust and that there can be confidence in the DVT results. Sometimes the tests involved are destructive and cannot be repeated on the same sample by multiple operators. In this case, it is common to use duplicate or triplicate testing on samples from the same batch. For example, during a prefilled syringe project, a technician might test 20 syringes for dose accuracy, and break-loose and glide forces on three different occasions (this could be on consecutive days). For a thorough validation, this would normally involve three technicians with each carrying out the test on three different occasions. Statistically concordant results should be achieved between technicians and instances of testing.

Although your chosen test facility may have carried out your chosen tests on numerous occasions and have several GR&R studies on file, your device may not be identical to those tested previously. In this case, you will need to consider (in order to keep costs down and timelines tight) if your notified body could accept these previously run GR&R studies.

Once the test procedure is approved, the DVT can proceed. The use of a laboratory with ISO 17025 accreditation will ensure that there is a good, fully-audited quality management system (QMS) and that equipment is qualified and calibrated, whilst processes are subjected to internal audits. It is entirely possible that not all tests will be specifically accredited. However, as long as these are carried out to an agreed protocol under the ISO 17025 QMS, there can be confidence in the results.

Some of the difficult questions relating

to testing revolve around whether multiple batch testing is required and what kind of pre-conditioning is required. It may be possible to combine multiple batch testing with pre-conditioning. For instance, the ISO 11608 standard for injector pen testing has pre-conditioning at 70°C and -40°C. If the risk analysis shows that testing at these conditions is indeed necessary, the opportunity to test different batches at the different conditions presents itself. The total amount of testing is then reduced, by examining batch 1 after high temperature conditioning and batch 2 after low temperature conditioning.

REPORTING

Test reports can be succinct or extensive. For regulatory submissions, a certificate of analysis will be too brief whereas as a hundred-page report will not be helpful. The report should include at least:

- Reference to the test protocol (the full protocol can be an appendix)
- Rationale for analyses included and excluded
- Any deviations from protocol
- Details of equipment and technicians
- Details of the product tested (batches, dates, description, etc)
- Test results
- Summary.

A report may not finish with a conclusion. If testing has been carried out following a standard with acceptance criteria or if there were definitive acceptance criteria described in the protocol, then it is possible for your laboratory to conclude whether these criteria were met or not. For example, ISO 11608 defines the required dose accuracy for injector devices quite clearly and gives a statistical concordance requirement as well. However, if subtle exceptions are found, such as an oral spray producing an aerosol 10% less dense than the design specification, the clinical knowledge of the pharmaceutical company is needed to assess the importance of this data.

SUMMARY

This article does not end with a conclusion. When developing a combination device, a pharmaceutical company must decide whether to carry out testing in-house or externally. There is no compulsion for independent testing, as long as a company's own laboratory is fully equipped, has all the control systems in place and will act without bias.

The advantages of using an experienced, well informed external laboratory are:

- Clear independence
- No capital costs
- Efficiency of project management, testing and reporting
- Good advice from a knowledgeable source.

Things to look for when selecting a laboratory are:

- A good QMS and good quality control
- Informed and helpful staff
- Rapid, accurate responses to queries
- Openness of access
- A comprehensive range of services (to reduce multiple sourcing and adding several companies to your supplier list).

MET's staff have developed plans for many projects and a wide variety of devices. These have been successfully implemented within an ISO 10725 QMS, helping clients to achieve a smooth entry into the market.

ABOUT THE COMPANY

Medical Engineering Technologies has successfully delivered design validation testing to medical device and pharmaceutical companies in 20 countries across Africa, Asia, Australasia, Europe and the US. 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 complete confidence in the quality and accuracy of the results.

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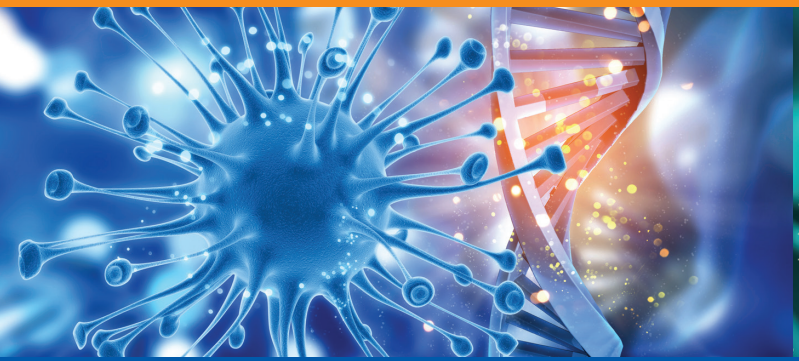
ABOUT THE AUTHOR

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. 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 (UK) in 1983 and has also studied astronomy, business administration, cosmology and opto-electronics.

- CCIT
- ISO 8009
- ISO 11040
- ISO 11608
- Glide Force
- Connectivity
- Trigger Force
- Needle Testing
- Dose Accuracy
- Human Factors
- Break Loose Force
- Performance Testing
- Transit /Altitude Testing
- Design Validation Testing
- On Body Delivery Systems
- Extractables and Leachables



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MITSUBISHI GAS CHEMICAL

ADVANCED MULTILAYER POYLMER VIAL & SYRINGE FOR BIOLOGICS

In this article, Tomohiro Suzuki, Associate General Manager, Mitsubishi Gas Chemical, explains how MGC has developed OXYCAPT™ Vial & Syringe to overcome the current weaknesses of glass and cyclo-olefin polymer containers, developing a product that provides the advantages of both.

There are some problems with existing vials and syringes made from glass and plastic. For example, glass suffers from breakage and delamination, whereas plastic lacks a sufficient oxygen and ultraviolet light (UV) barrier. Especially with glass, the US FDA has pointed out these problems, which have led to more than 50 incidents of recall. To address these problems with glass, a lot of suppliers have launched plastic alternatives, however the oxygen barrier has failed to meet the demands of customers. Given this situation, Mitsubishi Gas Chemical (MGC) has developed multilayer plastic vials and syringes with an excellent oxygen barrier, high UV barrier, very low extractables, high breakage resistance and other excellent features (Figure 1).

> "The OXYCAPT™ Vial & Syringe consist of three layers. The inner and outer layer are made of COP, the most reliable polymer in pharma industry. The middle layer is made of a novel polyester that has been developed by MGC."

Figure 1: OXYCAPT™ Vial & Syringe.

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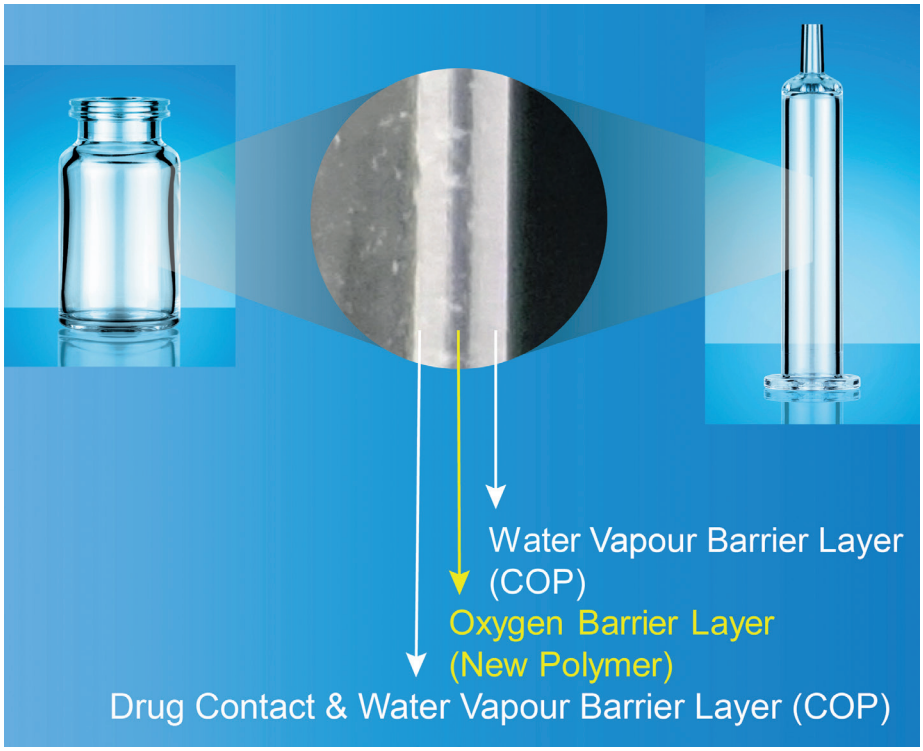


Figure 2: Triple layer structure of OXYCAPT™ including the middle polyester oxygen barrier.

OXYCAPT™ Vial & Syringe consists of three layers (Figure 2). The inner and outer layer are made of cyclo-olefin polymer (COP), the most reliable polymer in the pharma industry. The middle layer is made of a novel polyester that has been developed by MGC. The characteristics of COP give OXYCAPT™ the traditional advantages of polymers and the new polyester plays a role as an oxygen and UV barrier to address the weaknesses of COP alone.

The oxygen barrier quality of OXYCAPT™ is almost equivalent to glass and more than a hundred times better than COP (Figure 3). According to internal studies using antibodies, OXYCAPT™ outperformed glass and COP in terms of preventing oxidation. As biologics are often sensitive to oxygen, OXYCAPT™ can contribute significantly to the stability of such drugs over time. OXYCAPT™ also provides a UV barrier. For example, although about 70% of 300 nm

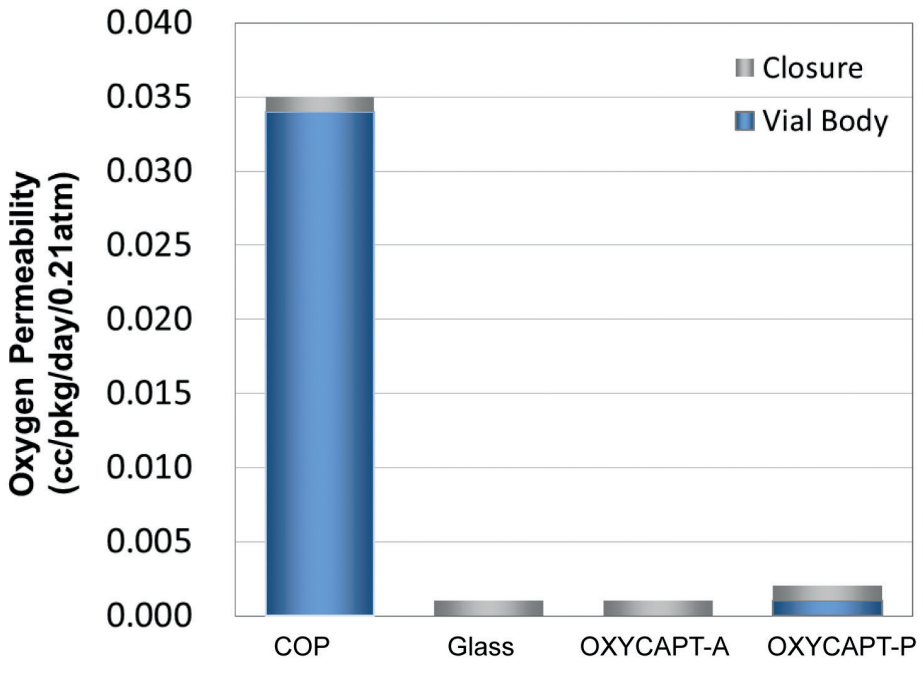


Figure 3: Comparison of oxygen barrier properties of COP, glass and OXYCAPT™.

"The oxygen barrier quality of OXYCAPT™ is almost equivalent to glass and more than a hundred times better than COP. According to internal studies using antibodies, OXYCAPT™ outperformed glass and COP in terms of preventing oxidation."

UV light transmits through glass and COP, only 1.7% transmits through OXYCAPT™ (Figure 4). This further contributes to biologic stability. With respect to the water vapour barrier, OXYCAPT™ cannot equal the performance of glass. However, it is similar to COP, easily meeting the water vapour barrier requirements set out in the ICH guidelines.

Studies have shown that OXYCAPT™ generates extremely low levels of extractables. One study was conducted to measure volatile, semi-volatile and non-volatile impurities from OXYCAPT™. Five solvents – water, 50% ethanol, NaCl, NaOH and $H_3PO_4^-$ – were selected and impurities were measured by gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-UV spectroscopy-mass spectrometry (LC-UV-MS) after 70 days at 40°C. Compared with the control, no impurities were detected in any of the OXYCAPT™ containers. A second study was conducted to measure inorganic extractables from OXYCAPT™. The level of extractables was similar to those from COP, which is well known as an extremely pure polymer, and less than that of Type I glass (Figure 5).

The OXYCAPT™ Syringe consists of tip cap, barrel, PTFE-laminated stopper and plunger rod. Although a very small amount of silicone-oil is coated on the stoppers, no silicone-oil is baked on the barrel. According to our internal studies by using antibodies, we have found this feature noticeably reduces instances of protein aggregation, compared with existing Type I glass syringes.

OXYCAPT™ Vial & Syringe are produced by co-injection moulding technology. Although this technology has been applied to beverage bottles for many years, MGC is the first company to succeed in developing multilayer plastic

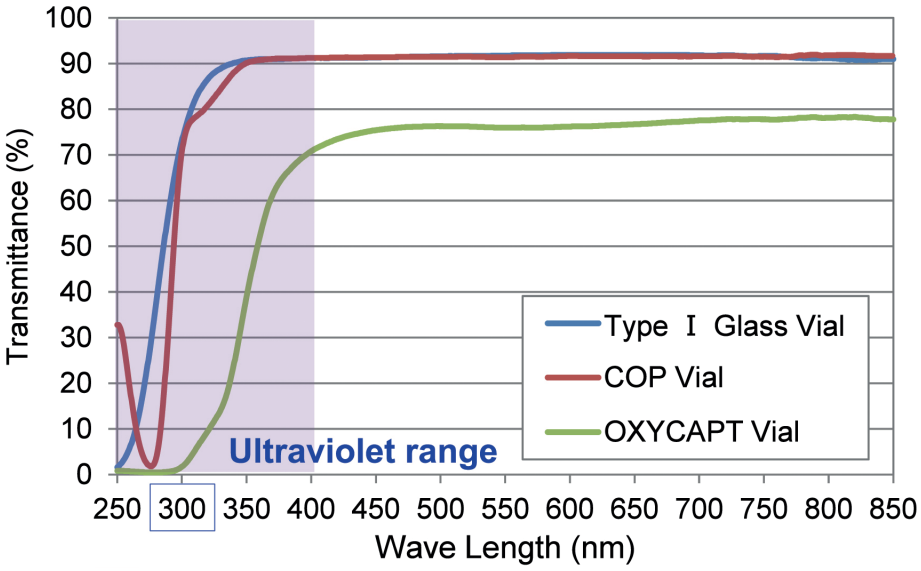


Figure 4: UV barrier properties of OXYCAPT™ vial compared with Type I glass and COP.

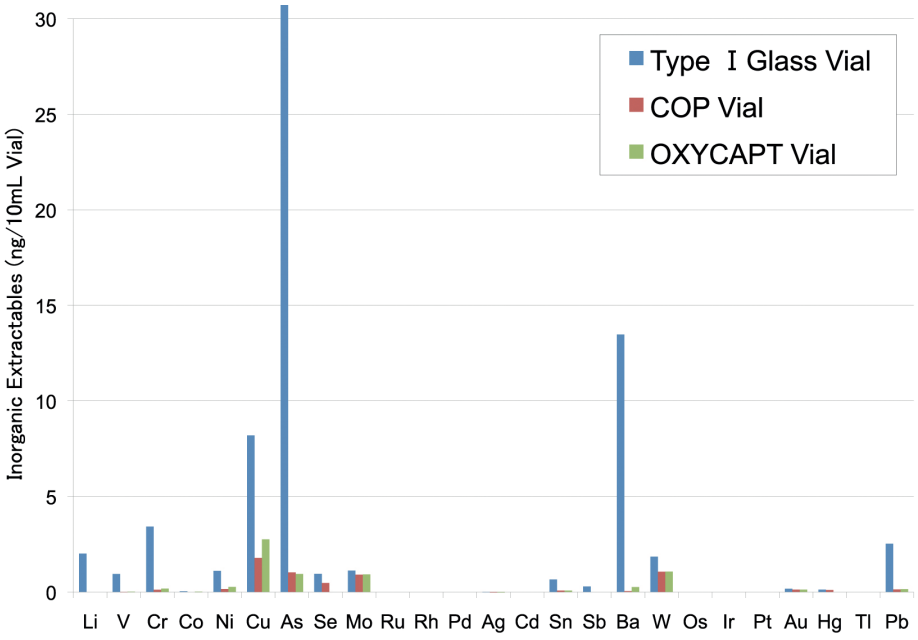


Figure 5: Inorganic extractables analysis of OXYCAPT™ vial compared with Type I glass and COP.

syringes. We have also developed inspection methods for the oxygen barrier layer. All of the containers are 100% inspected by state-of-the-art machinery.

MGC can offer bulk vials, ready-to-use (RTU) vials and RTU syringes. Regarding the RTU products, vials and syringes are provided in ISO-based nest and tub formats. The nest and tub are primarily sterilised by gamma ray. There are 2 mL, 6 mL and 10 mL variants for vials, and 1 mL long and 2.25 mL variants for syringes. Each polymer meets the requirements of USP661, USP87, USP88, EP and has been filed in the US FDA's drug master file (DMF). The vials and syringes are also compliant with each pharmacopoeia. The syringes are produced and controlled in accordance with ISO 13485.

The target therapeutic application for OXYCAPT™ is biologics. As the ICH guideline "Stability of Biotechnological/Biological Products Q5C" mentions, oxidation is a cause of protein instability. Some features of OXYCAPT™, such as its high oxygen and UV barrier properties contribute to the stability of biologics. Furthermore, we believe OXYCAPT™ can be applied to epinephrine, as it is well-known as an oxygen sensitive drug. Additionally, the breakage that can occur with glass syringes is not ideal for emergency drugs, so some suppliers have tried to develop new pen injectors using plastic.

Customisability is one of the features of plastic. Naturally, OXYCAPT™ incorporates this. MGC is able to consider developing specially designed OXYCAPT™ containers, as requested.

In conclusion, OXYCAPT™ has been developed to meet an unmet need in the pharmaceutical industry. In addition to the special features of COP, such as high water vapour barrier, high break resistance, very low extractables and low protein adsorption, OXYCAPT™ can provide a high oxygen and UV barrier. We believe OXYCAPT™ brings a lot of benefits to the rapidly growing field of biologics.

ABOUT THE COMPANY

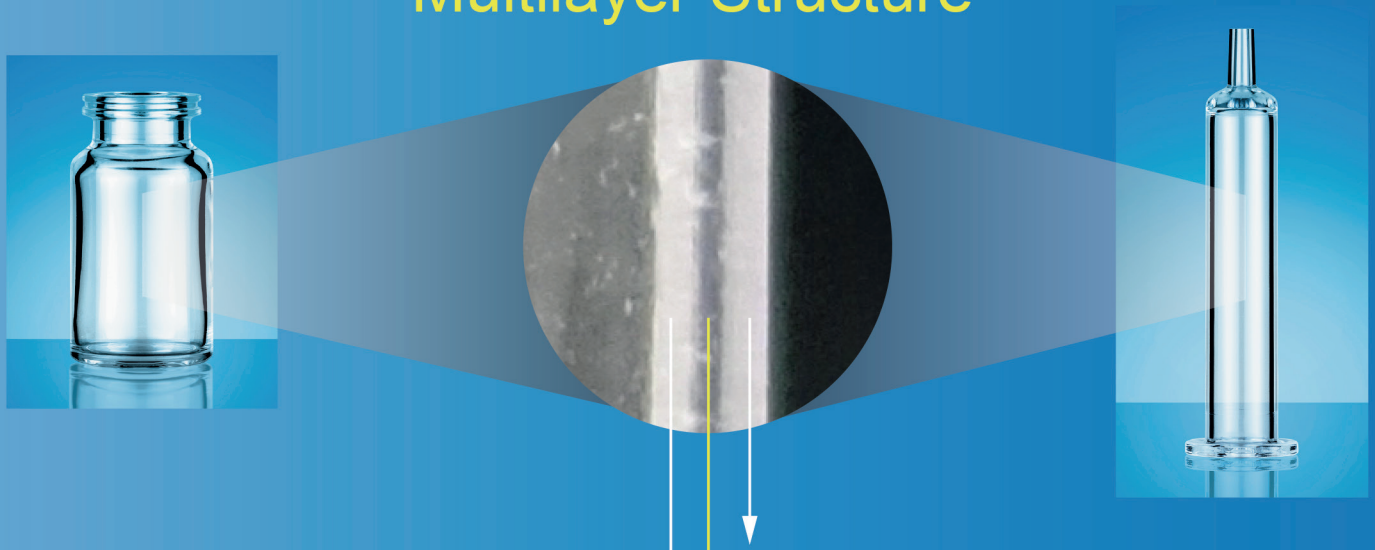
Mitsubishi Gas Chemical does business in a wide range of fields, from basic chemicals to fine chemicals and functional materials. MGC established its Advanced Business Development Division in 2012 as a centre for continually creating new businesses, and developed OXYCAPT™ Vial & Syringe as an alternative to glass containers.

ABOUT THE AUTHOR

Tomohiro Suzuki joined Mitsubishi Gas Chemical in 1998. He belonged to the oxygen absorbers division until 2011, after which he was transferred to advanced business development division in 2012 to be a member of the OXYCAPT™ development team. Since then, he has been in charge of marketing for OXYCAPT™ Vial & Syringe. His current position is Associate General Manager.

OXYCAPT™ Plastic Vial & Syringe

Multilayer Structure



Water Vapor Barrier Layer
(COP)

Oxygen Barrier Layer
(New Polymer)

Drug Contact & Water Vapor Barrier Layer
(COP)

- ✓Excellent Oxygen Barrier
- ✓High Water Vapor Barrier
- ✓Low Extractables & High pH Stability
- ✓High Break Resistance & Lightweight
- ✓Excellent UV Barrier
- ✓High Transparency
- ✓Silicone Oil Free Barrel
- ✓Low Protein Adsorption & Aggregation
- ✓Suitable for Biologics
- ✓Customizable

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A MODEL FOR TRANSFORMING BREAKTHROUGH INNOVATIONS IN SUCCESSFUL PRODUCTS

Here, Eric Dessertenne, Chief Operating Officer, Philippe Lesaulnier, Business Development Manager, and Arnaud Guillet, Business Development Manager, all of Biocorp, outline Biocorp's approach to device design and detail two products in the company's portfolio, Newguard and Easylog, which are anticipated for market launch next year.

A major concern for pharmaceutical companies is the comfort and safety of patients during the administration of their treatment. All too often, noticeable weaknesses in this area, including needlestick injuries or dosing errors, are observed.

Biocorp strives to offer reliable solutions to improve patients' lives. After a thorough research and development phase together with experimental collaborations with different partners, the company is now expecting its first market launches in 2019. In order to ensure it never loses sight of the patient, Biocorp works systematically to understand the needs of patients and propose the most suitable devices. To illustrate this approach, let's have a closer look at two key devices in Biocorp's portfolio: Newguard, the integrated safety system for prefilled syringes, and Easylog, the connected add-on device for pen injectors.

NEWGUARD – ANSWERING THE NEED FOR SECURITY

Enhancing safety for syringe use has been an increasing concern for pharmaceutical companies and healthcare providers, as handling prefilled syringes (PFS) all too often leads to needlestick injuries. The concept of needlestick protection is not new but, during the last decades, we have seen a significant modification of technical solutions available to reduce those risks. Early devices were manually activated, meaning that additional movements and manipulation of the device were required to activate the safety features.

A second generation of device was later developed, designed to be passive systems but still part of the overall concept of adding an additional element to the PFS. These systems do not require any additional action by the user, with the safety mechanism activated upon complete administration of the drug.

For many years, the "add-on safety principle" was the main answer to protect end-users against needlestick injuries when using PFS. These systems widely contributed to needlestick injury reduction in hospitals and during self-injection. However, they generated some burdens for pharma companies, such as additional costs, manufacturing complexities and increased product size.

Recently, a new trend in safety systems appeared: integrating the safety system at the syringe manufacturer site before the sterilisation cycle. Integrated safety systems are active or passive, pre-assembled on syringes by the glass suppliers and ready to use. The main benefit for pharmaceutical companies is that they receive a ready-to-fill system that comes already equipped with safety protection for the staked-needle PFS format.

That led Biocorp to develop Newguard, an integrated passive safety system for prefilled syringes. In doing so, Biocorp transformed a simple idea into a concrete innovation for the pharmaceutical industry.

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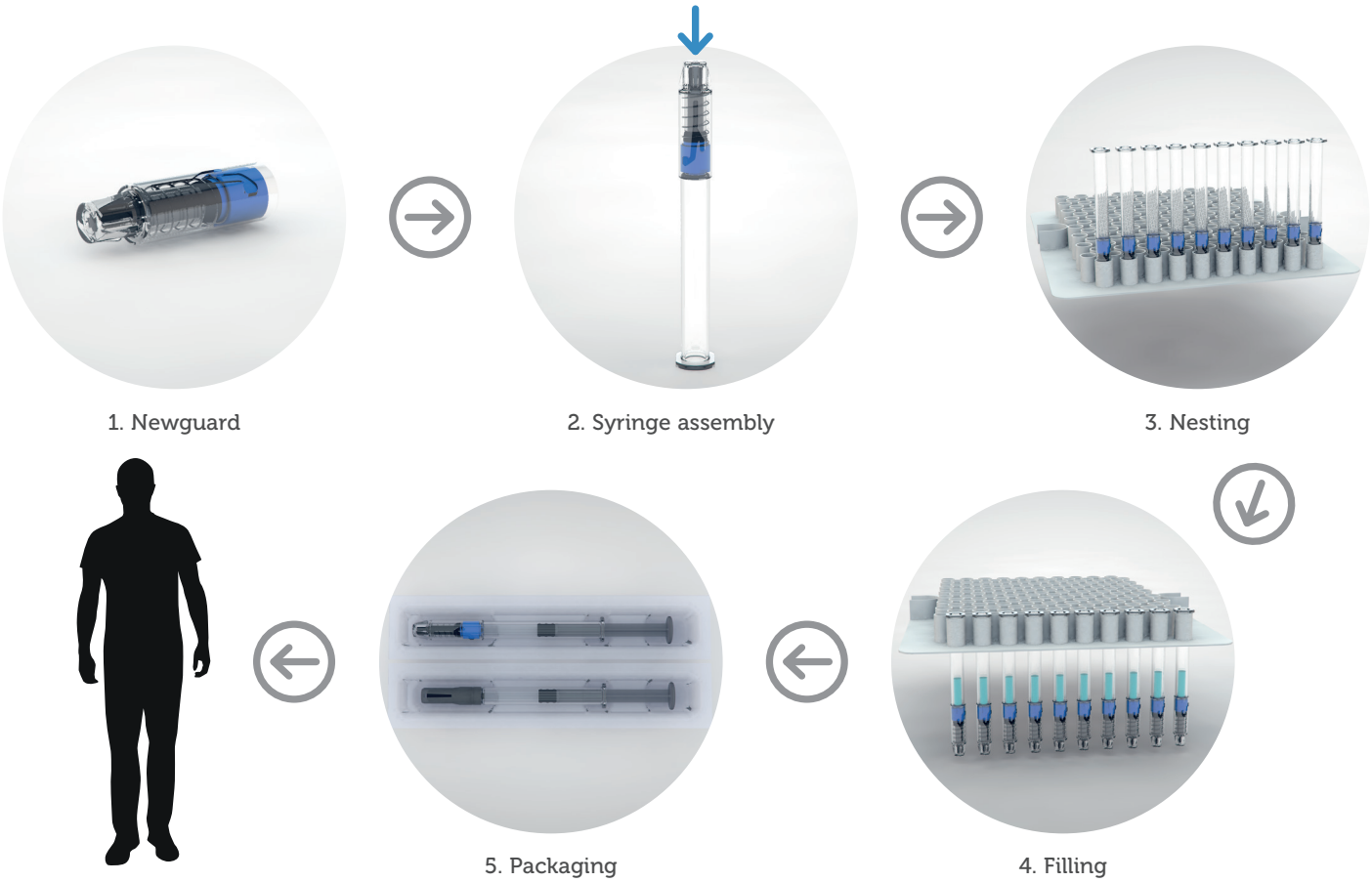

Figure 1: Newguard assembly process.

"After finalising several major steps of the development process, the Newguard design has been finalised and currently offers recognised technological advantages for optimal patient comfort."

There were numerous challenges to design a system that could both answer customers' requirements and that could be integrated into pharmaceutical processes with easy validation and limited impacts on regulatory aspects.

The user-friendly Newguard device is a system designed to be compatible with any standard PFS. It combines two functions in a single product: a rigid needle shield and a safety device. This all-in-one concept is highly appreciated by end-users, providing a reliable safety solution in a compact format.

The Up and Coming Standard Device On the PFS Market

Biocorp aims to work on innovative and cost-effective solutions. By adding Newguard to the syringe, every step of the PFS production process remains unchanged. Indeed, Newguard is produced and assembled at Biocorp's manufacturing site and then shipped to glass manufacturing partners for final assembly (Figure 1). The model is very similar to the existing model of assembling a rigid needle shield (RNS) to a standard syringe. After the nesting process of these assembled syringes, they will then go through the ethylene oxide (EtO) sterilisation process before being shipped to the end pharma customer. As Biocorp uses standard nest and tub formats, the filling process is also similar on the customer filling line, reducing the upfront conversion cost from a customer's previous safety system to Newguard.

After finalising several major steps of the development process, the Newguard design has been frozen and currently offers recognised technological advantages for optimal patient comfort. During this phase, Biocorp had extensive interaction with major technical partners to propose a ready-to-use product for pharma companies. Biocorp is now fully engaged with implementing an ambitious industrial model to serve a large market.

From Designing to Manufacturing

Biocorp's strength is not to deliver a mere concept, but specifically to take into consideration the design for manufacturing and industrialisation process from the very beginning of development. As a vertically integrated structure, Biocorp puts an emphasis on lean and effective collaboration between R&D and industrialisation teams to pave the way for an efficient manufacturing process.

This vertical integration is in Biocorp's DNA and offers a very specific positioning of the company within the drug delivery technology landscape.

Biocorp's Easylog has also been developed and moved along via the same methodology.

EASYLOG – IMPROVING PATIENTS' COMPLIANCE

Easylog is a smart cap compatible with all pen injectors that captures the exact dose dialled and delivered to the patient, together with time and date, and transfers that data automatically to a mobile app, utilising Bluetooth technology (Figure 2). Easylog is representative of Biocorp's "from design to production" approach.

Figure 2: Easylog, the connected add-on device for pen injectors.

"Easylog will be ready for distribution in the coming months. CE Mark and US FDA applications will be filed for the first ones before the end of the year."

The final assembly process relies on Biocorp's internal capacities together with the support of leading electronics integrators. Biocorp sees great benefits in manufacturing the first series of devices itself: it allows the industrial team to validate the production equipment, identify and correct any production incident and master the process, before potentially relying on external providers once the production volume increases.

Focus On What Really Matters for Patients and All Healthcare Stakeholders

Across the different therapeutic areas Biocorp is working in, diabetes and insulin injection is the first where the value of Easylog has been widely recognised, being integrated in a global ecosystem where diagnosis, insulin delivery and coaching advice will form a revolutionary offer to the patient.

Based on strong market knowledge and evidence collected from patients and healthcare providers (HCPs), the team mainly focuses on the most valuable and relevant functionalities for patients. For instance, right from the early stage of development, the team focused on the most critical factor for pen injector monitoring: capturing the exact dose delivered by the patient together with the time and date. The design of the device also allows for proper differentiation between priming doses and injection doses – delivering the patient or the HCP the injection data only.

"Easylog is of huge benefit, as it circumvents the danger of a patient forgetting their logbook and relieves the burden of constantly keeping track and reporting their doses, knowing that this effort is taken care of automatically and accurately by the Easylog connected device."

This data is key information for the patients, therefore Easylog is of huge benefit, as it circumvents the danger of a patient forgetting their logbook and relieves the burden of constantly keeping track and reporting their doses, knowing that this effort is taken care of automatically and accurately by the Easylog connected device. It's also crucial for HCPs, who can get reliable information thanks to Easylog's accurate recordings, improving the precision of the data on which they can base their diagnosis, for instance the measurement of the impact of the evolution of insulin dosages among their diabetic patients. The quality of their diagnosis and support of the patient depends on this key factor.

But beyond the traditional duo of patients and HCPs, many actors, such as blood glucose monitoring (BGM) and continuous glucose monitoring (CGM) actors, pharma companies, drug delivery networks and probably payers as well in the near future, are increasingly involved in the diabetes management space and propose a revolutionary approach: the "closed-loop system" or "semi-closed-loop system". The principle is to pull all the information and data from key devices and solutions involved in the management of diabetes (glucometers, titration solutions, coaching, activity trackers, dietary solutions, pen injectors and/or pumps) and gather them in a single platform for analysis, support and real time decisions. It goes without saying that the value of the entire service relies on the accuracy of the information reported; analytics and algorithms are only as good as the input data they utilise. Biocorp intends to be part of this effort and has already built strong connections with some of these players to bring Easylog on board. The 100% accuracy of the system is the key selling point for Biocorp's partners, who want to feed their systems with input data to provide the most relevant analysis and the best level of services.

Device to be Launched in 2019

Easylog will be ready for distribution in the coming months. First CE Mark and US FDA applications will be filed for the first before the end of the year. Easylog will cover all the major insulin pen platforms on the market. After Easylog gets approval from the regulatory authorities, Biocorp will commercialise the solution with partners, and connect to any diabetes support platforms, fulfilling its purpose of facilitating treatment management for the patient.

Nonetheless, whereas the Easylog device will be marketed first as an accessory to insulin pen platforms for diabetes, the add-on will be adapted to other indications. Biocorp has already engaged in developing tailored-made adaptations of Easylog for use in other therapeutic areas.

CONCLUSION

Over the years, Biocorp has been developing a firm idea of bringing innovative products to the market with a continuous mindset of making these devices simple. Newguard and Easylog reflect this philosophy and our long-term commitment for making patients' lives easier.

ABOUT THE COMPANY

For 20 years, Biocorp has been designing, developing and manufacturing medical devices for the pharmaceutical industry, enhancing drug reconstitution, safety, packaging and delivery. Today, Biocorp continues to innovate in medical plastics, bringing new solutions to the market such as the Newguard™, an integrated passive safety system for PFS compatible with nest, and Biopass, a reconstitution system with an integrated needle ready to inject.

Recognised for its expertise in device R&D, Biocorp has incorporated software development capacities to develop connected drug delivery systems, including the DataPen®, a reusable smart pen injector that automatically transmits data to a treatment mobile app, helping patients to manage their treatment, and a range of add-ons, smart sensors for existing drug delivery devices (pen injectors, MDIs).

In addition to its R&D activities, Biocorp also provides manufacturing services for plastic injection, process assembly and blister packaging.

ABOUT THE AUTHORS

Eric Dessertenne, Biocorp's Chief Operating Officer, holds a pharmaceutical degree from the University of Clermont-Ferrand (France), an MBA from ESSEC Business School (Paris, France) and is a graduate of the Therapeutic Chair of Innovation at ESSEC Business School. He began his career in the pharmaceutical industry working for Servier in France in the Corporate Strategy department and then moved to the Chinese subsidiary in Beijing, where he handled positions in the marketing and sales force department. Mr Dessertenne then joined LEK Consulting where he worked as a consultant in the Life Sciences and Private Equity practices. In 2014, he brought his experience and insights on market opportunities to Biocorp as Head of Business Development & Commercial Operations.

Philippe Lesaulnier is Business Development Manager at Biocorp, in charge of finding opportunities for non-connected devices from Biocorp's range and customised solutions for pharmaceutical companies. Operating in the pharmaceutical packaging sector for 25 years, Philippe has worked for companies like West, Rexam and Gerresheimer, in charge of major pharmaceutical accounts on a worldwide basis. Specialised in primary packaging for parenteral products, he has a combined technical background (electronics and mechanics) and numerous business experiences.

Arnaud Guillet is Business Development Manager at Biocorp, in charge of finding partnerships and license opportunities for Biocorp's range of connected devices. Previously, Guillet worked for a healthcare consulting firm with a strong focus on connected health strategies for pharma and insurance companies and has additional past experience in the pharmaceutical industry (with Sanofi) and the insurance industry (with AXA). He graduated from HEC Paris, a major European business school.

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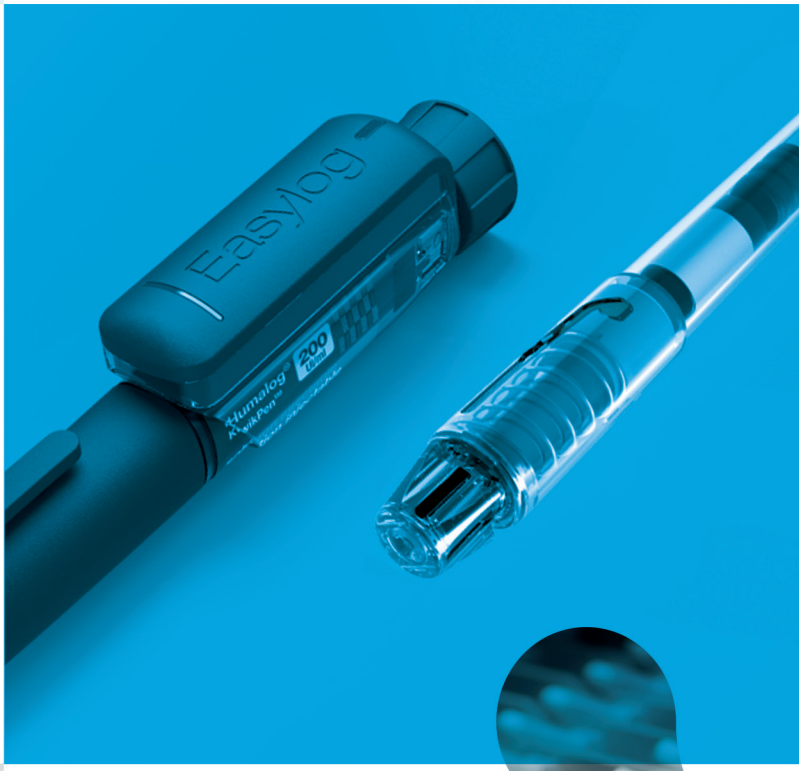

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INJECTION DEVICES & PAIN PERCEPTION

In this article, Severine Duband, Category Manager, Nemera, discusses the issue of patient comfort and pain perception in relation to injectable drug delivery and how the features of Nemera's two-step autoinjector, Safelia®, help take on this challenge.

Based on a presentation given by Séverine Duband at SMi's Prefilled Syringes West Coast Conference, San Diego, CA, US, June 4-5, 2018.

INTRODUCTION

In today's healthcare world, there is an ever-increasing emphasis on patient-centricity. A key aspect of this is pain perception; in order to be truly patient-centric, we must seek to minimise the pain experienced by the patient. With the shift towards moving healthcare out of the clinical setting and into the home as much as possible, designing devices with minimal pain perception becomes important than ever before, as it has a direct impact on a patient's willingness to administer their prescribed treatment.

> "With the shift towards moving healthcare out of the clinical setting and into the home as much as possible, designing devices with minimal pain perception will become more important than ever before."

FACTORS INFLUENCING PAIN PERCEPTION

The factors that play into the pain a patient perceives when administering a drug can be broken up into three categories based on their origin:

- The drug
- The user
- The device.

Factors Originating from the Drug

The first factor defined by the drug is the required volume to be injected. When considering prefilled syringes and autoinjectors, which typically inject their full payload in ten seconds or less, pain is most frequently associated with filling volumes of greater than 2.5 mL. Such devices rarely go above these volumes, with modern biologics requiring higher fill volumes targeting the wearable injector space, which tackles this problem via injection speed instead.

Secondly the formulation needs to be considered. There is limited relevant data on this subject, however it can be said that certain characteristics of formulation do have an impact on pain perception. One of the most notable of these, especially given the biologics market, is viscosity. Another factor known to have a direct impact on pain perception is the pH of a formulation.

Finally of consideration here is the injection site defined by the drug. The hypodermis is a highly variable tissue, significantly differing across body sites and skin types. For example, injection in the thigh is associated with a lower pain perception than injection in the abdomen. A secondary factor to this is injection depth, which may also play a role in how painful the injection is.

Factors Originating from the User

Injection speed is primarily a user-defined factor but is intrinsically linked to injection volume and can be influenced by device design. Slower injections are considered to

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be less painful. For example, 2 mL injected over 10 seconds would be more painful than 2 mL over 15 seconds, but less painful than 2 mL injected over 5 seconds. The total time is not the only aspect to consider however, the speed profile, in particular the beginning and end of the injection, also plays a role.

The temperature of a drug is another factor. Many drugs require refrigeration for storage but should be injected at room temperature to minimise pain perception. Patients often fail to follow instructions for use (IFU) in this regard and end up increasing the pain they experience because of it.

The patient themself is, naturally, a factor in this category. Every patient is unique, and part of that is how sensitive they are to injection pain. There are myriad aspects that play into this, as it is often a subjective problem. A patient may experience higher pain because they are tense due to unfamiliarity with a device or simply because they have a lower pain threshold. Training is a potential solution to the former scenario and a pre-treatment with anaesthetic is a possibility for the latter.

User skill is the last factor originating from the user to mention. This is another ill-defined factor, with little in the way of significant data to suggest how much of an impact it has. However, it is worth mentioning that for a device to be patient-centric, it should aim to minimise the skill level required for optimal use and ensure that painful mistakes, such as needlestick injury, are rare or impossible.

Figure 1: Nemera's Safelia® two-step autoinjector.

Factors Originating from the Device

When discussing injection devices, the most obvious device-derived factor influencing pain perception is the needle itself. Thinner needles with five bevels are associated with lower pain perception. The needle insertion speed is a difficult factor, as it varies from patient to patient whether faster or slower insertion is associated with less pain.

The device type may also be a factor, although no relevant clinical data is available. It is however worth considering that patients may display a preference for prefilled syringes, pen injectors or autoinjectors and subjectively associate their favourite with less pain. The device type also defines the designer's ability to build in systems to control other factors.

Device human factors studies also show that a device without proper feedback leads to patient anxiety and stress, thus often increasing pain perception. To minimise pain perception a patient should be able to be sure that the needle has been inserted correctly, when an injection starts and finishes and that the full payload of drug has been delivered, all of which should be done in a way that is not upsetting or disturbing for the patient.

NEMERA'S SOLUTION – SAFELIA®

To optimise patient comfort, Nemera has designed the award-winning Safelia® two-step autoinjector (Figure 1). Safelia® works by the patient simply removing the rigid needle shield and applying the autoinjector to the skin, with a single click signalling proper needle insertion at the start of injection and a second click to signal complete delivery at the end of injection (Figure 2). Safelia® is compatible with 1 mL and 2.25 mL prefilled syringes, is able to deliver extremely viscous (>100 Cp) formulations and is highly customisable to formulation and patient requirements.

> "To optimise patient comfort, Nemera has designed the award-winning Safelia® two-step autoinjector."

Safelia® has been designed to optimise patients' self-injection experience whilst allowing for tailoring of the injection to deliver even the most challenging drugs. What makes Safelia® different from other autoinjectors?

1. A powerful engine – To deliver viscous formulations through thinner needles in 15 seconds or less.
2. Limits the risk of glass breakage – Force transmitted on the syringe shoulder instead of the flange.
3. Delivery of the right dose at the right depth – Disconnection between the needle insertion and the injection.
4. Thinner needles for patient comfort – Reduced needle gauge and tailored needle insertion and injection speed.

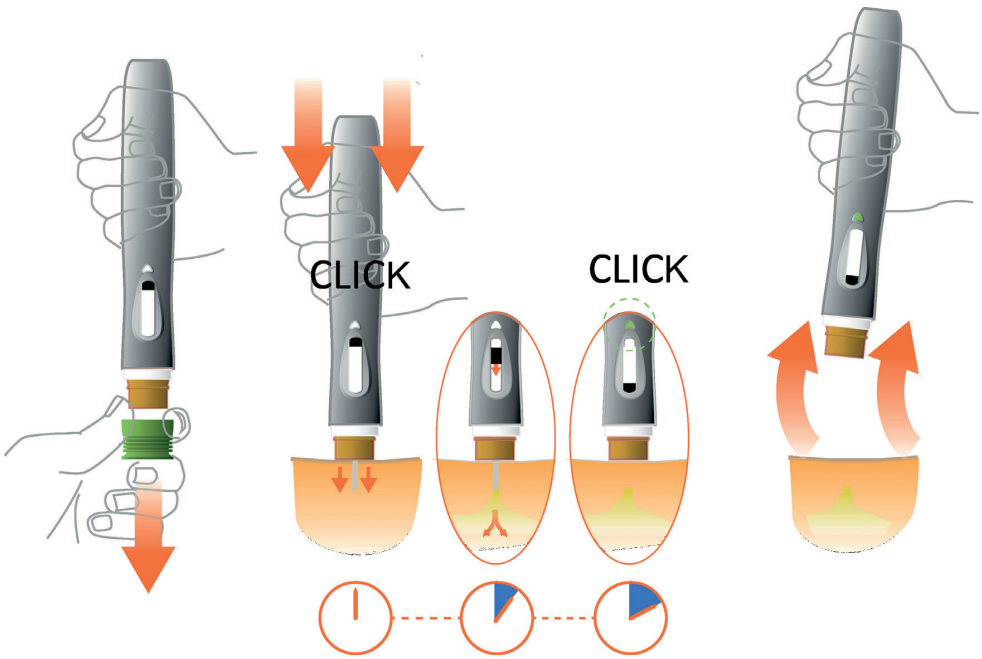

Figure 2: Operation of Safelia®.

5. Safety – The needle is never exposed throughout automatic needle insertion, delivery and needle retraction.
6. Ergonomic and easy to handle – for optimal patient comfort.

Safelia® uses a cam-based design in order to enable control of several injection process parameters (Figure 3). The cam allows tailoring of both needle insertion and injection speeds, as well as disconnecting needle insertion from the injection itself, which allows for fine control of the needle insertion depth. These factors are key in being able to design in lower pain perception for patients, along with more obvious factors like Safelia's ability to use thinner needles.

CONCLUSION

Whilst there is little in the way of concrete data concerning patient pain perception due to its highly subjective and variable nature, it is nonetheless a key factor to manage when designing a patient-centric device. Several factors affecting pain perception can be influenced by the device design, such as thinner needles, controlled needle insertion speed, precise injection depth and tailored injection profiles. There are further factors that require exploration, but Nemera has made a strong start with its Safelia® platform.

ABOUT THE COMPANY

Nemera is a world leader in the design, development and manufacture of drug delivery devices for the pharmaceutical, biotechnology and 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).

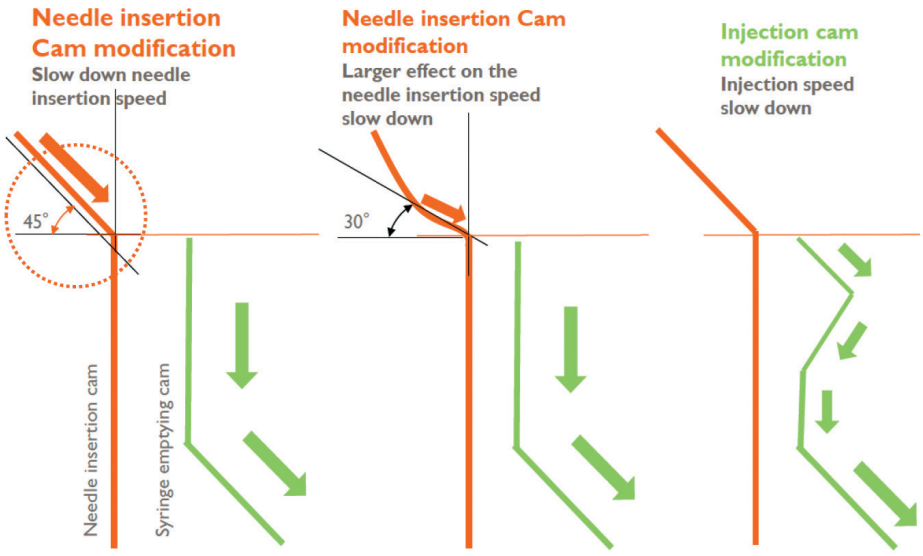

Figure 3: Safelia's cam-based design.

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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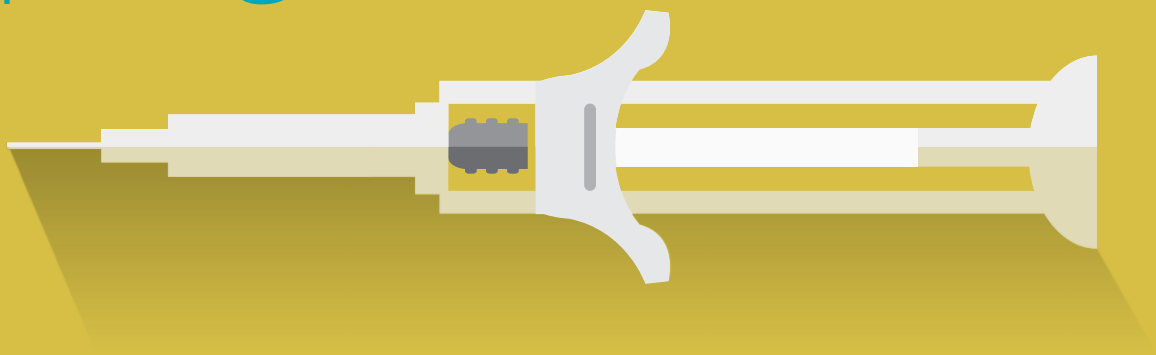

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PATIENT-CENTRICITY – A WINNING FORMULA

In this article, Justin Schroeder, Senior Executive Director of Global Marketing and Design at PCI Pharma Services, discusses patient-centricity, particularly how it relates to clinical trials in the modern global landscape of the pharmaceutical industry.

There has been considerable discussion about the concept of patient-centricity in the pharmaceutical community. The industry has taken a collective pause in an effort to re-evaluate and rethink longstanding approaches to drug development and commercialisation, with attention being recalibrated on the ultimate goal: making it easier for the patient to reach improved health outcomes. This perspective is underpinned by the recognition that what is best for the patient will lead to beneficial outcomes for all stakeholders, including the pharmaceutical company, the healthcare provider and the supporting community of associated service providers.

There is a famous quote from former US Surgeon General, C. Everett Koop: "Drugs don't work in people who don't take them." It is estimated that less than one third of all prescriptions written are actually filled at the pharmacy by patients. Wide ranging studies have shown medication adherence rates for life-threatening diseases including diabetes, heart disease and oncology can be as low as 30–40%. With the benefit of interventional techniques and developing technologies, adherence rates have been shown to improve, however these programmes have not been broadly adopted within the industry at scale and have not had significant impact decreasing the overall cost of healthcare, nor have they benefitted large populations.

Patients may be non-adherent, some consciously so and some unconsciously, for a variety of reasons. Certainly, we are all admittedly forgetful when it comes to taking our medicine on time or being diligent about timely refills of those prescriptions. Cost can also be a significant factor, whereby patients will consciously stretch out their medication supply or simply go off therapy. In either instance, doing so will hamper the health impact of their prescribed therapy or worse, in a case such as taking a drug holiday while prescribed an anticoagulant, potentially put their life in jeopardy.

> "Wide ranging studies have shown medication adherence rates for life-threatening diseases including diabetes, heart disease and oncology can be as low as 30–40%."

Other considerations may be unwanted side-effects or a lack of understanding about how to take the medication optimally, such as with food or alternatively avoiding food for some period of time, resulting in reduced effectiveness. Fear, or general lack of understanding, can also inhibit the path to improved health by affecting the patient's perception of the medication and their willingness to be compliant.

Likewise, the patient may not physically experience the benefit of the drug, and in some instances may have a negative perception due to the unwanted side-effects. Hypertension is the classic example where a patient may have high blood pressure, but generally not feel the effects of their disease. However, they may experience considerably unpleasant side-effects as a result of their course of treatment. A similar scenario plays out in popular cholesterol-lowering medications. By scale, these two examples are noteworthy, as in the

> "Fear, or general lack of understanding, can also inhibit the path to improved health, by affecting the patient's perception of the medication and their willingness to be compliant."

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"When one looks at the situation from a broader perspective, the focus on patient-centricity clearly generates tangible value and outweighs the short-term inefficiencies created by opting for a solution solely on speed or cost."

US, with a population of more than 300 million people comprised of 75% adults, it is estimated that one in every three adults has hypertension, while 10–20% of adults have high cholesterol. A large-scale patient-centric approach to benefit medication adherence would have significant positive health and economic impacts.

PATIENT-CENTRICITY IN CLINICAL TRIALS

In addition to challenges with patient adherence to medication in clinical trials, sponsors and study organisers are also constantly faced with hurdles such as patient recruitment and patient retention. As the industry is tasked with further expediting drug development and decreasing clinical study duration, the US FDA is increasingly requiring additional studies and additional data to prove long-term safety and comparative effectiveness, including post-market studies once the drug is commercially available in the market. This trend is coupled with an increasing percentage of drugs being brought to market for very specialised disease states and narrow therapeutic indications. This wave of specialised medicines and the ongoing need for treatment-naïve candidates, paired with cost pressures in the R&D sector more broadly, has increased the use of multi-national studies. These complex studies in turn create the requirement for multi-language labelling. This can result in the creation of investigational pharmaceutical product (IMP) study materials that may contain upwards of 16–20 languages on a single label.

Clinical trial professionals are left to balance all of these demands and creatively identify initiatives to keep the focus on the patient. At a surface level, these competing priorities may seem to be in direct conflict. However, when one looks at the situation from a broader perspective, the focus on patient-centricity clearly generates tangible value and outweighs the short-term inefficiencies created by opting for a solution solely on speed or cost.

PATIENT-CENTRICITY IN PACKAGE DESIGN

A practical example of patient-centricity in action can be found in package selection for investigational study. When looking to initiate a clinical study, a sponsor company may be evaluating choosing a bottle or a unit-dose blister in a calendarised format for their clinical study material. Looking simply at the short-term criteria of expediting material for study initiation, where a difference of mere weeks or days can be considerable, the path of selecting a bottle would be a logical solution. It is a cost-effective packaging option, it is relatively "off the shelf" in its availability, it can be hand-filled by a clinical packager with minimal start-up costs, it has an acceptable stability profile for barrier properties and is proven to be child resistant. Conversely, when one evaluates the development of unit-dose adherence packaging, there may be a longer lead time for development and it might be more costly to produce. If looking from a short-term perspective and the immediate pressures of cost and expediting, the choice leaves little room for debate. However, if the sponsor company is taking a holistic approach with a focus on patient-centricity, the broader economics absolutely point to use of the patient-centric package.

"Utilisation of a calendarised unit-dose blister format, or compliance/adherence packaging, offers sponsor companies considerable benefit in both addressing the needs of the patient as well as positively impacting the quality of the data."

Utilisation of a calendarised unit-dose blister format, or compliance/adherence packaging, offers sponsor companies considerable benefit in both addressing the needs of the patient as well as positively impacting the quality of the data, leading to more efficient studies, and lowering total delivered cost. The use of this style of package allows patients to take medication exactly as prescribed and track their usage, much more easily than with a bulk approach in a bottle format. Physicians can capture vital information on the package, including the specific date to start the therapy and any other pertinent notes for the patient. With the returned package, the patient can physically demonstrate to clinical providers that they have taken the product as prescribed. Furthermore, technologies are available that can provide real-time tracking of patient dosing, allowing for clinical interventions to ensure proper adherence while the study is in progress.

These technologies and principles extend to other delivery forms, including injectables. Increasingly, drug delivery is being driven to allow patients freedom to dose away from the clinical setting, creating new wrinkles and challenges in the way of ensuring proper compliance and adherence, ensuring proper self-administration and realising maximum benefit. The recent scandal with EpiPen raised awareness about how Mylan's technology had substantially changed the market for emergency epinephrine administration and what a distance it had created from its competitors. Amazing new developments are being developed in commercialised prefilled syringes, autoinjectors and pen technologies, as well as new forms such as wearable injectors and infusion pumps. Technologies such as Amgen's Neulasta® (pegfilgrastim) Onpro® demonstrate that drug companies are truly listening to patients and delivering patient-centric solutions to ease the burden of the traditional medical experience. Further developments are being realised in connected health, an exciting new frontier.

The ability to prompt, monitor and even track real-time information is a powerful tool. Likewise, with the advent of Bluetooth and near-field communication (NFC) technologies, packages with integrated technology can capture real-time information about side effects or other vital information as patients take the medication over the course of treatment.

Better adherence leads to healthier patients, and more valuable study data, and may lead to opportunities to change the way studies are administered, such as adaptive trial design. Poor adherence can be rectified and corrected as it happens. Better information gathering can lead to improved patient retention, a significant cost in clinical trial administration and a persistent challenge in study duration. It is estimated that in the industry, clinical studies have, on average, a 30% drop-out rate. With more adherent investigational study patients, health outcomes will be improved and better retention will be realised, translating into reduced total delivered cost, more valuable data generated, and studies executed more efficiently.

PATIENT-CENTRICITY IN CLINICAL SUPPLY CHAIN LOGISTICS

Another area of focus for realising patient-centricity in clinical trials is in the area of study design and administration. Considerable interest is being focused in "direct-to-patient" models, where patients may minimise, or in some instances entirely avoid, the need to come to a hospital or clinic to receive the study drug, as well as to provide critical health feedback. In this scenario patients are engaged by clinical trial or healthcare professionals in a home setting and the study drug is physically delivered to their home by a trained specialist. Clearly this model is not applicable for all studies and disease states, but for certain programmes there can be considerable benefit to the patient and the study. In certain geographies, patients in a traditional clinical study may have to travel significant distances to participate in a study, which can considerably hamper patient recruitment and retention. In a direct-to-patient model, the study effectively comes to them. This model may increase the cost of study administration for the sponsor company. However by executing the study in a more patient-focused approach the sponsor company can realise significant benefit through patient recruitment and retention, again translating into better data, more efficient studies and a faster path to completion.

"In certain geographies, patients in a traditional clinical study may have to travel significant distances to participate in a study, which can considerably hamper patient recruitment and retention. In a direct-to-patient model, the study effectively comes to them."

PATIENT-CENTRICITY IN A GLOBAL WORLD

One of the significant challenges in taking a patient-centric approach to clinical study execution is the growth in multi-national study execution. Often supplies are designed to pool so that multiple languages are provided, such that materials can be directed to individual countries as needed. This scenario forces sponsor companies either to manage a multitude of language specific supplies, or focus on common supplies where they are forced to condense information due to the shear amount of text being added, often squeezed into a multi-page booklet. Careful consideration must be paid to graphics common to all languages and cultures to ensure patients can clearly comprehend considerably distilled opening instructions, dosing regimens and other key information. Rather than a traditional pooled supply approach, some companies have developed newer strategies for "just-in-time" (JIT) labelling or late-stage customisation logistics, whereby they label study materials according to country-specific requirements at the time of drug dispatch. This can reduce the complexity of a scenario where they would be trying to accommodate 16 different languages on the same label in a multi-page booklet approach. This JIT strategy may decentralise supplies, but may bring other benefits in meeting the language and cultural needs of patients in their geography, as well as those of the study administration.

PATIENT FOCUS YIELDS POWERFUL RESULTS

The industry is in the infancy of its patient-centricity journey, but it is clear that, with a focus on the patient, many tangible benefits are realised by drug companies in their development and commercialisation of life-saving medicines. Encouraging relationships are being formed with patient advocacy groups, providing valuable insights for drug development and clinical trial administration, resulting in considerable breakthroughs being brought to market. With so many significant advances over the past decade, it is exciting to see where this patient-focused journey will lead, as new patient breakthroughs are happening every day.

ABOUT THE COMPANY

The global healthcare industry trusts PCI for drug development solutions that increase their products' speed to market and opportunities for commercial success. PCI has proven experience that comes with more than 50 successful product launches a year and over five decades in the healthcare business. Leading technology and continued investment enable the company to address global development needs throughout the product lifecycle — from Phase I clinical trials through commercialisation and ongoing supply.

ABOUT THE AUTHOR

Justin Schroeder is Senior Executive Director of Global Marketing and Design at PCI Pharma Services, responsible for global marketing, creative package design and new account development, with a focus on the development and commercialisation of new products. Mr Schroeder has over 20 years' experience in outsourced pharma services in various roles, including engineering, project management, marketing and development. He holds a Bachelor of Science from the School of Packaging at Michigan State University, US, and an MBA in marketing from Northern Illinois University, US. Mr Schroeder is a certified Packaging Professional from the Institute of Packaging Professionals, US, and is Vice-Chairman of the US Healthcare Compliance Packaging Council.

A SMART PLATFORM TECHNOLOGY FOR THE FOUR-STEP INJECTION PROCESS

For a drug delivery device to be successful today, it needs to be able to be adapted to an ever changing and evolving set of market and user needs, whilst remaining financially attractive. Here, Tobias Morlok, Head of Development, Medical Devices, /H&B/ Electronic, explains how /H&B/'s patented device with toothed gearing rises to this challenge.

INTRODUCTION

Development of new devices, or even just features, is very often a slower process than the flow of constantly changing customer and patient expectations. Hence, sometimes having a thorough understanding of current needs, upcoming requirements and future growth opportunities is still insufficient for keeping products up to date. In addition, companies also need to have options ready and available in order to react quickly, in a customer-friendly way, to the growing and continuously changing pharmaceuticals market.

To meet the challenges presented by this rapidly shifting market, /H&B/ has developed high-quality injection devices with toothed gearing. These devices are the logical next step forward after more than 20 years of developing innovative injection systems with patented solutions for reusable mechanical and electromechanical devices. All of the recent devices utilise /H&B/'s proven "Four-Step-Technology" – insertion, injection, dwell time and needle withdrawal, as discussed in /H&B/'s article in ONdrugDelivery's May 2018 "Injectable Drug Delivery: Devices Focus" issue.

"To meet the challenges presented by this rapidly shifting market, /H&B/ has developed high-quality injection devices with toothed gearing."

INJECTION DEVICES WITH TOOTHED GEARING

Here follows an overview of the features and possible variations of /H&B/'s patented mechanic for injection devices with toothed gearing to illustrate the many possibilities the design offers to customers to suit a variety of needs. There are too many aspects to cover each with sufficient depth, so a selection of the most important has been made.

Technical Implementation

The injection device was originally developed and optimised for single use, but with only a small number of changes it is equally well suited to a reusable system. One of its major advantages is that it contains only a few components, which not only makes the system financially attractive but also limits the potential sources of error.

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The device's defining element is the gear transmission:

- Needle insertion
- Decoupling of the syringe holder and ram holder
- Injection of medication
- Dwell time
- Recoupling of the syringe holder
- Needle retraction.

These elements all work together to perform the "Four-Step-Technology" injection process. This major feature was achieved with a reversal of the rotation direction of the gearwheel by fixed toothings, arranged on opposite sides. A damping element is integrated in the housing of the device which enables constant operational force.

Rapid needle insertion is initiated after exceeding a required starting force in the manual version. To facilitate this procedure the device can be equipped with a spring to replace the manual operation. The damping adapts to the applied force to ensure the actuation element operates at a constant, consistent speed. The insertion depth is also adjustable depending on the medication or site of injection. The insertion depth can be pre-set or made adjustable by the user.

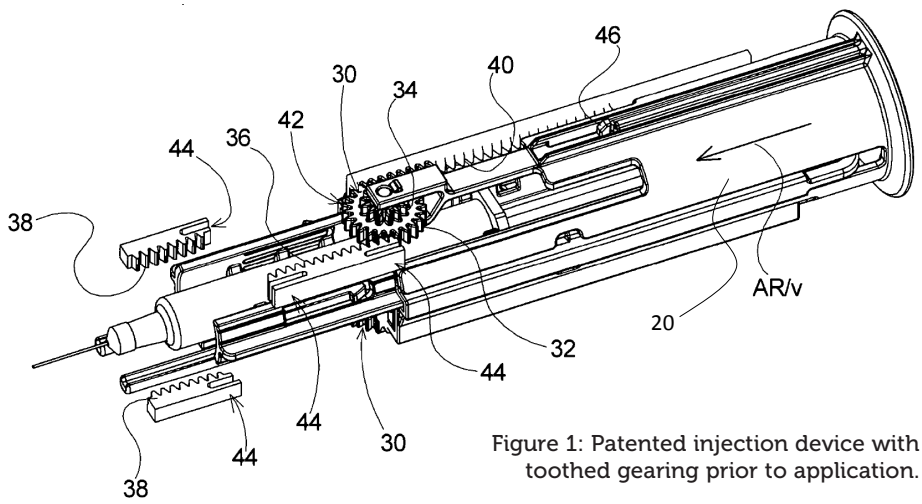

Figure 1: Patented injection device with toothed gearing prior to application.

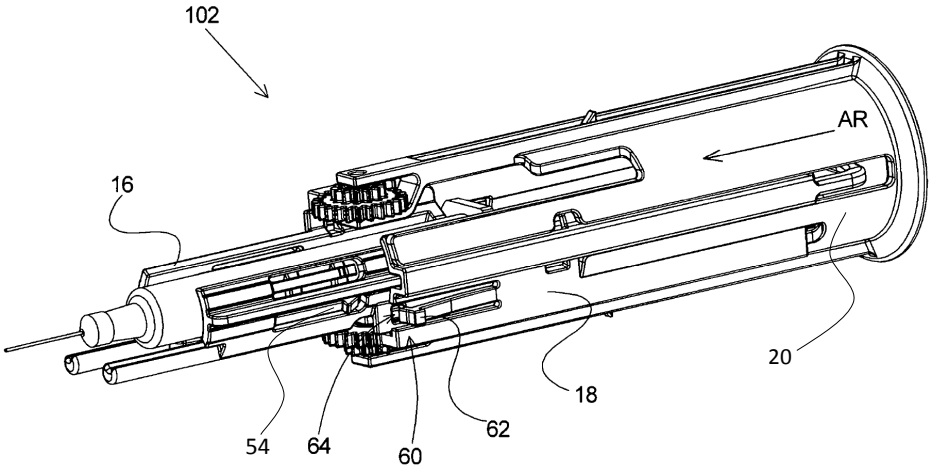

Figure 2: Patented injection device with toothed gearing during application.

The Injection Process

The needle is never visible to the patient. That not only prevents contamination, but also – even more importantly – hinders needle phobia and prevents patients from hesitating during the injection process. If desired, a protection cap can be attached to the needle to avoid any accidental or incorrect use. The required activation force can be adapted and must be exceeded to activate the device.

The device has an integrated damping element for constant progress of applied force. This is especially important in case of manual use, as even in this case there is almost no noticeable difference from one step to the next. The movement itself can be adapted in its behaviour, depending on the viscosity of the medication, the desired speed of injection and, last but not least, the abilities of the patient.

At the beginning of the injection process the actuation element (20) is being moved with a force in the direction AR (Figure 1). The two-tier gearwheel (30) meshes with the first housing-side toothing (36) and the ram-holder-side toothing (40). The effect is that the ram holder (18) moves with double the speed of the actuation element (20) in the direction AR (Figure 2).

The ram holder (18) is linked through an engagement element (62) with the syringe holder (16). The engagement element (62) is being moved alongside the housing (not shown).

After the insertion stroke is completed (Figure 2), the engagement element (62) evades into a recess in the housing. That interrupts the interconnection between syringe holder (16) and ram holder (18). The ram holder (18) keeps on moving, empties the syringe and remains for a reasonable dwell time. This dwell time is adjustable over a wide range, using the relation between driving force, distance between the housing-side toothings and damping behaviour.

After the syringe is drained, the two-tier gearwheel (30) leaves the first housing-side toothing (36) – start of the dwell time – and then meshes with the second housing-side toothing (38) – end of the dwell time – but still stays in contact with the ram-holder-side toothing (40). This now opposing arrangement of the toothing together with the different sizes of the gearwheels (32) and (34) leads to a reversal of direction of the two-tier gearwheel (30) and thus to a withdrawal of the ram holder (18) against the moving direction AR. This retraction is facilitated by a reduction of the necessary driving force.

> "Of course, even these simple devices are equipped with /H&B/'s "Four-Step-Technology". The logical and simple working principle allows for the same intuitive handling as with a standard syringe."

The syringe holder (16), which attaches via a coupling arrangement (54) with the ram holder (18) after the injection, is consequently also pulled back and thus the needle is withdrawn.

To avoid any danger of injury by the needle, the syringe is locked in the end position. In single-use systems that final step prevents any further use. Reusable injection systems can be brought back into the starting position again after removal of the empty syringe or cartridge.

EXAMPLE DEVICE VARIATIONS

Manual Single-Use Device

Of course, even these simple devices (Figure 3) are equipped with /H&B/'s "Four-Step-Technology". The logical and simple working principle allows for the same intuitive handling as with a standard syringe.

The device is ready-to-use, with a prefilled syringe is already installed, so that the patient only has to remove the protection cap (optional), position the device on the desired spot and then – as with an ordinary syringe – press the plunger. The distance covered when pressing the plunger provides direct feedback about the progress of the injection and a safe fixation at the end position guarantees that there is no danger of injury.

For patients, healthcare providers and pharma companies who like to track injection parameters, such as date and hour or duration of injection, possibly on a smartphone health app, the device provides a characteristic and easy to perceive click sound for communication with the app.

With this model, there is an extensive variety of options the customer can choose from:

- The dwell time is adjustable according to a wide variety of requirements by adapting the distance between the housing-side toothings and the damping behaviour.
- The design and size of the device are adaptable to customers' and patients' wishes and needs.
- A viewing window to control the medication before application is mandatory, and a second viewing window to display the progress of the injection is optional.
- In cases where the medication has to be cooled constantly prior to use the devices could be constructed differently so they can be sent to the customer without the container. Container and syringe would be inserted in the devices on-site. That would save valuable space during shipping and storage.
- The devices are typically equipped with syringes; however, cartridges and dual-chamber cartridges can be used instead.

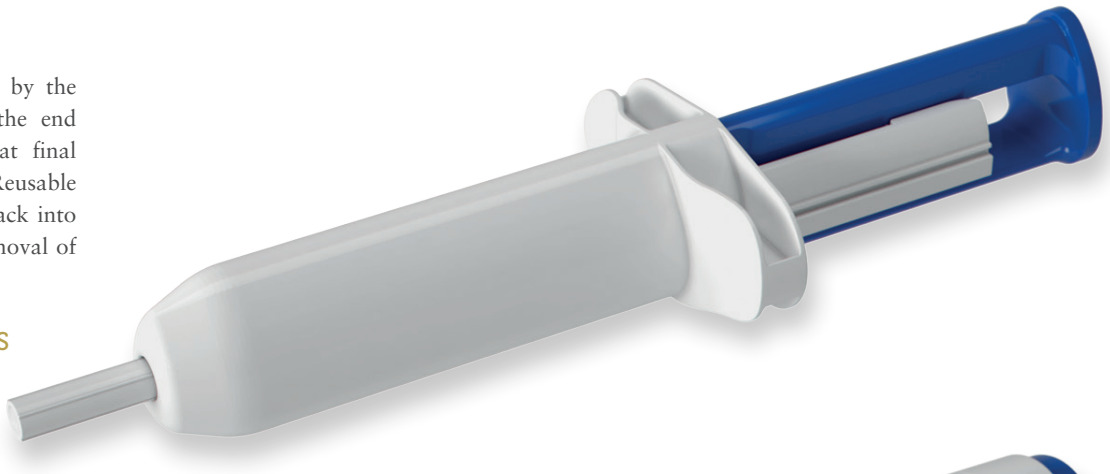

Figure 3: Manual single-use device.

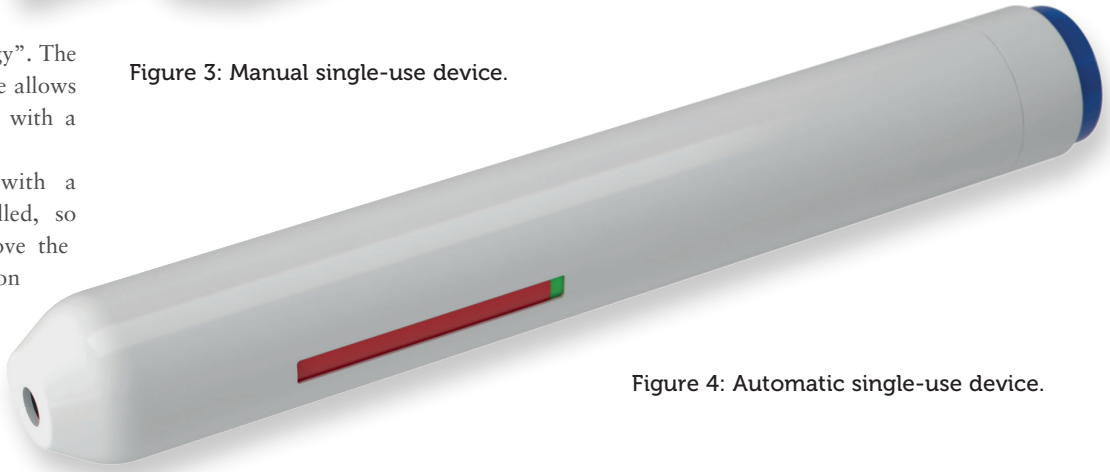

Figure 4: Automatic single-use device.

Automatic Single-Use Device

All of the automatic, single-use device features and possibilities are identical to the manual. The only difference is that the actuation element is activated by a start-button and driven by a spring, rather than manually by the user (Figure 4).

Reusable Injection Systems

Reusable injection systems use the same technology as the single-use systems. Both systems will be locked in the final position to prevent any misuse or injuries. However, the reusable device can be brought back into the starting position after removal of the syringe or cartridge. Only a few extra components have to be installed in the reusable devices. According to the material used for these components, more than 1000 injections are possible, if required.

CONCLUSION

With its variety of devices and the Four-Step-Technology /H&B/ already offers a wide range of products. However, further advances in design and manufacturing technology are necessary. The requirement to be able 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, output attained must not only meet the desired device specifications and market regulations, but also the requirements of the end-user.

One way to achieve that goal is to develop systems which provide maximum flexibility. With /H&B/'s patented technology of toothed gearing, its devices offer exactly that. Adaption to customers' needs can not only be achieved quickly, but can also be financially attractive.

"In an increasingly competitive landscape, output attained must not only meet the desired device specifications and market regulations, but also the requirements of the end-user."

Needless to say, with this system the safety and protection of end-users and healthcare professionals is guaranteed and meets the highest possible standards. /H&B/ has brought together product design and manufacturing engineering to create an injection system that will 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 metal and polymer hybrid components 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 – EN ISO 13485 and EU Directive 93/42 EEC Annex II.

/H&B/ is situated at the north rim of the Black Forest region in southern Germany. Its 13500 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 innovation 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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ANSWERING THE CONTAINMENT CONUNDRUM: QUALIFYING PREFILLABLE SOLUTIONS

In this article, Royce Brockett, Director, Product Management, at West Pharmaceutical Services, discusses the prefilled syringe market sector, how pharma companies looking to use a single drug product across multiple containment options face difficult issues, and how partnering with an experienced containment and delivery expert may be the solution to them.

When you think of injectable medication, a classic image may include a set of hands holding both a vial and a syringe to withdraw medication prior to injection. Advances in both drug products and self-injection options – including autoinjectors, pens and other self-injection devices – have helped to draw a new picture for injectable delivery (Figure 1).

While vials are still a preferred container format for many injectables, the use of a glass or polymer prefilled syringe (PFS) offers a variety of benefits, including ease of use thanks to a reduction in steps, less over-fill volume of the drug product to help reduce cost per dose and a more precise dosage to help ensure patient safety. Along with the rapid growth in biologic medicine, technical advances in containment and a rising patient preference for easy-to-use options for self-administration, these benefits have helped to fuel market growth for prefilled syringes.

"The use of a glass or polymer PFS offers a variety of benefits, including ease of use thanks to a reduction in steps, less over-fill volume of the drug product to help reduce cost per dose and a more precise dosage to help ensure patient safety."

Figure 1: Self-injection systems, such as the SelfDose® patient controlled injector, provide patients with an easy-to-use, safe and convenient option for self-administration, making them a popular option that may encourage brand loyalty and ensure product differentiation for pharmaceutical manufacturers.

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"Such systems present an array of containment challenges. Primary containment components, including syringe plungers, were typically made for manual injection, which can pose a problem for autoinjectors due to variability."

According to Pharmacircle (Encinitas, CA, US), more than 50% of drug products currently undergoing clinical development are likely to reach the market as injectable medications. Many of these products, including biologics such as monoclonal antibodies (mAbs), vaccines and anticoagulants, are large molecule solutions that need to be administered via parenteral injection to achieve the desired therapeutic effect. Many of these doses will suit common PFS sizes, including 1 mL and 2.25 mL syringe options, and may come to market in combination with an autoinjector or pen system that enables patient self-administration. In addition to ease of use, such devices offer patients safety and convenience, making them a popular option that may encourage brand loyalty and ensure product differentiation for pharmaceutical manufacturers.

But such systems present an array of containment challenges. Primary containment components, including syringe plungers, were typically made for manual injection, which can pose a problem for autoinjectors due to variability. In addition, as pharmaceutical manufacturers strive to make a fast move to market, the need to qualify a variety of containment options – including primary containment such as glass or cyclic-olefin polymer (COP) syringes, and secondary delivery options such as pens or autoinjectors across multiple syringe sizes – all while ensuring that a variety of regulatory requirements are met, can create additional challenges. To have a platform of delivery options available for a single drug product, pharmaceutical manufacturers are faced with the challenge of qualifying multiple containment options.

By aligning with the drug pipeline, selecting the proper materials for the drug product and the delivery system and managing the qualification process, pharmaceutical manufacturers can make a smooth move to market with an effective drug product and delivery system.

ALIGNING CONTAINMENT WITH THE DRUG PIPELINE

Whether preparing for clinical trials or preparing for drug product launch, different containment options may be needed to align with drugs in the pipeline. Characterisation and qualification of a variety of options can help to solve the containment conundrum and ensure a smooth transition from R&D testing, through clinical trials, to commercial scale up. Partnering with an expert in containment solutions and analytical testing can help ensure that the limitations of a drug product are known and can help to characterise and qualify a proper system that can be used throughout the drug product lifecycle.

Material Choice Makes a Difference

When characterising a system, pharmaceutical manufacturers must first look at the needs of the drug product itself and then the needs of the delivery system. For example, a drug product may be compatible with glass for primary containment, but the dose delivery requirement via an autoinjector may demand a force that would damage the syringe. In such a case, a polymer may offer the advantage of strength, tighter tolerances and improved functionality.

With a long history of use in the pharmaceutical industry, glass has many known benefits and is a well characterised choice for a variety of molecules. Multiple suppliers offer an array of glass syringes and elastomer components for PFS systems. However, these components may not be optimised for use in an autoinjector. Selecting the wrong component may result in breakage, or potential chemical interactions with tungsten or silicone oil used in the processing of glass syringes. While glass quality has increased, with many vendors offering syringes of greater strength, lower tungsten and more controlled silicone oil applications, these containers still pose a risk to certain drug products. With the complex and sensitive nature of many biologics, and as drug product viscosities increase, design factors for the complete systems will need to be thoroughly understood.

COPs offer advantages over glass in strength and break resistance (Figure 2). In addition, the systems are typically free of tungsten and silicone and may weather cold storage better than glass. Flexible design options also enable a wider variety of dose volume options, including 0.5 mL for ocular injection or up to 10 mL for viscous biologics that needs to be delivered over a longer period of time. However, COPs also have a few disadvantages, including scratching and less permeability, which could potentially alter a drug product.

MANAGING THE SELECTION PROCESS

The process of selecting and qualifying a component varies with the stage of the drug during the development lifecycle.

"The process of selecting and qualifying a component varies with the stage of the drug during the development lifecycle. During the preclinical process, component selection is critical, while ongoing technical and regulatory support are vital during commercial manufacturing scale up."

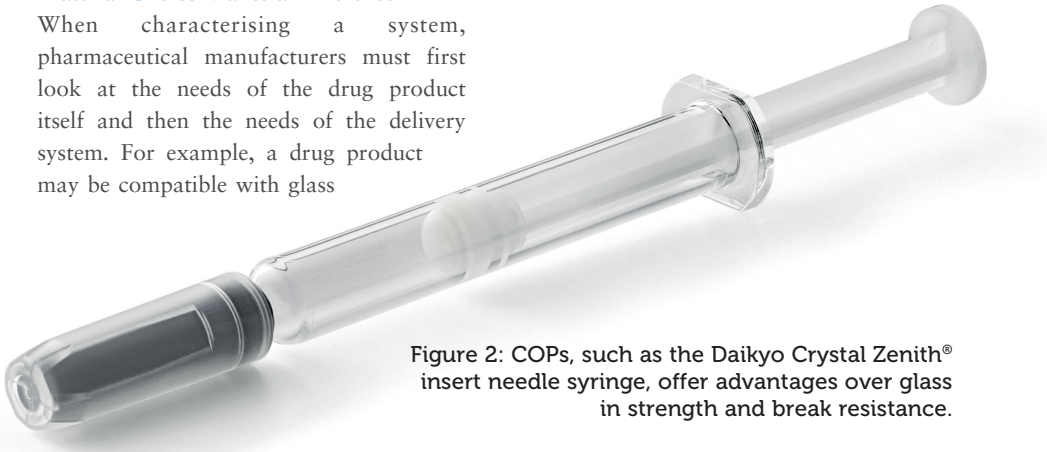

Figure 2: COPs, such as the Daikyo Crystal Zenith® insert needle syringe, offer advantages over glass in strength and break resistance.

During the preclinical process, component selection is critical, while ongoing technical and regulatory support are vital during commercial manufacturing scale up. West uses a four-stage interaction process to help its customers qualify a PFS system.

Stage 1: Preliminary Assessment

During the preclinical and development activities, the need to select, assess and procure parenteral packaging components is critical. A product requirement questionnaire can help to define the needs, while functional testing – including tests for container closure integrity, dimensional fit, break-loose and glide forces, and any other necessary performance evaluations – is critical to ultimate success.

West's NovaPure™ plungers are commonly recommended during preliminary assessment for biologic/protein-based drugs that need the highest level of drug product protection, performance and consistency in PFS delivery systems. NovaPure plunger characterisation includes comprehensive extractables and leachables studies, design controls with design history file and performance testing, all of which can be shared to support customer development activities.

Stage 2: Verification

At this stage, clinical supply begins and machinability assessments help to establish and optimise the filling line. Much of the verification stage is dedicated to process development and determining the needs for pilot-scale filling lines, inspection parameters and testing, and the evaluation of the target delivery system. Choosing the target delivery system for a drug application can be a complicated undertaking. While many drug products do not initially launch with a delivery device, it is important that the primary container selection aligns with the long-term lifecycle management strategy of the drug. Safety systems, autoinjectors and wearable injectors all have their own benefits as part of the delivery system and can be evaluated proactively as part of a device technology assessment.

Stage 3: Implementation

With the anticipation of a successful approval of the drug product and its delivery system, it's time to begin scale-up activities, including process transfer and verification and validation of process parameters on commercial-scale filling lines. Delivery system performance is also verified at this stage. As a leading partner in integrated containment and delivery, West can support these development activities and help mitigate risk across the container and delivery selection process.

Stage 4: Ongoing Support

At this stage, the primary focus is on ensuring the drug manufacturer's commercial manufacturing is uninterrupted by supply issues. Strategic inventory planning is critical, as is ongoing regulatory support for customers in the form of managing requests for West drug master files (DMFs) and responding to any agency questions.

CONCLUSION

As the industry continues to see growth for products developed for delivery via PFS, there is a trend for pharmaceutical companies to require deeper understanding of the drug delivery system as a whole, especially as the number of biologics in development continues to increase. Pharmaceutical manufacturers may find that partnership with a containment and delivery expert with in-house expertise in contract manufacturing will help mitigate risk and provide solutions, not only during development, but also around scale up, tooling and automation that will help to streamline the move to market.

Regardless of which delivery system is eventually selected, an integrated approach from R&D to clinical and commercial scale up is a best practice. By using high-quality components, a staged approach to testing and an in-house expert to build the delivery system, making the move to market becomes a matter of working the process – and not a containment conundrum.

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Daikyo Crystal Zenith® is a registered trademark of Daikyo Seiko, Ltd.

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ABOUT THE AUTHOR

Royce Brockett has 16 years of experience working in the pharmaceutical industry with a focus in sales and marketing. He is currently the Director, Product Management, Prefilled Systems & Delivery at West Pharmaceutical Services. His responsibilities include supporting business development efforts, defining new products, and executing marketing strategies. Mr Brockett has published articles related to sterilisation techniques for elastomer components, particle reduction strategies and cartridge technology. Prior to joining West, Mr Brockett held various positions within the sales and marketing organisation at AbbVie, Solvay, and Pfizer. He holds a BS in Biochemistry from Lehigh University and an MBA in Health Sector Management from Boston University.

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PLATFORM DEVICES AND THE PATIENT JOURNEY

In this article, Mark Tunkel, Partner and Business Development Director, Insight Product Development, discusses the benefits of mapping the patient journey when looking to select a platform device for a new drug-device combination product.

Whether you are looking to develop a novel device or select a platform solution, it should always begin with a thorough understanding of the patient journey. Having knowledge of the patient, their capabilities and limitations, and how they change over time is fuelled by a contextual understanding of their experiences. A map of the patient journey provides a very powerful tool to drive inputs and decisions, especially when utilised in the earliest stages of a development programme. For companies developing drugs, both branded and generic, for virtually any patient population, this process will inform the selection of platform solutions as well as generate design requirements for novel device development.

Additionally, the same information can be used to help enhance usability, adherence and provide differentiated solutions. These factors help to design the complete delivery system, including functional packaging, training strategies, instructions for use (IFU), quick reference guides and methods for longitudinal patient engagement.

> "Mapping the patient journey can be achieved by utilising a technique called applied ethnography. This method relies on a combination of interviews and in-context observations of practices, processes and experiences within the patient's home or any natural setting."

Mapping the patient journey can be achieved by utilising a technique called applied ethnography (Figure 1). This method relies on a combination of interviews and in-context observations of practices, processes and experiences within the patient's home or any natural setting.

Figure 1: Applied ethnography can help designers to learn about the context of use in self-administration through observations and interviews to get a broad understanding of the patient journey.

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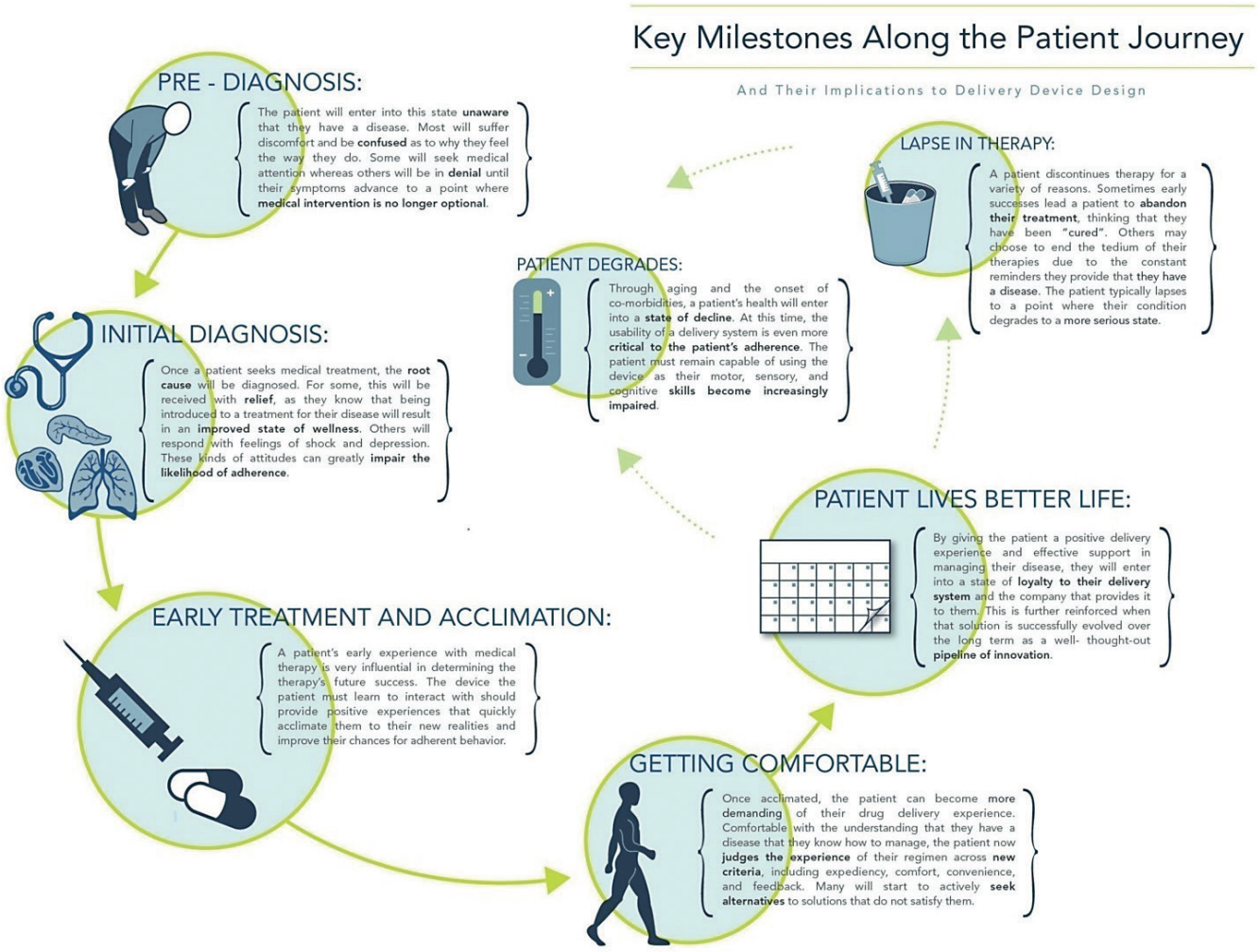

Figure 2: The output from ethnography is a patient journey map that allows the development team to identify opportunities for improving the user experience or mitigating risk.

To achieve this level of understanding, every learning opportunity must be capitalised on, no matter what size lens the investigators are looking through.

This process allows for the gain of significant understanding of the environment, social/emotional contexts and all the other factors that influence a patient's use of a delivery system (Figure 2). At this early stage, use cases are looked at broadly, potentially from when a patient receives their device, through the entire process of preparing, administering and disposing of that particular device. This gives the most natural view of the patient experience in use and in context. This is supplemented by gaining an understanding of the experience of healthcare professionals, as they are critical in helping with device selection and training for a specific patient population. A good example of this is Bigfoot Biomedical's (Milpitas, CA, US) connected ecosystem, a comprehensive solution that addresses every stage of managing diabetes. Without looking at the "big picture" and observing each sub-set group and treatment methodology, this integrated system could not exist.

> "Ultimately, these processes and outputs are used to develop innovative devices or to select the right platform device."

Understanding both the patient and healthcare provider experience enables development of these patient journey maps, which demonstrate the complete process patients go through in managing their disease – both from an administration standpoint and from a longitudinal perspective – as they progress with their condition and treatment.

These journey maps help to:

- Understand and prioritise user needs to drive development of novel device strategies.
- Select and possibly customise the proper platform device in combination with technical characterisation of the drug product.
- Identify experiential gaps at a very early stage, which can then be addressed through the development of IFU, novel training methods, value-added packaging or other methods.
- Uncover patient engagement opportunities that can be supported with connectivity and mobile applications.
- Provide an early indication of areas where risk might be present in clinical trials.

Ultimately, these processes and outputs are used to develop innovative devices or to select the right platform device. In both cases, user research is relied upon to gain an understanding of where opportunities for differentiation might exist.

Companies who select a platform solution for their combination product all too often

"The matter of differentiation is key, particularly in generics and biosimilars, where competitive companies may be targeting the same reference drug, perhaps even the same platform device."

assume that all of the human factors, risk management and characterisation of performance relative to their specific drug patient attributes has already been completed. This is simply not the case, as platform devices are in most cases very well designed devices, but they are meant to be broadly applicable to as many potential patient and drug attributes as possible. Ultimately, drug companies are responsible for their own drug-device combination and the platform device at that stage is really only half of the picture. It's incumbent on the pharma company to ensure that the platform device, in combination with their drug, is appropriate, safe and effective for the target population. This includes all technical characterisation, risk management, human factors and design verification.

The matter of differentiation is key, particularly in generics and biosimilars, where competitive companies may be targeting the same reference drug, perhaps even the same platform device. In this scenario, the foundation of the patient journey can be harnessed to understand potential areas of differentiation for device attributes with both functional details and patient interface features such as form, dosing windows, dial counters, grip architecture, etc. Even if the actual device is fixed, some measure of differentiation can be driven by adding utility to packaging, IFU, quick reference guides, and device training and onboarding, all while taking advantage of the many benefits that platform devices

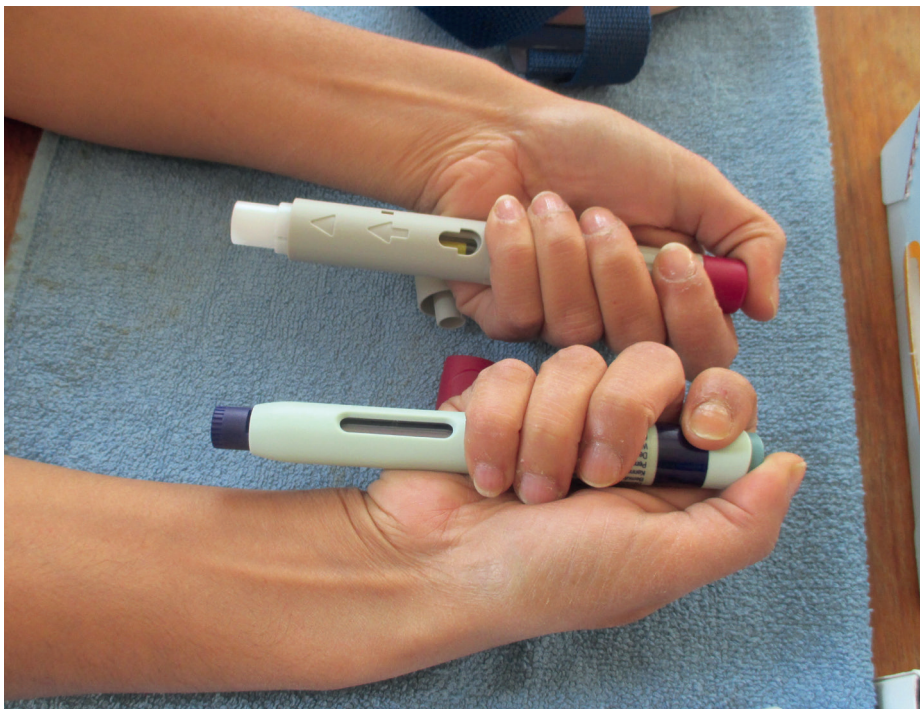

Figure 3: To support human factors submissions, evaluate the impact of innovative packaging, IFU, etc, and differentiate beyond a platform device, it is necessary to work with patients.

provide (Figure 3). Developing a holistic and comprehensive patient experience strategy can often times create competitive advantage.

So, although platform devices provide many benefits, they also require a lot of work to commercialise for the target population, whilst also considering means of differentiation. Utilising the understanding of user needs as characterised by the patient journey mapping process is a great way to inform the development of safe, effective, usable and differentiated platform-based systems for drug delivery.

ABOUT THE COMPANY

Insight Product Development is a design innovation consultancy focused on the medical device and drug delivery sectors since 1988. Capabilities include human factors engineering, design research, industrial design, engineering and prototyping. Insight supports its client's device strategy across novel and platform devices. The company has expertise in contextual research and human factors driven understanding of the patient journey as well as design and development of autoinjectors, wearable injectors and inhalation devices across multiple chronic disease states.

ABOUT THE AUTHOR

Mark Tunkel is a Partner and Director of Business Development at Insight Product Development. With more than 20 years of global business development experience and a deep understanding of the marketplace challenges and trends impacting the pharmaceutical industry, Mr Tunkel has advised many of the world's leading companies on their product development and innovation strategies with an emphasis on driving realisation and the most favourable business outcomes.

DEVELOPING DEMONSTRATORS TO INCREASE PATIENT CONFIDENCE AND REDUCE ANXIETY

In this article, Joe Reynolds, Research Manager at Noble, using Noble's collaboration with BD as an example, discusses the value of demonstrators for making patients comfortable and effective with their prefilled syringe, leading to a significant improvement in treatment adherence and patient quality of life.

According to recent research, the global prefilled syringe market is estimated to reach US$22.5 billion (£17.3 billion) by 2025. Driving forces in the market's expansion include technological advancements in drug delivery and the growing use of prefilled syringes for biologic and large molecule medications.[1] While these medications can significantly improve patient quality of life, the WHO estimates that 50% of patients diagnosed with chronic conditions do not take their medications as prescribed.[2] Whilst myriad factors influence patient adherence and outcomes, research has shown that demonstrators and education can positively influence patient acceptance and adherence to treatments using prefilled syringes, safety systems and other forms of drug delivery.

Through advancements in usability and human factors engineering, the overall understanding of patient adherence and, in particular, the value of device demonstrators and onboarding education has greatly improved. While Instructions for Use (IFU), package inserts and other content-based collateral are effective, it is estimated that only 12% of patients have the health literacy needed to understand and manage their treatment using these materials alone, resulting in training gaps that can adversely affect the use of prefilled syringes and safety syringes by patients and other stakeholders.[3]

From experience, Noble has found that confidence and anxiety are two key variables that influence a patient's perception toward drug delivery devices and their overall

"Through advancements in usability and human factors engineering, the overall understanding of patient adherence and, in particular, the value of device demonstrators and onboarding education has greatly improved."

therapy. The onboarding period (or the first 30, 60, 90 days of treatment) is where these attitudes and usage behaviours are first established, becoming key predicators of long-term adherence and outcomes (Figure 1). During the onboarding phase, 45% of patients skip or avoid injections due to needle anxiety or fear,[4] which can subsequently lead to ingrained avoidance behaviours and, ultimately, the discontinuation of treatment.

REDUCING NEEDLE ANXIETY THROUGH THE USE OF DEVICE DEMONSTRATORS

Needle anxiety is a common adherence barrier for patients who use prefilled syringes and other injection-based delivery systems. To help patients overcome the emotional barriers of self-injecting, novel

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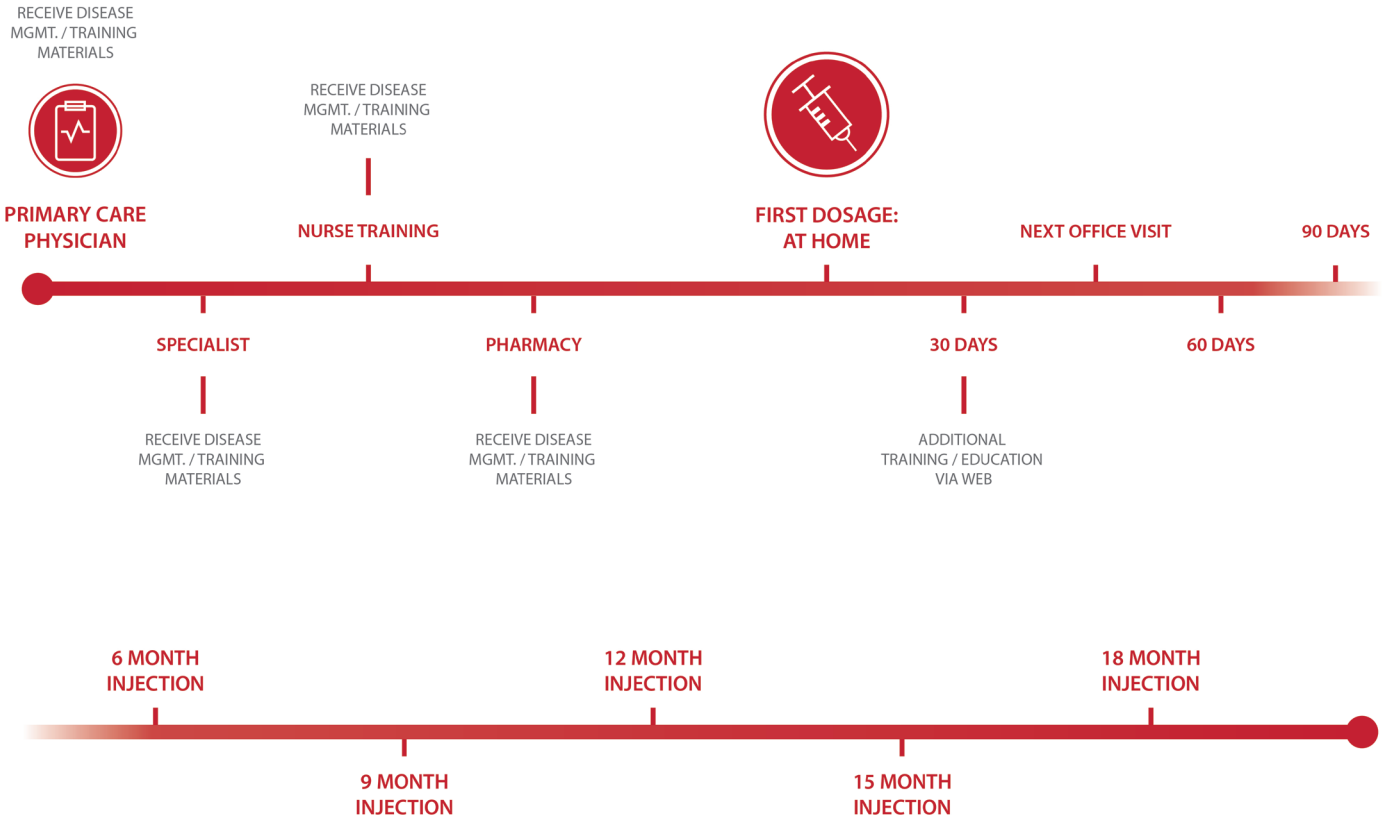

Figure 1: Onboarding timeline.

needle simulation technologies have been developed to fully mimic the deformation, puncture and insertion force characteristics of syringe needles. When applied to prefilled syringe training, these proprietary technologies allow patients to learn, safely, the force and technique required to insert a needle into subcutaneous tissue. A study announced by Noble revealed that demonstrators that incorporate needle simulation technologies result in a greater reduction in patient anxiety compared with traditional training.

COLLABORATIONS THAT FOCUS ON PATIENT SUCCESS

As the pharmaceutical market continues to grow, so too does the need for injection devices that support both the complex properties of molecules and the needs of the end-user performing the injection. By providing a best-in-class user experience, pharmaceutical manufacturers can ensure that patients have access to resources that promote meaningful outcomes and build confidence in their ability to self-mange treatments and use drug delivery devices.

Noble collaborates with Becton Dickinson (BD) to provide advanced patient onboarding solutions, including demonstration devices (Figure 2).

> "Through the ongoing collaboration, Noble leverages its onboarding solutions to develop novel demonstrators based on BD UltraSafe™ technology, thereby improving the patient experience and confidence."

Through the ongoing collaboration, Noble leverages its onboarding solutions to develop novel demonstrators based on BD UltraSafe™ technology, thereby improving the patient experience and confidence. Noble's market expertise and BD's passive needlestick safety devices allow for a platform approach for drug delivery devices and access to dedicated onboarding systems. BD has been an early innovator

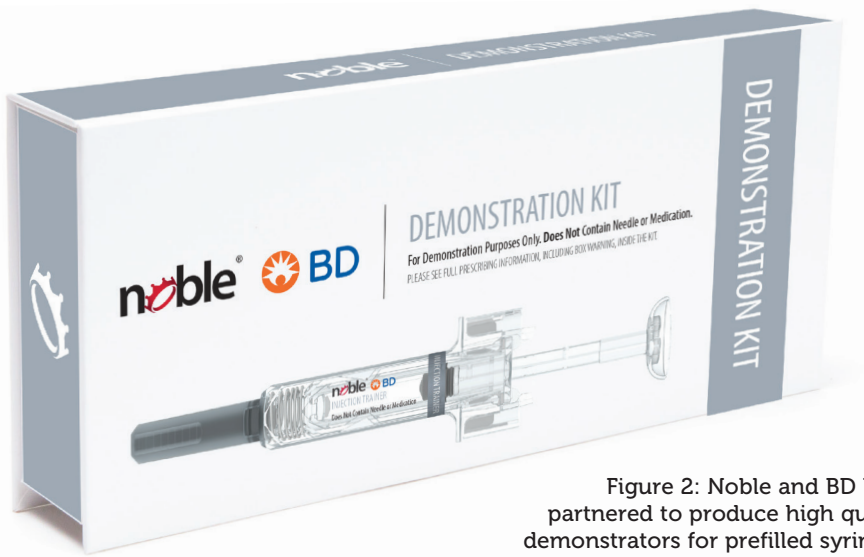

Figure 2: Noble and BD have partnered to produce high quality demonstrators for prefilled syringes.

in developing safety-engineered solutions for the market, partnering with numerous customers to ensure product success.

Partnerships and collaborations like the one between Noble and BD provide the expertise needed to develop optimal treatments from start to finish. In a recent market survey conducted by Noble, 89% of patients reported that it was very important to them to have the most realistic demonstrating device possible. By having a deep understanding of complex device engineering and patient needs, companies are better able to create positive and impactful onboarding solutions for patients. User-centric companies like BD and Noble have the patient in mind as they begin the onboarding process for treatment all the way to the final step, the administration of treatment.

One example of how this collaboration benefits patients is BD's UltraSafe Plus™ Passive Needle Guard. The overall design of the product was validated by performing handling studies with both nurses and self-injecting patients. Results from the user study confirmed that the BD UltraSafe Plus™ Passive Needle Guard was intuitive and easy to use with a 100% activation success rate for all 500 injections. Noble's device demonstrators will compliment BD's syringe and help instil another level of confidence during the onboarding process through hands-on experience that fully mimics the actual device (Figure 3). Device demonstrators have become the foundation for effective education and onboarding strategies, allowing patients and healthcare providers to safely learn how to use prefilled syringes and other forms of drug delivery.

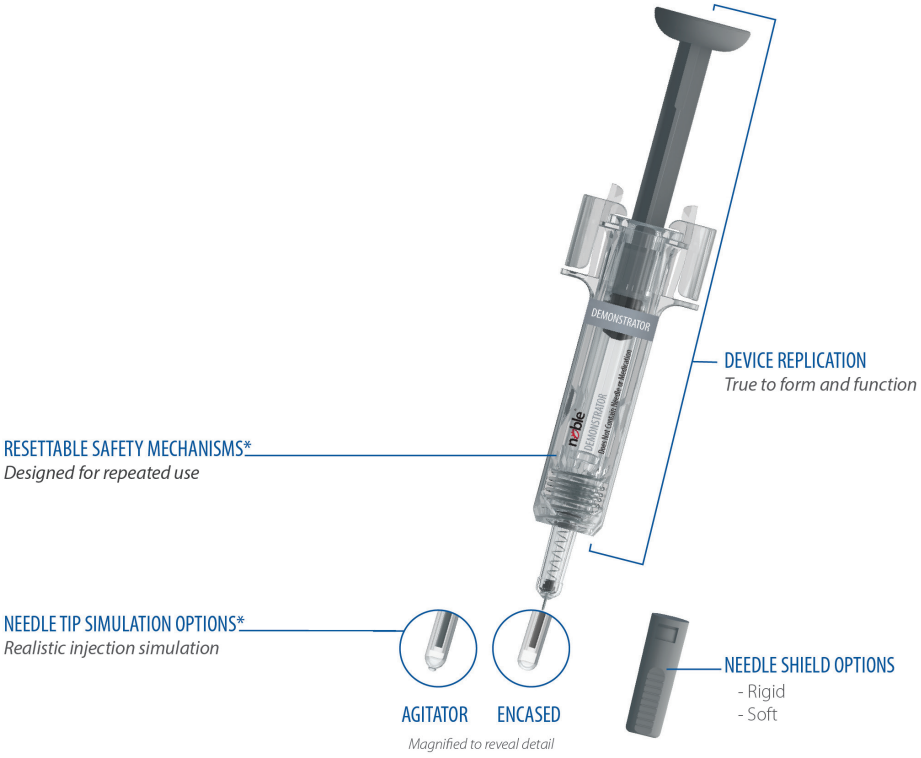

Figure 3: Noble offers a variety of innovative features designed to simulate BD UltraSafe™ technologies with the goal of familiarising and preparing patients to self-inject.

DEVELOPMENT OF DEMONSTRATORS FOR PREFILLED SYRINGE SYSTEMS

Noble's prefilled syringe demonstrators simulate the attributes of real prefilled syringes and are available as off-the-shelf or customised platforms, which include proprietary technologies. With the ability to be customised, brands are able to include capabilities like audio, tactile feedback, sensors, syncing and error detection features. They also offer customisable options for syringe angle training that can be custom-fit to shape and design, colour, and 45- and 90-degree angularity.

These demonstrators are custom developed to mimic standard prefilled syringes and prefilled syringes with safety systems. A few key features include:

- **Locking Needle Shield & Resettable Safety Mechanisms** – Demonstrators are intended to replicate the device safety and shielding systems with the capability for users to reset the mechanisms for repeated use.
- **Replication** – Demonstrators are designed to be true to form and function of the real prefilled syringe, able to simulate all aspects of the patient experience including form, colour adjustments, window size and actuation force.
- **Needle Tip Simulation Option** – Demonstrators should also offer the option to exhibit realistic injection simulation designed to simulate the feel and forces involved with an injection.

> "By setting high quality standards when designing medical demonstrator devices, companies are able to prioritise user needs and translate those needs into effective onboarding solutions."

BEST PRACTICES IN QUALITY

Noble adheres to a strict quality control process to ensure patients are provided with best-in-class demonstration devices. All device demonstrators are tested to guarantee that needle simulation and other features accurately simulate those of real drug delivery devices. By setting high quality standards when designing medical demonstrator devices, companies are able to prioritise user needs and translate those needs into effective onboarding solutions.

The industry will continue to evolve, giving patients the opportunity to gain confidence in their treatments, overcome adherence barriers and, in the end, achieve an improved quality of live. Through partnerships and collaborations that put the patient at the centre, like the relationship between Noble and BD, patients will have a better onboarding experience for treatment all the way to the last step as they administer their medication. Industry leaders like BD and Noble, partners who know the power of incorporating human factors into engineering and experiential training, inspire the industry to innovate design and onboarding practices and ultimately provide patients with better overall treatment options.

ABOUT THE COMPANY

Noble is a full-service, user-centric advanced drug delivery training device and patient onboarding company. Noble works closely with the world's leading drug delivery device original equipment manufacturers and pharmaceutical companies to develop educational and training solutions designed to provide positive patient onboarding experiences, reduce errors and improve patient outcomes.

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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, pharmaceutical and biopharmaceutical manufacturers. Mr Reynolds earned his Bachelor of Science in Business Administration from the University of Central Florida, a Master of Science in Marketing from the University of South Florida, and a Master of Science in Pharmacy and Master Certificate in Drug Regulatory Affairs from the University of Florida.

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TOM VAN GINNEKEN, SCHOTT

Tom Van Ginneken studied Chemical Engineering in Antwerp, Belgium and holds a MBA from the University of Sankt Gallen, Switzerland. After working in the chemical and pharmaceutical sector in Belgium for three years, he joined Schott in 2008. Following different positions in the pharmaceutical product development department, he joined the product management team as global product manager for the polymer syringes Schott TopPac®.

Interviewed here, Mr Van Ginneken discusses the advantages of polymers as a material for primary pharmaceutical packaging and how the company supports pharma manufacturers with engineering capabilities for individualised containers and rapid prototyping.

Q What fascinates you about polymers as a material for primary packaging?

A Polymers, specifically cyclo-olefin copolymer or "COC", offer a number of attractive benefits when designing pharmaceutical containers. Its features, such as its transparent glass-like appearance together with its physical stability and the diverse design options, make it an ideal alternative to package pharmaceutical products. In particular, the market for prefilled syringes made of polymers has seen a steady growth in recent years and is growing in market share.

Q For which applications are polymers used?

A The application fields are quite diverse and include a variety of therapeutic areas within the clinical setting or in home-based care. In the form of a prefilled syringe, polymers are used for emergency pharmaceuticals and diluents due to their break-resistance and for infusion therapy due to the large format options of 10, 20 or 50 mL. Polymer syringes are also suitable for highly viscous medications, such as hyaluronic acid, which is used in the cosmetic industry. Besides those traditional markets, we also see that the growth is driven by a broader range of applications. For example, highly sensitive biologics or immunoglobulin benefit from the material's inertness and large size syringe formats. The material's flexibility in terms of its form opens the door for improved functionality and compatibility with drug delivery devices, such as wearables.

COC offers great design flexibility, which means that it can be fitted to meet the specific requirements of the drug and application. This is particularly important for applications including a device. Devices are being developed for a specific patient group, who might have physical limitations. During the development stage of the device, it is of high importance that the device is ergonomic and easy-to-use, as this will contribute to the success of the patient's therapy. Polymers offer the needed design freedom to ensure that the container will be developed around the ergonomic device and that no compromises are needed from the device development team in choosing a container. The result is a container that works seamlessly with the device.

> "COC offers great design flexibility, which means that it can be fitted to meet the specific requirements of the drug and application. This is particularly important for applications including a device."

Q What sort of devices are you thinking of?

A Wearables are just one example that would benefit from individualised containers. To give you an idea, a customised COC packaging solution would be suited for needle-free injection devices, inhalers or insulin pumps among others. Due to their requirements, such as needing additional assembly steps in the case of an inhaler, design flexibility is a crucial aspect. Moreover, some devices require tight tolerances, such as for the nozzle dimensions of a needle-free injection device, which is best achieved with polymers.

Q Speaking about individualised solutions, what exactly can be customised?

A The cylindrical polymer container consists of three parts: the cone, the barrel and the flange. All three parts are customisable depending on the needs of the drug product, filling process or drug administration process. For example, if a pharma company has an innovative idea for

[Continued on Page 86...]

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[...Continued from Page 84]
an insulin pump, it will need a container that fits exactly into the pump. A standard container on the market might not meet those requirements, as it would have to be longer or shorter or have a reduced inner diameter. This is where we could support with developing a container that has the exact dimensions to work with the pump.

Another scenario could be a biotech company developing a wearable device to administer a drug over a longer period of time. Due to the large filling volume, the biotech company might be struggling to find a suitable cartridge without compromising on the dimensions of the wearable. We could jointly create a container with a bigger inner diameter to contain the large filling volume, while at the same time maintaining the ergonomic and easy-to-use design of the device.

Or imagine a dermal filler manufacturer who is looking to solve needle disconnection with standard luer-lock syringes. Together we could develop a syringe with a different thread in the luer-lock, which stabilises the needle on the syringe cone.

Q **Are there specific process steps for such a development project?**

A We classify the process in four stages with the aim to speed up the development while reducing financial and project risks for our customers. This means that the process is built on a "Go/No-Go" decision after each step. In the first stage, we offer rapid prototyping of samples within a few days. The second stage is focused on design freeze samples. This is an important step, as the concept is evaluated based on functionality tests. If the customer is ready to move forward, we reach the stage of small scale "for human use" production. This phase allows fast drug approval without heavy financial investments or long machine lead-times. The fourth and final step is the fully automated production to produce large quantities with economies of scale.

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.

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DIVIDELLA
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MONOMATERIAL PACKAGING: A SOLUTION TO THE GLOBAL PLASTICS CRISIS

In this article, Peter Grassl, Sales Director, Dividella, discusses the extent of environmental damage caused by plastic waste in the oceans, and explains how cardboard monomaterial packaging is not only a step towards tackling this issue, but also a potential source of extensive cost savings in pharmaceutical logistics and storage.

OVERVIEW

In February 2108, a young sperm whale washed up on a beach in south-eastern Spain. When scientists carried out a necropsy, they discovered the huge mammal had succumbed to a fatal infection caused by more than 30 kg of plastics in its stomach and intestines. The whale was far from alone; some 90% of dead sea birds are found to have plastic in their gullets. And the problem is only getting worse, an estimated 10 billion kg of plastics enter rivers and oceans every year – a quantity on course to double by 2025 (Figure 1).

The most obvious manifestation of this environmental crisis is the "Great Pacific Garbage Patch", an 80,000-tonne island of mostly plastic refuse swirling around between California and Hawaii. These plastics not only kill animals, but also decimate coral reefs and damage human health as they break down into microplastic

> "Dividella has long espoused the concept of using 100% monomaterials in its packaging solutions – not just for environmental reasons but also to deliver much lower total cost of ownership and total cost of package."

Figure 1: An estimated 10 billion kg of plastics enter rivers and oceans every year.

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particles that are now prevalent right across the food chain.

This is why enterprises increasingly aspire to become "plastics free" as part of their sustainability goals. For the pharmaceutical industry, the biggest use of plastics is, of course, in the packaging and logistics chain. Tackling this problem means embracing the use of monomaterials (essentially cardboard) to replace plastics in packaging.

MONOMATERIAL PACKAGING BENEFITS

Parenteral packaging specialist Dividella has long espoused the concept of using 100% monomaterials in its packaging solutions – not just for environmental reasons but also to deliver much lower total cost of ownership (TCO) and total cost of package (TCP). In-depth research and numerous case studies have enabled Dividella to calculate the actual savings from using monomaterial packaging with some precision.

In principle, the development of the packaging solution should take place right at the beginning of the decision-making process. The choice of a suitable packaging solution has considerable impact on several TCO points. Special attention must therefore be paid to it, as it may be one of the dominant cost drivers.

To explain this, consider the simple example of packaging three syringes and a pack insert. The choice is between a classic blister pack in a side-loading folding box or a 100% cardboard solution, consisting of a folding box with a glued corrugated flute, which can be produced on a toploader.

> "The NeoTOP monomaterials package has a volume about half that of the blister pack, partly because it is optimised for volume and also by eliminating the need to seal a blister with lidding foil."

Item	Blister Pack	NeoTOP 100% Monomaterial
Folding box	10¢	8¢
Plastic tray/cardboard flute	9¢	2¢
Aluminium lidding foil	5¢	0¢
TOTAL	24¢	10¢

Table 1: Packaging material costs.

Item	Packs per Container	Cost per Pack	Cost for 2.5 million Packs
100% monomaterial cardboard	20833	24¢	$600000
Blister pack	12315	40.6¢	$1015000

Table 2: Logistics costs.

Figure 2: Dividella's 100% monomaterial NeoTOP packaging solution.

Table 1 shows how the material costs differ.

Thus, for an annual quantity of 2.5 million packs, total costs are US $600,000 (£460,000) for the blister pack, compared with $250,000 (£190,000) for the monomaterials toploading pack, resulting in a saving of $350,000 (£270,000) per year.

This is from the chosen packaging solution alone, but there are consequent savings to be achieved in simplicity of manufacture and, not insignificantly, in logistics costs from weight and volume reductions, particularly in cold-chain storage, where both are at a premium (Table 2). By land, it costs some $5000 to shift a 9 m^3 refrigerated container over 3000 km. Now consider the number of packs such a container can carry. The NeoTOP monomaterials package (Figure 2) has a volume about half that of the blister pack, partly because it is optimised for volume and also by eliminating the need to seal a blister with lidding foil. These transportation savings are further magnified when moving goods by sea or air.

The TCP savings extend onwards into energy cost in packaging installation, which can also be determined fairly easily from manufacturers' information. The high heating demands for film forming and sealing mean that a thermoforming process for blister packs will cost more than a toploader for monomaterial packaging (cardboard) that is only glue sealed. In the example above, energy costs per shift, including compressed air, came to approximately $5000 (£3900) for the toploader, compared with $12000 (£9300) for the blister machine.

ENABLING MONOMATERIAL PACKAGING

Dividella has built up an impressive reputation across the global pharmaceutical industry for the quality and effectiveness of its NeoTOP topload cartoning machines. This success has been established on a holistic approach that recognises that machine and pack design go hand in hand.

The toploading concept also recognises that pack design, construction and appearance form significant added values for manufacturers, meaning that each pack deserves to be treated as a unique entity, supported by optimised handling and a complete packaging design.

Therefore, Dividella's packaging designers are accustomed to working in close co-operation with the customer's marketing departments to determine detailed specifications for individual packs and carton loading.

Dividella is thus able to address TCO and TCP concerns at multiple levels:

- The high-quality engineering of cartoners
- The flexibility and integration of modular design concepts
- Innovative package design expertise
- Extended machine capabilities allowing for wider choice of materials and formats
- User friendliness in operation

ABOUT THE COMPANY

Dividella AG, a member of the Korber Medipak Systems Group, has specialised in developing and manufacturing packaging machinery for the pharmaceutical industry for four decades, with specific expertise in packaging requirements for parenteral products. Dividella counts 20 of the world's largest pharmaceutical companies among its clients, including the entire top ten.

Dividella's production units at Grabs, Switzerland, exclusively design and manufacture machines for packaging pharmaceutical products, with total focus on the specific requirements of parenteral pack products, i.e. liquid pharmaceuticals that are packaged in syringes, flasks, vials, autoinjectors and the like. These are highly sensitive products that demand thoroughly developed solutions.

ABOUT THE AUTHOR

Peter Grassl is Sales Director at Dividella, having previously been very successful as Area Sales Manager in the field of automated inspection machines for the pharmaceutical industry. Mr Grassl has extensive experience in the pharmaceutical packaging industry in the fields of engineering and consulting. His expertise covers the capital equipment industry and, through extensive sales activities, he has an excellent knowledge of international markets. Mr Grassl was educated as a mechanical engineer and holds an additional degree in Business and Administration.

MARKET CHALLENGES AND OPPORTUNITIES FOR DELIVERY SYSTEMS AND INJECTION DEVICES

Here, Massimo Mainetti, Head of Strategic Marketing, Datwyler, presents a brief overview of the current state of play in the field of novel biologic medicines as they relate to drug delivery.

The healthcare industry is consistently oriented towards improving patient safety and future health with innovative drugs and treatments. New products and solutions are introduced to the market fast and often clearly indicate in which direction a market or industry is headed. But despite the high frequency, introducing a new and potentially ground-breaking product is a long and highly complex process, especially in the fields of high-end pharmaceuticals and biotech solutions.

The development pipeline for pharmaceuticals and biopharmaceuticals contains numerous promising and innovative treatments with the potential to address unmet medical needs. However, the amount of research and development that is necessary for these new treatments can be tedious, challenging, expensive and subject to substantial scientific and regulatory uncertainty. In fact, on average, only 12% of investigational new medicines entering the clinical trial phase are ultimately approved by the US FDA.

According to PhRMA, about 74% of drugs in clinical development can potentially be considered first-in-class medicines, which is to say that they use a different mechanism of action from any other already approved drugs. Such medicines offer new treatment options for patients, which is key for the care of those who have not responded to existing therapies or for whom no treatment options are presently available.

> "To ensure the efficacy and integrity of the drug, the packaging components have to meet the highest regulatory standards of the industry."

> "About 75% of drugs in clinical development can potentially be considered first-in-class medicines, which is to say that they use a different mechanism of action from any other already approved drugs."

The numbers of potential first-in-class medicines in all phases of clinical development are high, but the percentage decreases in the later stages. This is partly because medicines with new mechanisms are less likely to make it through the development process due to higher levels of uncertainty. Among others, these uncertainties include the chemical composition of the drug and the reaction potential with interacting materials such as packaging components or other external factors. Therefore, primary packaging and the method of administration are crucial for the success of the drug product.

Due to their nature and composition, many of these innovative drugs – especially biotech drugs – tend to be administered by injection. To ensure the efficacy and integrity of the drug, the packaging components have to meet the highest regulatory standards of the industry. However, with the fast development of new medicines, the requirements for parenteral primary packaging are ever-evolving and constantly changing, especially in the growing field of biosimilars and biologics. At the same time, novel injection devices have been emerging fast.

For these new treatment options, prefilled syringes and innovative injection devices for at-home use have become the go-to choice for administration, especially for chronic

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> "Prefilled syringes and innovative injection devices for at-home use have become the go-to choice for administration, especially for chronic diseases, as they provide patients with more comfortable and flexible treatment options."

diseases, as they provide patients with more comfortable and flexible treatment options. To ensure the integrity of the contained drugs at all times, the right choice of primary container, elastomer closure, coating technology and aluminium or plastic outer seal is crucial in drug development and across the entire lifecycle of the drug – from development and manufacture, through transport and storage, to the application. Elastomer components especially are a key element for parenteral packaging and drug administration systems, therefore they have to fulfil strict criteria in terms of chemical and functional performance.

In the growing area of biosimilars and biologics primary packaging solutions must provide an optimised extractables and leachables profile. In most cases, these drugs are administered via prefilled syringes to ensure the highest level of safety for sensitive biosimilars and biologics. This is a crucial factor with regard to storage and packaging. The increasingly specialised demands for the primary packaging material performance drive the developments of high-quality components.

Components for prefilled syringes, such as barrels and plungers, in many cases have to be siliconised to ensure low break-loose and smooth glide forces. However, there are applications of closures and pharmaceutical components where siliconisation is not a preferred method of surface treatment. This is especially true for biologics and biosimilars, which consist predominantly of therapeutic proteins and, as such, may have undesirable interactions with a siliconised surface. Thus, more suitable alternative methods are applied.

For therapeutic proteins, the exact chemical make-up and three-dimensional conformation can influence the efficacy of the drug. The interaction of proteins with silicone oil can present a risk to the safety and efficacy of therapeutic proteins. Conformational changes, degradation and aggregation can lead to the inefficacy or immunogenicity of the protein, ultimately impeding or preventing the success of the drug. Therefore, many manufacturers of biologics or biosimilars are already relying on fluoropolymer coated closure solutions today. The reduction and elimination of silicone oil and silicone-oil-based subvisible particles (SbVPs) has become a legitimate concern for any pharmaceutical and medical manufacturers.

ABOUT THE COMPANY

Datwyler Group is an international supplier of state-of-the-art industrial components with leading positions in global and regional market segments, with a global manufacturing footprint on three continents, sales in over 100 countries and more than 7,000 employees. In its Sealing Solutions division, Datwyler provides customised sealing solutions to manufacturers and companies which operate in the healthcare and automotive industries, among others. The products and services of Datwyler are built on high-quality material, innovative technologies, outstanding engineering and process know-how.

ABOUT THE AUTHOR

Massimo Mainetti is Head of Strategic Marketing at Datwyler Sealing Solutions. He holds a Master's degree in business administration from the University of Milan, Italy. In January 2015, he joined the global sales team of Datwyler Pharma Packaging as Key Account Manager, Injection-Systems. Since June 2017, he has been acting in his current position. He brings to the company broad experience from diverse backgrounds in key account managing, distribution and strategic and international marketing.

ZAHORANSKY
PERFECTLY DIFFERENT

FROM GRANULATE TO PACKAGED PRODUCT

In this article, written by Michaela Gnann of gnann text+page, ZAHORANSKY runs through the options and advantages conferred by Z.BLIZZARD and its other automation technologies, with further explanations from Berthold Schopferer, Business Development Manager – System Technology at ZAHORANSKY.

There does not exist one single Z.BLIZZARD (Figure 1). This fact is important to Berthold Schopferer, Business Development Manager at the mechanical engineering specialist ZAHORANSKY Automation & Molds. Z.BLIZZARD machines manufacture ready-to-fill prefillable syringes from cyclo-olefin polymers (COPs) or copolymers (COCs) with a very high degree of autonomy. For the original equipment manufacturer (OEM) or contract manufacturing organisation (CMO), this not only means efficient and safe production of their pharmaceutical products, but also the assurance that they have invested in a sustainable solution.

> "No two Z.BLIZZARD's are alike – each one consists of many functional units, which are individually adapted to the wishes of the OEM or CMO and put together to suit their needs."

However, as Mr Schopferer explains, "No two Z.BLIZZARD's are alike – each one consists of many functional units, which are individually adapted to the wishes of

Figure 1: The Z.BLIZZARD manufactures ready-to-fill prefillable syringes from COCs/COPs with very high autonomy.

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the OEM or CMO and put together to suit their needs." The customer determines for themselves what is the orientation of the needle; is it straight or bent? What areas have camera cover? Is the Z.BLIZZARD equipped with access doors or not? These and other details are defined in close co-operation with the customer and then implemented as desired. The involvement of the customer begins at the early stages already, with theme being part of the entire manufacturing process, which usually takes 12 months.

"Of course, we also proactively make suggestions and recommendations if the customer cannot or does not wish to be such an intensive part in the design of the machines," Mr Schopferer says, explaining how a customer of ZAHORANSKY needs only be as involved in the design process of their Z.BLIZZARD as they wish to be.

All recommendations are analysed in terms of their causes and consequences in the form of medical documentation, including a risk assessment in accordance with GMP guidelines. Proof is provided that the proposed solution will be implemented for the customer in a secure manner. "We have to be able to show why something works or why it does not. That's what distinguishes a good machine builder from the rest. 100% means 100% for us. We also think into the future for the customer's sake. In other words, after we have delivered the Z.BLIZZARD to our customer and have installed it, it is paramount for us to know that the customer is in possession of an innovative and future-proof machine," explains Mr Schopferer.

This also applies to the use of plastics, which has several advantages over glass. In essence, the needle is over-moulded and not melted down. The melting process, which usually uses a high-temperature-resistant material such as tungsten, operating at temperatures as high as 1000 °C, can lead to trace heavy metals passing into the glass container and can later be found in the product – thus the containers are subsequently washed, dried and sterilised.

"The Z.NFS can isolate between four and 32 needles or cannulas at up to 12 cycles per minute – that is, up to 400 per minute."

Although this results in a partially longer shelf life for the syringe made of glass, the plastic variants offer further advantages due to minimised risk of breakage and, in particular, a greater freedom in design (Figure 2).

In addition, the needle isolation system Z.NFS (Needle Feeding Systems) of Z.BLIZZARD guarantees the "first in first out" principle. This means that the system is filled with the required quantity of cannulas and processed in series. This prevents the needles from remaining in the system for an extended period. The Z.NFS can isolate between four and 32 needles or cannulas at up to 12 cycles per minute – that is, up to 400 per minute. At present, diameters from 0.2 mm and lengths up to 40 mm can be processed. If the Z.NFS is integrated into the Z.BLIZZARD, it also becomes an integrated system that guarantees the highest level of purity in the production process, since there is no human contact and the process can take place in line with cleanroom regulations (Figure 3).

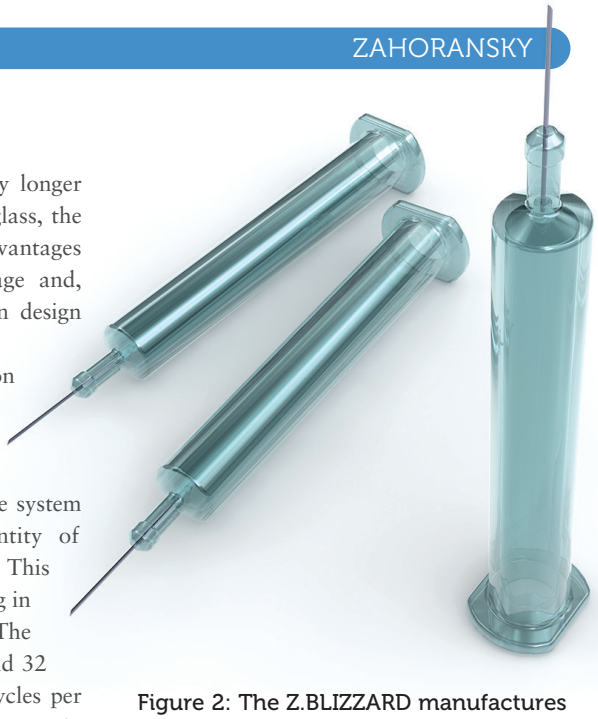


Figure 2: The Z.BLIZZARD manufactures PFS from plastics that have several advantages over their glass variants, such as the fact that the needle is over-moulded and not melted down.

"It goes without saying that we meet the essential GMP requirements with our machines, which is the standard requirement for our customers," explains

Figure 3: If the Z.NFS is integrated into the Z.BLIZZARD as shown here, it is an integrated system that guarantees the highest level of purity in the production process, as there is no human touch and the process can be carried under cleanroom conditions.

"If the Z.MISTRAL, which is responsible for the downstream, and the Z.LODOS palletising system are also connected, it is possible to cover the entire process chain, from the granulate to the finished, packed, ready-to-fill syringe – a real one-stop solution."

Figure 4: If the Z.BLIZZARD is still connected to the Z.MISTRAL, which is responsible for the downstream, and the palletising system Z.LODOS, it is possible to cover the complete process chain, from the granulate to the finished packed PFS.

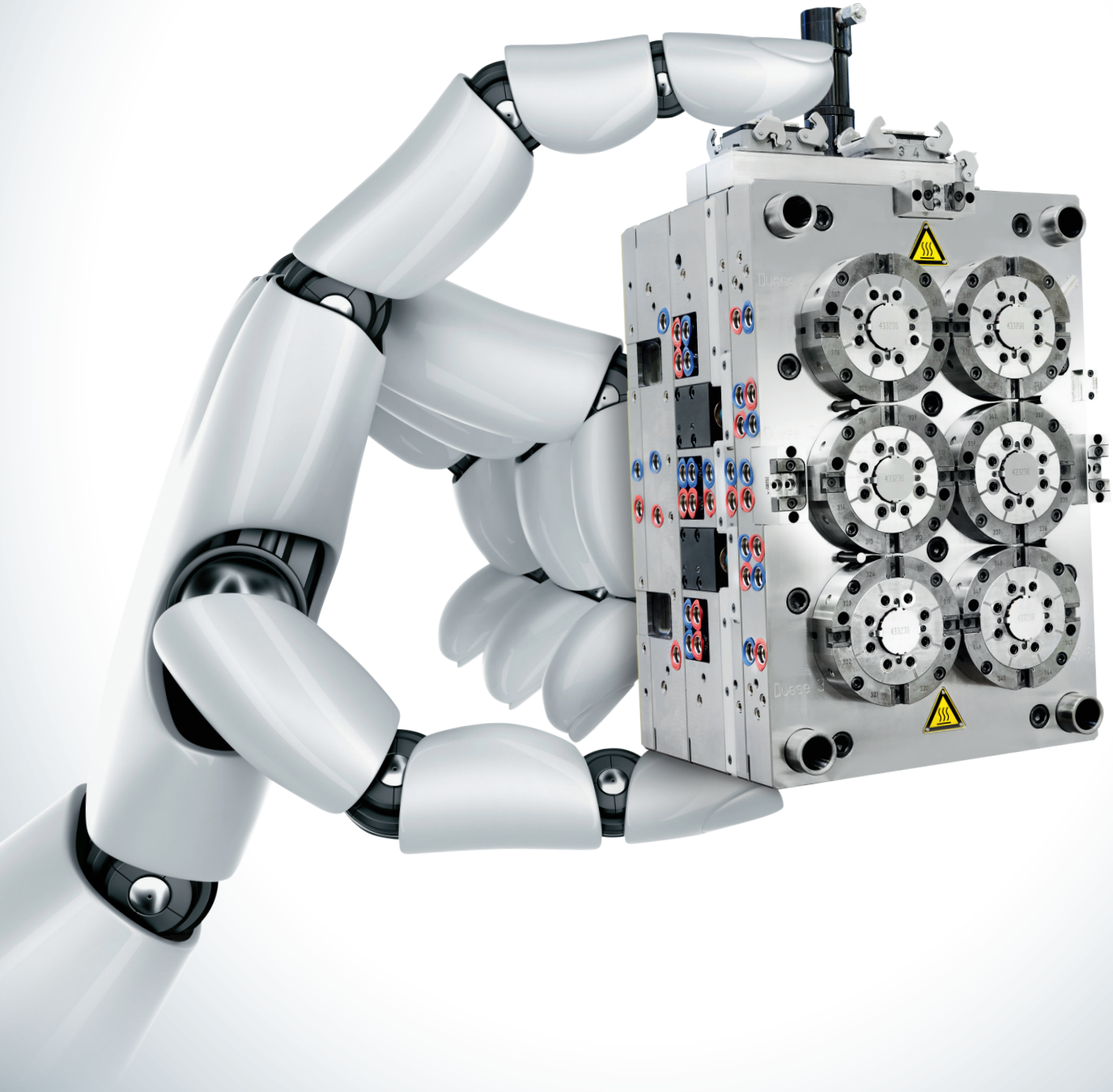
Schopferer. "We play an important role in ensuring that our customers' products meet the high-quality specifications that are required and demanded in medical technology." If the Z.MISTRAL (Figure 4), which is responsible for the downstream, and the Z.LODOS palletising system are also connected, it is possible to cover the entire process chain, from the granulate to the finished, packed, ready-to-fill syringe – a real one-stop solution.

As a matter of course, all relevant prerequisites have to be met, so that the system will not pose a danger to the product, and therefore to human beings. ZAHORANSKY ensures that all components that come into contact with the product are suitable for the application and that the software demonstrably does what it needs to do. Mr Schopferer explains this key but subtle difference by saying, "This also ensures that the system is built exactly as it was designed and developed. For example, if a technician finds that there is a borehole missing, they must ask and find out why that is the case – they are not allowed to simply add a borehole."

ABOUT THE COMPANY

ZAHORANSKY AG is a full-range supplier in machinery and production lines, sophisticated, innovative injection moulds and automation equipment. The company operates with over 700 associates at production sites in Germany, Spain, China, India and the US. The company's system technology offers cross-system solutions for injection-related automation. These systems are based on injection moulds by ZAHORANSKY Automation & Molds GmbH and on established systems from different modules of automation. Intelligent and injection-related automation solutions can be composed with these modules. ZAHORANSKY Automation & Molds GmbH serves the areas of industrial automation and medical devices, with pre-configured solutions provided for medical engineering. Z.BLIZZARD, for example, is an integral solution for making ready-to-fill prefillable syringes as primary medical packaging.

The One-Stop Solution Provider
for Automation & Molds



Passion and Perfection in Molds, Machinery and Automation.
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