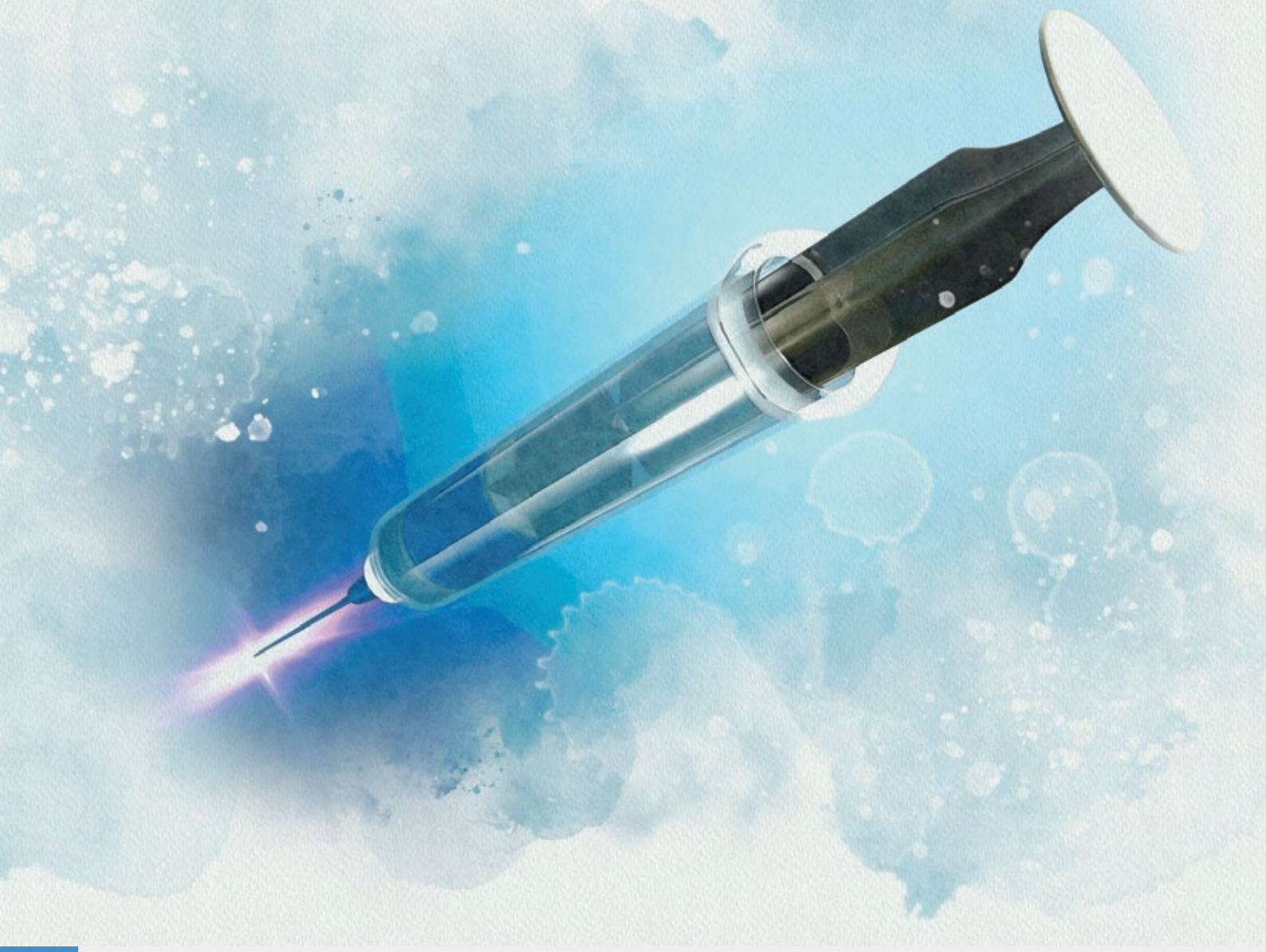
INJECTABLE DRUG DELIVERY

ON drugDELIVERY



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ONdrugDelivery Issue N° 120, May 31st, 2021

INJECTABLE DRUG DELIVERY

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

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HOW TO ENSURE THE FUTURE DEMAND FOR BIOLOGICS CAN STILL BE DELIVERED BY INJECTABLES

Here, Anthony Vico, Technical Customer Support & Quality Management Supervisor, and Enrico Barichello, Product Management Specialist for Syringes and Components, both of Stevanato Group, discuss the demands that high-viscosity biologic formulations place on prefilled syringes, and how pharmaceutical companies can make the most of this growing market segment to deliver improved quality of life for patients.

Global biologic sales are expected to grow from a market size of US$325 billion (£230 billion) in 2020 to $425 billion (£300 billion) by 2024. That represents an estimated compound annual growth rate (CAGR) of 7%, and a significant opportunity for pharmaceutical companies.[1]

Biotech drugs, especially monoclonal antibodies (mAbs) and recombinant proteins, have enabled the pharma industry to treat incurable critical and chronic diseases, such as osteoporosis, rheumatoid arthritis and hypercholesterolemia, meeting previously unmet needs and delivering better outcomes for pharma companies and patients in equal measure. Because most biologics are primarily administrated parenterally, particularly via the subcutaneous route, prefilled syringes (PFSs) have gained strong acceptance as the preferred delivery system.

Market trends have led pharma companies to formulate concentrated biologics that reduce the required frequency of injections for those who suffer from chronic conditions. These complex biologics are characterised by high chemical sensitivity and strong dynamic characteristics (i.e. viscosity), which pose significant challenges to PFS technology. As a leading provider of primary packaging and drug delivery systems, Stevanato Group is consistently challenging itself to deliver best-in-class, optimised solutions to improve patients' lives.

This article reviews the current state of the PFS market and discusses the challenges associated with biologic drug delivery, before covering a case study on how to optimise needle design to mitigate a patient's discomfort perception while guaranteeing acceptable administration performance for higher viscosity medicine. Finally, this article considers the key drivers in the choice of PFS, advocating an early-phase, full-system approach to mitigate risk and speed time to market for these life-enhancing therapies.

The burden of chronic disease continues to weigh heavily on populations across the globe. In Europe alone, these illnesses are the leading cause of mortality by far,

> "Managing a chronic condition can place a high demand on patients, often requiring regular visits to a clinical setting to receive their therapies, frequently via intravenous methods. Self-administration via the subcutaneous route relieves a great deal of this burden by handing greater control to the patient."

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accounting for 77% of the total disease burden and 86% of all deaths.[2] Cross-referencing these statistics with demographic trends, such as increasing life expectancy, has further implications for the future of healthcare provision.

By 2100, the proportion of those aged 65 years and over is projected to increase. This is despite forecasts that the overall population across the EU will decline in comparison with 2019 levels. As such, this age group will grow its share from a fifth of the current total (20.3%) to almost a third (31.3%),[3] equating to an additional 39.7 million people who are at risk of living with some form of chronic disease, or even multiple chronic diseases, over the coming decades.

Given the damaging impact of these conditions on citizens' wellbeing and the associated negative consequences for economic health, it is understandable that prevention and early detection of chronic disease is a clear focus among policymakers, who are seeking to tackle the issue as close to its source as possible.

At the same time, there is a growing requirement to address chronic diseases from the patient's perspective through long-term management and sustained treatment regimes. Pharmaceutical companies are pursuing innovative R&D programmes in these areas that, with supply chain partners, aim to uncover new treatments and drug delivery techniques that will ease many of the obstacles facing patients and healthcare professionals.

THE RISE AND RISE OF BIOLOGICS

Biologics are at the forefront of these developments. Between 2014 and 2018, the share of net medicine spending on biologics grew from 30% to 42% of the total. Over this same period, the Center for Drug Evaluation and Research (CDER) within the US FDA approved the biologic licence applications for 59 novel biologics. This more than doubles the 26 approved in the preceding five-year period.[4] A further 10 biologics were approved in 2019, as well as 10 biosimilars based on previously approved therapeutic biological products.[5] Cancer and orphan diseases (indications affecting 200,000 patients or fewer) are the most targeted therapeutic areas.

Since parenteral delivery is the typical route of administration, the demand for syringes is predicted to rise in line with the growth in biologics. Forecasts suggest this will result in the global PFS market expanding at a CAGR of 9% from 2020 to 2025, when it will be valued at $8.6 billion.[6]

> "When dealing with biologics bringing these benefits to the patient is not necessarily as straightforward as it sounds. The main sticking point being the high viscosity of the formulations in question."

There are several trends that are driving the uptake of biologic treatments delivered via PFSs, one key example being patient convenience. Managing a chronic condition can place a high demand on patients, often requiring regular visits to a clinical setting to receive their therapies, frequently via intravenous methods. Self-administration via the subcutaneous route relieves a great deal of this burden by handing greater control to the patient.

However, adherence remains an obstacle to effective treatment, particularly where preparation is required using a vial and syringe. In comparison with vials, PFSs deliver a ready-made, high-concentration dose that has been prepared to precise tolerances. These benefits mean medication errors and overfill waste are reduced and adherence is increased, with the potential for further improvements in adherence when used in conjunction with autoinjectors and as part of a connected combination product platform.

SOLUTIONS FOR HIGH VISCOSITY

When dealing with biologics, however, bringing these benefits to the patient is not necessarily as straightforward as it sounds. The main sticking point is the high viscosity of the formulations in question. This is due to the strength of the intermolecular forces at play in highly complex, long-chain biologics, such as mAbs, combined with the fact that protein concentration is deliberately formulated very high in order to meet dosing requirements. While viscosity is seen to increase moderately in low-concentration formulations, in high concentration formulations of greater than 100 mg/ml, viscosity increases exponentially.[7]

At higher viscosities, difficulties can arise for parenteral delivery mechanisms, including the need for additional force to be applied to the plunger rod. This can mean injections take longer and some traditional or more conventional autoinjector technologies may be rendered unfit for purpose if the force required is too high. Solving this challenge typically requires compromise on the part of the patient, such as increasing the frequency of injections, and/or when it comes to the PFS, such as increasing the needle gauge or selecting specific low-friction plunger stopper components; both scenarios have clear drawbacks in terms of compliance, comfort and ease of use. It has been down to innovators in the field of primary packaging and drug delivery systems to find a pathway that satisfies patient expectations from the perspective of both biologic drug delivery and user experience.

Stevanato Group, as a leader in this field, has carried out a detailed analysis of design developments intended to manage these issues. Its work looked closely at the morphological features of thin-walled needles, which offer the advantage of simultaneously maintaining flow rates and reducing needle gauge. However, they also increase the risk of both needle-tip deformation (e.g. hooks) and coring (the formation of elastomer particles caused by the needle tip piercing the elastomeric needle shield). The research identified that needle-tip deformation is a product of the reduced mechanical strength of the cross-section. In parallel, Stevanato Group confirmed that coring propensity is linked to aspects including the sharpness and geometry of needle-tip bevels, the mechanical characteristics of the elastomeric needle shield, and the tribology between the needle tip and the elastomeric needle shield – all of which are critical to quality.

In a further study, Stevanato Group attempted to determine how varying the needle-tip geometry would mitigate the risk of deformation and coring propensity when moving to a thin-walled configuration. This involved comparing the geometries of a five-bevel and a three-bevel needle tip. The research investigated the mechanical performance of the two designs, examining their hooking propensity in the context of the required penetration force.

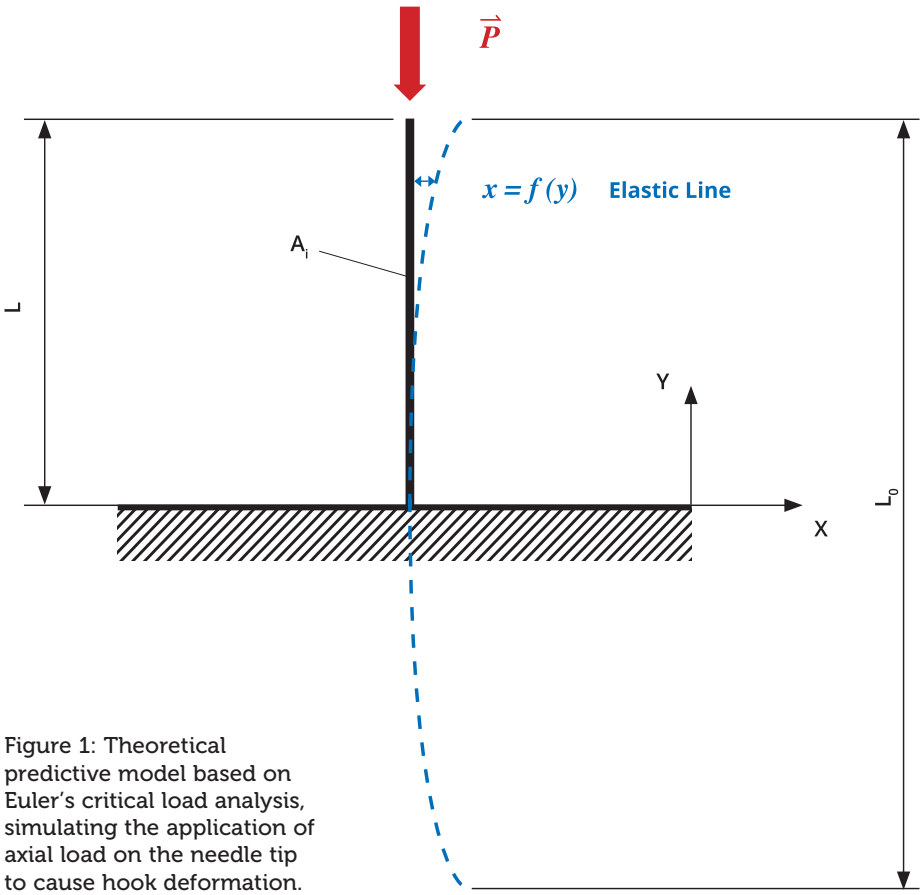

Figure 1: Theoretical predictive model based on Euler's critical load analysis, simulating the application of axial load on the needle tip to cause hook deformation.

The study used theoretical finite element analysis (FEA) predictive models to determine the difference between the two needle-tip designs in terms of hooking propensity. Both models were based on the experimental test setting, with a vertical load applied to control deformation. The theoretical prediction model was based on Euler's critical load analysis, simulating an axial load applied to the needle tip to cause hook deformation (Figure 1). Based on this model, the five-bevel needle design withstood an axial load 83% higher than the three-bevel needle design before achieving the same deformation magnitude (50 µm), as shown in Figure 2. This finding was confirmed by the numerical predictive model, which indicated that the axial load required to arrive at the same deformation magnitude (50 µm) would be 555% higher for the five-bevel needle than the three-bevel needle.

The five-bevel needle's lower propensity for hooking was further underlined by subsequent experimental testing. This testing also demonstrated that the predictive models overestimated the performance gap between the needle tips (Figure 3).

To analyse the penetration force, the different needle types were inserted into a specific fixing tool and moved at constant speed towards a plastic substrate (Figure 4). The insertion force was recorded as a function of penetration depth through a calibrated load cell, with the five-bevel needle registering a slightly lower needle penetration force (median of 1.12 N) compared with the three-bevel needle (median of 1.12 N). The conformance (variance) was found to be consistent between the two needle designs.

MATCHING PFS CHARACTERISTICS WITH FORMULATION

From a device design perspective, one of the clear takeaways from Stevanato Group's research is the importance of factoring primary container selection into the development process for injectable drugs. The ultimate end goal is to achieve a unified solution that incorporates all aspects of the container closure system and device at the desired tolerances and performance levels. This is dependent on a range of analytical techniques that must be used to understand the interplay between the various elements,

"Stevanato Group's SG Alba® and SG Nexa® product lines, for example, have been designed specifically to meet the requirements of high-value biologics, accommodating even large-volume (2.25 mL) high-viscosity formulations."

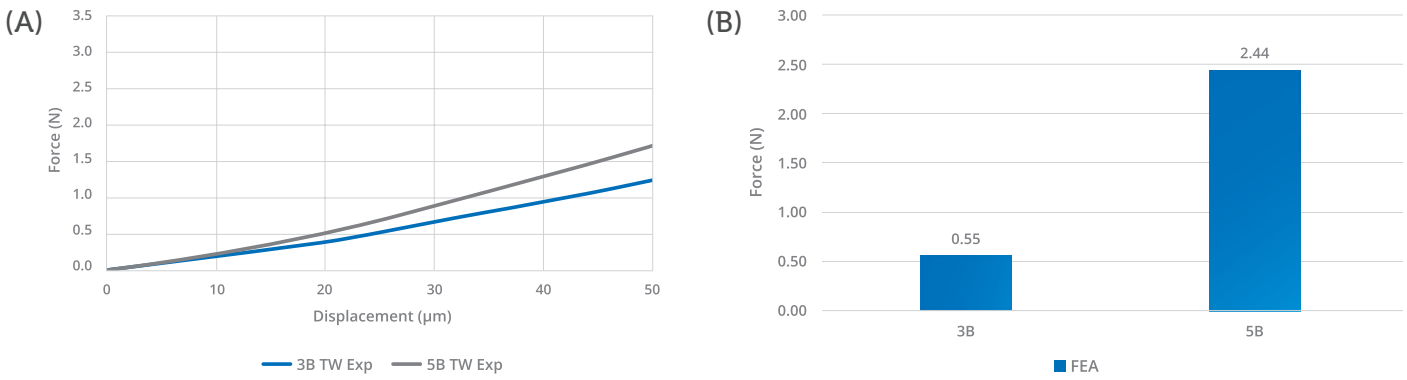

Figure 2: The finite element analysis confirmed a significantly lower hooked needle propensity for the five-bevel needle tip design compared with the three-bevel needle tip design. The trend (A) and external load (B) required to generate a hooked needle at 50 µm is significantly higher – approximately five times – for the five-bevel needle tip design than with the three-bevel needle tip design.

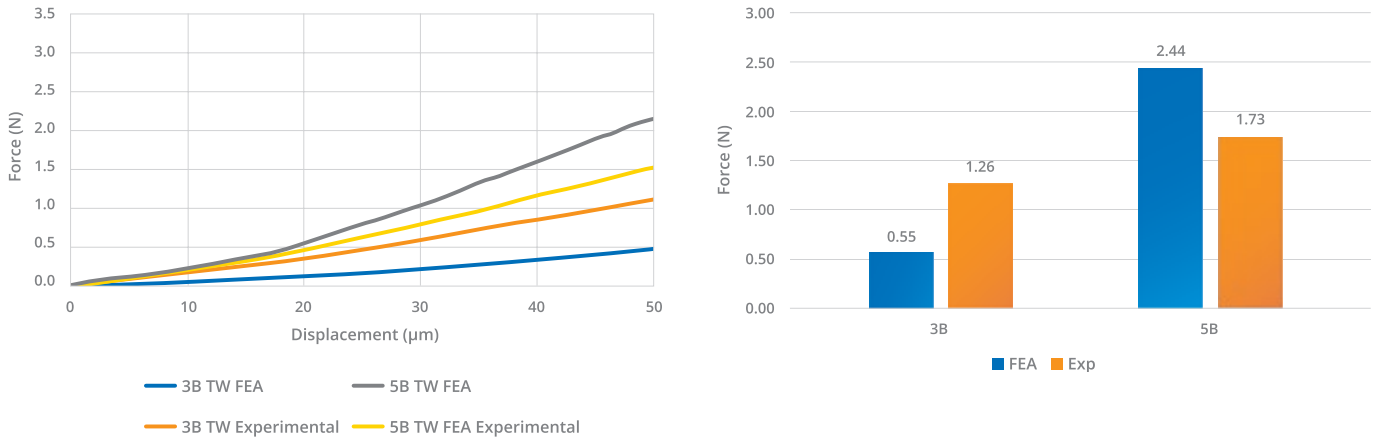

Figure 3: Comparison between numerical and experimental hooking propensity testing.

which in turn provides the knowledge base to optimise the choice of container for the specific drug product in question. If considered in the early stages of a project, this ensures the overall process is as streamlined as possible, avoiding potential disruption further down the line.

The need to bring specialist knowledge to the table early in proceedings underlines the importance of the relationship between project owners and supply chain stakeholders. Stevanato Group understands this dynamic, and is focused on its mission to provide its partners with a comprehensive suite of systems, processes and services that guarantee medicine integrity.

Stevanato Group's SG Alba® and SG Nexa® product lines, for example, have been designed specifically to meet the requirements of high-value biologics, accommodating even large-volume

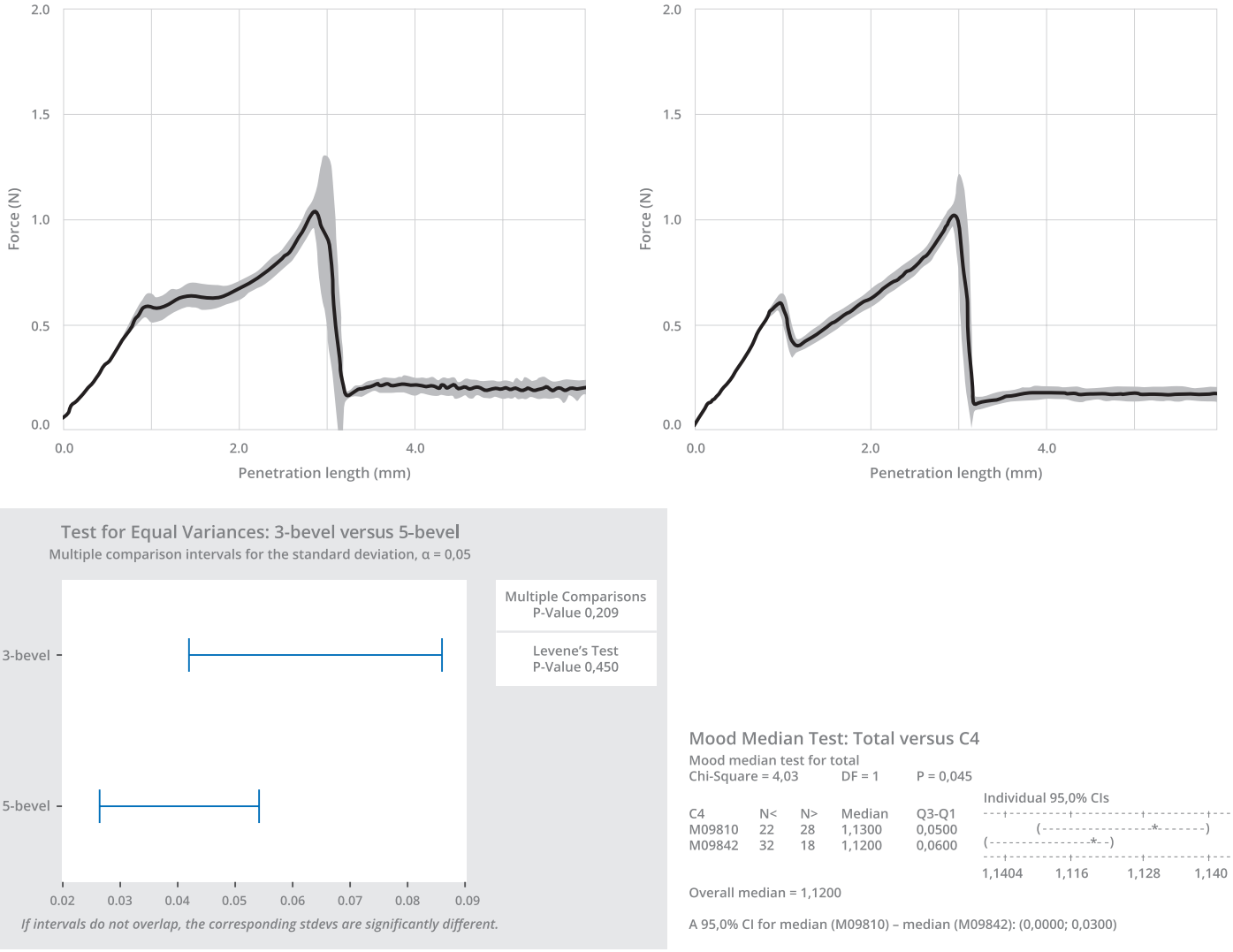

Figure 4: A penetration force test was performed to compare the three-bevel and five-bevel needle (thin walled). The penetration test is described by ISO 7684.

(2.25 mL) high-viscosity formulations. This is due to their high dimensional and geometrical accuracy, as well as enhanced properties relating to glideability, frictional fluid dynamics and extractables profiles. In addition, both product lines can be easily integrated into active and passive needle safety systems and into automatic drug delivery devices, such as spring-based autoinjectors.

These qualities ensure that Stevanato Group can de-risk the development process for its pharma partners, saving costs and accelerating product time to market. However, the ultimate stakeholder in this process is, of course, the patient. Chronic conditions affect the lives of millions of people and Stevanato Group's research serves as a reminder of the need to continually evaluate the injection experience with a view to reducing the discomfort that patients must repeatedly endure over an extended period. By continually identifying ways to advance needle technology, and by presenting this in a convenient, patient-friendly proposition – one that integrates syringe, needle closure and device – Stevanato Group will continue to help pharmaceutical partners deliver the day-to-day patient benefits that, together, add up to an enhanced quality of life.

ABOUT THE COMPANY

Founded in 1949, Stevanato Group is one of the world's largest providers of integrated containment and delivery solutions for the biopharmaceutical industry. From the beginning, Stevanato Group has developed its own glass-forming technology to ensure quality of the highest standards. Stevanato Group is home to a wide range of skills dedicated to serving the biopharmaceutical and diagnostic industries. It offers glass containers with its historic Ompi brand, plastic components for diagnostics and medical devices and contract manufacturing services for drug delivery systems, up to inspection, assembly and packaging machines. Stevanato Group also provides analytical and testing services that study the interaction between the container and drug and the integration into delivery systems, supporting the drug development process. By bringing together several skills under the same umbrella, Stevanato Group is able to offer unique solutions to companies and reduce time-to-market and overall cost.

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ABOUT THE AUTHORS

Anthony Vico is Technical Customer Support and Quality Management Supervisor at Ompi of America, Stevanato Group. He moved to the US to support Stevanato Group's growth in glass primary packaging. In his previous role he spent five years as part of the technical and quality assurance front end team at Stevanato Group in Italy. He has a wealth of experience in glass container technology for pharmaceutical use, supporting the design, development and manufacturing of ready-to-fill glass containers (syringes, cartridges, vials and special containers). He has strong expertise in technical and quality support, including regulatory and compliance from early-stage development to lifecycle management, dealing with parenteral medicines in drug delivery systems based on prefilled glass containers. He received both his Masters in Mechanical Engineering, Thermodynamics and Heat Transfer, cum laude, in 2011 and his Bachelors in Mechanical Engineering, cum laude, in 2009 from the University of Padua (Italy).

Enrico Barichello has a background in industrial engineering and a Masters in Management from the University of Padua (Italy). He has acquired a broad spectrum of skills in technical concepts and complex processes. Mr Barichello joined Stevanato Group in 2017 on an undergraduate internship. He has since worked on defining and co-ordinating all the activities required to bring products to market, bridging gaps between different functions within the company and aligning internal teams. He is now Product Management Specialist for Syringes, Components and Analytical Services.

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April/May	Drug Delivery & Environmental Sustainability	Mar 17, 2022
May	Delivering Injectables: Devices & Formulations	Apr 7, 2022

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FROM PROCESS TO PRODUCT: OPTIMISING PROCESS DEVELOPMENT STRATEGIES FOR VARIABLE DRUG-DEVICE REQUIREMENTS

In this article, Markus Goldinger, Senior Director of Process Development, and Erik Alexandersson, Assistant Manager of Process Development, at SHL Medical, discuss the benefits to process development provided by SHL's fully in-house, vertically integrated model, and how those benefits are applied throughout the process from initial design work to final assembly of the drug delivery device and primary container.

Combination product development follows a two-pronged approach: pharma takes the lead in drug discovery and formulation development and device companies do the same for the drug delivery system. On the device side, process development (PD) takes centre stage in ensuring tangible and intangible resources are translated into self-injection devices that reach the hands of patients across the many disease areas that require them. While changes relating to the device development process and/or its intermediary products entail myriad risks, SHL Medical takes a scientific and engineering-based PD approach to safeguard the execution of all stepwise procedures undertaken in autoinjector development.

In the autoinjector industry, where buzzwords like "streamlined operations", "end-to-end processes" and "vertically integrated services" are common and loosely used, device companies need to be challenged to substantiate such claims. For SHL Medical, three crucial elements are of prime consideration in its device development strategy:

- Formulation and mapping of processes
- Execution of these processes
- Ensuring the quality of the output of each step-by-step event leads to the carefully developed, final assembled device.

Early in the planning stages of a device project with a pharma partner, a sound PD strategy is required to ensure in-process controls are well integrated with the intended qualifiable and quantifiable outputs in the manufacturing stream. Although not commonplace, SHL believes that this should be the norm in the autoinjector industry.

CONVENTIONAL PROCESS DEVELOPMENT AT A GLANCE

In brief, PD refers to the exercise of creating a means to manufacture a specific product in a given quantity, involving the selection and

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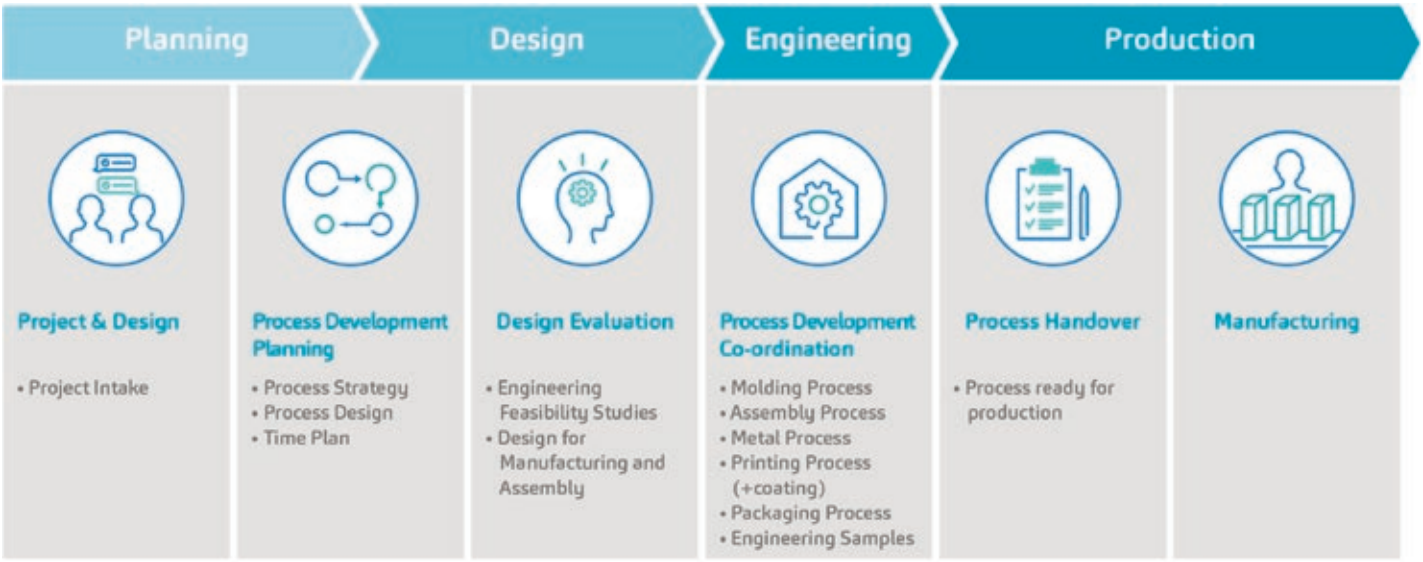

Figure 1: SHL Medical's overarching PD streams. *The validation phase and final assembly are not shown in this figure.*

sequencing of process steps from a repertoire of unit operations.[1,2] Conventionally, what this means is that a device will take a highly specific development stream contingent to the project requirements – a project that requires low-volume production will undertake a distinct manufacturing process different from that which requires high-volume production. Likewise, the overarching development process for a fully bespoke device project will differ from a project that leverages the technology of a modular platform offering.

Interestingly, when a device project requires not just one but a combination of these factors, the dependencies and interdependencies of upstream and downstream processes exponentially multiply and the complexities become increasingly apparent. In drug device development, the competencies of a device developer to address the requirements of the customer, primary container, branding or patient become important to the project's success.

When the research, development and formulation of a drug can take 10 or more years, a PD strategy that can adapt to the customer's needs is crucial to meet or even shorten timelines in combination product development, as well as mitigate project risks. For SHL Medical, the flexibility of processes is key to addressing the varying requirements of stakeholders, as well as ensuring that the manufacturing and assembly process is fully scalable.

A SCIENTIFIC AND ENGINEERING-BASED PROCESS DEVELOPMENT APPROACH

The PD strategy at SHL Medical (Figure 1) takes a scientific and engineering-based approach to ensure that the following critical considerations in combination product development are taken:

1. Delineate the primary function of the device with the end-user requirements in mind during early design work
2. Establish design requirements of pharma partners, establish robust and efficient processes, and deploy these into the manufacturing streams
3. Ensure successful design transfer and guide the execution of the penultimate steps for the customer to undertake in the combination product development process (i.e. final assembly).

> "SHL's participation in the market launch of more than 47 combination products – designed for a wide variety of disease areas and end users – provides the company with a contextual perspective that translates to cycles of assessing, verifying and testing devices and iterating designs of its device technologies."

A key highlight of SHL Medical's PD strategy is that it comprises both the device development aspect of a combination product project as well as the processes that directly concern its pharma partners. Specifically, this means that the PD strategy is streamlined not only for activities that constitute its autoinjector development streams, but also for the processes which would be undertaken by its customers, such as the final assembly of the autoinjector sub-assemblies with the syringe. It could be said that this PD strategy, which covers both the upstream and downstream processes of combination product development, draws from SHL Medical's years of experience in supporting the regulatory approval and launch of a myriad of self-injection devices.

SHL's participation in the market launch of more than 47 combination products – designed for a wide variety of disease areas and end users – provides the company with a contextual perspective that translates to cycles of assessing, verifying and testing devices and iterating designs of its device technologies. The depth and breadth of its cumulative experience have fortified SHL's focus on a scientific and engineering-based device development approach with the end user in mind.

MANAGING DEVELOPMENT RISKS THROUGH DFMA PRINCIPLES

On the device side of combination product development, the robustness of a device technology is just one side of the story. The other side relies on an informed system of processes and procedures. An informed

system means that the way the steps are undertaken downstream of the device project relies on insights from data upstream of the whole device development process. With an informed set of procedures, root causes can be identified from the upstream processes, preventing the impact of change versus the cost of change casualties.

In brief, various experts are sought to ensure that the manufacturing stream is seamless. This improves device manufacturability and mitigates project risks in relation to the impact of design changes versus the costs of running a device project. Changes brought about by data gathered from simulations in the early stages of a project will impact costs less than when a device part is already produced, or when the combination product is already launched on the market (Figure 2).[3]

While design for manufacturing and assembly (DFMA) concepts are not new, the PD structure at SHL Medical continuously adapts its scientific and engineering-based approach for DFMA. As a systematic solution to device projects, engineering feasibility studies, as well as DFMA evaluations, are carried out at the earliest practicable stages of product design.

An important highlight of this system is that DFMA concepts are explicitly outlined during the design proposal step in preparation for a device project's engineering phase. This ensures that tools and process flows are well co-ordinated and integrated with mass production requirements and tuned to manufacturing capabilities, ultimately supporting the original device design requirements.

An SHL device project will undergo stringent reviews by various subject-matter experts during its design phase, well before it enters the mass manufacture stage. This would include:

1. A review of the input materials, such as the plastic and metal components to be used throughout the manufacturing process
2. Injection moulding and assembly simulations by computational engineers
3. Moulding and assembly process reviews in accordance with historical data or prior knowledge from similar projects
4. Toolset review of mould structure by tooling experts
5. Review by process and automation experts of the assembly process, as well as equipment considerations for mass production.

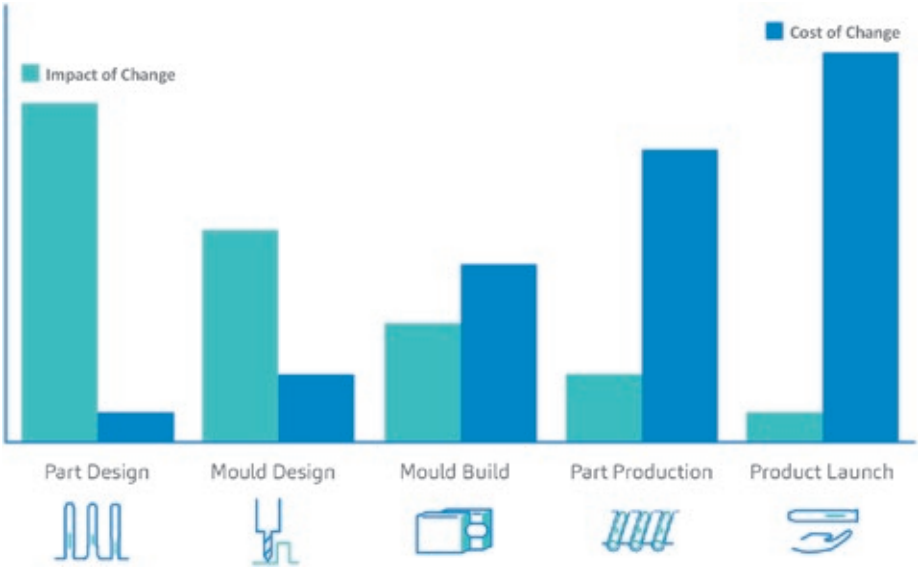

Figure 2: A generalised comparative graph representing the relationship between the impact of a change versus the cost of that change in combination product development, with a focus on the device aspect.

This framework generally serves as a "robust anchor" that guides the development – and prevents unintended issues – of an autoinjector project for a pharma partner. In accordance with the project and end-user requirements, a draft design will be made by the design engineers and a feedback loop will commence to evaluate the manufacturability of that draft design, as well as ensure that, downstream of the process, such a device can be fully assembled with the primary container carrying the drug.

Starting from the raw materials to be used, computer-aided engineering allows SHL's subject-matter experts to understand the injection processability of the input polymers, as well as minimise warpage and shrinkage of the moulded parts. Injection moulding simulations are run to analyse and visualise how much shrinkage and warpage to expect, given the current part material, design and expected processing conditions. The results of these simulations make it possible to consider a wider range of possible solutions early in the design phase of a project, and to come up with an optimised combination of design, material and processing parameters to produce the desired part.

A keen understanding of the assembly of each moulded autoinjector part is also developed early in the device development process. Similar to injection moulding PD, computer-aided engineering is used to understand and analyse the physical force requirements of the device assembly process, such as the assembly and separation force, given the known parameters of the part material and design. This way, the functional requirements for the assembly equipment are defined and automation experts can proceed with developing the right assembly equipment for small-scale studies, as well as the mass-production phase.

When it comes to establishing the actual process, scientific injection moulding is carried out to design, as well as to produce, the right tools that conform to the design specifications, based on the initial simulation results. The first iteration of the tool is constructed and the design of experiments (DoE) is performed to test variables in the moulding process and ultimately come up with a consistent approach that would not require any modifications once the process is set. On the other hand, assembly process assessment testing is also carried out on the autoinjector prototype to support the establishment of the requirements and acceptance testing for the equipment to be used in the actual assembly process.

For SHL, consistency in results is tantamount to ensuring a robust PD strategy. This comes from understanding the whole combination product development process and the causes of issues within its streams, leading to an informed PD strategy where both simulation and actual results meet – indicating a robust process that guides the fate of the stepwise procedures along the whole device development.

Figure 3A shows warpage trend simulation data for a specific part of SHL's modular platform device technology, and Figure 3B shows warpage data for its actual moulded part. This indicates a highly similar

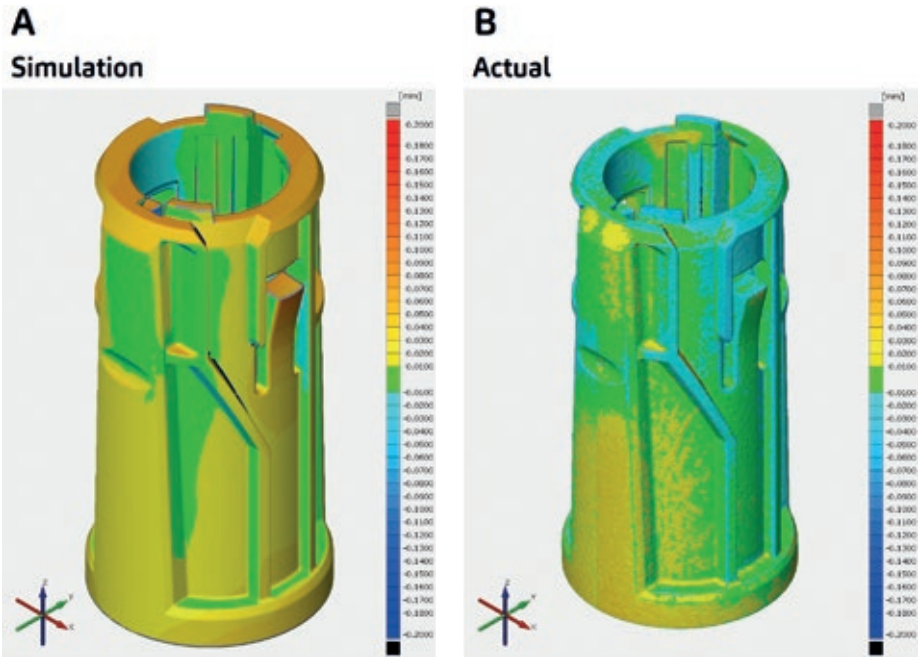

Figure 3: From simulation to actual results, a robust PD strategy ensures the desired output of the stepwise procedures along the whole device development.

> "In contrast to a linear device development process, SHL device projects are supported through an array of in-sourced capabilities, resulting in a parallel development process. These in-house capabilities ensure a vertically integrated system at SHL Medical, enabling various product development activities to have parallel, overlapping timelines."

warpage trend for both the simulation and the actual process output, validating the robustness of checkpoints put in place along the device development stream.

FULLY IN-HOUSE CAPABILITIES

In contrast to a linear device development process, SHL device projects are supported through an array of in-sourced capabilities, resulting in a parallel development process. These in-house capabilities ensure a vertically integrated system at SHL Medical, enabling various product development activities to have parallel, overlapping timelines. For SHL, these are what truly constitute an end-to-end system of processes. This is reflected in the establishment of PD from planning through to the validation stages of a device project.

Subsequently, this vertical integration of core capabilities enables intra-organisational communications where information, whether technical or not, can be relayed directly between different functions. Using this model, communication failure is minimised. Likewise, this means that feedback, such as verifying or confirming the information received, can be provided in a timely fashion to avoid process errors. While various organisational models suffer from asynchronous communications, the vertical integration of PD capabilities equips SHL Medical with streamlined, highly responsive lines of communication across the project. This presents a considerable improvement in logistics management and helps lessen lag or idle time over stepwise work operations.

A suitable analogy for describing PD within SHL is the relationship between the "spider and its web". With most device development functions in-house (representing the spiderweb), PD experts are able to "spider" over all the steps in the autoinjector development – optimising procedures and leveraging the know-how of each specialist department (tooling, automation, verification, testing, etc) to create a robust device. In a grander scheme, this presents a multitude of advantages, including an improved time to market for customer projects, as well as enabling SHL to execute various device projects in parallel to meet their independent timelines.

INTEGRATING PROCESS DEVELOPMENT AND FINAL ASSEMBLY

As a device developer with fully in-house capabilities, SHL's insight into the processes involved in the whole combination product development is unparalleled. Early in the autoinjector development, SHL's final assembly experts synchronise with project teams to ensure successful design transfer and execution of the final assembly of the autoinjector with the primary container. This ensures synchronisation of deliverables during various phases of the project's lifecycle, where SHL ensures a successful final assembly process for the pharma partner by guiding them through the process, as well as providing them with the design verification master report – technical documentation which is a suite of test methods, protocols and reports detailing the particular device.

There is depth and breadth in the informed device data that SHL analyses prior to releasing sub-assemblies to customers. This level of comprehensiveness is made possible by the expertise of SHL's design verification and testing experts, as well as the SHL-built testing machines and in-house test method development. The composite of these also enables SHL to better understand and dissect the complexities of device design. At present, SHL the flexibility in device testing options that extend to fully automatic device testing.

It was mentioned earlier that a key element of SHL's PD strategy is the integration of processes that have an impact not only on SHL but also on its customers. To reduce lead time for equipment design and procurement, SHL has the capacity to develop the client's device and the required final assembly equipment in parallel. This means that in the initial stage of the device development, SHL's in-house PD engineers collaborate closely with the equipment engineers to provide guidance on the assembly process and acceptance testing, ensuring that the final assembly process effectively aligns with the specifics of the device.[4]

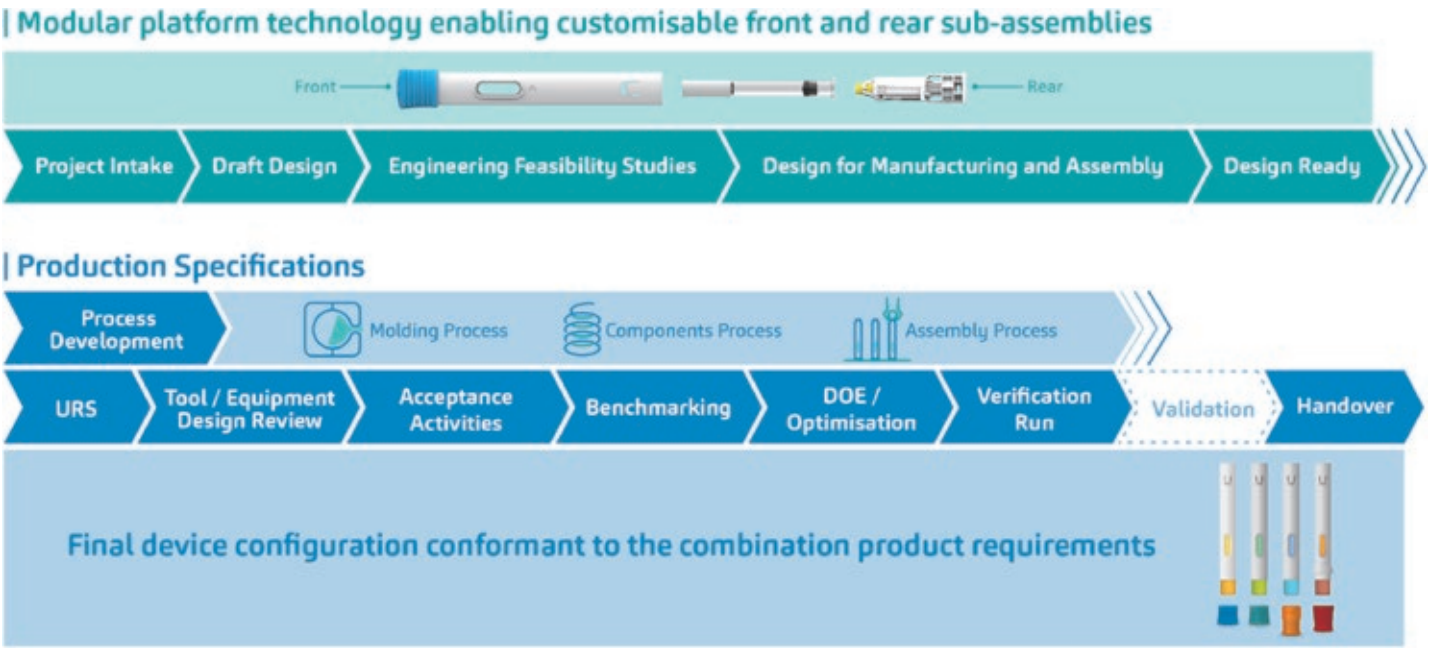

Figure 4: From process to the product, the Molly® modular platform technology, along with its robust PD strategy, allows for device configurations that conform to the highly specific requirements of any combination product. *Device renderings only, not representative of final product.*

A MODULAR PLATFORM AND A STREAMLINED PROCESS STRATEGY

It should not be forgotten that PD is always entwined with a device technology. In 2020, SHL Medical published a review of a modular platform technology; the Molly® autoinjector device.[5]

First launched in 2010, Molly® has since supported the development and regulatory approval of around 16 combination products covering a range of disease areas. Over the years, the Molly® technology has matured to become a modular platform that allows an appreciable level of freedom for customisation while maintaining its rotator-based mechanism. The device technology is a modular platform in the sense that both the front and rear sub-assemblies comprise five to six intricately designed parts that are configured to support flexibility in both design and manufacturing.

Molly® is a device technology with proven successes and launches in the market, demonstrating its credentials as a platform device offering that has been optimised over the years. This goes hand in hand with a robust PD strategy that ensures quality in the combination and interaction of its input variables. When it comes to autoinjectors, these input variables pertain to various layers of elements that are involved in device development, including the interacting parts that constitute a final assembled device and the network of processes involved.

With more than 20 years of experience developing drug delivery devices, SHL Medical is able to leverage a wealth of resources from within its organisation, coming in the form of platform data, subject-matter experts per variables in the PD stream and historical data that can be pulled from a multitude of past device projects that have shared various common elements. For SHL, this translates to a modular platform technology that enables the Molly® device to draw upon years' worth of testing platform parts and sub-assemblies, as well as iterating designs, to ensure a robust device offering. This has allowed SHL to develop a platform technology that allows for customisations in the front and rear sub-assemblies of the autoinjector, supporting an autoinjector device that can address the requirements of the primary container, industrial design and usability needs of the end user (Figure 4).

"Molly® is a device technology with proven successes and launches in the market, demonstrating its credentials as a platform device offering that has been optimised over the years. This goes hand in hand with a robust PD strategy that ensures quality in the combination and interaction of its input variables."

CONCLUSION

SHL believes that the key to delivering self-administrable medicines in the comfort of one's home is not only innovative device technologies, but also the sound processes that support the design, development and manufacture of combination products.

With the ever-changing needs and varying complexities in combination product development, an end-to-end process stream that includes a proven device technology enabled by a streamlined process that extends to the final assembly of the device and the primary container will be crucial to maintain a continuous and sustainable supply chain on both the drug and device development sides. SHL is disrupting the norms of the medtech space by providing solutions that cater to the end-to-end requirements of combination product development.

The authors would like to thank Kai Kiutra, Robin Wang and William Wang for their contributions to this article.

ABOUT THE COMPANY

SHL Medical is a world-leading solutions provider in the design, development and manufacturing of advanced delivery

devices, such as autoinjectors, pen injectors and wearable drug delivery systems. It also provides final assembly, labelling and packaging services for leading pharmaceutical and biotech companies across the globe. With locations in Switzerland, Taiwan, Sweden and the US, SHL has successfully built a strong international team of experts that develops breakthrough drug delivery solutions for pharma and biotech customers. These include advanced reusable and disposable injectors that can accommodate high-volume and high-viscosity formulations – and connected device technologies for next-generation healthcare.

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Erik Alexandersson is an Assistant Manager of Process Development at SHL Medical. He is responsible for assembly process development, a key stream in the design, development and manufacturing of parts and sub-assemblies that make up SHL's autoinjector device technologies. Mr Alexandersson brings a wealth of subject-matter expertise in process development relating to medtech devices, having 15 years of experience in the medical device industry. He holds an MSc in Embedded System Design.

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Nemera

THE ADDED VALUE OF A PLATFORM APPROACH: PEN INJECTOR CASE STUDY

In this article, Radosław Romańczuk, MD, Pen Platform Business Development Director; Severine Duband, Category Director, Devices; and Audrey Chandra, Category Project Manager, all at Nemera, discuss the development of the company's pen-injector platforms and how they are tailored to meet the customer's needs.

INJECTION AND PATIENT ADHERENCE

Parenteral administration is preferred in emergencies related to cardiac diseases or anaphylactic shock, and, in certain therapies, it is the only possible route of administration (monoclonal antibodies (mAbs), insulin, etc). In comparison with oral administration, injection has a number of significant advantages, such as better bioavailability, faster onset of effect, more predictable pharmacokinetic and pharmacodynamic profiles and avoiding the first-pass effect. The subcutaneous route of administration is highly preferable for many injectable drugs, such as trastuzumab, rituximab, bortezomib, granulocyte-colony stimulating factor (GCSF), immunoglobulins, epoetin alfa and heparin. For some drugs (e.g. insulin), the choice of administration route depends on the clinical circumstances.[1]

Over the last decade, we have witnessed a dynamic increase in therapies that make use of biological drugs – medicines derived from living cells or through biological processes.[2]

Polypharmacy and dosing frequency appear to be rate-limiting factors in patient satisfaction and subsequent adherence.[3] For self-injected drugs, the user interface plays an important role in the catalogue of factors that influence patient compliance, while reducing the complexity of the drug administration procedure has been highlighted as particularly important.[4]

A PLATFORM APPROACH TO MEET KEY USERS' NEEDS

In order to increase patients' compliance and adherence, as well as to accommodate pharmaceuticals' needs, developing a device platform needs to be strategically defined to ensure that it is designed for the maximum possible range of potential therapeutic areas and patient populations. This is to ultimately assure the device effectiveness. With this in mind, through user-evaluation studies, a platform should be tested by a broad, representative range of participants that reflects the diversity of potential device end-users. After performing this upstream work and early-stage diligence, a platform can be further examined using risk analysis to mitigate negative surprises in the late-stage development process.

"In order to increase patients' compliance and adherence, as well as to accommodate pharmaceuticals' needs, developing a device platform needs to be strategically defined to ensure that it is designed for the maximum possible range of potential therapeutic areas and patient populations."

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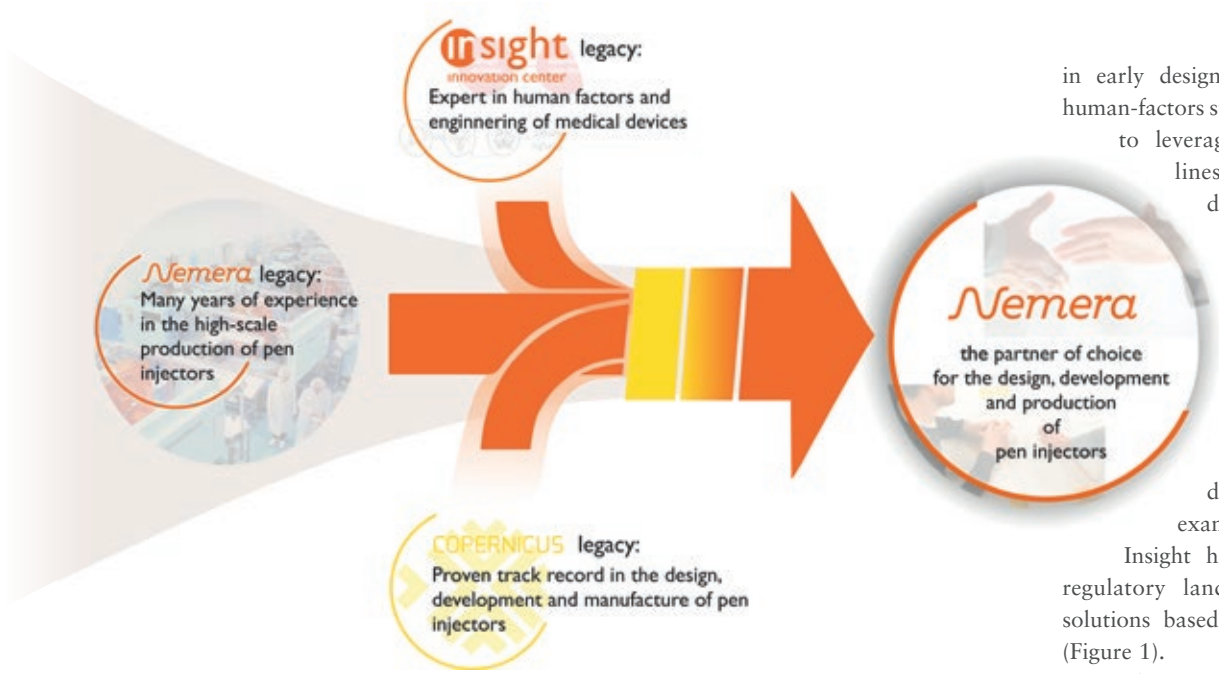

Figure 1: Comprehensive capabilities in the design and manufacture of pen injectors built through years of experience and targeted acquisitions.

Nevertheless, a platform should go through several adjustments and a few customisations to further translate it into a suitable combination product for both its target drug and the intended user population. The goal is to leverage baseline knowledge and generated data throughout the development of a device platform, then tailor it into a specific combination-product to meet pharma's needs.

NEMERA PEN INJECTOR PLATFORMS: DESIGNED FOR VARIOUS THERAPIES AND APPLICATIONS

Innovative technological solutions that offer a simple and intuitive user interface are easily adopted by patients. This favours adherence to therapy as well as safe and reliable dose delivery. Furthermore, successful technology can be applied to the development of other medical devices.

> "Nemera's long-standing experience in the high-scale production of tailor-made pen injectors serves as a strong foundation and legacy that steers the company to go the extra mile, continuing its story."

In this way, the combination of technological solutions that ensure functional parameters are specified in defined ranges that provide a platform for the development of new products.

The use of the existing platform for the development of other pen injectors based on technological solutions invented in the course of the development of this platform is associated with a number of significant benefits, amongst which the following deserve special attention:

- Reduced development time
- Lower development costs
- Reduced risks of developing a new pen
- Implementation of a user interface with market-proven acceptability.

By fostering the platform approach, coupled with Nemera's integrated end-to-end service programme offerings, the company helps its customers accelerate their specific combination product development programmes in the sprint to market.

Nemera's long-standing experience in the high-scale production of tailor-made pen injectors serves as a strong foundation and legacy that steers the company to go the extra mile, continuing its story. Thanks in large part to the two strategic acquisitions made in the last couple of years, Nemera is well on its way to fulfilling its vision of becoming one of the most patient-centric drug delivery device companies worldwide.

Due to the acquisition of Insight Product Development in 2019, Nemera's strength in early design research framework and human-factors strategy enables the company to leverage and tailor its product lines and platforms across different administration routes, including the recently acquired former Copernicus's (Szczecin, Poland) pen platforms. Insight Innovation Centre (Chicago, IL, US) brings its experience from the earliest development phase. For example, within the US market, Insight helps navigate through the regulatory landscape to develop fitting solutions based on US FDA prerequisites (Figure 1).

Furthermore, Copernicus's proven track record in the design, development and manufacture of pen injectors boosts Nemera's parenteral product portfolio and small series capabilities. The acquisition strengthens the company's proprietary product platform offering and establishes an operations footprint in Eastern Europe.

Nemera's story continues to reinforce its focus and purpose of always putting the patient at the centre of everything it does by becoming the partner of choice for the design, development and production of devices, including pen injectors.

Acquired by Nemera in October 2020, Copernicus has developed four product platforms for pen development and manufacturing. These include PENDURA AD®, PENONE®, PENVARIO® and PENHV®, which are designed for reusable and disposable devices for various therapies to meet key users' needs (Figure 2).

PENDURA AD® is Nemera's product platform, dedicated to the manufacturing of market-proven, reusable pen injectors, which integrates an automatic, spring-driven feature coupled with a side-activation button. The range of products developed from the PENDURA AD® platform includes pen injectors dedicated to the administration of insulin and its analogues, growth hormones and PTH analogues, amongst others.

In the disposable segment, PENONE® has been marketed for its multiple-use fixed-dosing feature, including a dose counter in addition to the ergonomic side-activation button, as well as the automatic, spring-driven delivery. Thanks to the presence of a dose counter, the user of each pen from the PENONE® platform has ongoing

Figure 2: Four pen injector platforms for various therapies to meet key user needs.

control of the number of doses remaining in the pen. As a result, the PENONE® platform is regularly chosen for the development of pen injectors dedicated to various drugs with a fixed therapeutic dose.

Continuing Nemera's story within the disposable pen injector space, its standard platform, PENVARIO®, is designed to be suitable for any drug with standard manual variable dosing. It is highly customisable for a wide range of applications, to match any drug administration. Thanks to its high flexibility in scaling production, Nemera is capable of meeting its customers' needs in both low- and high-scale production.

> "Developing a pen device based on existing platforms facilitates the application of such technological solutions that can significantly foster patient adherence to the therapy, hence the competitive positioning of the drug used for administration with a given pen."

Along with the rise of high viscous drugs and larger-dose volume administration, Nemera identified the need for low-force spring-assisted disposable pen injectors designed for ease-of-use. Therefore, using its long-standing experience in spring-assisted pen injectors, Nemera has developed the PENHV® platform, which incorporates a spring-assisted, non-extendable push-button on top of the pen to facilitate seamless, low-force injection. It provides constant speed delivery for both fixed- and variable-dose pens and is highly customisable.

Depending on the functional parameters defined together with the customer, a platform is selected that will be used to develop the pen injector with parameters strictly defined in the user requirement specification.

Each product platform can be used to design pen injectors dedicated to both generic and innovative drugs. Having Nemera's own design and development, own tool shop for the production of moulds, fully equipped plastic injection moulding setup and the possibility of both semi-automatic and fully automated production, means the company is able to provide a short time-to-market and cost-effective development of the pen injectors, based on its proven product platform, and to scale the production according to the actual customer needs.

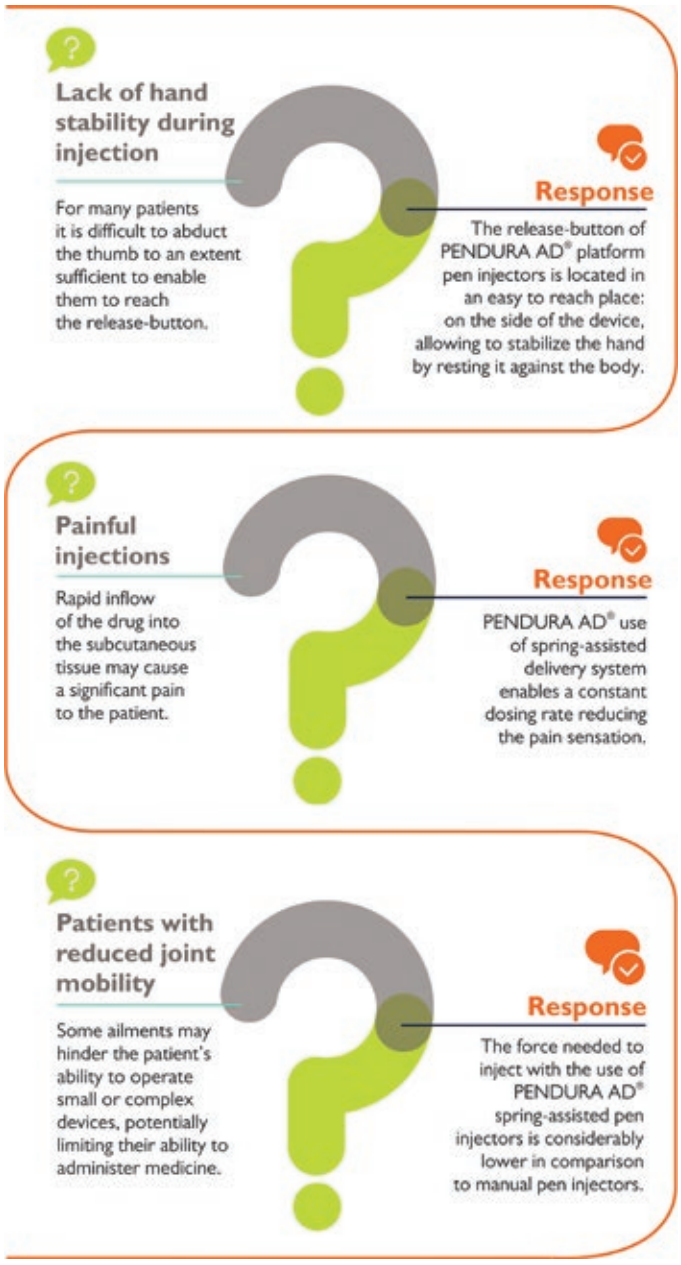

Figure 3: Improving patients' adherence through ergonomic solutions.

CASE STUDY: PATIENTS' BENEFITS TRANSLATED INTO SALES INCREASE

Innovative, user-friendly technological solutions invented during the development of the product platform are used in all pen injectors from a given platform. For this reason, the customer can be more confident both in terms of development timelines and its final results. Moreover, developing a pen device based on existing platforms facilitates the application of such technological solutions that can significantly foster patient adherence to the therapy, hence the competitive positioning of the drug used for administration with a given pen (Figure 3).

An example is the introduction of a pen from the PENDURA AD® platform to the European market. The manufacturer of the drug, whose domestic sales growth was three times lower than that of the market leader, decided to change the pen injector previously offered for use with its drug to a pen from the PENDURA AD® platform.

Within two years after the introduction of the pen injector from the PENDURA AD® platform, there was a decrease in the official drug price, which have could have significantly jeopardised the sales results of all the drug manufacturers. However, thanks to the introduction of the PENDURA AD® platform pen injectors, the sales value of the drug used with this pen increased, while the sales value of the company's competitors significantly dropped. This example shows the value for the user of the pen injectors from the PENDURA AD® platform, as well as the role of the injection devices in the choice of the brand within a therapy area (Figure 4).

It is worth mentioning that some detailed technological solutions can be imported

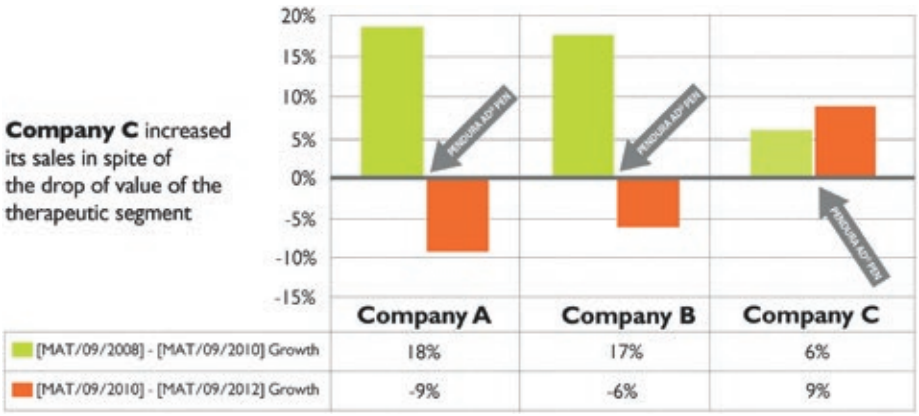

Figure 4: The impact of introducing a pen injector from the PANDORA AD® platform on the dynamics of drug sales.

to the new platform, dedicated to the production of other types of pen injectors. For example, the use of a technological solution that allows the ergonomic location of the dose-release button on the side of the pen, allowing the user to stabilise their hold on the pen by resting their hand against the body during dosing.

The positive assessment of this technological solution used in reusable pen injectors from PENDURA AD® platform, expressed by users in several post-market surveys, meant that the technological solution enabling the location of the dose-release button on the side of the pen was also used in the PENONE® product platform dedicated to disposable fixed-dose pen injectors.

NEMERA: YOUR PARTNER OF CHOICE IN DESIGN, DEVELOPMENT AND MANUFACTURING

With the integration of Copernicus and Insight Product Development, Nemera offers the highest quality standard for its customers and patients. The pen injectors are developed based on proven technological solutions, and their development is carried out by experts in the field of human factors engineering, design and production.

Looking to the future, Nemera is actively working on innovative platforms, by leveraging existing and discovering novel techno-bricks. Tapping into the converging trend of digital health and connectivity, the company is currently developing advanced solutions with the ultimate purpose of improving patient outcomes through offering robust and easy-to-use solutions.

ABOUT THE COMPANY

As a world-leading drug delivery device solutions provider, Nemera's goal of putting patients first enables it to design and manufacture devices that maximise treatment efficacy. Nemera is a holistic partner and helps its customers succeed in the sprint to market with their combination products. From early device strategy to state-of-the-art manufacturing, Nemera is committed to the highest quality standards.

Agile and open-minded, the company works with its customers as colleagues. Together, they go the extra mile to fulfil its mission.

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ABOUT THE AUTHORS

Radosław Romańczuk, MD, Pen Platform Business Development Director, has over 20 years of experience in the life sciences industry. He is the author of the concept of a series of pen injectors, produced by Copernicus, which was acquired by Nemera in 2020. The development and usability of medical technologies is perceived by Dr Radoslaw in three dimensions, representing his versatile experience – the perspective of a medical doctor, the perspective of the person managing marketing and business development in a biotechnological company, and the perspective of a person in charge of development of pen injectors franchise within a patient-centric device manufacturing organisation.

Séverine Duband is Marketing Director for drug delivery Devices at Nemera, steering overall category strategy, product portfolio and innovation development for five key delivery routes. She has been leading the parenteral segment at Nemera since 2018, focusing on proprietary products such as safety systems, pen injectors and on-body injectors. Ms Duband graduated from Emlyon Business School (Lyon, France) in 2004, and joined Nemera's Global Marketing team in 2018 as a Global Category Manager, focusing on the parenteral segment.

Audrey Chandra is the Category Project Manager at Nemera. She joined Nemera in 2019. Ms Chandra graduated from the Faculty of Medicine, Atma Jaya University (Jakarta, Indonesia) and pursued her master's degree in strategy and business development at Toulouse School of Management (France). With her dual competencies, she is in charge of providing strategic support for various targeted marketing projects. Additionally, Ms Chandra actively works on diverse content management along with communication activities co-ordination.

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CAMBRIDGE DESIGN PARTNERSHIP

FORMULATION & DEVICE DEVELOPMENT: A SYMBIOTIC RELATIONSHIP

In this article, Caroline Zakrzewski, Drug Delivery Devices Scientist at Cambridge Design Partnership, considers the interaction between formulation and device development and the challenges that drive innovation in the field. Her work frequently sits in the overlap between formulation and device development, navigating the interwoven steps that lead to the sweet spot, where formulation and a device work in tandem, providing safe and effective delivery of the drug.

It's often been said that formulation development would be easier with the "final" device, and developing the device would be easier with the "final" formulation. It's a nice idea, but it could miss the symbiotic effect that each can have on the other – driving innovation in both fields (Figure 1).

Here we will explore some of the key topics that arise when developing a drug and device combination product, and how the iterative development of formulation and device can be beneficial for all the key stakeholders.

PRIMARY CONTAINER SELECTION

In its most basic presentation, a liquid formulation can be stored in a vial or ampoule and extracted by a syringe just before administration. This is easy to manufacture but does not consider all the needs of the end user. It was the method used 100 years ago, when the first insulin injections were carried out in humans and, whilst the fundamental mechanism remains the same, the development in primary containers has significantly improved.

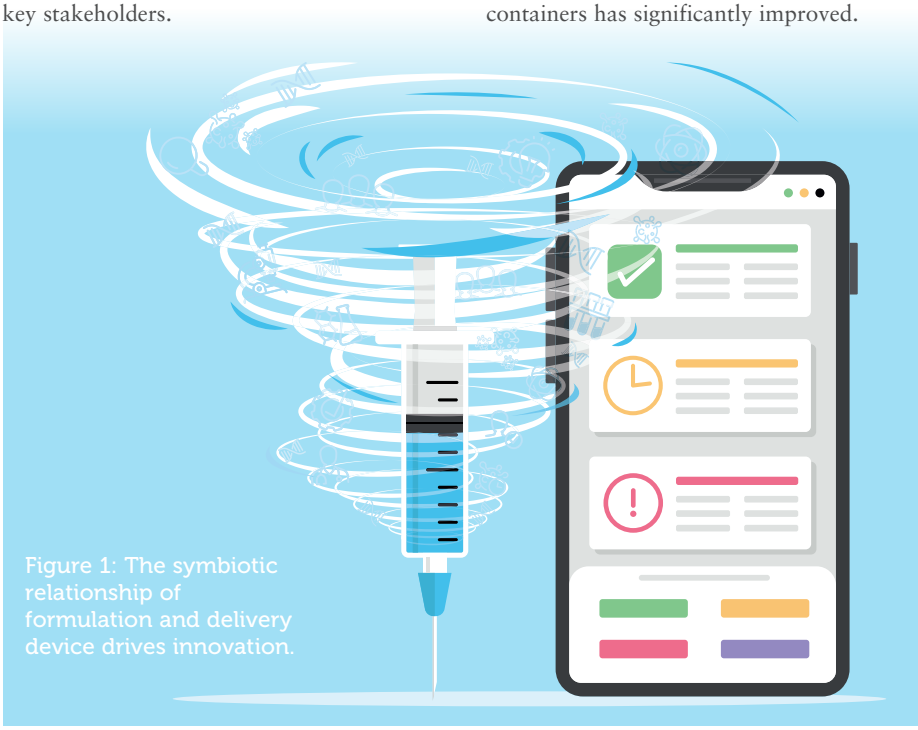

Figure 1: The symbiotic relationship of formulation and delivery device drives innovation.

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Most primary containers used for storage of small-volume injectables are made of glass. The formulation's influence on the choice of glass primary container can be as simple as UV sensitivity, driving the use of amber ampoules or vials, or more complex, with interactions on a molecular level seen with silicone or tungsten oxides. Commonly, liquid silicone is used to coat the inside of syringes and cartridges so that the plungers can advance to administer the dose. The silicone can form microdroplets in the formulation, providing nucleation sites and initiating agglomeration of larger molecules, such as biologics. Overcoming this interaction may involve moving to a primary container coated with baked-on silicone, which is chemically bonded to the glass surface, or to more recent silicone-free developments such as the GORE (Newark, DE, US) ImproJect Plungers with Schott's (Mainz, Germany) syriQ BioPure® silicone-free syringes. There's a similar consideration for the sensitivity of the drug to tungsten oxide residues deposited during the glass-forming process. Spiking the formulation with representative residues can give an early warning of whether this will be an issue, and alternative manufacturing methods can be used, although this increases cost.

The requirements for a sterile, single-use syringe to draw up from an ampoule or vial led to the development of plastic syringes, which are cheap to mass produce and customise, and much more robust for handling and transport. Typically made from polypropylene, these can be unsuitable for prefilled syringes (PFSs) because the moisture vapour transmission rate can cause concentration changes over time and absorption of the molecules onto the internal surfaces of the syringe can occur.

More recently, advances in polymer technology have sought to overcome these issues. Cyclic olefin copolymer (COC) and cyclo olefin polymer (COP) are gaining traction in the pharmaceutical industry as viable alternatives to glass PFSs. The tighter dimensional tolerances and more flexible customisations of these syringes give them advantages in more complex delivery devices, with a growing body of stability evidence behind them to address business risk concerns.

DELIVERABLE VOLUME

For subcutaneous or intramuscular injection, the delivered volume has perhaps the largest influence on the type of device selected to administer the formulation. There is a broad classification in the USP that small-volume parenterals are those which have a volume under 100 mL, but the volumes discussed here focus on the range of 0–10 mL.

Consider a delivery volume requirement of a straightforward liquid formulation. The most basic presentation would be a vial or ampoule and a syringe, where the vial (not reasonably constrained by size) could hold several doses. But what if this isn't suitable? As well as reducing the number of required components, PFSs reduce the number of use steps and the potential for use error associated with the vial and syringe presentation. However, they do bring additional challenges related to formulation stability. The requirement to be able to inspect the contents of the syringe prior to administration prevents the use of amber-coloured materials, which would have been present in the vial format to prevent the formulation being degraded by UV light. This can be resolved either through tertiary packaging or changes in the formulation – the former being easier than the latter.

PFSs can be used on their own or within autoinjectors that carry out many of the use steps required in a repeatable and reproducible way, improving patient compliance. It's possible, as shown by Teva (Petah Tikva, Israel) with Copaxone® (glatiramer acetate injection), to launch the PFS as a stand-alone presentation prior to investing in the development of an autoinjector. Most autoinjectors currently on the market are for delivery volumes up to 1 mL, either subcutaneously or intramuscularly. There are systems that can deliver larger volumes, but these come with challenges; a high flow rate during administration can cause local pain and discomfort at the injection site, and for slower flow rates it may be difficult to maintain the injector position for the time it takes to inject.

As the delivered volume requirement increases to 2 mL and above – particularly common in biologics – there's a decision to be made. With an injection of up to 2 mL completed within 15 seconds, the reaction of the injection site to the introduction of this volume becomes a factor in the ability to effectively deliver the formulation. The 5 mL subcutaneous injection of Roche's (Basel, Switzerland) Herceptin (trastuzumab) has shown that changes to the formulation, such as the addition of hyaluronidase, can help subcutaneous dispersal, but this isn't always possible or acceptable to the patient. There's a tendency to increase the formulation concentration to reduce the volume, which can be effective but goes hand in hand with an increase in viscosity. Increasing the viscosity affects the force required to deliver the formulation, particularly through thinner needles, hindering the appropriate administration in a manual injection and stretching the capabilities of many autoinjectors. In response to this, thin or ultra-thin walled needles have been developed, but there are physical limits constraining innovation in this area.

If the requirement is for delivery of more than 2 mL, particularly for a subcutaneous delivery, it's sensible to consider whether a bolus injector would be appropriate. Attached to the body for a short period of time, these devices deliver a larger-volume injection over a set time of minutes or hours, and have capacities up to 10 mL, sometimes more. Examples of these types of injector can be seen in the development of West Pharmaceutical Services' (Exton, PA, US) SmartDose®, the Enable Injections' (Cincinnati, OH, US) delivery device and BD's Libertas™. In a similar class are the ambulatory pumps which provide a consistent, fixed-rate infusion of a drug into the body and are commonly used for insulin delivery.

DRUG CHARACTERISTICS

So far, the consideration has been for formulations that are stable as liquids, but this isn't always possible due to either the nature of the active ingredients or the time available in development. The current crop of covid-19 vaccines is a good example of this latter point.

> "The move towards more patient-centric treatments, where the patient is not constrained to having their treatment delivered in a healthcare setting or even by a healthcare professional, is driving innovation in both formulations and devices."

Lyophilisation is a well-established process with the drug presented to the user in a dry powder form for the addition of a diluent to reconstitute the formulation immediately prior to administration. The knowledge and experience of manufacturers around the lyophilisation in vials, as well as the capital investment needed for the infrastructure to support this, creates inertia in the introduction of this type of formulation. The number of use steps required for reconstitution is significantly more than for just a vial drawn up into a syringe, requiring transfer of the diluent from a second container followed by agitation to ensure a homogenous solution. This increases in significance if the resulting solution is to be administered in several small doses. The need for a more user-friendly administration of this type of formulation drove the development of dual-chamber systems and the devices that contain them. Taking inspiration from the PFS model, dual-chamber systems were developed to reduce the use steps and materials required to reconstitute and administer this type of formulation.

Dual-chamber systems contain both the dry powder drug and diluent in separate chambers during storage to maintain the shelf life and stability of the drug product and facilitate the integral reconstitution though a simple use step prior to administration. Common systems include a glass syringe or cartridge with an external bypass – a channel that allows the diluent to transfer past the separating plunger and into the dry powder chamber. Adding only enough components needed to facilitate the administration, devices such as Vetter's (Ravensburg, Germany) Lyo-Ject® embody the core functionality of this type of system. Systems such the Credence MedSystems' (Menlo Park, CA, US) Companion® series build on this principle, linking novel internal bypass technology with the passive needle safety that is becoming a requirement in many healthcare settings.

Like the PFSs on which they are based, dual-chamber systems are expanding into autoinjectors, with products such as Pfizer's Genotropin® (somatropin) pen guiding the user through the reconstitution steps and enabling them to dial subsequent doses for delivery. The challenge of the current dual-chamber systems goes back to deliverable volume. In the current format, the need for both the diluent and dry powder chambers to have sufficient space to contain the deliverable volume makes the devices bulky, particularly as volumes increase.

HOW WILL THE DEVICE BE USED?

The move towards more patient-centric treatments, where the patient is not constrained by having their treatment delivered in a healthcare setting or even by a healthcare professional, is driving innovation in both formulations and devices. This can be seen most clearly in the range of treatment options that exist for Type I diabetic patients. Although the basic vial and syringe format is still common, disposable and reusable injector pens, such as Eli Lilly's KwikPen (insulin lispro injection) or Novo Nordisk's NovoPen respectively, are widely available with on-body pumps, such as Medtronic's MiniMed™ providing additional options. The device developers have challenged formulators to develop insulin formulations that are stable at body temperature, to support the use of ambulatory pumps. In return, the formulators have challenged device developers to accurately deliver single doses of increasingly concentrated solutions, with the move from a standard U-100 to U-500 and even U-1000 formulations.

No discussion of devices would be complete without mentioning connectivity. The recent trend towards connected devices allows feedback to the user – normally using an app – on how well they are adhering to their regime. This can also provide information to the monitoring physician on the suitability of the treatment format, with the potential to provide in-market trends that drive further formulation and device innovations.

THE FUTURE

So, what is next? Innovation in formulations and their devices is far from finished, as therapies become more complex and current markets experience a trend towards patient-centric self-administration. We've seen how previous limits of acceptable subcutaneous injection have been stretched by Roche's 5 mL Herceptin (trastuzumab) formulation, how devices have assisted in the delivery of highly viscous formulations previously unable to be administered by manual injection, and how the introduction of integrated reconstitution has allowed patients more freedom over their treatment profile.

On the horizon are integrated systems that overcome the challenges still present in reconstitution by the patient, devices that help to maintain a formulation suspension over time in a bolus injector, connected devices that provide tangible data on patient compliance, and more cost-effective primary container technology to support the next generation of formulations.

"Innovation in formulations and their devices is far from finished, as therapies become more complex and current markets experience a trend towards patient-centric self-administration."

The challenges that formulators and device developers set for each other are driving innovation in the field, and it is exciting to play a part in this process.

ABOUT THE COMPANY

Cambridge Design Partnership (CDP) is an end-to-end innovation partner focused on helping clients grow. Some of the world's largest companies trust CDP to design and develop their most important innovations. Located in Cambridge (UK) and Raleigh (NC, US), CDP specialises in the consumer, healthcare and industrial markets. Its multidisciplinary teams have expert knowledge to identify opportunities and overcome challenges throughout the product development and manufacturing process.

ABOUT THE AUTHOR

Caroline Zakrzewski is a Science Consultant with Cambridge Design Partnership. Holding masters degrees in Chemistry and Pharmaceutical Engineering, she specialises in drug delivery devices. Her career includes the co-ordination of multidisciplinary groups involved in the design, development, industrialisation and commercialisation of PFSs, autoinjectors, pen injectors and a range of inhalation devices. Ms Zakrzewski has a keen interest in the establishment of robust processes to facilitate the technical transfer of products into manufacturing.

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PATIENT-CENTRICITY: THE IMPORTANCE OF HUMAN FACTORS IN THE PANDEMIC ERA

In this article, Marcus Agunloye, Senior Human Factors Engineer & Industrial Designer at Oval Medical, and Asmita Khanolkar, Senior Director, Cambridge Pharma, SMC Technical Strategy & Commercialization, discuss how patient-centricity is at the heart of drug delivery device design and innovation, and how the global pandemic has highlighted the importance of patient-centric development in this field.

The drug delivery device market is expected to grow tremendously, bringing novel technologies and therapies to life. The key factors driving this innovation peak include a trend towards moving care out of hospitals and into patients' homes, adoption of smart devices, predictive data analytics, targeted therapeutics and personalised medicine. Patient focus is a common theme in all these drivers. As we begin this decade, it is clear that patient-centricity is at the heart of all innovation and one of the most important considerations throughout the development process. However, there is a lot of work still to be done in this field to truly understand the concept, process and what exactly the success criteria are towards a patient-centric development. The pandemic has opened our eyes to the importance of human factors considerations even further.

> "There is a lot of work still to be done in this field to truly understand the concept, process and what exactly the success criteria are towards a patient-centric development. The pandemic has opened our eyes to the importance of human factors considerations even further."

MARKET TRENDS

Global trends continue to move medical care from hospitals to homes, with the pandemic threat of covid-19 the push for virtual care, longer time between hospital visits, and at-home care for chronic diseases has increased. An example is the transfer of chemotherapy treatment from hospitals to homes, which has led to a requirement for subcutaneous delivery of cancer treatments as opposed to intravenous delivery in a hospital setting. This trend is generating a need for devices for self-administration that can deliver large volumes of formulation and drug containers that can withstand high pressures in order to provide acceptable delivery times. Successful high-pressure delivery device systems will determine the success of this important transition from hospital to home.

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> "The three effects of the covid-19 pandemic, namely isolation, virtual care and remote learning, are all elements that amplify the problems of self-administered devices."

Smart devices are an area of opportunity to enhance user engagement with their treatment process. Using a smartphone or other digital device can offer the patient an expanded user interface, including useful functionality such as dose tracking, reminders and training information, and can also offer opportunities for the prescriber to understand adherence when care is moved to the home. However, this relies on two things from the patient – access to technology and their engagement with the smart system. Whilst the adoption of smartphones is becoming more and more widespread, there are still patient populations that may struggle to afford an up-to-date smartphone, so understanding patient access to technology must be a key consideration in the inclusion of this type of technology into a drug delivery device.

Whilst adding further functionality and data information for the user through a connected device may seem like an easy way to improve the patient experience, it is important to understand if the patient wants to engage with this. Some patient populations may find the steps required to set up a connected device confusing or taxing, or may have a general reluctance towards technology that might make a connected device a barrier to adherence rather than a motivator. Overall, there may be compelling use cases for the integration of digital systems into drug delivery devices, but it is important to understand how the patient population will respond to it by exploring the area with them and considering the full range of costs and benefits associated with this type of integration before moving forward with it.

HUMAN FACTORS CONSIDERATIONS IN THE PANDEMIC

Human factors considerations are even more important than ever in identifying specific patient needs, particularly in the current global pandemic. The three effects of the covid-19 pandemic, namely isolation, virtual care and remote learning, are all elements that amplify the problems of self-administered devices. Under the conditions of the pandemic, patients couldn't be trained in hospitals and overall access to healthcare practitioners (HCPs) was limited, yet more and more therapies started moving towards home care. The pandemic emphasised the need for intuitive devices that need only very minimal training. Crisis devices are often used by a carer, a teacher or even a passer-by, and again, in such cases, intuitive-to-use devices are needed for effective dosing.

In addition, the effect of isolation and emotion on the use of the device requires a non-threatening, welcoming, integrated functional approach. The pandemic also highlighted the effects of disparity where technology may not be universally available. Not everyone is technology savvy, and digital literacy may be a big factor in the correct use of the device. In addition, diversity factors are more exaggerated with remote site limitations, spread of information and patient involvement. It is clear that the one-size-fits-all approach does not work with diverse patient populations, including paediatric and geriatric populations, and a range of users from patient to carer to community pharmacist, and a variety of dose regimens are required.

ELEMENTS OF A "PATIENT-CENTRIC" MODEL

The four important areas of considerations for human factors include patient safety, patient outcomes, patient adherence or compliance, and finally, the overall patient experience (Figure 1). Patient safety and therapy outcomes are the first layers of consideration. Current complaints vary with the application and include both crisis and chronic use. For life threatening diseases, obviously this can be profoundly serious and have serious consequences. For emergency-use devices, it is imperative that the accurate dose is injected at the correct depth, intramuscularly or subcutaneously. Some of the human factors considerations in these applications focus around patient populations. Patient physiology is different in children compared with adults, and important considerations of needle-to-muscle depth accuracy repeatability when overcoming population diversity is an important factor.

Some of the challenges with glass containers include breakage and repeatability issues due to siliconised rubber. In high-pack glass syringes, patients have experienced variability of injection times, resulting in wet injections. In the case of biologic drugs, this can potentially cause immunological response due to wet injections. Other impurities such as tungsten in needle-staked glass containers can pose issues for the stability of delicate drugs, such as biologics, and result in degradation of the drug and unwanted therapy outcomes. Finally, use errors are on the rise due to the pandemic and lack of training, this demands intuitive devices.

Patient adherence and overall experience are the second layers of considerations and equally important. Particularly with self-administered devices, ease of use becomes a priority. Devices need to be easy to use without training, or with minimal training, should promote adherence, be non-intimidating and perform robustly and reliably every time for a positive overall experience.

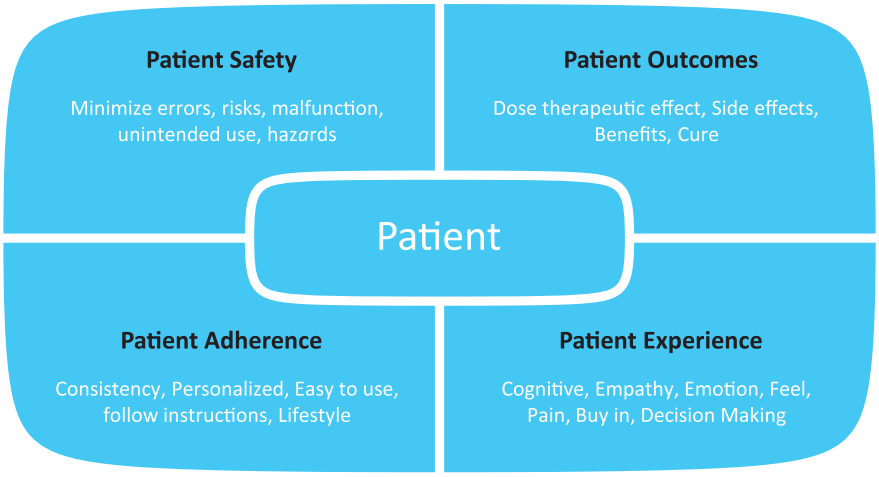

Figure 1: Elements of a patient-centric model.

"Using patient insights on cognitive and emotional needs, lifestyle, population diversity, technology access and adoption skills, reliability and sustainability can help add further benefits to the therapy."

Long-acting injectables provide a better overall patient experience due to a reduced number of injections. However, it is important to focus on adherence and if the patient will remember to administer their injection regularly each month, and to create a feedback loop so the prescriber knows that the patient is receiving their treatment. Training decay can also be an issue if the patient only uses the autoinjector once a month – will they be able to remember how to use it again a month later?

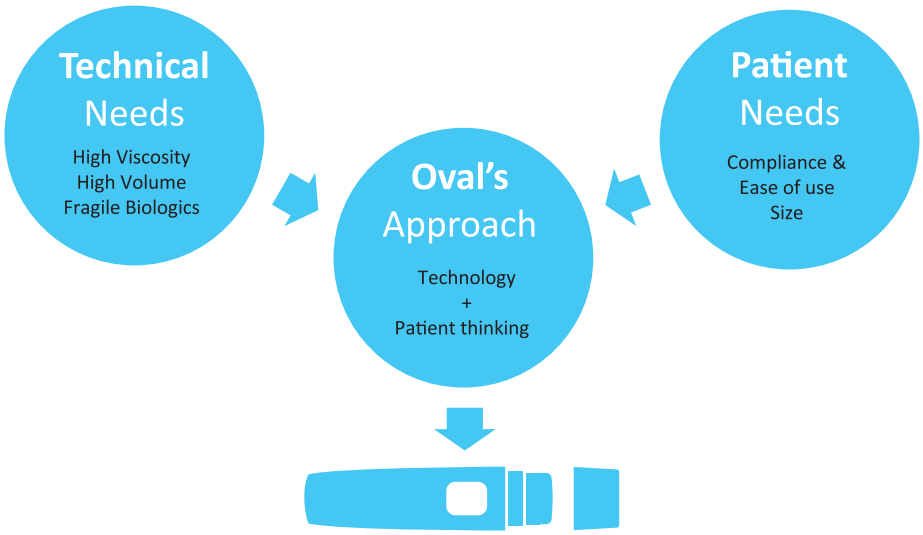

Figure 2: Incorporating patient needs for intuitive autoinjector designs.

First and foremost, the best approach to solve this is to make the device as simple and intuitive to use as possible. This can also be supported with training the patient, such as having an HCP guide the patient through the first few injections and by having robust information available for the patient to support themselves, such as training videos and clear instructions for use.

A patient-centric model requires additional elements with the patient at the heart of the thought process, and designing around the patient. Using patient insights on cognitive and emotional needs, lifestyle, population diversity, technology access and adoption skills, reliability and sustainability can help add further benefits to the therapy. Oval's approach to device development combines a deep understanding of the patient's needs, coupled with the technical needs when developing patient-centric autoinjectors that can be customised to deliver a wide range of drug formulations, including fragile molecules for both subcutaneous and intramuscular injection with high viscosities and a wide range of delivered volumes (Figure 2).

Figure 3: Key design features with a human approach.

PATIENT-CENTRIC DESIGN THINKING

To put the user case at the heart of the process, the device design must satisfy functional, cognitive, aesthetic and emotional balance. This requires flexibility in the design space for both the inside and outside of the device. Moulded primary drug containers provide both flexibility of container size and shape, and control of tolerances for reliability of repeated use. The inside mechanics need to deliver the therapy in optimised delivery time, depth and bolus size.

The outside is equally important for key design features with a human approach, such as those shown in Figure 3. Figure 4 shows the human factors attributes applied to the product design.

Key Characteristics

1. Curved Top Body
2. Tactile Waist
3. Cap smile
4. Cap Tactile Proudness
5. Frosted Cap
6. Front View Symmetric Body
7. Crisp Edges (For smaller devices)
8. Tension Viewing window
9. Down Force Dexterity Friendly

Figure 4: Human factors attributes applied to design.

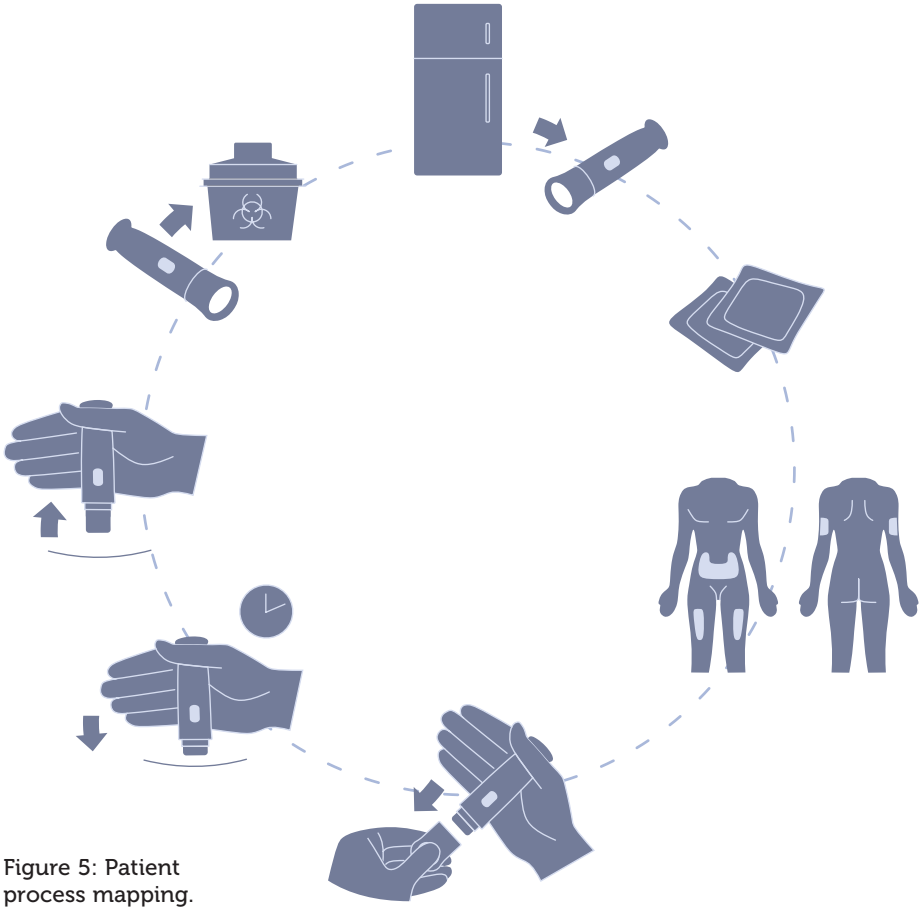

Figure 5: Patient process mapping.

The combination of innovative design coupled with small footprint, quiet devices that provide consistent delivery performance for patient safety, outcome, adherence and preference is a crucial consideration.

PATIENT PROCESS MAPPING

Patient process mapping is a method that outlines the process of how the autoinjector is used, such that the inputs of the three elements that affect device use – the user, the use environment and the user interface – are captured in the process. Early-stage field work is a must to put the patient's needs to the forefront at each stage of autoinjector design.

A key focus in the early stages is getting feedback and input from patients and users as soon as possible. Through fieldwork, such as interviews with patients, caregivers and HCPs in their living and working environments, insight into the patient's treatment journey can be gained. This can be used to map out each of the touchpoints the patient interacts with during their treatment, identifying pain points and difficulties they may encounter along the way. From this, the patient's needs throughout the process can be identified, taking into account the basic need to receive the dose, along with their emotional needs related to their treatment, and an understanding of issues with treatment that may become barriers to adherence (Figure 5).

There are many examples of such early-stage insights that can have a real effect on the design approach of an autoinjector. Chronic versus crisis applications pose different requirements. Looking at a crisis autoinjector that patients must always carry with them, Oval found users adopting a range of coping strategies for how to store their devices when carrying them day to day – they were using anything from pencil cases to zip-lock bags to Tupperware containers in attempts to make sure that their life-saving device was protected and ready in case they needed to use it. This pointed to an unmet need – many users didn't feel their autoinjector was safe enough in the packaging materials they were provided with by the manufacturer – and one that may not have been uncovered in a formative evaluation in the development of the autoinjector, as few users vocalised these feelings until they were directly asked how they were currently carrying their autoinjector.

> "...with detailed device-user input, supporting materials can be developed, while the internals of the device are developed to meet the needs of the drug formulation."

A range of packaging concepts were developed at the same time as the crisis autoinjector. Concepts were selected and prototyped, giving a range of materials that could be brought to an early-stage formative evaluation, provoking further conversations with users about their full range of needs from end to end of their treatment process, while at the same time developing an understanding of how they were able to use the device.

This approach can be applied to both platform customisation and bespoke device development, with early-stage user research occurring in parallel with the drug formulation characterisation process, providing a strong understanding of both key inputs: user needs and technical needs. From there, with detailed device-user input, supporting materials can be developed, while the internals of the device are developed to meet the needs of the drug formulation. Depending on the identified patient needs, a number of design solutions may be developed encompassing device packaging and labelling details, with a view to bringing one or more concepts to an early-stage formative evaluation.

> "This feedback loop of design development and user interaction allows both the development of a thorough understanding of the users' interactions with the device and use-related risk, while also continuing a conversation with the patient and user population about their needs beyond just the delivery of their medication."

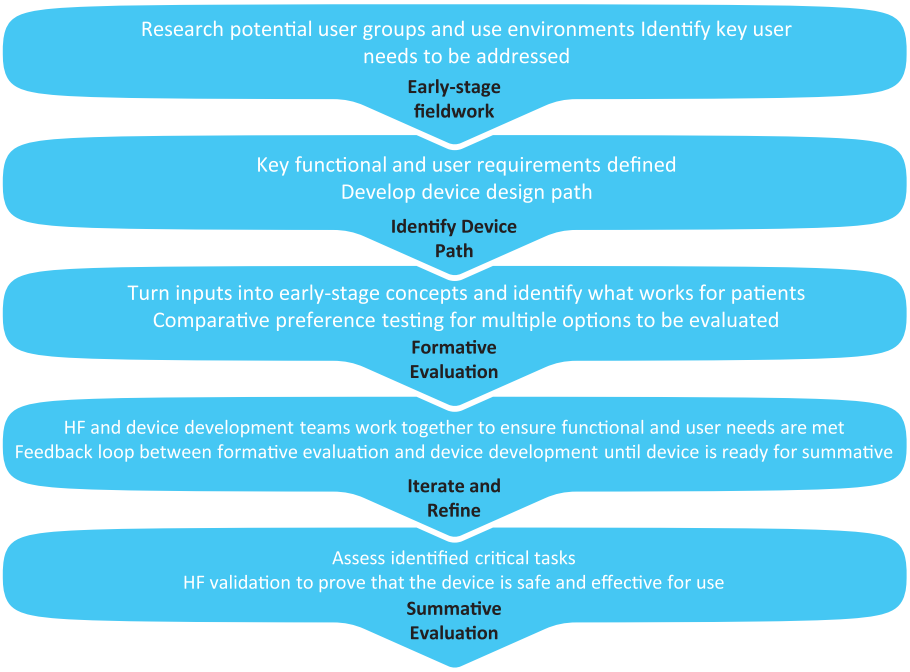

Figure 6: Human factors process.

PATIENT-CENTRIC DEVELOPMENT STRATEGY

These early-stage activities then form a crucial input for the rest of the human factors process. Early concepts are refined and narrowed down and, as the autoinjector design develops, subsequent formative evaluations can be undertaken with increasingly high-fidelity prototypes. This feedback loop of design development and user interaction allows both the development of a thorough understanding of the users' interactions with the device and use-related risk, while also continuing a conversation with the patient and user population about their needs beyond just the delivery of their medication (Figure 6).

As the device reaches maturity, a thorough understanding of the use of the device user interface and its associated risks has been developed, with mitigations applied where necessary, ready for validation. At the same time, this process maintains the user and patient's voice throughout, putting focus not just on the device but on the wider environment and scenarios that affect the patient's experience, resulting in an end product that is both safe and effective for the user, and optimised to the needs of the patient throughout their treatment journey.

> "Patient input will always be key to developing the best possible autoinjector. By involving the patient in the process early and often, you have the best chance of uncovering their full range of needs and ensuring that what you are designing responds to them."

Figure 7: Design evolution through multiple user studies and patient populations.

PATIENT USABILITY STUDIES

Formative usability studies are an important part of the feedback loop in patient-centric development, providing insights into device handling and patient preference. The use steps of the device can be tested, with prototype variants of the device provided with packaging, labelling and instructions for use, allowing the evaluation of injection site preference, observation of use errors for safety, improvement areas for the user interface, effectiveness of training and population diversity factors. Examples of feedback measurements may include successful dose delivery and an understanding of the visual and audible feedback provided by the device. The feedback from these studies can then be used to inform device design, developing a device that users can understand and feel comfortable using.

Late-stage user studies can then be used to further analyse the design of the user interface once it has matured. Through the use of tools such as use-related risk analysis, critical tasks can be identified, and, by testing these with the intended user population, it can be determined if the device is safe and effective for use and ready for human factors validation. Alongside this, late-stage user studies can also be used to verify that the design decisions made in response to early-stage observations work for the patient population's wider needs through discussion on the use of the device.

This approach was taken in the case study shown in Figure 7, where three user studies were conducted on early-stage device designs. The results from these studies eventually led to the design of the ArQ platform, with its user interface undergoing further refinement through another two user studies (Figure 8).

Through this process, findings were made, both about how the device functions and how it fits into the patient's daily life. In the early stages, user feedback led to the development of the key user interface elements, now found across Oval's platforms, such as the audible and visual feedback mechanisms. The process also involved testing an autoinjector variant tailored to patient populations with low manual dexterity, the learnings from which

Figure 8: Optimised user interface design elements for ArQ.

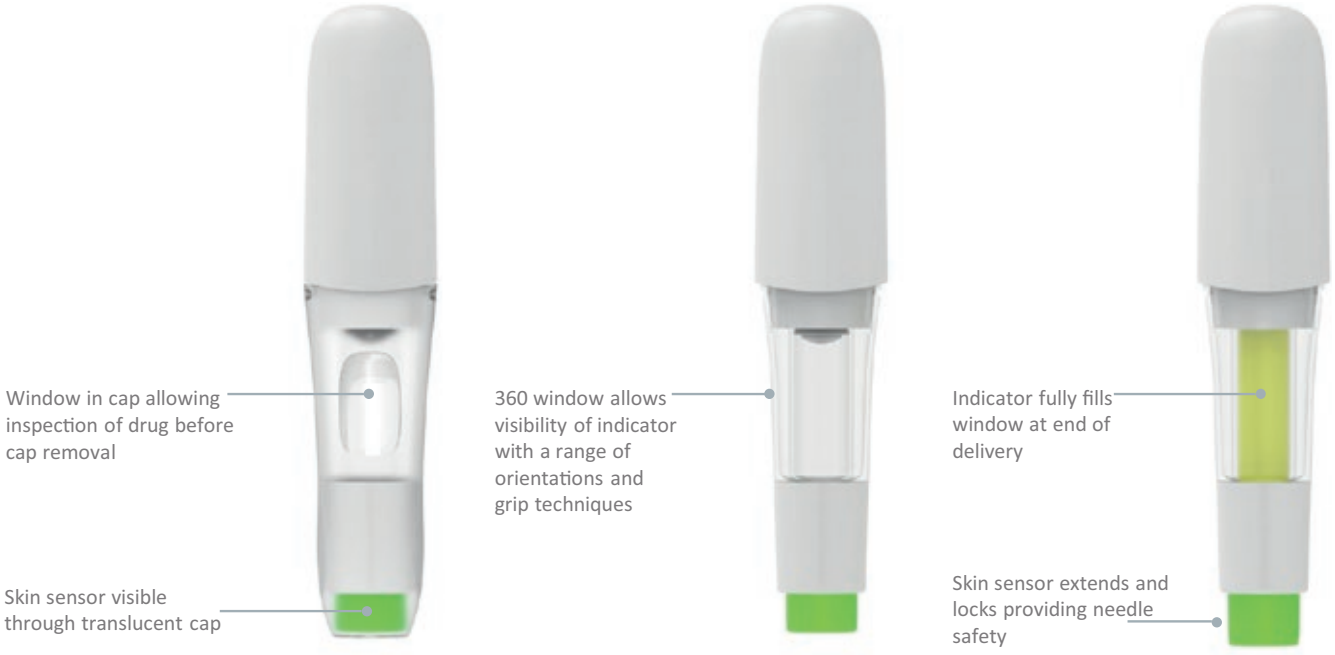

Figure 9: Optimised user interface design elements for ArQ-Bios high viscosity/volume.

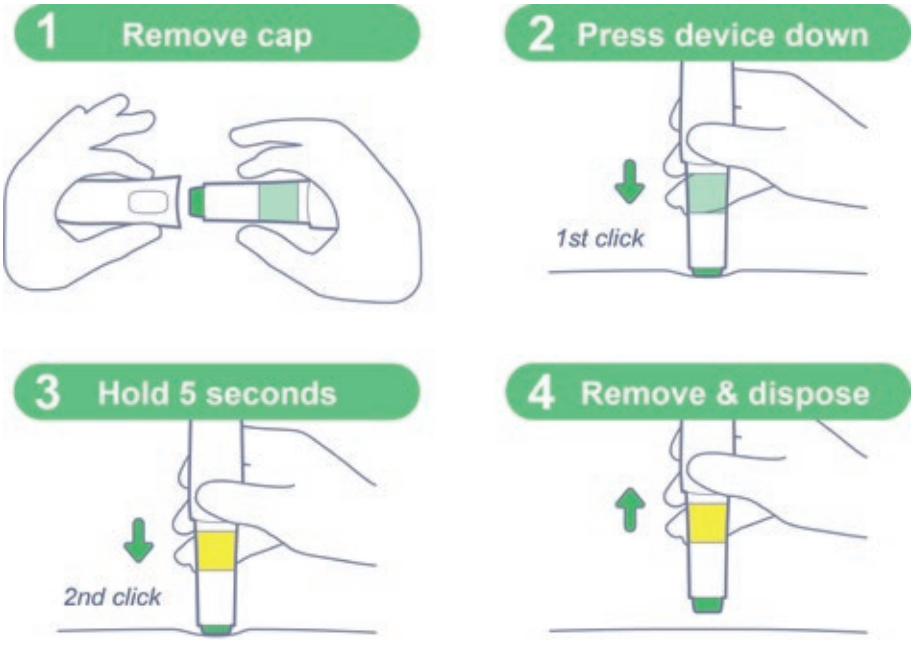

Figure 10: "Easy-to-use" steps for a patient-centric design.

influenced Oval's approach to building an understanding of patient's specific needs and customising devices to patient populations (Figure 9).

PATIENT FEEDBACK

Patient input will always be key to developing the best possible autoinjector. By involving the patient in the process early and often, you have the best chance of uncovering their full range of needs and ensuring that what you are designing responds to them. By making sure this input is implemented throughout the design process, you can reach validation with a device that is not just safe and effective to use but fits properly into the patient's life and eases some of the issues they may have previously experienced with their treatment (Figure 10).

ABOUT THE COMPANIES

Oval Medical Technologies, an SMC Ltd company, is a drug delivery company whose patient-centric autoinjector platforms enable pharmaceutical companies to deliver a wide range of drug formulations for both subcutaneous and intramuscular injection. Oval's flexible, robust drug delivery platforms can be tailored precisely, providing unprecedented scope for pharmaceutical companies to address the needs of current patient populations and develop and market new products. With its patented integrated primary drug container technology at their core, Oval's devices are safe, reliable and easy to use in their target patient populations. The company is certified to ISO 13485 (2016).

SMC is a global device manufacturer for the healthcare industry specialising in drug delivery, medical devices, diagnostics and pharmaceutical services. With over 33 years of experience, SMC provides an "End-to-End" integrated solution for clinical and commercial product manufacturing. SMC provides product services from initial concept through the final packaged device; including programme management, design and development, product manufacturing, clinical manufacturing, electronics integration and global supply chain management. SMC has global GMP manufacturing sites in the US, UK, Costa Rica and India for moulding, assembly and automated package integration. SMC's service offerings have been established to ensure the company offers superior value to its customers.

ABOUT THE AUTHORS

Marcus Agunloye, Senior Human Factors Engineer & Industrial Designer, Oval Medical Technologies, is a human factors engineer, with experience working in industrial design and human factors in the medical device industry. He joined Oval in 2017, where his focus has been on improving patient experience and safety through user interface design. He graduated with a BA in industrial design and technology from Brunel University (UK).

Asmita Khanolkar, Senior Director, Cambridge Pharma, SMC Technical Strategy & Commercialization, has a master's degree in materials science & engineering from Worcester Polytechnic Institute in Worcester, MA, US. With over 24 years of manufacturing experience specialising in the medical device and pharmaceutical industry, she has managed various device projects from concept to commercial launch. Her product portfolio includes single-use, wearable and implantable devices, and drug device/device-biologic combination products for drug delivery, biotech and pharmaceutical applications. Ms Khanolkar has held various engineering and management roles in new product development, manufacturing engineering, advanced quality planning, operations, supply chain and product life cycle management. Her current responsibilities include technical strategy and commercialisation of innovative technology platforms for drug delivery and fill-finished combination product.

TOWARDS USER-CENTRIC SPECIFICATION OF AUTOINJECTOR TECHNICAL ATTRIBUTES: INSIGHTS FROM EMPIRICAL WORK

Here, Andreas Schneider, PhD, Innovation & Business Development Director, of Ypsomed Delivery Systems, discusses an empirical study into both users' ability to remove the cap from an autoinjector and the difficulty those patients perceived in doing so. Furthermore, the study builds a quantitative model relating the empirical data to patient perception.

Although user-centricity has been a guiding paradigm in the development of new drug delivery devices, little is known about how technical attributes of spring-actuated prefilled autoinjectors shape patient perceptions about the ease of handling them. To shed further light on the subject, Ypsomed conducted an empirical study[1] that explored users' ability to remove an autoinjector's protective cap and quantitatively assessed how patient characteristics, such as dexterity, age, and sex, influence self-reported ease-of-use. In so doing, the empirical work provides much-needed insights into how clinically relevant technical attributes relate to user perceptions and, ultimately, device preferences. The study concludes with selected recommendations for new product development and considerations for device specification on the basis of patient-specific needs.

PATIENT-CENTRICITY – FROM WORDS TO ACTION

"Putting the patient at the centre of everything we do" may sound like a very bold statement, but this mindset has nevertheless permeated throughout drug delivery device development, be it with device manufacturers, pharmaceutical companies or regulators. In fact, patient-centricity has become the standard guiding paradigm in the development of new prefilled autoinjectors. For example, formative and summative usability studies have proved to be indispensable tools for effective new product development, and research has provided rich insights into how patients, caregivers and healthcare professionals administer drugs subcutaneously with the help of innovative self-injection devices.

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A great deal is known about if and how autoinjectors can be used safely and effectively for their intended uses and use conditions. However, there is limited understanding of how user perceptions shape the specification of clinically relevant technical attributes of autoinjectors.

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The lack of relevant studies is surprising, given that industry is acutely aware how clinically relevant technical attributes may shape design preferences and drive treatment choices. A misleading specification of clinically relevant technical attributes may negatively impact the perception of the device, and also limit its safe and effective use.

The study discussed in this article[1] puts the autoinjector cap-removal process under the microscope – a critical step for effective device use. Specifically, the empirical work studied whether patients, caregivers and healthcare professionals with a range of disabilities were able to remove the autoinjector protective cap with target removal force up to 55 N. The study also shows how the cap-removal force and participant characteristics, such as age, sex and dexterity impairment, shape self-reported perceived ease of cap removal, and ultimately device preferences.

REMOVE THE NEEDLE CAP FROM THE AUTOINJECTOR – INTRODUCING THE EXPERIMENTAL DESIGN

The single-site simulated-use study included 42 participants across five user groups:

- Adolescent patients
- Adult patients
- Elderly patients
- Non-professional caregivers
- Healthcare professionals.

Participants were sampled to assess the potential effects of user characteristics, such as dexterity, age, sex and professional education, on the cap-removal process. All patients were diagnosed with at least one chronic disease for which autoinjector-based drug products are being commercialised, such as rheumatoid arthritis, diabetes or multiple sclerosis. Each participant was asked to remove the protective needle cap of four non-functional devices with cap-removal forces in the range of 25–55 N. Effective task completion and user-reported ease of cap removal were documented for each cap-removal process.

The study included non-functional mock-up devices of the prefilled YpsoMate 2.25 mL autoinjector platform (Figure 1). The US FDA-approved and commercialised two-step YpsoMate 2.25 mL autoinjector is based on a push-on-skin principle to initiate the injection; users then sustain a minimum force to hold the device against the skin to complete the injection.

Figure 1: The YpsoMate 2.25 mL autoinjector platform included in the empirical study. The device platform is marketed as a prefilled two-step autoinjector device for Teva's migraine-treatment drug AJOVY® (fremanezumab).

"Interestingly, and contrary to expectation, the upper limit of cap-removal force that might prevent effective device usage was apparently above the range included in the study. With respect to the ability to remove the cap of the autoinjector, no differences were found based on patient characteristics."

CAP-REMOVAL FORCES OF UP TO 55 N ENABLE EFFECTIVE DEVICE USAGE

The empirical study shows that all participants were able to effectively remove the autoinjector cap with target cap-removal forces of up to 55 N with the YpsoMate 2.25mL autoinjector and its unique protective cap design. Interestingly, and contrary to expectation, the upper limit of cap-removal force that might prevent effective device usage was apparently above the range included in the study. With respect to the ability to remove the cap of the autoinjector, no differences were found based on patient characteristics, such as age, professional education or dexterity impairments.

Although other studies have identified use difficulties and use errors due to the cap-removal process, the results of this study were consistent with earlier anthropometric research on finger pull strength. Here, scholars observed that healthy male volunteers applied up to 98 N when pulling with one hand on a device equipped with force sensors. Previous anthropometric work has also demonstrated the importance of a device design that accommodates different types of pinch grips to maximise the pull force. The results of the empirical study summarised here similarly underscores the need for flexible protective needle cap geometry to allow for different pinch grips during the cap-removal process.

TOWARDS A QUANTITATIVE MODEL FOR USER-CENTRED SPECIFICATION OF CAP-REMOVAL FORCE

In addition to the findings on users' ability to remove the protective cap, the empirical work also modelled the relationship between the cap-removal force and user-reported ease of cap removal. This was done as a basis for a user-centred specification of cap-removal force. Specifically, users rated the perceived ease of

"Users whose hands were affected by rheumatoid arthritis reported higher discomfort when removing the autoinjector cap compared with other user groups – despite the fact that all users effectively removed the protective needle cap independent of dexterity impairments."

cap-removal for each cap-removal process on a five-point scale (one being very difficult and five being very easy). A linear model was then built to quantitatively relate the cap-removal force to the user-reported ease of cap removal (Figure 2).

The statistical analysis not only confirms a negative relationship between cap-removal force and user-reported ease of cap removal, but also quantifies this relationship. The results show that a 1 N increase in cap removal force results in a 0.064 point lower self-reported ease of cap-removal on the five-point scale. This model is a first step towards establishing a comprehensive toolbox for device development teams to predict user perception of clinically relevant device attributes, such as the cap-removal force. Consider an illustrative example. A cap-removal force of 25 N corresponds to a mean of 4.62 on the five-point scale for user-reported ease of cap removal. If the specification of this force was increased by 9 N, for example due to the use of an alternative rigid needle shield, it would still maintain an average value of 4.0 on the five-point scale for ease of cap removal.

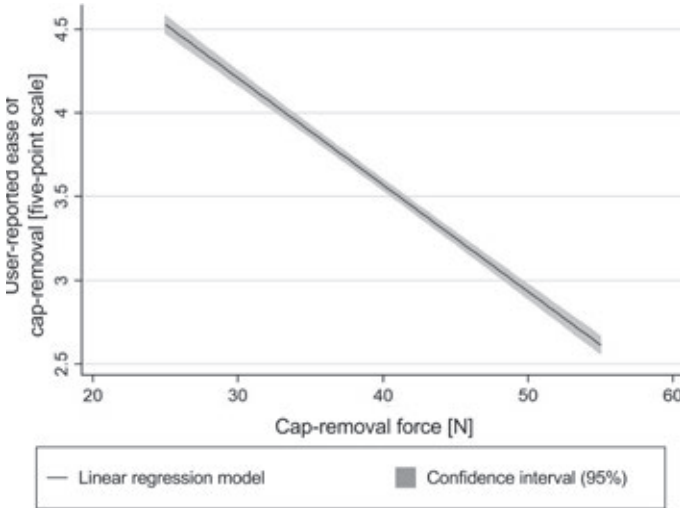

Figure 2: Graphical representation of the relationship between cap-removal force and user-reported ease of cap removal.

USER CHARACTERISTICS MATTER – WATCH FOR DEXTERITY-IMPAIRED PATIENTS

The linear model also uncovered a negative effect of dexterity impairment on perceived ease of cap removal. Users whose hands were affected by rheumatoid arthritis reported higher discomfort when removing the autoinjector cap compared with other user groups – despite the fact that all users effectively removed the protective needle cap independent of dexterity impairments. These findings are critical for the design and development of drug delivery devices for chronic debilitating disease states, such as multiple sclerosis or rheumatoid arthritis. This patient group is expected to be most sensitive to higher cap-removal forces, as this may have stronger effects on device perception and preference. In addition, cap-removal force deserves close attention as these disease areas are characterised by especially strong intra-class competition between treatment options.

EMPIRICAL INSIGHTS TO GUIDE FUTURE DEVICE DEVELOPMENT

The simulated-use study provided important insights for the user-centric specification of clinically relevant technical attributes, such as the cap-removal force. The results show that users were able to effectively remove the device's cap with target forces up to 55 N. Because the study distinguishes between users' ability to remove the autoinjector cap and their perceived ease of cap-removal, it provides a more nuanced understanding of the autoinjector cap removal process. As such, the simulated-use study provides a measure of how increasing the cap removal force reduces the user-reported ease of cap removal.

The resulting model is a starting point for building an advanced toolbox for predicting user perceptions based on device technical attributes. Finally, while the study suggests that dexterity impairment does not affect users' ability to remove the protective needle cap, it reveals a negative effect of dexterity impairment on users' perceived ease of cap removal. These insights have important implications for the design and development of new autoinjectors and injection devices, such as those developed by Ypsomed (Figure 3), as they re-emphasise the importance of involving users early in new product development.

ABOUT THE STUDY

The empirical study summarised here was funded by Ypsomed and conducted in collaboration with Design Science (Philadelphia, PA, US). As a leading developer and manufacturer of self-injection systems for subcutaneous drug delivery, Ypsomed has established a scientific research & communications programme with the purpose of advancing new insights relevant to industry and academia. The results regularly appear in peer-reviewed scientific forums, such as Expert Opinion on Drug Delivery, Patient Preference

Figure 3: Ypsomed's leading portfolio of drug delivery device platforms to facilitate subcutaneous drug administration.

and Adherence, and Medical Devices: Evidence and Research, and are presented at leading medical device and drug delivery conferences, such as the PDA Universe of Prefilled Syringes and Injection Devices.

ABOUT THE COMPANY

Ypsomed's comprehensive drug delivery device platforms consist of autoinjectors for prefilled syringes in 1 mL and 2.25 mL formats, disposable pens for 3 mL and 1.5 mL cartridges, re-usable pen injectors, ready-to-use prefilled wearable patch injectors and injection devices for drugs in dual-chamber cartridges. Unique click-on needles and infusion sets complement the broad self-injection systems product portfolio.

With over 30 years of experience in the development and manufacture of innovative injection systems, Ypsomed is well equipped to tackle digital healthcare challenges and has strategically invested in the development of connected solutions and therapy-agnostic digital device management services. Anticipating the future needs of patients, pharmaceutical customers, payers and healthcare professionals, Ypsomed moves beyond manufacturing connected sensors. Ypsomed's smart device solutions strive to transform patients' lives by capturing therapy-relevant parameters, processing them to facilitate self-management of chronic diseases, and integrating these insights with third-party digital ecosystems.

The company leverages its in-house capabilities in electronics, software and connectivity for the development of new devices and digital product systems. Ypsomed is ISO 13485 certified and all processes comply with design control and cGMP guidelines with operational QA/QC experts on-site at each location. Ypsomed's FDA-registered manufacturing facilities are regularly inspected by pharma customers and regulatory agencies to supply devices for global markets including the US, Europe, Japan, China and India.

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ABOUT THE AUTHOR

Andreas Schneider, PhD, is Innovation & Business Development Director at Ypsomed Delivery Systems. He leads a team that drives the definition and development of new drug delivery device platforms, such as next-generation pen and autoinjector devices, wearable patch injectors, connected systems and digital solutions. Dr Schneider has published various articles and given presentations in the areas of innovation management and drug delivery. He holds a PhD in innovation management and organisational sciences from ETH Zurich, Switzerland.

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HOW OWEN MUMFORD CARRIED OUT USABILITY TESTING UNDER COVID-19 RESTRICTIONS

Miranda Newbery, Director and Founder of Inspired Usability, describes working with Owen Mumford Pharmaceutical Services on usability testing for a platform autoinjector under covid-19 restrictions.

When lockdown measures were first introduced in 2020, human factors professionals were faced with the challenge of carrying out usability testing remotely. There is certainly a wide range of human factors tools that can be employed without any contact with end users, such as use risk assessments, expert reviews and device comparisons. Also, known use problems for similar or previous devices can be researched.

However, first-hand user feedback is invaluable and usability testing is a regulatory requirement for most drug delivery devices. It is only when a potential end user tests a prototype that it is possible to truly understand issues with the device, and to make important design decisions. For medical device development to continue, usability studies needed to be reimagined as we entered into the "new normal". Any new solution still needed to fulfil the required standards for human factors studies, to satisfactorily demonstrate device safety and usability.

SUCCESS FACTORS

Owen Mumford Pharmaceutical Services was in the latter stages of working on a platform autoinjector when lockdown measures were introduced. Inspired Usability had conducted a large-scale formative study in January 2020 and Owen Mumford wanted to confirm that the subsequent design changes had improved the design and did not cause any unforeseen problems. The best way to do this was via a follow-up formative usability study with potential end users. Cancelling the usability study was an option but both companies were keen to see if there was a solution that would get them the feedback they really needed.

> "Cancelling the usability study was an option but both companies were keen to see if there was a solution that would get them the feedback they really needed."

The work began with an assessment of the requirements of an effective usability study to be able to prepare a study design:

- **Representative participants:** to ensure that participants were representative of end users, it was important to brief recruiters thoroughly. As well as the type of device being researched, they had to have a good understanding of what is involved in human factors studies and how they differ from market research. For their part, participants also needed to be briefed fully about what the study would entail so that they could give informed consent.

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"It was important to be able to see elements of the autoinjector up close, and to be able to hear feedback clearly at the start and end of an injection."

- **Clear protocol and study design:** a clear protocol and discussion guide would make it easier to repeat the study multiple times, allowing user actions and behaviours to be compared. The aim was to ensure that the study itself was not too complicated, and to focus on evaluating key parts of the device design.
- **A comfortable environment:** although the setting had to simulate where the device would be used, participants needed to feel relaxed and not under pressure. Building up a rapport between participants and moderators running the study would put participants at ease so that they felt free to interact with the device as if they were at home (or in their place of work) and to express their views.
- **First-hand observation:** the moderator, observer and client had to be able to see and hear first-hand what was occurring during the usability sessions. It was important to be able to see elements of the autoinjector up close, and to be able to hear feedback clearly at the start and end of an injection. This also needed to be recorded on video at a high quality to allow for thorough review after the study.
- **Device safety:** the safety of participants and moderators had to be ensured during the sessions by completing a risk assessment beforehand and putting risk mitigations in place. This was especially important for handling the autoinjector as needles and injectable liquids were involved.

ADAPTING TO COVID-19

For platform devices, it is important to be as inclusive as possible during testing to cover as many usability problems as possible. In this example, the aim was to test the most challenging cases. The cohort included children, older adults, people with musculoskeletal conditions, people with neurological conditions, people with visual and hearing impairments and healthcare professionals, all with and without injection experience. To increase participation, the chosen venue was in a suburban area with parking, and participants were encouraged to walk or drive rather than use public transport.

In terms of the practical considerations, extra time was needed for each session to allow for cleaning and for the room to be ventilated. There was also additional preparatory work, as the prototypes were all packed at least three days in advance of the study by engineers wearing PPE – and remained sealed until needed. Rather than being handed prototypes for different parts of the study, each participant was allocated a set of trays that contained all the devices they would need (in this case, 15 autoinjectors). The prototypes were numbered and placed in colour-coded sections of the trays so that the moderator could easily direct participants during the session.

Although the general flow of the study remained the same, there were some noticeable changes. The moderator had to describe actions that would normally be done for them, such as handing out prototypes. Both working and non-working prototypes may be used during a study, so it is critical that the correct one is used at each stage. This particular study

"The prototypes were all packed at least three days in advance of the study by engineers wearing PPE – and were kept sealed until needed."

even included gathering anthropometric data to inform the design input requirements, so the moderator described to participants how to use the equipment. Since needlestick injury was a risk during the study, the moderator was highly vigilant when participants handled the prototypes and there were no incidents.

Despite social distancing measures, rapport seemed easy to build as participants appeared to enjoy being out of their homes – and enjoyed the process of testing the device and providing feedback. To allow for observation of the testing process, a local video company was recruited to help with live video streaming. There were production-equivalent cameras that could transmit high-definition video feeds simultaneously. The picture-in-picture facility showed a close-up view of the autoinjector going into the injection pad, and a wide view of the participants and their interaction with the device. High-quality microphones captured audible feedback and participant responses. Inspired Usability used Microsoft Teams to stream the content so that the Owen Mumford team could ask the moderator questions about participant behaviour during the sessions.

"Despite social distancing measures, rapport seemed easy to build as participants appeared to enjoy being out of their homes – and enjoyed the process of testing the device and providing feedback."

CONCLUSION

Overall, the study was a success. It allowed the Owen Mumford team to move to the design freeze stage, ready for product launch in 2021. The restrictions and changes did not seem to impact the flow of the study, participant recruitment or how the participants interacted with the autoinjectors. The restrictions imposed by covid-19 were a concern at first – but the measures in place soon became second nature, showing people's ability to quickly adapt to the change in conditions. It is likely that some of these restrictions will stay in place for some time – particularly guidelines on hygiene and infection control, which will become best practice – so the lessons learned over the past year may continue to be useful for future testing.

ABOUT THE COMPANIES

Inspired Usability was founded by Miranda Newbery to support the medical device and pharmaceutical industry as it reaches beyond the regulatory human factors requirements to create effective and inspirational products. The company combines knowledge of product development and human factors regulations with a sensitive and creative approach. The team is inspired by the users and the complex, ever-changing world around us. Using a range of human factors methods, Inspired Usability can apply insight and rigour to inform the design process and create medical devices and submission files that are fully compliant with regulations and that delight the people using them. The company has experience with a range of drug delivery devices, hospital-based medical devices, surgical equipment, smart devices, apps, wearables and consumer health products.

Owen Mumford is a major healthcare company and device manufacturer that commercialises pioneering medical products in its own brand and custom device solutions for the world's major pharmaceutical and diagnostic companies. Owen Mumford's goal is to enhance access to diagnostics, encourage adherence to treatment and reduce healthcare costs, making a world of difference to a world of people.

ABOUT THE AUTHOR

Miranda Newbery is a creative human factors and user research consultant with over 10 years' product development experience. She firmly believes in putting the user at the heart of the design process and combines her expertise in medical devices, human factors regulations, design and user research to creatively identify unmet needs. Ms Newbery has a wealth of experience in combination drug delivery devices. She originally studied Mechanical Engineering at Cambridge University (UK) and Industrial Design at the Royal College of Art (London, UK). She is a chartered ergonomist with the CIEHF and founded Inspired Usability in 2016.

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REUSABLE ELECTRONIC AUTOINJECTOR – FLEXIBLE PERFORMANCE

In this article, Bjarne Sørensen, Director, Front-End Innovation at Phillips-Medisize, discusses the ability of electronically driven injection devices to cater for a broad range of liquid drug properties within a single device platform.

In a previous ONdrugDelivery article, Phillips-Medisize argued that there are several changes in the market that might accelerate a transition from disposable mechanical to electronic reusable autoinjectors. Beyond megatrends around sustainability, connectivity and self-administration of drugs, pharmaceutical companies continue to pursue broad range platform devices that can be reused across multiple drug formulations with widely varying properties. This article focuses on this aspect of electronically driven injection devices; the ability to cater for a broad range of liquid drug properties within a single platform device. Data from a mathematical model will be presented to support this hypothesis.

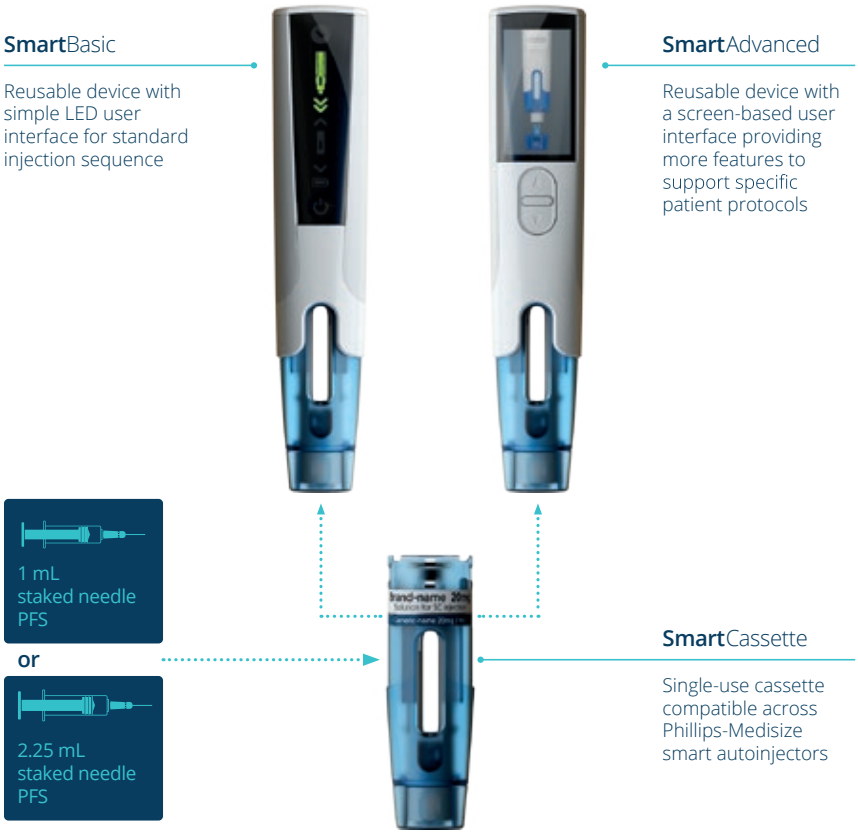

Figure 1: Key elements of the Phillips-Medisize smart autoinjector.

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Phillips-Medisize has been developing a new smart autoinjector that is small and easy to use for patients and provides a powerful and flexible platform for pharmaceutical companies. This new development presents a very different take on the challenges with injection devices that follow new agendas like connectivity and sustainability, but it also presents a powerful approach to addressing the challenges and compromises coming from autoinjectors with spring-driven drive trains.

KEY ELEMENTS OF THE SMART AUTOINJECTOR

As shown in Figure 1, the device consists of a single-use, disposable cassette that contains the prefilled syringe and an electronic reusable device that contains all the electronics and offers product customisation through different versions of the user interface, including the possibility of a full graphical display.

Cassette

The disposable cassette, which incorporates needle safety features, can include either a 1.0 mL (all flange types) or 2.25 mL (small round flange) syringe. The cassette is discarded in a sharps container after use, as usual. It is compatible with a range of standard prefilled syringes and components, according to ISO 11040. This is a true platform opportunity for the pharmaceutical industry, as the same cassette can be used to deliver a wide range of drug products with different injection volumes and viscosities.

The cassette is made of plastic and lacks metal springs. It is significantly smaller and lighter than current disposable devices. During transport and storage, the cassette is not under any load, allowing for a minimal approach to packaging.

The cassette can be loaded with a syringe by axial insertion, and with automated locking in the cassette. Phillips-Medisize can supply cassettes in bulk or handle the complete process of fitting syringes into cassettes in a controlled environment, including serialisation, if desired. The cassette label can include a radio frequency identification (RFID) tag, readable from the device, and selected data can be submitted to a connected system.

Device

The reusable device includes an electronically controlled drive train, powered by a rechargeable battery, with Bluetooth Low Energy (BLE) connectivity options. RFID reading of cassettes is an option as well.

The device is available in two versions:

1. The SmartBasic device with LEDs and audible support, which is similar to typical disposable autoinjectors but with an extended user interface.
2. The SmartAdvanced device with a graphical user interface and a menu-driven operation, also including audible support. It is possible to have a custom-designed user interface, including buttons and further functionality, with this version.

Both device versions have the connectivity option embedded and can convey selected information to an app and a secure backend platform. Phillips-Medisize offers a complete connected health solution or customers can connect the devices to other systems.

Drive Train Description

The drive system is microprocessor controlled and features a brushless DC motor that, via gearing, drives a threaded spindle. There is an encoder embedded in the motor, so the position and speed of the plunger is known by the processor. Furthermore, the processor can tightly control the applied force on the syringe, so all aspects of the plunger movement are controllable from parameter settings in the firmware of the device and can be configured to the specific requirements of the drug and therapy.

"A key advantage of the motor drive is that high forces can be applied in a fully controlled manner, so it is possible to optimise delivery of even highly viscous drugs and still minimise the needle size."

"The injection sequence also provides for a configurable dwell time with a specific force on the stopper to minimise dead volume before the end-of-dose signal is indicated to the user."

A key advantage of the motor drive is that high forces can be applied in a fully controlled manner, so it is possible to optimise delivery of even highly viscous drugs and still minimise the needle size.

The algorithm prioritises the target injection time, varying the force as required to achieve this time (up to the configured maximum force). The injection sequence also provides for a configurable dwell time with a specific force on the stopper to minimise dead volume before the end-of-dose signal is indicated to the user.

The configuration of the device during manufacturing will include the following parameters:

- Target injection time
- Maximum force applied
- Target dwell time and plunger force.

In the advanced device, the target injection time and other settings can optionally be adjusted by the patient. The battery in the reusable device is a rechargeable lithium-ion cell which can be charged from a USB port.

DIFFERENCES BETWEEN ELECTRONIC DRIVE TRAIN AND SPRING-DRIVEN DRIVE TRAIN

Electromechanical drive trains offer several potential benefits when compared with spring-driven systems. Configuration of the latter requires a delicate balance between several, sometimes counteracting, aspects whereas the important parameters of an electronically driven system can be configured to consistently deliver the target requirements, with headroom available to account for real-world variation encountered via the full system interactions, including primary container, drug, needle and injection site.

Function	Electronic drive train	Spring driven
1.0 mL and 2.25 mL compatibility	The device and cassette accommodate both 1.0 mL and 2.25 mL syringes, so it is a true platform, with sufficient power to drive both syringe sizes.	Different devices are usually required due to the increased power (approximately 4 x force if all other factors, such as needle gauge and injection time remain equal) and hence size required.
Engagement with the stopper	The plunger moves at a constant injection speed, and thus engages with the stopper in a controlled manner, gradually building up the required force on the plunger to achieve and maintain the target injection speed.	At the start of an injection, the plunger is released with the full force of the compressed spring, quickly accelerating towards the stopper. At impact, the plunger strikes the stopper with a considerable impulse force that creates a shock wave in the drug and stresses within the prefilled syringe.
Partially filled syringes	As above, the plunger moves at a constant injection speed, regardless of syringe fill volume, and therefore the stopper engagement is controlled and gentle across all syringe fill volumes.	In a partially filled syringe, the additional flight distance between plunger rod and plunger stopper generally occurs over the highest force profile of a compressed spring, increasing the impact and shock forces on the syringe assembly.
Break-loose force	The electronic drive system has a large and controlled power reserve, meaning it can overcome the break-loose force while still controlling the rate of injection immediately after stopper movement commences.	Spring-driven systems are generally sized to overcome the break-loose force but have little ability to control the rate of injection once stopper movement commences. At this point, injection rate is driven by spring-force decay versus the resistive forces of the syringe barrel and liquid flow through the needle bore.
Variations in siliconisation	The electronic control maintains a constant injection speed, adjusting motor current and hence plunger force to deliver a consistent injection time. Because the full force is available throughout the entire stroke, the electronic system is able to accommodate changes in resistive forces from sources such as siliconisation variations.	As the majority of spring-driven devices use compression springs, the available force tends to decrease over the stroke length. Springs need to be sized to overcome potential resistive forces encountered throughout the stroke, such as siliconisation. Variations in these resistive forces tend to impact injection time as it is the parameter that can't easily be controlled in spring-driven devices.
Different drug viscosity ranges	The electronic drive and motor system has the power to cope with very high viscosities, which can allow a thinner needle to be used in some applications. The same device can work with both low and high viscosities without any changes as the drive algorithm will adjust the force output to maintain the programmed injection time.	Spring-driven systems for high viscosity drug delivery can require large, powerful springs to be maintained in a compressed, or energised, state until activation. This places a constant high load on the plastic device body throughout transport and storage.
Dead volume in syringe at end of stroke	Configurable force on plunger at end of stroke, to compress stopper as required, minimising dead volume.	Dependent on remaining force from spring at end of stroke.
End-of-dose indication	The end-of-dose indication is software controlled, encompassing full stroke travel, stopper compression followed by a programmable dwell time. Therefore, the audio-visual end of dose indication provides direct user feedback that it is safe to remove the injection device without a separate "hold" time. This should have the added effect of reducing "wet" injections caused by users removing the device too soon.	Typically, end-of-dose indication is provided by a mechanical sound initiated by the plunger movement nearing the end of its stroke. This typically happens slightly before the injection is complete, requiring an instruction for the user to "hold" the injector in place for a period of time before removing. Removal before the end of this time period may result in a "wet" injection.

Table 1: Functional differences between electronic drive train and spring-driven drive train.

In Table 1, some of the key functional differences are described.

SIMULATIONS PERFORMED ON THE SMART AUTOINJECTOR AND SPRING-DRIVEN SYSTEMS

To simulate the performance of mechanical and electromechanical autoinjectors, Phillips-Medisize developed a complete dynamic model like that published by Zhong X *et al* (2020).[1] The model assumes:

- A flight distance between the plunger rod and plunger stopper for the mechanical autoinjector of 3 mm
- An air bubble of 5 mm between the plunger stopper and the liquid in the prefilled syringe
- Injection into air (so no back pressure)
- The algorithm as embedded in the smart autoinjector.

In Figure 2, we show different key parameters for a 50 cP, 2.0 mL drug, 27GTW needle with a targeted injection time of 15 s, and for both drive train types. A spring rate of 1050 N/m for the spring-driven system was defined to suit these requirements.

As can be seen in Figure 2a (plunger rod force), the electronic autoinjector can deliver a soft controlled engagement with the stopper, and a constant force on the plunger throughout the injection. During

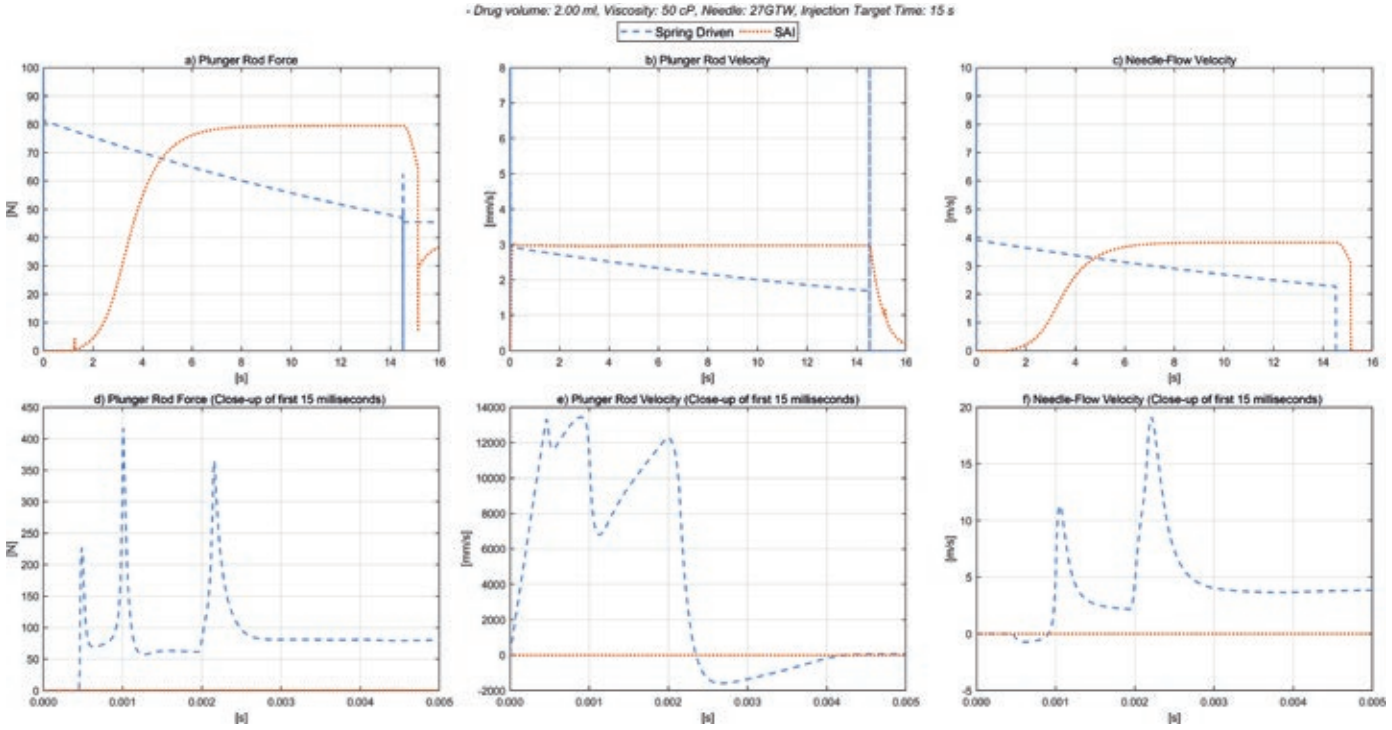

Figure 2: Spring-driven autoinjector versus smart autoinjector 50 cP.

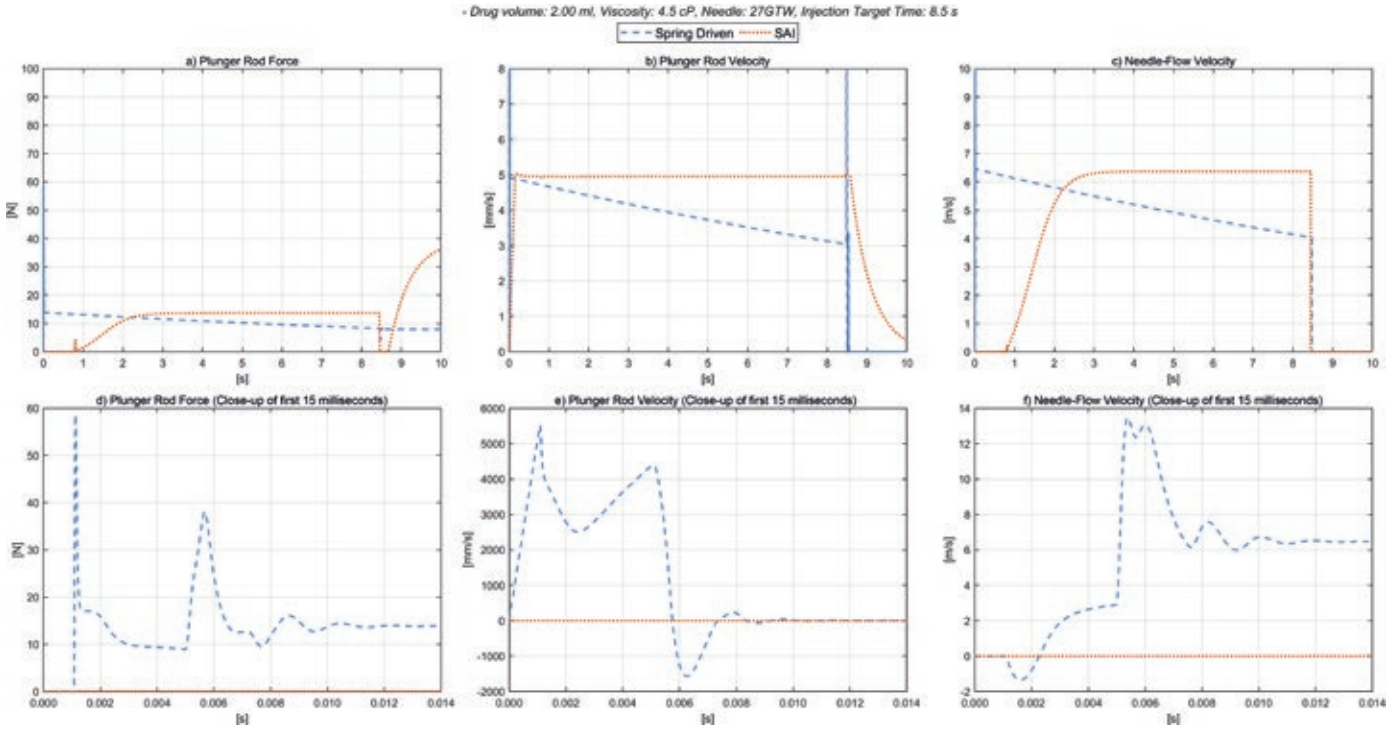

Figure 3: Spring-driven autoinjector versus smart autoinjector 4.5 cP.

the configurable dwell time, the force on the stopper can be optimised to minimise the dead volume – shown here as 35 N. It is also evident that the force available from the spring-driven system is significantly different at the start and end of the stroke.

Figure 2b (plunger rod velocity) shows the constant plunger speed of the smart autoinjector, and the declining plunger speed for the spring-driven one. Figure 2c (needle-flow velocity) shows the constant flow in the fluid path of the electronic drive train, and the declining flow rate of the spring-driven version.

As shown in Figures 2d, 2e and 2f, for the initial phase of the injection, the forces from the spring-driven plunger on impact with the plunger stopper, after the free flight distance, are approximately three to four times the nominal plunger force calculated during the actual injection. It is these higher forces that are likely to limit the performance of the drive train to deliver the drug without risk of damaging the prefilled syringe. For the electronic drive, the nominal force on the plunger stopper after the free flight gradually increases as the air bubble is compressed and then remains constant as the plunger stopper is driven along the barrel.

The additional force headroom for the electronic drive train enables a potentially shorter injection time in this example and increases the ability to work with higher viscosities. Furthermore, it is more straightforward to optimise the set-up for the required target injection time with the minimum possible needle size. The maximum force applied to the syringe can be configured to accommodate the specification of the actual syringe assembly which, in most cases, determines the overall limitations of the system. Given the large headroom, there are none of the typical issues with potentially excessive break-loose force or stalling plungers due to differences in siliconisation.

Figure 3 shows the same curves but for a 4.5 cP, 2.0 mL drug with 8 s injection time, and again for both drive train types. A spring rate of 172 N/m for the spring-driven system was defined to suit these requirements.

The only difference to the electronic drive train used for the 50 cP liquid and the 4.5 cP is that the target injection time was set to 8.5 s, with the other device parameters and settings unchanged, showing the superior flexibility of the electronic platform. The same settings in the smart autoinjector can be used for 1.0 mL syringes and 2.25 mL syringes.

Given the very different delivery requirements, the spring-driven drive train will require different spring rates of 1050 N/m and 172 N/m respectively, resulting in further development work to determine and verify the functionality for different drug properties and parameters such as break-loose force, changes in siliconisation, mechanical stability of the device and all other relevant design considerations

> "Beyond the sustainability and connectivity benefits offered by the smart autoinjector, it is evident from the simulations presented here that the electronic drive train offers performance and platform benefits for the delivery of injectable drugs."

SUMMARY

Beyond the sustainability and connectivity benefits offered by the smart autoinjector, it is evident from the simulations presented here that the electronic drive train offers performance and platform benefits for the delivery of injectable drugs. The approach offers a wider range of flexibility and suitability compared with traditional spring-driven autoinjectors, which are likely to be more sensitive to changes in drug delivery parameters, and thus also require more development efforts and fine-tuning to optimise the design for each new application.

The motor control algorithm, as developed for the smart autoinjector firmware, enables swift configuration of the system to the selected parameters such as injection time and maximum applied force on the plunger. The smart autoinjector provides a powerful platform device featuring a very high degree of flexibility on critical parameters, and wide suitability as the system can be used for both 1.0 mL and 2.25 mL syringes.

ABOUT THE COMPANY

Phillips-Medisize, a Molex company, is an end-to-end provider of innovation, developmentand manufacturing solutions to the pharmaceutical, diagnostics and medical device market segments. 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.

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ABOUT THE AUTHOR

Bjarne Sørensen, Bsc, ME, is a Director of Front-End Innovation at Phillips-Medisize, based in the company's Development Centre in Denmark. With more than 35 years of experience within Product, Strategy and Business Development, Mr Sørensen has a very visible track record within different business areas. At Phillips-Medisize he participates in customer programmes, typically involving electronic injectors and connected health systems. He is also deeply involved in new electronic platform programmes, especially on conceptual, technical and sustainability aspects.

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ADDRESSING THE CHALLENGES OF VISCOUS INJECTABLE ADMINISTRATION

Andrew Donnelly, PhD, Vice-President of Innovation, at Bespak by Recipharm, and Shahid Uddin, PhD, Director of Drug Product, Formulation & Stability, at Immunocore, look at the challenges of self-administration of injectable viscous formulations and the technology that is helping to overcome these issues.

To date, one of the key issues holding back the widespread adoption of self-administration for injectable formulations is that many of the available devices are not able to deliver the drug through a needle fine enough to be acceptable to the patient, particularly for viscous formulations. A wide-diameter needle is perceived as uncomfortable or even painful, to use, making many patients reluctant to use them. This reluctance can all too easily translate into non-compliance, with repercussions for the medicine's efficacy and, ultimately, the patient's health.

With this in mind, it is clear that there is a pressing need to create more user-friendly devices, even when the formulation is viscous. To achieve this, significant challenges must be overcome during drug development to improve ease of administration, and steps must be taken to create devices that can cater for more challenging formulations.

WHAT MAKES A LIQUID VISCOUS?

A liquid with high internal resistance to flow is described as having high viscosity. This internal resistance is created when the molecules move past one another, for example when the liquid is poured out of a container. Liquids made up of small, relatively simple molecules tend to have low viscosity, whereas liquids with larger, more complex long-chain molecules have a much higher viscosity. This is because the molecular chains get tangled up in each other as the liquid moves.

Viscosity is also governed by the strength of a liquid's intermolecular forces, especially the shapes of its molecules. Liquids with molecules that can form bonds with each other are usually more viscous. Honey, which mostly comprises of relatively small glucose and fructose molecules, is a good example of a liquid that owes its viscosity to internal bonding.

Liquid drug formulations can have different viscosities, depending on the nature of their APIs, the solvents used or the release profile they have been designed to achieve. The more viscous drug formulations in common use include:

- **Formulations containing high concentrations of large molecules.** Biologics, including monoclonal antibodies (mAbs), are a key example of formulations containing large, long-chain molecules. The nature of these therapies means that they often need to be delivered by injection. The impracticalities of intravenous administration mean that subcutaneous routes are more desirable when it comes to developing biologic treatments for self-administration. However, the volume of formulation that can be delivered in a single dose with a syringe or autoinjector is limited to 2 mL or less. The need for higher doses is driving the need for higher concentrations of the drug, especially when it comes to mAbs. This increase in concentration generally leads to formulations with much higher viscosities in the range of 20–100 cP.

> "The intrinsic nature of many high-viscosity formulations means that only so much can be done to optimise them for use in standard autoinjectors. This is driving the need for alternative devices that can offer a viable alternative when reducing viscosity is not an option."

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- **Formulations designed to provide sustained or controlled release.** For many therapeutics that are rapidly cleared from the body, it is desirable to control the rate of release of the active agent from the site of injection, thus reducing the need for multiple doses. However, many of these controlled-release formulations include polymers with a high molecular weight, which render the formulations extremely viscous. The viscosity of these formulations can be more than 1000 cP.
- **Non-aqueous formulations.** For some formulations, the solvent itself is highly viscous. Oil-based formulations, for example, may be needed to generate controlled-release characteristics or as solvents for drugs that are poorly water soluble. The viscosity of these formulations is similar to the viscosity of the oil – for example, the viscosity of castor oil is in excess of 2000 cP.

That said, it is clear that there are limitations on how much drug formulations, particularly those for biologic treatments, can be improved to reduce their viscosity. The intrinsic nature of many high-viscosity formulations means that only so much can be done to optimise them for use in standard autoinjectors. This is driving the need for alternative devices that can offer a viable alternative when reducing viscosity is not an option.

THE COMPLEXITIES OF MANUFACTURING HIGHLY VISCOUS FORMULATIONS

Increasing the concentration, and thus the viscosity, of biologic formulations has ramifications for the manufacturing process and the product's storage requirements, as well as how it is ultimately administered to patients. One example is the biologic therapies used to treat immunological and genetically related diseases. As previously mentioned, these are often delivered subcutaneously, which means the formulations must contain high concentrations of drug substance to overcome the limited volume of drug that can be administered in a single dose. To achieve these high concentrations within a formulation, diafiltration is used – a process that separates out different-sized protein molecules within a preformulation via micro-molecule permeable filters in order to concentrate quantities of the desired protein.

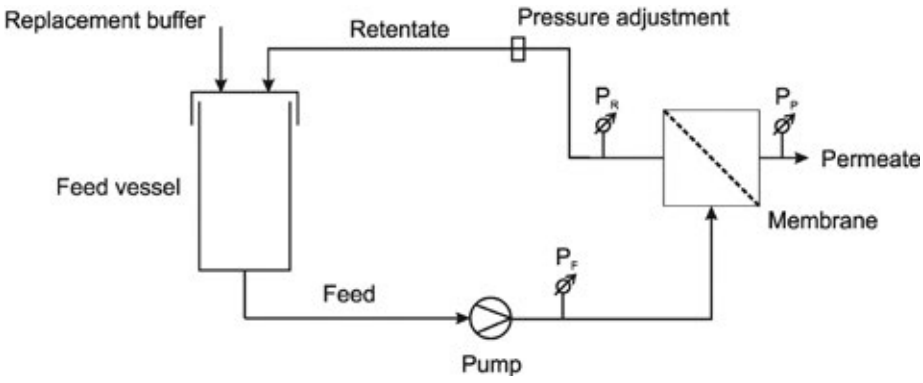

Figure 1: Representation of diafiltration setting.[2] (Source: WikipediaDorian).

However, diafiltration can pose challenges when it comes to manufacturing a formulation, particularly with regard to stability and aggregation, as protein-protein interactions become more likely when concentration increases. Ordinarily, instability and aggregation occur because diafiltration is a dynamic operation in which protein concentration increases by volume reduction and buffer matrix changes.[1] This instability can have significant repercussions in terms of product quality and shelf life. As such, the diafiltration process requires extensive expertise and should be highly controlled to ensure product quality is not impacted (Figure 1).

Manufacturing scalability is also a key concern with diafiltration. It is not a simple case of expanding the filter membrane surface area as the proportion of protein being processed is increased. The high viscosity of high protein concentrations increases operating pressure in diafiltration.[3] This can reduce the protein-loading capacity of the filter, which means that the protein load ratio must be decreased to achieve the same performance at higher scale.

In addition to these scalability issues, viscous biologics can lead to costly material waste during the filtration process, leaving behind unused but viable protein in the filters. Although this problem may be prevented by oversizing the membrane, a setup that uses low-concentration operations necessitates changes that promote high-concentration operations. Using a membrane with a low molecular weight cut-off may reduce protein loss during filtration.[4]

Furthermore, the high mechanical stress experienced during diafiltration can cause irreversible protein aggregation. This is a phenomenon that sees protein molecules group together into insoluble masses, negatively impacting their effectiveness in the finished formulation, as well as potentially increasing viscosity further.

To enable successful development of high-concentration biologics, a number of excipients can be added to formulations to stabilise proteins by suppressing aggregation and surface adsorption. In liquid formulations, buffers with phosphate or histidine and a small amount of detergent can be useful. Excipients for lyophilised formulations include sucrose, trehalose, mannitol and glycine, among others. However, these add complexity and cost to the formulation development process, further impacting on manufacturing efficiency (Figure 2).

On top of challenges when producing stable, high-concentration biologic formulations, viscosity can cause complications during processing. The transfer of viscous solutions via pumping can be challenging and can generate high back pressures during the filtration process. The physical stresses that these processes apply to the solution can also create stability issues. Clogging of the filling needle can

"Despite the development and manufacturing challenges posed by the viscosity of biologic drug formulations, they remain an exciting area for drug innovation. Steps can be taken not only to overcome manufacturing efficiency issues, but also useability issues for patients."

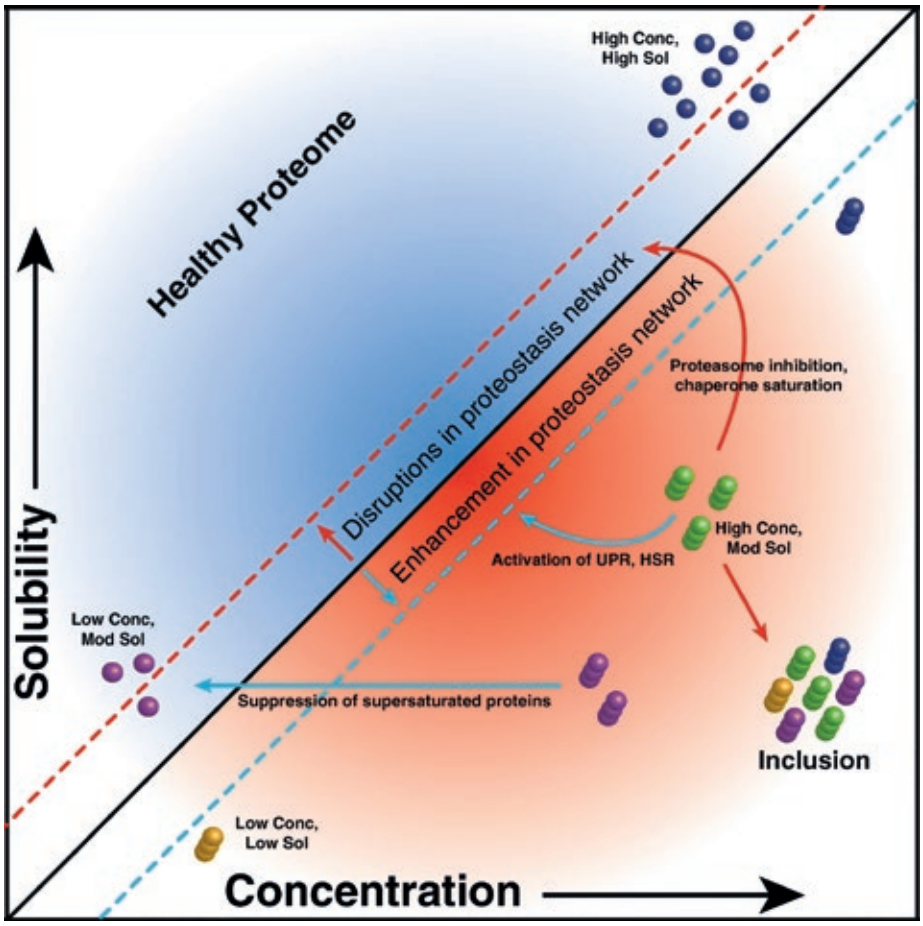

Figure 2: Protein aggregates.[5] (Source: Ciryam P, Antalek M, Cid F, *et al*, "A metastable subproteome underlies inclusion formation in muscle proteinopathies". Acta Neuropathol Commun, 2019, Vol 7(197)).

occur as solute is deposited in the needle with high drying rates, if temperature and humidity are not controlled.[6] Furthermore, the process-yield issues that this creates lead to significant economic losses.

These issues can be daunting for drug companies, creating a false perception that the overall profitability of parenteral drug products using viscous drug formulations may be lower than desirable. It may also lead them to believe wrongly that their options are limited when it comes to designing more patient-friendly parenteral drug products for self-administration, impacting on the adoption of autoinjectors.

ACHIEVING DRUG DELIVERY SUCCESS

Despite the development and manufacturing challenges posed by the viscosity of biologic drug formulations, they remain an exciting area for drug innovation. Steps can be taken not only to overcome manufacturing efficiency issues, but also useability issues for patients. Enhancing the effectiveness of the delivery device used for viscous medications can go a long way towards creating a better experience for patients, with or without changes to the formulation.

Viscous formulations need to be delivered with relative ease and cause limited pain, which is a challenge using standard devices. Many traditional syringes are only able to deliver viscous formulations by using a needle with a wider diameter, as this can significantly reduce the pressure required to administer the drug. These wider needles can cause unpleasantness for patients, particularly if they are self-administering, since they are not trained to manage the potential discomfort in the same way as healthcare professionals. This can lead to a poor patient experience, with potential negative consequences for patient adherence.

However, advances in technology can overcome this issue, to the benefit of the patients self-administering the drug. One such innovation involves devices that use a liquefied gas, rather than a spring, to push the formulation through the needle. This can allow greater pressure to be exerted to push the drug through a fine needle, while minimising the risk of the needle

> "By taking the patient experience into account from the beginning of the parenteral drug development stage, we can ensure that we do our part to create easier-to-use injectable drugs."

breaking, the device stalling or causing undue discomfort for the patient. As a result, they can eliminate the need for unpleasant wide-diameter needles.

One final hurdle that needs to be overcome is the design of the primary formulation container. Many standard autoinjector devices utilise glass prefilled syringes, which can be susceptible to cracking when high pressures are applied to deliver a viscous drug formulation. Improvements to container design in recent years have significantly reduced the likelihood of this happening, but there is still a risk.

An option to overcome this issue is to use polymeric primary containers, such as those based on cyclic olefin polymer and copolymer (COP/COC). These can better withstand the pressures experienced during the administration of viscous drugs. However, there are concerns with stability and leachables for some products, which means they are not yet a universal solution to the problem of drug container breakage.

TIME TO ACT: CREATING A BETTER USER EXPERIENCE

The growth of viscous formulations on the market shows no sign of slowing down, with many new treatments in development. Consequently, the need to keep patient-centricity front of mind grows ever more pressing, especially if we are to continue to develop drugs designed for self-administration. By taking the patient experience into account from the beginning of the parenteral drug development stage, we can ensure that we do our part to create easier-to-use injectable drugs. There may be limitations in terms of how far we can improve the formulations of drugs to reduce their viscosity, but there are many opportunities to enhance the design of the devices that deliver the finished formulations.

There are third-party device experts

available who can support drug companies in developing more useable, patient-friendly injectable treatments. By working with outsourced partners that specialise in the creation of high-quality autoinjector devices, drug companies can ensure that they have the help and guidance they need to overcome the administration and manufacturing challenges of viscous injectable drug formulations.

By working with such partners, companies can ensure that even viscous drugs are easy for patients to administer themselves with minimal discomfort, allowing them to truly harness the benefits of self-administration in the parenteral space. These will offer greater patient convenience and the liberation of healthcare professionals from the time-consuming need to administer injections on their patients' behalf. As such, better delivery devices have the potential to optimise patient adherence, transforming their health, while enhancing efficiency for resource-constrained public healthcare systems.

ABOUT THE COMPANY

Bespak by Recipharm delivers market-leading design, development and manufacture of drug delivery devices to the global pharmaceutical market. This includes inhalers, nasal technologies and autoinjectors, as well as development and manufacturing services. Recipharm is at the leading edge of drug delivery device innovation. Driven by customer and patient demand, the company's innovations have the potential to create new treatments and opportunities across the globe, as well as accelerating routes to market.

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ABOUT THE AUTHORS

Andrew Donnelly, PhD, is Vice-President of Innovation at Bespak by Recipharm. With 25 years of experience in the pharmaceutical industry and a PhD in drug delivery, Dr Donnelly is responsible for leading the Bespak by Recipharm innovation team of engineers and scientists, and working to identify needs for new technologies. As part of his role, Dr Donnelly is also responsible for creating and identifying new solutions, as well as working with the biopharmaceutical industry to develop combination products.

Shahid Uddin, PhD, is currently Director of Drug Product, Formulation & Stability within the Chemistry, Manufacturing and Controls department at Immunocore. Dr Uddin is responsible for commercialisation and bringing research candidates into the clinic. Prior to this, Dr Uddin held the position of Head of Formulation at MedImmune (AstraZeneca), where he supported the biologics portfolio covering mAbs, peptides, bispecifics and other proteins. He has extensive experience in preformulation/formulation, forced degradation and delivery of biologics both for early- and late-stage programmes.

Subcuject

SUBCUJECT WBI: LOW-COST, LARGER VOLUME, HIGH-VISCOSITY WEARABLE BOLUS INJECTOR – USING STANDARD GLASS PRIMARY PACKAGING

Here, Claus Schmidt Moeller, Chief Technology Officer of Subcuject, introduces the company's wearable bolus injector for single use and discusses the advantages of the device.

HIGHER VOLUME DELIVERY OPTIONS

Subcutaneous injection of volumes above 2 mL is becoming a reality. To administer this, a pharmaceutical company can choose one or more prefilled syringes, more than one autoinjector or a wearable injector.

The use of more than one device for a single injection sequence increases the risk of incorrect use by the user. Hence, a single injection device in the form of a wearable bolus injector may be preferable. However, several of the wearable injectors in development are either expensive to manufacture, use primary packaging materials that are not covered in standard stability documentation or involve additional user steps – such as assembly of parts. Furthermore, a number of wearable injectors in development are quite big in size due to the need to accommodate motors, gears and batteries or a large spring as the drive mechanism.

Subcuject has developed a purely mechanical wearable injector for single use (Figure 1), using forward osmosis as the drive mechanism and using a standard glass primary container. This achieves significant economic advantage, with the device cost expected to be in the range of a single-use autoinjector. Subcuject is currently collaborating with Phillips-Medisize to bring the wearable bolus injector (WBI) to market.

> "Subcuject has developed a purely mechanical wearable injector for single use, using forward osmosis as the drive mechanism and using a standard glass primary container. This achieves significant economic advantage, with the device cost expected to be in the range of a single-use autoinjector."

Figure 1: The Subcuject WBI (5 mL).

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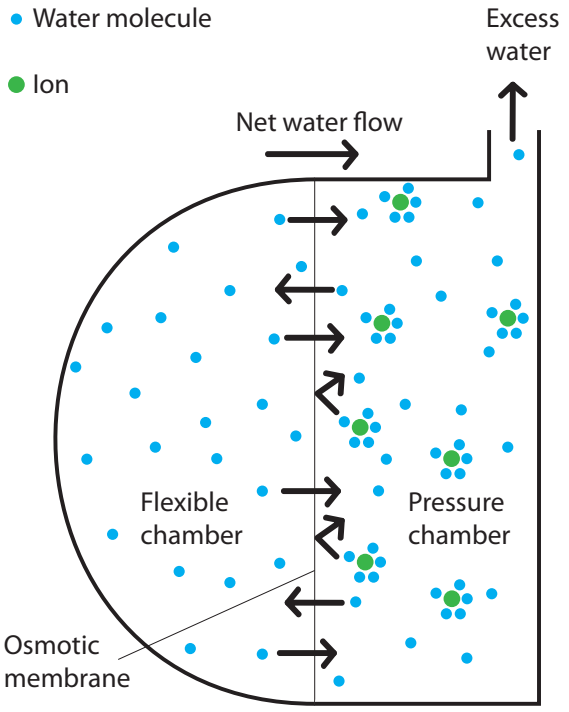

Figure 2: Schematic representation of the osmotic process in the Subcuject wearable injector.

SUBCUJECT WBI WORKING PRINCIPLE

The driving mechanism main elements are freshwater, salt and two semi-permeable forward osmosis membranes. Osmosis is a spontaneous process, where water molecules move around randomly and cross the membrane in both directions without spending any external energy (Brownian movements). When a salt (osmotic agent) is dissolved in the water on one side of the membrane, each ion of a dissolved salt crystal attracts and binds several water molecules. The permeability of these hydrated ions through the membrane is much lower than for the free water molecules, and they stay on one side of the membrane due to a combination of their size and the complex hydrophilic/hydrophobic properties of the membrane. As the salt molecules bind a high number of water molecules, the concentration of free water molecules is lowered, resulting in a spontaneous net flow of water molecules from the freshwater side to the saltwater side of the membrane. The attraction between the ions and the water molecules further increases the net flow of water molecules through the membrane (Figure 2).

> "As pressure needs to be built up before the plunger starts moving, there is a soft injection start for increased patient comfort and minimised risk of impact damage in the primary container."

In the Subcuject WBI, the osmotic agent is released to a "pressure chamber" when the activation button is pushed. A few seconds after activation, the osmotic process starts and water is driven through the membrane to the pressure chamber. The excess water flow builds up a pressure and moves the plunger in a drug-filled cartridge, pushing the content of the cartridge out through the connected needle mechanism. The speed at which the plunger is driven is determined by several factors such as membrane characteristic/permeability and area, osmotic agent and concentration. A patented design ensures that the flow is constant over the entire injection and independent of the device orientation.

ADVANTAGES OF USING AN OSMOTIC-DRIVE MECHANISM

From a user's perspective there are several advantages associated with using an osmotic/hydraulic-driven device. One of the most apparent advantages is the size of the device. As the drive mechanism is hydraulic, there is no need for a mechanical plunger rod, which is often a primary factor for defining the size of an injection device. A 5 mL version of the WBI has approximate dimensions of 84 x 48 x 18.5 mm, while a 10 mL version of the device is anticipated to have dimensions around 93 x 51 x 20 mm – which is expected to be significantly smaller than most competitive wearable injectors in development.

The absence of mechanically moving parts has the added advantage that no sounds are made during injection and, except for "click" sounds during activation of the device and at retraction of the needle, the device is completely soundless. Furthermore, as pressure needs to be built up before the plunger starts moving, there is a soft injection start for increased patient comfort and minimised risk of impact damage in the primary container.

As the device contains only a small number of parts, a non-toxic salt and no electronic parts, the device is as acceptable for disposal as a single-use autoinjector.

From the perspective of a pharmaceutical company, the use of inexpensive elements and the fact that no electronical components need to be handled during development, assembly, storage and disposal of the device is advantageous. As previously noted, the cost of the WBI is expected to be comparable with an autoinjector and, therefore, offers a considerably more cost-effective solution than most competitive prefilled wearable injectors.

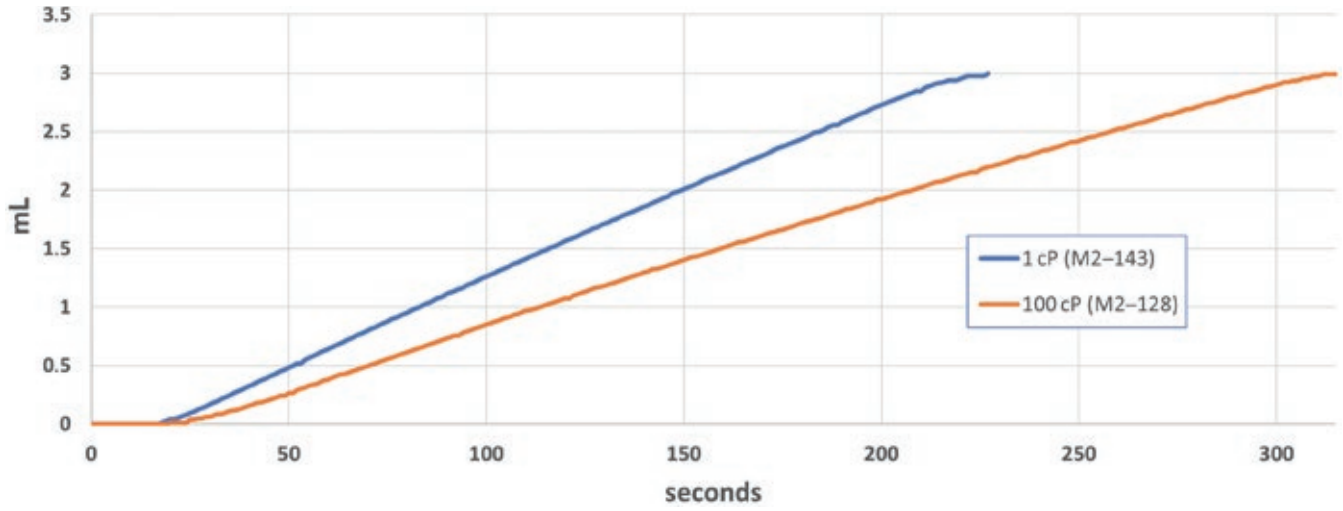

Figure 3: Delivered dose 1 cP and 100 cP examples.

> "An injection device is all about delivering a pharmaceutical product, often biologic, and this must be stable in the device during the shelf life of the product. Therefore, primary packaging is generally a major concern for pharmaceutical companies."

Osmotic processes can be very strong and easily create a pressure above 40 bars under the right conditions. The Subcuject WBI operates within an approximate pressure range of 0.2–1 bar, depending on the viscosity of the drug, and as this is in the lower pressure range of the osmotic process, the flow rate is relatively modestly affected by high viscosity. The flow rate when injecting a drug with a viscosity of 100 cP is just 25–30% lower than for a drug with a viscosity of 1 cP. Accumulated volume injection from the 3 mL device is shown in Figure 3 with typical examples of 1 cP and 100 cP fluids.

An injection device is all about delivering a pharmaceutical product, often biologic, and this must be stable in the device during the shelf life of the product. Therefore, primary packaging is generally a major concern for pharmaceutical companies. Most drugs are tested in glass and with standard rubber compounds during early stability testing and, as such, selecting a device using such preferred components and materials poses a low risk of experiencing drug stability issues. The Subcuject WBI is based on a glass cartridge and a plunger made of a standard rubber compound.

In manufacturing, the drug-filled cartridge is assembled as the last part and can be added to the device by the pharma company or CMO (Figure 4).

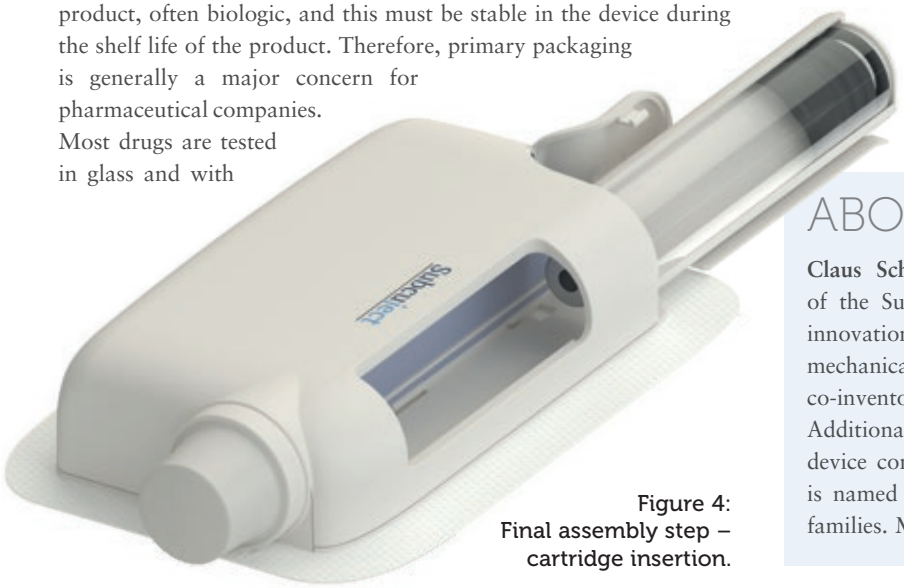

Figure 4: Final assembly step – cartridge insertion.

OUTLOOK

Subcuject has previously demonstrated a 3 mL wearable injector and is now working with Phillips-Medisize on a 5 mL device that will be ready for demonstration during 2021. The forward osmosis principle used in the Subcuject WBI is not limited to injection of certain volumes, and larger volume devices are planned for development.

Phillips-Medisize and Subcuject are ready for engagement into drug-specific development programmes with pharmaceutical companies

ABOUT THE COMPANY

Subcuject is a privately held company, developing an innovative and proprietary device platform for wearable bolus injection. The management team and board of directors have decades of experience and a track record in medical devices, pharma and drug delivery. Subcuject collaborates with Phillips-Medisize on development, commercialisation and manufacturing of the Subcuject WBI.

ABOUT THE AUTHOR

Claus Schmidt Moeller, Founder of Subcuject and inventor of the Subcuject device concept, has 25 years' experience in innovation of drug delivery devices. He is the inventor of the mechanical concept of Novo Nordisk's Novopen 4, 5 and 6, and co-inventor of the company's Flexpen and Flextouch insulin pens. Additionally, he has developed and licensed several injection device concepts for major pharma and device companies, and is named as inventor or co-inventor on more than 60 patent families. Mr Moeller holds a BSc in Mechanical Engineering.

SAFE AND AUTOMATIC DEVICE TO IMPROVE DRUG PREPARATION FROM MULTIDOSE VIALS

In this article, Benjamin Morel, Intellectual Property Manager, and Claire Authesserre, PhD, R&D Fluidics Manager, both of EVEON, discuss the challenges and opportunities presented by multidose vials.

The use of multidose vials (MDVs) versus single-dose vials (SDVs) has been the subject of a 40-year debate. Yet the industry has been slow to implement alternative formats to SDVs, even though alternatives are being developed and can challenge existing practices.[1,2]

In 1983, it was already outlined by Sheth *et al*[3] that MDVs could be used with relatively low risk of bacterial contamination. More recent studies demonstrate that using MDVs as packaging presentation for vaccines does not affect immunogenicity.[4,5]

However, this type of packaging is associated with some clinical outbreaks.[6,7,8] The resulting manual handling can induce dosing mistakes and increase the risks of drug contamination and needle-stick injury. Therefore, MDVs require more training and more stringent practices to ensure patient safety.[9,10]

Furthermore, this type of packaging presentation has often been questioned from an economical point of view. The use of MDVs brings an additional challenge of increased dose wastage if opened with lack of planification during a vaccination campaign,[9,11] and is inevitable, according to experts.[12] In addition, studies have revealed that, during the H1N1 pandemic, MDVs were not as economic as expected due to the additional cost of time spent on manual handling and administrative processes.[13]

Today, more than 10 years after the H1N1 pandemic, MDVs are at the centre of the global strategic plan to overcome the current global crisis. Since the beginning of the covid-19 vaccination race, MDVs have been at the forefront. Worldwide demand for glass vials, as well as the glass technicity required for vaccine stability, and the low number of vials providers, led to the situation of potential shortage if only SDVs were used.[12] To illustrate this point, a few weeks ago the US FDA approved two new MDVs, enabling a shift from six to 11-dose and 15-dose vials to overcome this situation.[14] This measure is another step toward avoiding a vial shortage, but also a proven efficient measure to reduce what is considered "inevitable waste".[15]

Indeed, the covid-19 crisis pushes forward the use of MDVs – but it is important to consider the beneficial aspect observed on the vaccination value chain and our ecosystem and to use them for more general purposes. We learnt from vaccination campaigns in low- and middle-income countries that MDVs enable a 40% packaging waste reduction[16] and a 47% storage volume reduction in vaccination centres and storage rooms.[16] Those benefits are key when you consider the waste management crisis, which has already started on a global scale.

That is why it would be of interest to see how to improve the use of MDVs and to challenge the current paradigm of SDVs. This global vaccination campaign is the right time to think out of the box, push innovations and overcome the drawbacks of MDVs. Identifying key learnings helps to further improve practices and bring new solutions for future local, regional or global vaccination campaigns.

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"EVEON's technologies dedicated to automated drug preparation and injection demonstrate key advantages to overcome cost efficiency, healthcare worker usability and patient safety challenges."

Dose (mL)	Expelled dose standard deviation (mL)	Dose accuracy (%)	n
3	0.1	3	n=6
1	0.01	1	n=6
0.3	0.005	2	n=30
0.02	0.0005	3	n=5

Table 1: Examples of doses expelled from EVEON devices for several targeted injected doses (3 mL, 1 mL, 300 µL and 20 µL) Errors bars correspond to standard deviations; n is the number of expelled doses used for standard deviation calculations.

One way to improve is to standardise the manual work performed by healthcare workers (HCWs) to get a repeatable, consistent, secure and cost-efficient vaccination process for each injection. This can be achieved through HCW training in best practice. Since manual work still remains user dependent, a medical device approach would enable the standardisation of preparation and injection steps by getting rid of inter-user variability and greatly limiting the number of manipulations.

One of EVEON's goals is to address the challenge raised by drug preparation and injection. How can medical devices bring answers to questions raised around patient safety and cost efficiency? How can medical devices be part of the solution for reducing product wastage and improving usability for physicians?

EVEON's technologies dedicated to automated drug preparation and injection demonstrate key advantages to overcome cost efficiency, HCW usability and patient safety challenges.

By developing electromechanical devices, EVEON enables the automation of drug preparation and/or delivery. All parameters – such as the injected dose, the injection flow rate and the process time – are highly controlled, leading to a very reproducible preparation or delivery and a standard process, thus avoiding user-dependent variability, manipulation risks and dosing mistakes.

EVEON devices, using the company's proprietary micropump, can deliver doses from 20 µL up to several millilitres with a high accuracy (<3%). The Intuity® Ject device has been used for several applications with different targeted injected doses. Table 1 shows the dose accuracy for four expelled doses. For example, a 1 mL bolus has been injected with ± 0.01 mL, leading to 1% accuracy (n-6), and a 300 µL dose has been injected with ± 5 µL, leading to <2% accuracy (n=30).

Such levels of dose accuracy with highly reproducible results allow optimisation of the filling of the drug container. In the case of MDVs, the extraction and delivery of an accurate dose allows for the same number of doses to be delivered every time, without requiring precise handling or losing time during the process. In the context of vaccine dose shortages, it also avoids the possibility of an HCW wasting a dose because of a wrong move.

The use of medical devices also enables control and reduction of dead volumes to maximise drug retrieval within the vial. EVEON devices are developed to be adapted to standard pharmaceutical containers. The design of the fluid path and the fluidic process is optimised to reduce dead volume and drug loss in both the containers and the device fluid path. EVEON's development within its Intuity® Mix platform (Figure 1) demonstrates a 56–66% reduction in drug wastage within the vial, compared with other products on the market.

As HCW time is precious, especially in the context of a pandemic, EVEON devices are also designed to minimise the number of manipulations and the process time required for use. For example, the Intuity® Ject device (Figure 2) is capable of injecting a 300 µL dose in less than three seconds.

Figure 1: The Intuity® Ject device.

Figure 2: The Intuity® Mix platform.

"An appropriate medical device, coupled with best-practice training, can fill the economic and patient-safety gap between MDCs and SDVs."

Usability is also an important factor for time efficiency and device acceptability on the part of the user. That is why EVEON works in close collaboration with HCWs to understand users' needs and the environment and use conditions of the device. EVEON is used to working with ergonomists and designers to take human factors into account, right from the first steps of device design, to be sure to design an appropriate and easy-to-use device.

An appropriate medical device, coupled with best-practice training, can fill the economic and patient-safety gap between MDVs and SDVs. EVEON can bring easy-to-use and robust medical innovation to standardise dose preparation (dilution) and injection – and turn MDVs into an attractive and competitive solution.

ABOUT THE COMPANY

EVEON is an ISO 13485-certified company that designs and manufactures safe, connected, automatic medical devices for the preparation and delivery of therapeutic treatments to improve patient quality of life. EVEON places the needs of patients and care professionals at the heart of its development by designing simple, intuitive devices to improve therapeutic performance, compliance and the conditions of at-home care. The company's expertise has been recognised by Forbes magazine, which ranked EVEON as the third most inventive company in France in the category of medical technology in 2019.

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Benjamin Morel holds a master's degree in Bioengineering, specialised in applied molecular and cellular biology, and an advanced master's degree in Biotechnology Management from Grenoble Ecole de Management (France). After working as a consultant in intellectual property strategy and business intelligence for the life science industry, he joined EVEON as Intellectual Property Manager in 2019. Part of his mission is to assist the R&D team by using tangible information to stimulate the process of innovation. This interdisciplinary role involves integrating multiple business-related aspects from the early stage of product development to generate solutions with strong potential to answer technical needs.

Claire Authesserre, PhD, is an engineer who graduated from ESPCI Paris, a major French institution of higher education that combines multidisciplinary scientific courses in physics, chemistry and biology. She is also a graduate of Imperial College London (UK), where she obtained an MSc degree in Biomedical Engineering in 2013. She then completed a PhD in Microfluidics at CEA Leti Grenoble (France). Since 2017, Dr Authesserre has been R&D Fluidics Manager at EVEON, leading a team of fluidics engineers and technician. Placed at the heart of EVEON's development, the R&D fluidics team works very closely with both the mechanical & plastics and digital teams to design medical devices with optimised performance to fit with customer and patient needs.

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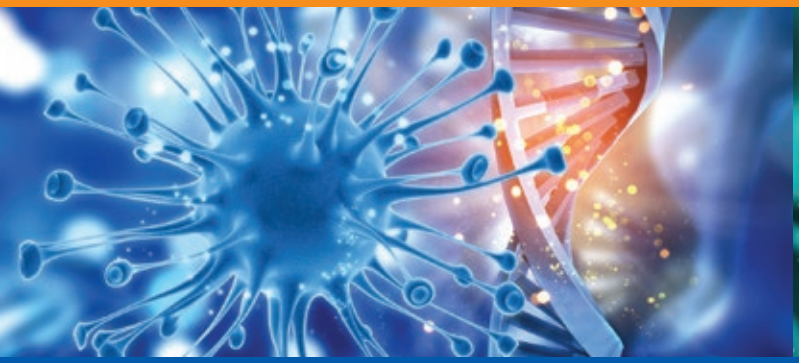

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ENSURING FUNCTIONAL PERFORMANCE AND REGULATORY COMPLIANCE OF ELASTOMER STOPPERS FOR MULTIPIERCING SITUATIONS

In this article, Bruno Morchain, Technical Center Manager, Aptar Pharma Injectables, Sébastien Cordier, Technical Product Manager, PremiumCoat®, and Estelle Verger, Business Development Senior Manager, PremiumCoat®, all of Aptar Pharma, discuss a series of experiments conducted on Aptar Pharma's PremiumCoat® vial stoppers to demonstrate their compliance with EU and US Pharmacopeia standards and their excellent performance in multipiercing situations.

When developing a drug product, be it a new drug, a generic or repurposing an existing drug, specifying the appropriate primary packaging is an essential step. Because it is in direct contact with the drug product, the primary container plays a critical role in preserving the drug's integrity throughout its lifecycle, from the initial point of production, through packaging, distribution, short- or long-term storage, up to the moment when it is administered to the patient. As such, any failure associated with the primary container has the potential to result in serious adverse effects for the patient or the healthcare practitioner, which, aside from the potential significant human impact, can also result in financial implications for the drug manufacturer.

Primary drug packaging for injectables is typically comprised of two parts: a glass container for holding the solution and an elastomeric component. In applications using vials, further to requirements that the container can be closed easily during the filling process and that container closure integrity be maintained throughout the product's lifecycle, the elastomeric stopper plays a critical role in facilitating easy and safe collection of the drug product by healthcare practitioners.

In the majority of cases, elastomeric stoppers are not removed from the vial in order to preserve the integrity of the drug product. Instead, a needle is inserted through the stopper to access the drug. However, this piercing action can lead to critical incidents, making the stopper's functional performance key in protecting both the drug and the patient.

In the first instance, the needle must pierce through the elastomer. Although the design of the needle contributes to reducing the insertion force required, the stopper material also plays an important role in easing the act of insertion. Furthermore, the use of hard rubber may bend the tip of the needle and increase patient discomfort during the injection.

An additional risk to patient safety is through coring (tearing off small fragments of the elastomer when the needle pierces the rubber), which leads to contamination of the drug solution. Furthermore, since glass vials can be used to package multiple doses, often the stopper must be pierced

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several times while maintaining a seal after the delivery of each dose. Elastomeric solutions providers, therefore, need to ensure that the self-sealing capabilities of their components continue to preserve the drug's integrity over time, avoiding the potential for contamination and oxidation that would be detrimental to patient safety. This is particularly true in the current covid-19 context, where the need to mass-vaccinate large populations has led pharma companies to choose multidose vials as their favoured type of vaccine container.

Over the course of 50 years of collaboration with pharma and biotech partners, Aptar Pharma has developed expertise to address such drug delivery challenges, working with vaccines, biotech drugs and small molecules. Aptar Pharma's latest innovation is PremiumCoat®, which combines start-of-the-art elastomer formulation with market-proven ethylene tetrafluoroethylene (ETFE) film-coating technology. Under testing, the functional performance of PremiumCoat® stoppers was shown to be fully compliant with the quality controls specified by EU Pharmacopoeia (EP) 3.2.9, demonstrating excellent properties for protecting drugs and patients, and facilitating the drug development process.

PREMIUMCOAT®: REDUCING PIERCING FORCES

When working with vial containers, healthcare practitioners need to pierce the elastomeric closure components to access the drug. The force required to insert the needle depends on factors such as needle diameter and tip design, but also on the mechanical properties of the elastomer. While this force is usually not a limiting factor for the health practitioner's activity, it may affect the integrity of the needle tip. Over the decades, injectables companies have worked to develop needle designs that minimise patient discomfort during an injection. This is usually achieved by using thinner needles or by increasing the sharpness of the tip. However, sharper tips and thinner needles are inevitably more fragile and therefore more likely to bend if excessive force is applied when piercing the elastomer. The discomfort and pain associated with a bent needle can be avoided by improving the mechanical properties of the vial's stopper to help reduce the needle insertion force required.

> "The need to mass-vaccinate large populations has led pharma companies to choose multidose vials as their favoured type of vaccine container."

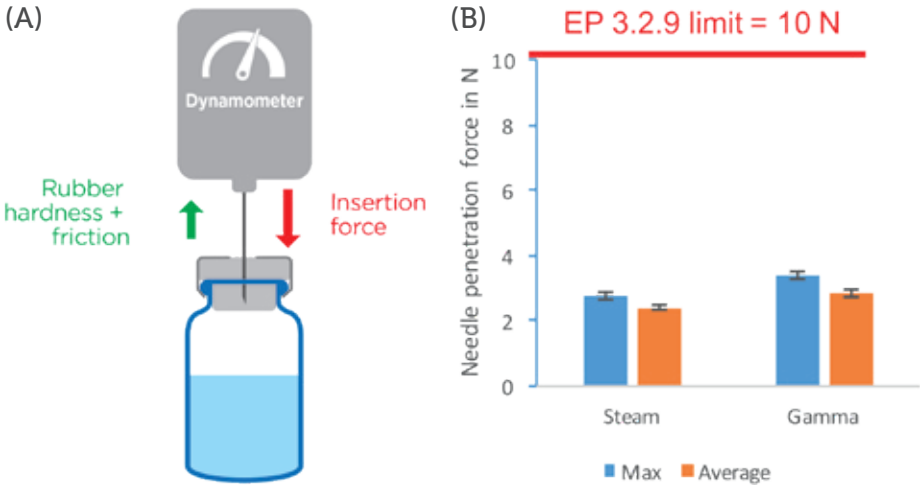

Figure 1: Measurement of needle insertion force. A) Representation of the experimental setup. B) Representation of the maximum insertion force and average insertion force measured for steam- and gamma-sterilised PremiumCoat® 20 mm stoppers. The data were collected after two years of ageing and using 21G 3-bevel needles.

Aptar Pharma's experts have evaluated the insertion force required to pierce PremiumCoat® stoppers using a 21-gauge needle, comparing stoppers that were sterilised using steam or gamma radiation processes after two years of ageing (Figure 1). The insertion force was measured using a dynamometer at an insertion speed of 200 mm/min, with recordings taken of the maximum force registered during the insertion. EP 3.2.9 sets the maximum acceptable force at 10 N.

Results showed that, regardless of the sterilisation method used with PremiumCoat® stoppers, the needle insertion force is significantly below the limit imposed by EP 3.2.9. The average insertion force reached 2.4 N (maximum at 2.8 N) for steam-sterilised stoppers, and 2.8 N (maximum at 3.4 N) for gamma-sterilised stoppers.

These results confirm that, despite the presence of an ETFE film, the force required to pierce PremiumCoat® stoppers remains well within EP 3.2.9 and US Pharmacopeia (USP) <381> recommendations. It was shown that PremiumCoat® stoppers are easy to pierce, facilitating ease of the injection process and potentially helping to reduce perceived pain among patients during the injection by preserving the needle tip's integrity.

> "Sharpness may become problematic when the needle punctures the elastomeric vial stopper as it may tear off fragments, which will end up in the drug solution and may compromise patient safety."

PREMIUMCOAT®: PROTECTING THE PATIENT AGAINST FRAGMENT CONTAMINATION

Sharpness is an essential quality for needles, allowing them not only to penetrate effectively through the rubber stopper but, most importantly, to limit the patient's discomfort during an injection. However, this sharpness may become problematic when the needle punctures the elastomeric vial stopper as it may tear off fragments, which will end up in the drug solution and may compromise patient safety. Therefore, manufacturers must ensure elastomer formulations are less prone to fragmentation to help limit the risk of coring without the need to compromise on the increased patient comfort provided by sharper needles.

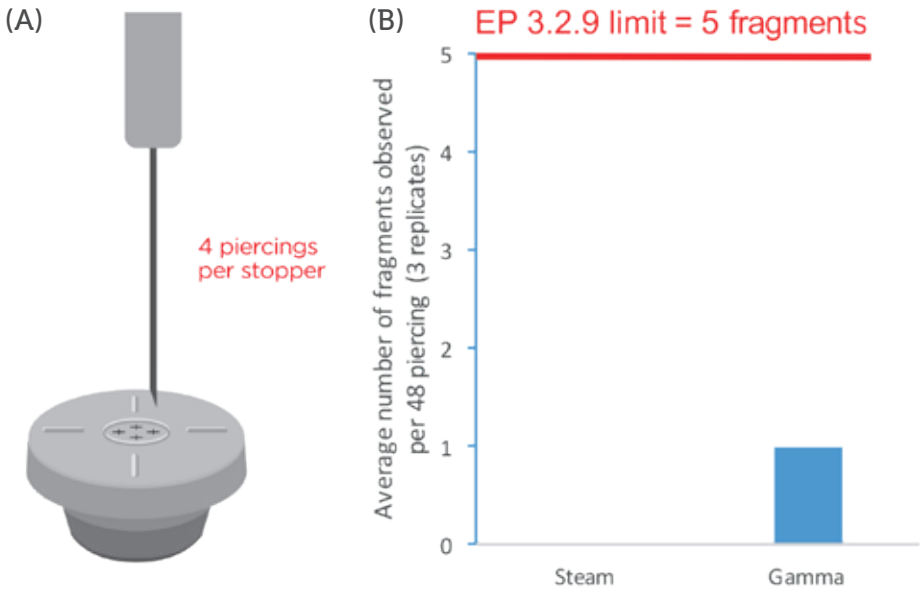

Figure 2: Evaluation of PremiumCoat® 20 mm stoppers piercing fragmentation. A) **Representation of the experimental design**: each stopper is pierced four times successively at a different spot and the vial's content filtrated to look for visible fragments. B) **Representation of the fragmentation results**: the data are represented as the number of fragments per 48 piercing events. Three sets of 12 steam-sterilised and three sets of 12 gamma-sterilised stoppers were each pierced four times with 21G needles.

Aptar Pharma's technical team evaluated the performance of PremiumCoat® stoppers in terms of the risk of coring (Figure 2), referring to the limits set out in EP 3.2.9. A total of 12 stoppers were manually pierced four times, each time at a different site. The EP 3.2.9 acceptance limit is set at five fragments over the 12 stoppers and 48 piercing events.

This experiment revealed that, regardless of the sterilisation method, the number of fragments recorded over 48 piercing events for the PremiumCoat® stopper was very clearly within the acceptance level of EP 3.2.9 and USP <381>. For the steam-sterilised stopper, no fragments were counted after performing the experiment three times (a total of 36 stoppers tested with 144 piercing events). In the case of gamma-sterilised stoppers, either zero, one or two fragments were counted after 48 piercings. After conducting the experiment three times, an average of one fragment was observed per 48 piercings.

The results demonstrate that the risk of rubber fragmentation is very low with PremiumCoat® stoppers and fully in accordance with EP 3.2.9 and USP <381> guidelines. PremiumCoat® stoppers reduce the risk associated with elastomer fragment contamination of drug products, contributing to improved patient safety and safe drug injections.

PREMIUMCOAT®: MAINTAINING OPTIMAL SEALING AFTER MULTIPIERCING

Multidose primary drug packaging is commonly used in the injectables market, especially in the case of vaccination campaigns or in settings that focus on waste limitation and cost savings. In principle, the stopper of a multidose vial will be pierced several times, and each piercing increases the risk of compromising the sealing properties of the stopper. Due to their elastic properties, elastomers demonstrate a level of resilience that allows them to reseal after being breached, and rubber-component providers have been working on specific formulations that ensure long-lasting protection for drugs in multipiercing applications.

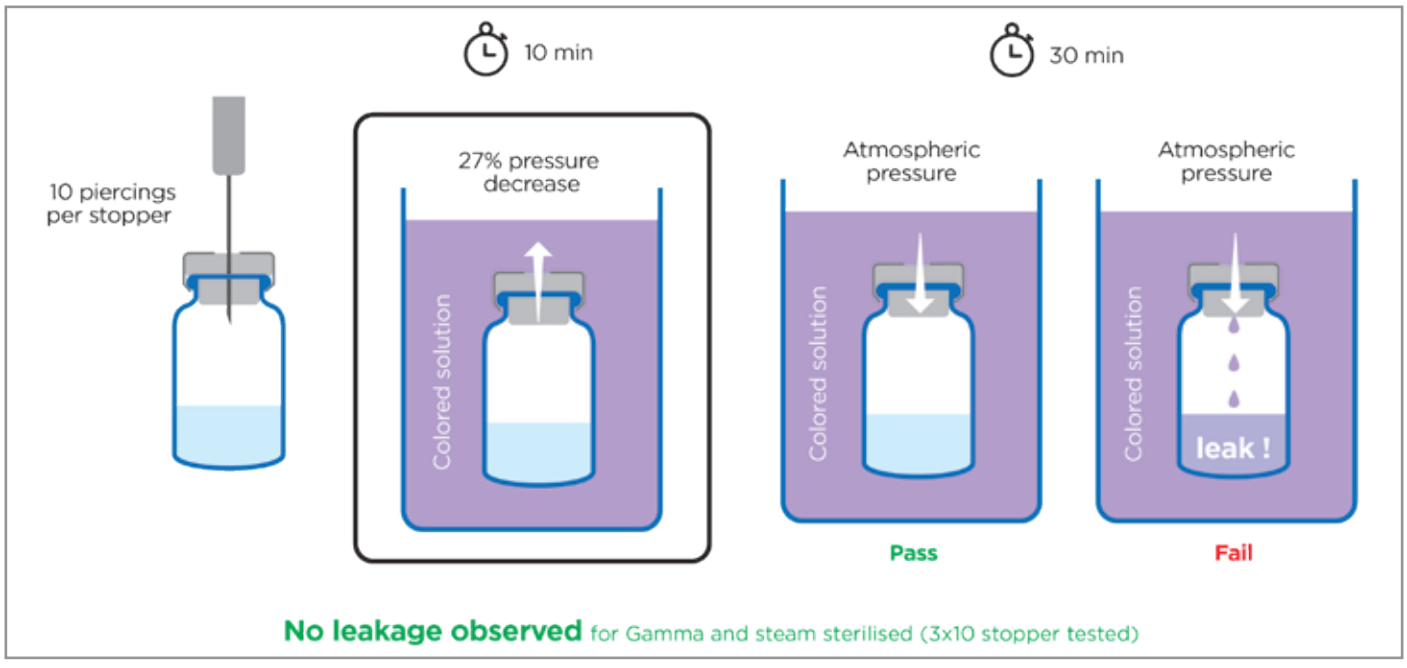

Figure 3: Evaluation of the self-sealing ability of PremiumCoat® 20 mm stoppers. Each stopper was pierced 10 times at a different site with a 21G needle then immersed in a coloured solution while reducing ambient pressure by 27 kPa in a vacuum chamber. Atmospheric pressure was then restored and the inside of the vials were monitored for evidence of potential leaks of the coloured solution. The arrow represents the pressure gradient. A total of 30 observations were performed for both steam-sterilised and gamma-sterilised stoppers.

BOX 1: APTAR PHARMA'S PREMIUMCOAT®

The function of ETFE films is to form a barrier to protect the drug from extractable and leachable chemicals. However, the presence of a film must not negatively affect the other key properties of stoppers. The results of the tests performed by Aptar Pharma's expert teams show that PremiumCoat® stoppers are fully compliant with the EP 3.2.9 recommendations. Regardless of the sterilisation method chosen and even in straining circumstances, such as the mass vaccinations for covid-19, PremiumCoat® is a reliable solution that ensures the success of Aptar's pharma partners by:

- Facilitating easier injections and potentially reducing perceived pain among patients by protecting the needle tip.
- Helping to protect the drug and patients against particulate contaminations, even in a multipiercing context.
- Safeguarding the drug's integrity throughout its lifecycle, even for multidose applications.

Aptar Pharma's experts evaluated the ability of PremiumCoat® stoppers to preserve the seal closure in conditions that simulate multipiercing applications (Figure 3). The stoppers were pierced 10 times with the same needle before the vial was submerged into a coloured solution. The system was placed in a vacuum and the pressure reduced. Upon restoring atmospheric pressure, any failures in sealing properties would be highlighted by a colouration of the contents within the vial.

The experiment clearly demonstrated the self-sealing performance of PremiumCoat® stoppers, with the seal closure maintained even after 10 successive piercings. No leakage was observed among the 60 stoppers tested, and the sterilisation method did not affect the performance of the stoppers.

These results highlight how, even in an extreme case where the rubber is pierced 10 times, the self-sealing capabilities of PremiumCoat® stoppers maintain container closure integrity. PremiumCoat® stoppers, therefore, provide an optimal solution for preserving the drug product – even in multidose applications – and ensuring patients receive safe injections (Box 1).

All data referenced in this article are from Aptar Pharma's internal report #TR20-0206, conducted in 2020 in Villepinte, France.

ABOUT THE COMPANY

For pharma customers worldwide, Aptar Pharma is the go-to drug delivery expert, providing innovative drug delivery systems, components and active packaging solutions across the widest range of delivery routes including nasal, pulmonary, ophthalmic, dermal and injectables.

Aptar Pharma Services provides early-stage to commercialisation support to accelerate and derisk the development journey. With a strong focus on innovation, Aptar Pharma is leading the way in developing connected devices to deliver digital medicines. With a global manufacturing footprint of 14 manufacturing sites, Aptar Pharma provides security of supply and local support to customers. Aptar Pharma is part of AptarGroup, Inc (NYSE:ATR).

ABOUT THE AUTHORS

Bruno Morchain is Manager of the Technical Center in Villepinte (France) for Aptar Pharma's Injectables division. A graduate in mechanical engineering from the University of Technology of Compiègne (France), Mr Morchain has over 18 years' experience in the pharmaceutical industry. He joined Aptar Pharma in 2012 as a Technical Support Engineer, where he was in charge of supporting customers with elastomeric primary packaging selection, validation, filing and use during the product lifecycle. In 2018, he became Technical Center Manager, where he leads a technical team involved in developing new products, evaluating their performance and conducting studies to support customers and their projects.

Sébastien Cordier is the Technical Product Manager for PremiumCoat® projects at Aptar Pharma's Injectables division. A graduate of MINES ParisTech and EDHEC Business School in France, Mr Cordier first spent over 15 years in the automotive industry, where he developed a strong expertise in plastics and elastomers, before joining Aptar Pharma in 2020. In his current role as Technical Product Manager at Aptar Pharma, Mr Cordier is responsible for the PremiumCoat® platform of vial stoppers and syringe plungers, and is dedicated to supporting customer development projects involving coated elastomeric solutions.

Estelle Verger is the Business Development Senior Manager for PremiumCoat® coated solutions for Aptar Pharma's Injectables division, and is responsible for the growth of the PremiumCoat® platform in the global injectable market. A graduate from ESSEC Business School (Cergy, France) and Fachhochschule Dortmund (Germany), with a masters degree in International Business Management, she joined Aptar Pharma in 2011 as a Sales Manager, Injectables. Ms Verger then moved to Aptar Pharma's Consumer Healthcare division as a Product Manager, where she was responsible for airless dispensing solutions for pharmaceutical applications for a number of years, before returning to the Aptar Pharma Injectables division in 2020.

DRIVERS FOR CHANGE IN ASEPTIC AUTOMATION

Here, Dave Seaward, Projects Director, and David Phasey, Projects Director, both of 3P innovation, discuss the factors that have led to recent growth in aseptic automation within the pharmaceutical industry.

MACRO TRENDS

The last few years have seen a significant shift in focus by aseptic machinery vendors as they respond to their clients' demands. This is merely a reflection of structural changes within the pharmaceutical industry. Parenteral drug delivery remains an area of significant growth, with the trend towards home healthcare and self-administration of injectables (to reduce administration costs and improve the "patient journey").

Overlaid upon this, is a rise in insoluble small molecules and biologics driving more parenteral applications. In turn, this is leading to growth in aseptic automation dominated by fill-finish.

The rise of biologics and, more recently, some of the cell and gene therapies – also known as advanced therapy medicinal products (ATMPs) – has driven much of this change within aseptic machinery vendors.

> "A rise in insoluble small molecules and biologics [is] driving more parenteral applications. In turn, this is leading to growth in aseptic automation dominated by fill-finish."

Manufacturing facilities are having to adapt to ever-smaller batch commercial manufacturing. Vendors are developing flexible automation systems to serve the growth of biologics, orphan drug products and personalised medicines.

This has led to the need for flexible machinery capable of smaller batch sizes (see Figures 1 and 2), the rise of robotics and the need for custom

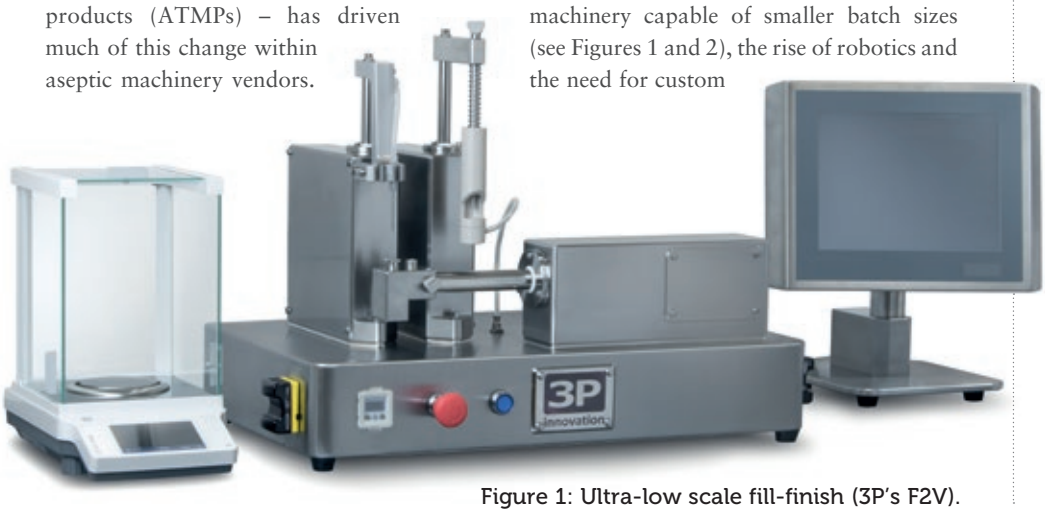

Figure 1: Ultra-low scale fill-finish (3P's F2V).

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machinery to assemble novel administration devices. While some products still require high-speed, high-volume and relatively inflexible fill-finish machinery, vendors are increasingly offering smaller footprint flexible machines filled with reconfigurable robotic processing.

The borosilicate glass vial remains the go-to primary drug container for many of these medicaments, especially during clinical trials and initial commercial manufacture. There is, however, a continued trend towards prefilled syringes (PFSs) and cartridges that typically are then used within autoinjectors, dual chamber/reconstitution applications and wearable devices. This trend can be traced back to the early 1980s, when Sanofi and Rhône Poulenc-Rorer (now Sanofi-Aventis) successfully introduced them as the primary drug container for heparins. Prior to this, PFSs were very much a niche market product.

The use of plastics and, in particular, cyclic olefin copolymer (COC), is opening up many new primary drug container opportunities – this material can enable the elimination of silicone oil lubricants that interact with some drugs (~10% of the biologic pipeline drugs are ultra-sensitive to silicone), it is more robust at cryogenic temperatures, and injection moulding provides for the addition of features to be moulded onto the primary drug container. The ability to add features via injection moulding to the primary drug container enables the medical device designer to get really creative – in particular, this is leading to more compact devices.

The trend towards PFSs from vials is likely to continue as they enable easier and safer injections. Since the drug is already filled in the container in its exact dose, this prevents the risk of dosing error and reduces overfill during the production of a potentially very costly drug.

Many of these drugs are high value and low volume. As such, the space and capital equipment cost required to depyrogenate/sterilise primary drug containers ahead of a fill-finish line is falling out of favour for all but the largest volume production facilities. In its place are the use of presterilised tubs containing nests of primary drug containers (according to ISO11040-7:2015[en]). This has led to smaller fill-finish production equipment focused on the rapid sanitisation of the outside of the tubs prior to removal of the Tyvek™ (DuPont, Wilmington, DE, US) lids and the fill-finish process. Robots are the natural solution to de-nesting (and re-nesting) tubs of primary drug containers. Simple changes to the robot end effector also enable the same line to process vials, cartridges, PFSs and novel primary drug containers when packages are in ISO-standard tubs. To minimise development, many vendors of aseptic automation have elected to use "standard" robots, albeit to cleanroom/sterilisable standards (3P uses a Stäubli (Freienbach, Switzerland) integrator). Typically, these six-axis or SCARA robots are relatively large for the application, leading to larger-than-necessary isolators. More recently, vendors have begun to introduce their own compact robots (3P has recently introduced the "Crabot" tub-handling robot).

Figure 2: Low-scale fill-finish (3P's F2V-W-N-S).

"Industrial robotics are seeing a boom across many industrial sectors. This is driven by a need for improved product quality, greater assembly precision and greater automation flexibility. In previous decades, the cost of robots often precluded their implementation. However, ever lower cost robots can now lead to very rapid paybacks."

Industrial robotics are seeing a boom across many industrial sectors. This is driven by a need for improved product quality, greater assembly precision and greater automation flexibility. In previous decades, the cost of robots often precluded their implementation. However, ever lower cost robots can now lead to very rapid paybacks. Notwithstanding the desire for more consistent process aseptic processing, robots enable a reduction in particulates. Numerous articles have demonstrated that human operators are the main contamination risk in cleanrooms, particularly through the shedding of particles from personal clothing (even undergarments) and skin, exacerbated by movement. A typical person sheds around one billion skin cells every day and 10% of them have micro-organisms on them.[1] Meanwhile, every minute, microorganism-loaded liquid droplets are released from the mouth and nose (10 million/g of saliva or nasal fluid).[1] Hence, manual aseptic tasks are increasingly being converted to non-shedding robotic tasks typically within an isolator.[2] To paraphrase another machinery company, "if it can be automated, it will be automated!"

THE TREND TOWARDS CUSTOM AUTOMATION

The previous paragraphs refer to the macro trends that all aseptic automation companies are observing. As experts in custom aseptic automation, 3P has some unique insights into many of the niche applications – in many cases, these have been under development for several years and they are now starting to appear on the market. These applications require assembly and fill-finish equipment that simply did not exist before 3P "invented" it. Aseptic processing equipment and automation has to be developed from first principles for these applications.

The trend of self-administering injectable drugs and the goal to reduce injection frequency has driven the development of wearable/large volume injectors. These are designed for administering injectable drugs in large volume, typically more than 2 mL, and/or injection over an extended time. Many of these devices use conventional cartridge-based primary drug containers.

"In connection with the trend towards COC, there are a number of novel devices in development taking advantage of the flexibility of injection mouldings to create patient benefits. Some of these unique features are driving the need for custom automation and custom fill-finish solutions."

In connection with the trend towards COC previously mentioned, there are a number of novel devices in development taking advantage of the flexibility of injection mouldings to create patient benefits. Some of these unique features are driving the need for custom automation and custom fill-finish solutions. As the drug substances are denatured by terminal sterilisation, the custom automation and fill-finish need to be accomplished aseptically.

Linked to desire of reduced injection frequency, some daily injections are moving to "depot"-based sustained-release products. The drug is mixed with a polymer, which biodegrades safely to release the drug over many days or weeks. These technologies are typically based around poly lactic-co-glycolic acid (PLGA), which is now used in many US FDA-approved devices owing to its predictable and tuneable biodegradability and biocompatibility (safety profile).[3] Such technologies have the ability to deliver small molecules and biologics, including proteins, vaccines, DNA, RNA and peptides. Typically, these devices rely upon some form of reconstitution between a powder (often freeze or spray dried) and a diluent to form a subcutaneous sustained-release gel following injection.

The recent success of covid-19-related vaccines has brought into sharp focus the challenges of cold chain logistics. It is well recorded that cold chain logistics can be challenging, especially in hot and developing nations. Even within developed nations the "last-mile" is a recognised problem leading to cold chain breaches. Drug substances tend to be significantly more shelf-stable at ambient conditions as a powder rather than as a liquid and, clearly, parenteral injections are predominantly liquids delivered through a needle. This has led to the rise in reconstitution devices, which mix a shelf-stable powder with a diluent just prior to administration. These are dominated by lyophilisation within vials or cartridges. Some applications use spray drying as a means of improving the speed of reconstitution (for poorly soluble materials). The reconstitution within vials is a complicated multistep process for caregivers, which can lead to errors. Numerous reconstitution "twin chamber" systems are under development with some form of bypass/valve between the chambers. These enable liquid/liquid or powder/liquid reconstitution just prior to administration. This trend has given rise to the need for precise aseptic powder dispensing. In addition, the physical properties required for solubility tend to go hand in hand with a sensitivity to humidity and poor flow characteristics, meaning these powders tend to be a challenge to dispense from bulk into a primary drug container such as a twin chamber cartridge or novel device.

Another area that has grown in interest is the generation of small diameter extruded depots. In these applications, a small depot similar in size to a grain of rice is first extruded into a continuous length prior to drying and cutting operations. Such devices are clearly limited in the size of the payload. They are typically injected under the skin to deliver sustained-release hormones or vaccines. As above, these drug substances are typically denatured by terminal sterilisation, such that these novel processes must be produced in an aseptic manner.

THE RISE OF CELL AND GENE (ATMP)

One cannot discuss trends within parenteral administration without discussing what tends to be called "cell and gene" in the US and ATMPs in Europe. These therapies encompass a wide range of treatments including genetic editing techniques and chimeric antigen receptor (CAR) T-cell therapies. They use engineered cells to boost a patient's own immune system to fight diseases such as cancer. These intravenous therapies are currently seeing an explosion in activity with billion-dollar acquisitions, IPOs and investments. It is only a few years (2017) since the FDA made its first approval of a gene therapy.

The growth is very reminiscent of the not-so-distant biologics boom in monoclonal antibodies. By way of example, in 2017 there were reported to be ~2,600 ATMP trials across 38 countries[4] and market surveys suggest over 30% annual growth between 2020 and 2027 from around US$2.5 billion (£1.8 billion) to $25 billion (£18 billion).[5] In 2020, there were 154 reported trials within the UK alone.[6] The technology is moving rapidly from the lab to patients, and that hints at some of the challenges. Poorly defined semi-automatic and manual processes developed by academics in university laboratories are currently being industrialised, scaled and validated. The pharmaceutical sector is a highly regulated environment used to high-volume production, with formal procedures for the simplest of tasks. Knowledge and the guidance are having to be developed for these novel ATMP treatments. Meanwhile the rapid expansion of the sector has led to a skills shortage drawing in staff from traditional high-volume manufacture.

Manufacturing costs and complexity of manufacturing tend to be high in a nascent industry launching products made with an innovative technology. For the ATMP companies, working through the scale-out/scale-up challenge is a priority.

For autologous treatments the batch size is one. Cells are harvested from a patient, modified and expanded and then returned to the patient, typically intravenously. As discussed, laboratory processes can be very manual and there is currently no scale. As such, the introductory price for ATMPs can range from $18,950 (£13,650) to $1.2 million (£869,256) per patient.[7] There is a real and present need to reduce the cost of production by a factor of 10–20. The situation is reminiscent of bespoke car production before Henry Ford introduced the production line in 1913.

The jury is currently "out" on what the equivalent efficient production system is for ATMPs. Some believe the future lies in closed single-use ecosystems designed to only run upon dedicated processing machines. This is an Apple business model, whereby all items of the ecosystem need to be procured from a single source. Others are investigating robotic processing within an aseptic isolator, agnostic to the consumable vendors: think open-source Android. What is clear, is the future will require significant amounts of automation technology. The goal is to create a repeatable manufacturing

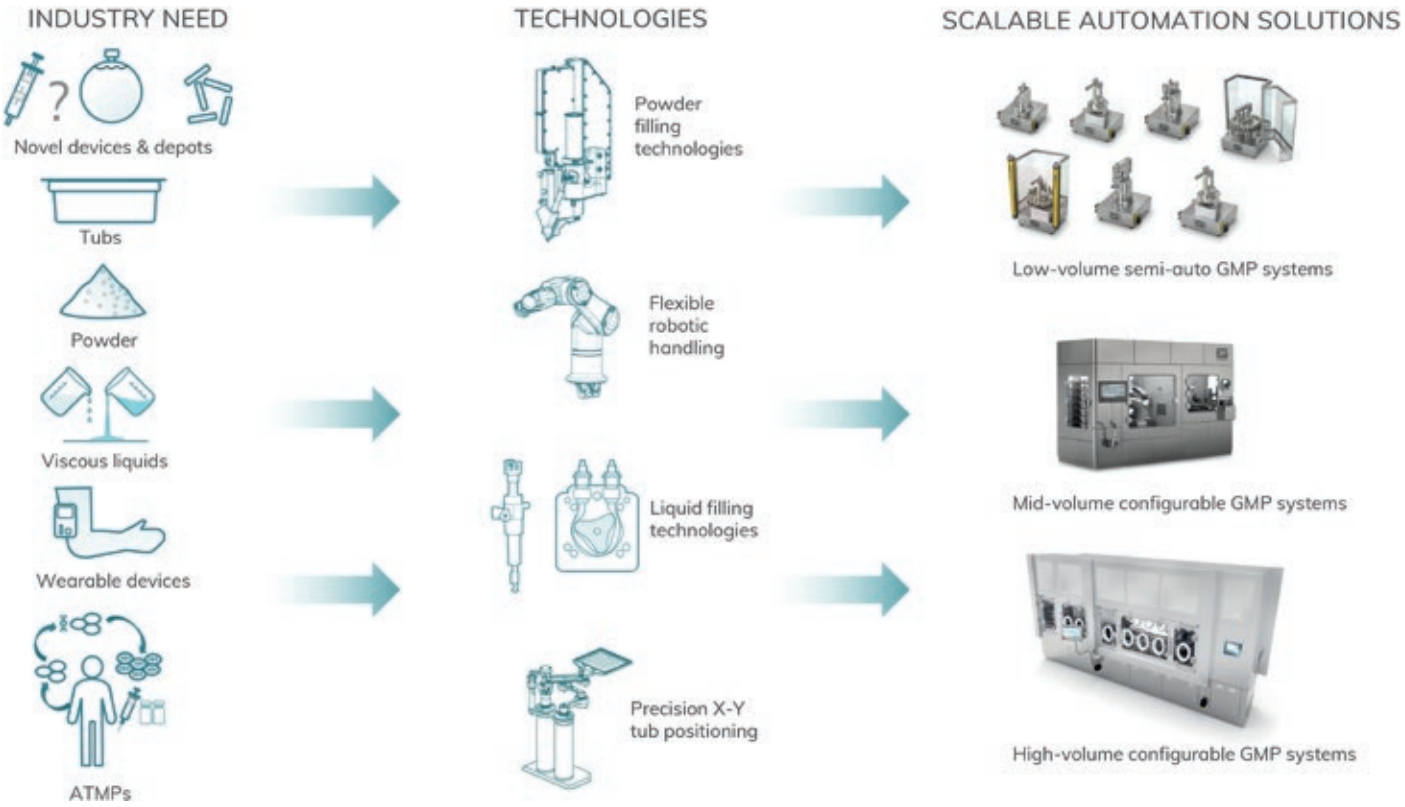

Figure 3: Drivers for change in aseptic automation and 3P's response.

platform for ATMPs that many companies can replicate. Aseptic equipment manufacturers have their part to play in responding to this new market need with innovative solutions.

A SUMMARY OF ASEPTIC AUTOMATION TRENDS

The parenteral market for aseptic automation is changing, as shown pictorially in Figure 3; this is being driven by a number of factors. As described, this is partly due to the trend of new medicaments being higher value but lower volume. Tubs are now available from numerous vendors to hold arrays of primary drug containers. The introduction of COC primary drug containers and large-volume (on-body) devices is requiring custom automation solutions. Depot-based and reconstitution-based technologies also require custom automation solutions, and often, this also includes the need for aseptic powder dispensing. The current explosion of ATMP application is also driving the need for automation innovation – this is particularly the case for autologous applications where the batch size is one. Overlaid on top of these device-driven trends is the need to minimise the number of manual operations to reduce particulates and product-to-product variability.

ONE COMPANY'S RESPONSE

As a custom automation house, 3P is, and has been, well placed to respond to the above trends and challenges. A significant proportion of the company's work remains the development of highly engineered custom solutions for its clients. These systems are developed to enable clients to scale-out and/or scale-up, depending upon need. The automation is developed specifically for the needs of the client's product. Some recent custom examples include:

- Aseptic ram-die and aseptic twin screw extrusion of depots
- Aseptic cutting of depots
- Manufacture of COC-based primary drug containers (for terminal sterilisation)
- Helium leak testing of primary drug containers
- Aseptic liquid and powder filling of standard and custom primary drug containers:
  - Including device assembly
- Aseptic cell processing
- Vision inspection systems of the product in Grade A.

Like many automation houses, 3P has a range of "standard" aseptic modules that can be employed as required, each an evolution in known technologies with a focus on low-particulate generation and class-leading precision. Hence, the company has a range of modules to de-lid tubs, to manipulate tubs, to de-nest and to re-nest devices into tubs. 3P has a range of pumps and lift/rotate modules to enable aseptic liquid dispensing (and some unique powder dispensing technology – see Figure 4). There are stopper feed bowls and stoppering modules (including vacuum). Finally, the company has low-particulate generating crimping modules. Systems can then be "glued together" by its robotic solutions and placed into an isolator from a range of isolator vendors with a range of sterilisation methods (iHP/vHP/HPV etc). To this end, 3P has focused on aseptic robotic solutions from a particular vendor; the company's default is to use the Stäubli TX2 range of aseptic six-axis collaborative robots, so called "cobots". The cobot feature enables the safe integration with manual operations and enables the guard line to be within the reach of the robot (to minimise the size of any isolator). These are also sealed against hydrogen peroxide sanitisation and have an exterior that is a specialist non-shedding white coating. For some space-constrained tub-based solutions, 3P has developed its own compact "crabot" robot. This system has a small footprint and can remove devices from an ISO-tub filled with devices.

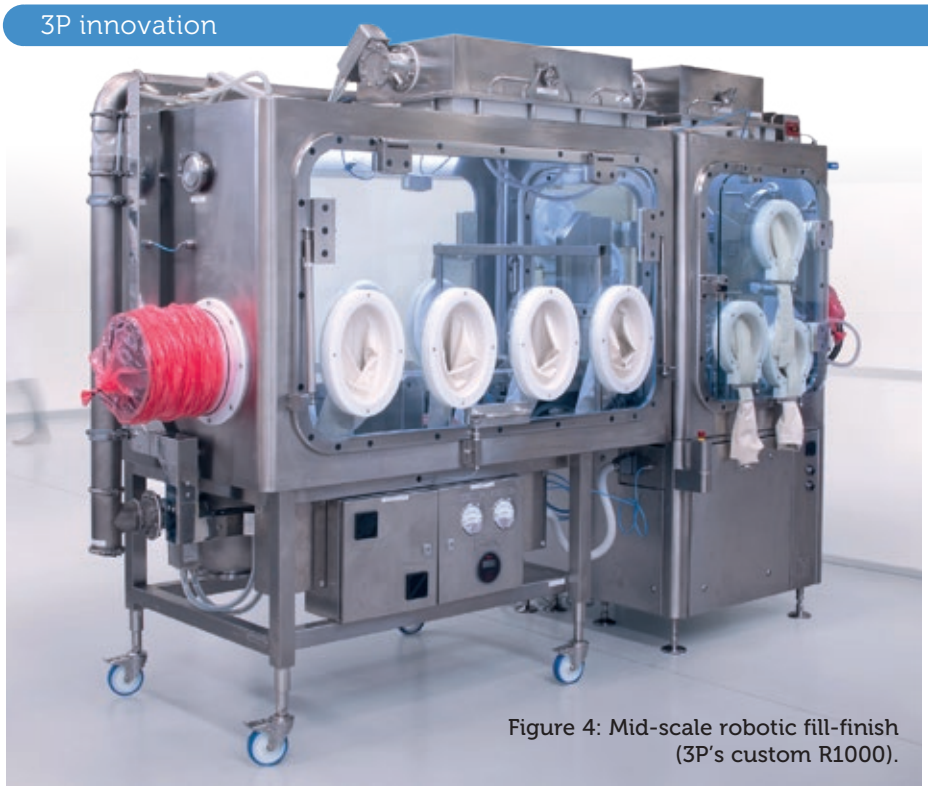

Figure 4: Mid-scale robotic fill-finish (3P's custom R1000).

3P's award-winning Fill2Weight powder dispensing technology (originally developed for inhaled applications), has been used in aseptic processing applications for over 10 years. The narrow form factor is ideal to maintain unidirectional air flow within an isolator and it is fully sealed for sanitisation or clean in place (CIP). Expertise has been developed to ensure powder is not released, even within low-humidity environments and under unidirectional air flow. 3P's patented aseptic gravimetric powder dispensing is one of the company's unique offerings to the market.

"By creating a configurable platform comprising state-of-the-art technologies, these systems address the need to provide solutions for new products/devices, such as an aseptic spray-dried powder into a dual chamber syringe, in a way not yet seen by the industry."

Figure 5: Commercial-scale robotic fill-finish.

With the need for flexible tub-based fill-finish systems, 3P repackaged some of its "standard" fill-finish modules described above, into a flexible multi-format robotic powder or liquid-filling system with integrated stoppering/capping and crimping – the F2/F5 range of fill-finish equipment (Figure 5). By creating a configurable platform comprising state-of-the-art technologies, these systems address the aforementioned need to provide solutions for new products/devices, such as an aseptic spray-dried powder into a dual chamber syringe, in a way not yet seen by the industry. This filling platform is then encapsulated within an isolator with tub loading via NTT (Neweco, Warsaw, Poland) or a decontamination chamber to suit the product and operator protection requirements. While these could be gloveless systems, clients still prefer the insurance that gloves provide, in case a rare intervention is required.

To address the very low-volume ATMP requirements, the "standard" modules described previously have been repackaged as stand-alone pieces of semi-automatic machinery. These can be single stations or integrated with a small indexing carousel to increase throughput. They are designed to be very compact for integration into small isolators and to be operated via glove ports.

CONCLUSION AND OUTLOOK

It is clear that it is an exciting time for the aseptic automation sector. Automation vendors need to embrace the changes brought about by a wide range of factors:

- New and innovative injectable devices taking advantage of the trend for home administration and caregiver convenience.
- A move from glass to plastic (COC) primary drug containers. This is partially led by robustness against cryogenic temperatures, advances in polymers, market acceptance and also because they enable additional features to be moulded onto the primary drug container.
- A reduction in batch sizes taken advantage of by tub-based supply of primary drug containers. This, in turn, leads to a requirement for more compact fill-finish lines to reduce the size of very costly aseptic clean room facilities.
- A reduction in human variability (and error) by automating manual processes. The drive to robotics and automation

is also driven by a desire to reduce operators and gloves to reduce particulate generation.
- A desire to avoid cold chain is leading to investment in engineered particles such as those produced by spray drying, bulk freeze drying and cryo-milling. This, in turn, is leading to a growth in precision aseptic powder-filling technology.
- Huge investments are being made in cell and gene therapies (ATMPs), which have only recently emerged from the lab. The commercialisation of these ultra-low volume and ultra-high value products is being hampered by the lack of "open-source" (think the Apple ecosystem) automation solutions.

All the above has led to an explosion of innovative aseptic automation solutions, of which 3P innovation is at the forefront with a wide range of liquid and powder fill-finish automation platform technologies. These platform technologies can be configured for benchtop solutions for clinical and ATMP applications. Similarly, they can be integrated within a higher volume robotic solution, typically with a tub-based infeed. Aseptic liquid and powder dispensing can be added to these fill-finish lines as required. Finally, custom modules can be developed as required to deal with innovative injectable devices.

What is clear is the outlook for aseptic automation companies is one of innovation and change. Fun times ahead!

ABOUT THE COMPANY

3P innovation is a life sciences engineering and custom automation company. It works collaboratively with pharmaceutical and medical device customers to develop and industrialise new products through the design, manufacture and support of production equipment. Based in a purpose-built facility in Warwick, UK, this award-winning business employs over 70 people and services a multinational customer base with machines installed worldwide. 3P's specialisms include aseptic processing machines, powder- and liquid-filling technologies, custom device manufacture, assembly and test.

ABOUT THE AUTHORS

Dave Seaward, PhD, is a chartered engineer and 3P innovation's founding director. He has a first degree in electrical and mechanical engineering and a control theory PhD (applying servo motors to automation). Dr Seaward's 35-year career has focused on developing custom automation for numerous industries, including the pharmaceutical and MedTech sectors. He is named inventor on over 20 patents including Unilever's pyramid teabag patent, which is included in the UK Patent Office book "Inventing the 20th Century". Many of Dr Seaward's projects have included powder or liquid dispensing, and recently he worked on numerous dry powder inhalers, drug eluting and injectable drug delivery projects.

David Phasey joined 3P innovation in 2010 as a project development engineer to help develop automation for a novel healthcare device. In the subsequent 10 years, Mr Phasey has risen to Projects Director, delivering projects across a spectrum of industries, each of which has contributed to the development of 3P's range of platform of technologies. This breadth of experience has enabled Mr Phasey to develop a valuable set of capabilities across manufacturing processes, such novel vaccine delivery and ATMPs, with a specialist knowledge of sterile manufacturing.

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OPHTHALMIC DRUGS: PATHWAY TO OVERCOME PRIMARY PACKAGING AND DRUG PRODUCT MANUFACTURING CHALLENGES

In the second in a series of two articles, Rainer Glöckler, Chief Technical Officer, swissfillon, Carole Delauney, Director Business Development, swissfillon, Nicolas Eon, Senior Technology Development Manager, Terumo Pharmaceutical Solutions, and Katsuyuki Takeuchi, Associate Product Manager, Terumo Pharmaceutical Solutions, discuss the myriad complexities of developing drug products for intravitreal injection, and how the partnership between swissfillon and Terumo can ease and accelerate these products to market. The first article, published in April, covered how swissfillon's state-of-the-art filling line meets the complex requirements of ophthalmic drug products.

With the trend towards personalised medicines, there is a growing demand for highly complex drugs to treat a wide variety of diseases, each with a relatively small number of patients. In the case of injectables, highly flexible production filling lines are needed for different categories of drugs which will be ultimately presented in combination with tailored primary packaging. This could include vials, prefilled syringes and cartridges, which may then be assembled into medical devices such as pens, wearable devices or autoinjectors. These drug products (DPs) require a high level of process know-how and state-of-the-art technologies.

Advanced DPs with a small to mid-size annual demand (fewer than 500,000 units) and innovative containers and devices pose a major challenge to existing manufacturing business models based on large throughputs. The regulatory requirements for the DP in combination with the medical device are particularly stringent in the case of ophthalmic products, and must be fully understood before a product can be brought to market. By working together, swissfillon and Terumo Pharmaceutical Solutions are exceptionally well positioned to provide innovative DP manufacturing solutions to satisfy previously unmet market and patient needs.

OVERVIEW OF THE OPHTHALMIC MARKET FOR RETINAL DISORDERS

The ophthalmic drug market can be broken down into segments based on therapeutic area. The largest sector in terms of market share is retinal disorders, which are responsible for some of the most common causes of blindness in the world, including:

- Diabetic retinopathy – the most common cause of blindness in the working-age population of industrialised countries
- Age-related macular degeneration (AMD) – the third most common cause of blindness in the world
- Retinopathy of prematurity – a notable cause of blindness in children in middle-income countries
- Retinal vein occlusion.

Retinal disorders are caused partly by over-production of a protein called vascular endothelial growth factor (VEGF) and are treated with anti-VEGF drugs, which are administered by intravitreal injection into the back of the eye. AMD may recur after anti-VEGF treatment, and require multiple rounds of treatment (once every two months).

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"The use of ophthalmic injections is increasing, but it is extremely challenging to develop the necessary very low dose syringes which are silicone-oil free, and which need to be filled to an extremely high level of precision, while minimising the presence of particles and bubbles."

The global ophthalmic drug market is forecasted to grow from US$28.4 billion (£20.5 billion) in 2020 to $36.2 billion in 2025, and to reach $47.6 billion by 2030. In 2020, retinal disorder drugs accounted for the largest share of the market, with sales of $13.1 billion and 46% market share.[1] Growth in the market will be driven by the rapidly ageing global population, the increasing prevalence of diabetes and ocular diseases, unmet clinical needs in many disease areas and economic growth resulting in increased demand in developing countries, particularly in Asia. At present, North America and Europe together make up 68% of the global market.

The most common drugs for retinal disorders are Regeneron's Eylea (aflibercept) and Genentech's Lucentis (ranibizumab) and Avastin (bevacizumab). Eylea accounted for 62% of the retinal disorder drugs market in 2020, replacing Lucentis as the ophthalmic pharmaceutical product with the greatest revenue. OSI Pharmaceuticals' Macugen (pegaptanib) and Bausch & Lomb's Visudyne (verteporfin) also continue to be used to a lesser extent. The patent for Lucentis will expire in 2022, and Eylea's patent will expire in 2025 in Europe. The opening up of the market to biosimilar drugs once patents expire represents a major opportunity for new players wishing to enter the sector. There is already interest from biotech companies in producing biosimilars, not only in Western Europe and the US, but also in Eastern Europe and Asia. At the same time, a number of pharma companies are working on next-generation ophthalmic formulations.

The R&D pipeline for drugs to treat retinal disorders also includes new classes of therapeutic agents. It is likely that the dominance of blockbuster products will diminish as medicines become more focused, and the potential growth in ophthalmic drugs will be driven by innovative products developed by biopharma companies.

SPECIFIC REQUIREMENTS AND COMPLEXITY IN OPHTHALMIC DRUG PRODUCT MANUFACTURING

The use of ophthalmic injections is increasing, but it is extremely challenging to develop the necessary very low dose syringes which are silicone-oil free, and which need to be filled to an extremely high level of precision, while minimising the presence of particles and bubbles. The following sections discuss the key considerations for primary packaging and DP manufacturing in ophthalmic projects.

Regulatory Requirements and Recommendations on Subvisible Particles and Endotoxins

Ophthalmic solutions should be essentially free from particles that can be observed on visual inspection. US Pharmacopeia (USP) 789 relates to particulate matter in ophthalmic solutions and describes tests for enumerating extraneous particles within specific size ranges. The ophthalmic solution is first tested by the light obscuration procedure and, if it fails to meet the prescribed limits, it must pass a microscopic procedure. Sampling plans need to be based on consideration of product volume, particle numbers historically found to be present in comparison with limits, the size distribution of particles present and variability of particle counts between units.

The US FDA has issued a Guidance for Industry[2] which specifies recommended endotoxin levels for intraocular ophthalmic devices. The recommendations specify a limit of no more than 0.2 endotoxin units per millilitre (EU/mL) for all ophthalmic viscosurgical devices.

Visible and subvisible particulates may be present in the drug formulation or may arise from the primary packaging or during the filling process. If the formulation is not stable, particulates may develop over time. The primary packaging manufacturer and the contract development and manufacturing organisation (CDMO) must guarantee that their products are in accordance with the relevant standards, and a great deal of experience and expertise is needed to minimise all possible risks. Subvisible particle testing using the light obscuration method is one of the pre-release tests carried out by Terumo for its ready-to-fill syringes.

Use of Silicone-Oil Free Syringes to Avoid Floaters and Subvisible Particles

Silicone oil has traditionally been used as a lubricant for syringes so that the plunger can move smoothly in the syringe barrel. However, in the case of ophthalmics, it is known that silicone oil would be deposited in the eye's vitreous body after repeated

injections and cannot be evacuated.[3] Silicone-oil droplets which remain in the eye are called "floaters" and avoiding them is one of the unmet needs in ophthalmic injection treatments. There are recent studies which recommend the use of silicone oil-free syringes for intravitreal injections to address this concern.[4]

In addition, silicone-oil droplets may react with the DP in the syringe and create subvisible particles. Studies show that silicone oil plays a role in both the denaturation of proteins, and the initiation of aggregation processes in proteins.[5,6] As soon as the protein is denatured or the configuration is changed, the efficacy of the treatment will be reduced, or it may no longer work at all. Any increase in the level of subvisible particles will also increase the risk of failing to comply with USP 789.

Technologies such as crosslinked silicone oil, baked-on silicone oil, or plasma treated silicone oil have been developed by the industry to minimise free silicone oil in drug solutions. But experience shows that even these silicone-oil layers using plasma or other treatments are not suitable for drugs that are extremely sensitive to silicone oil, and in such cases a silicone oil-free system is the only option. During the development of new formulations, it is impossible to tell in advance whether or not the drug will be sensitive to silicone oil. Pre-stability studies could be carried out, but the safest option is to use a silicone oil-free solution so that the question does not arise.

Figure 1: Terumo's PLAJEX™ 0.5 mL Luer lock silicone oil-free, ready-to-fill syringe system with i-coating™ stopper.[6,7]

These considerations are a major driver in deciding the most suitable system for ophthalmic projects. The PLAJEX™ 0.5ml Luer lock syringe is supplied silicone-oil free, with Terumo's proprietary i-coating™ lubricant on the plunger stopper (Figure 1).

Use of Next-Generation Syringes to Ensure Safe and Easy Ophthalmic Injection

As ophthalmic injections are directly administered to the eye, it is vital to minimise the potential risks around the injection process. With the trend of injectable drug development towards more viscous formulations, and with thin needles (for example, 30 or 31 gauge) being used for ophthalmic injections, it may be necessary to apply high pressure to the syringe. One of the major advantages of using a polymer syringe is that the Luer lock and the syringe barrel are a single moulded component, known as an integrated Luer lock, such as PLAJEX™ Luer lock syringes. In the case of a glass syringe, a polycarbonate Luer lock adaptor is assembled onto the syringe, known as an assembled Luer lock, and there is a risk that the Luer lock adaptor pops off from the syringe barrel when high pressure is applied to the syringe, such as during the injection of viscous formulations.

Another advantage of a polymer syringe is the wider design flexibility, so it is possible to design syringes that are easier to handle by adjusting the inner diameter, outer diameter and length of the syringe as required for the intended use.

Ensuring Accurate, Low-Volume Doses

Very low fill volumes are required for ophthalmic injections. The range of the fill volume is usually in the range of 100–200 µL, and filling syringes with such small volumes requires high-precision systems.

A speciality of swissfillon is that its filling line transports through syringe by syringe. This allows every syringe to be weighed using the tare and gross weigh installed on the machine, and the volume in each syringe to be calculated. Depending on the gap between the target and actual weight of the syringes, a feedback loop corrects the pump automatically. In practice, an average of three to five syringe weights is used to smooth the curve, rather than correcting for each syringe. This approach means that swissfillon can achieve exceptionally high accuracy during filling, despite such low fill volumes, and typically has an accuracy well within ±2%.

This monitoring of individual syringes is very unusual. Most CDMOs carry out nest filling, for which such a tight specification on fill accuracy is not possible. With nest filling, there is usually a 2% fully automatic in-process-control (IPC) weigh calculation, so only two out of every 100 syringes are checked. This means that any overfill or underfill will result in 50 syringes being rejected, rather than a single syringe on the swissfillon filling line.

> "A speciality of swissfillon is that its filling line transports through syringe by syringe. This allows every syringe to be weighed using the tare and gross weigh installed on the machine, and the volume in each syringe to be calculated."

> "Wastage due to overfilling is extremely costly for pharmaceutical companies in the case of both ophthalmic drugs and other very expensive DPs. By working together, the syringe manufacturer and filling company can reduce overfill and thereby achieve significant savings for the client."

Filling accuracy is driven by the pump, the tubing and the filling needle. The pump is one of the most critical considerations in the filling process. A peristaltic pump has a press release mechanism and, over time, particulates may occur due to damage to the pump tubing. This must be considered when deciding how long a filling process can run, as the particulates enter the system after the filter. The process uses very specific high-quality silicone tubing, but with the pump running at around 500 revs per minute in order to guarantee that syringes can be filled within two seconds, each fast start/fast stop causes extreme stress to the tubing. For this reason, the tubing must be checked and changed if necessary after 8–10 hours' run time.

An accuracy of ±5% is usually guaranteed because fill accuracy depends to some extent on the product solution. For critical, higher risk solutions, there needs to be very well-defined accuracy. If required, improved levels of accuracy could be achieved by changing from a peristaltic pump to a rotary piston pump. Stainless steel or ceramic rotary piston pumps offer exceptional accuracy and remove the risk of particulates as no tubing is placed under stress.

Minimising Overfill

Minimising overfill in ophthalmic prefilled syringes is a challenge. Given the very small volumes which are filled and administered, even a reduction in the filling volume of 10–20 µL will have a significant impact in percentage terms.

Typically, only a third of the filled DP is injected into the eye – in other words, syringes are overfilled by a factor of three in order to guarantee the expected administration volume. Two-thirds of the DP is wasted due to the hold-up volume (dead space) of needles and syringes, the priming process for expelling air bubbles from the syringe and overfilling to address variation in the filling process. For example, in the case of Lucentis, syringes are prefilled with 165 µL but only 50 µL are injected. Some wastage is unavoidable – even with extremely thin needles, there will be residual drug inside the needle, needle hub, and syringe Luer bore – but it is important to ensure that residual drug in the needle and syringe is minimised.

Wastage due to overfilling is extremely costly for pharmaceutical companies in the case of both ophthalmic drugs and other very expensive DPs. By working together, the syringe manufacturer and filling company can reduce overfill and thereby achieve significant savings for the client. The primary packaging has an important role to play because overfill is necessary not only to compensate for any variation of the filling process, but also to allow for any variation in the dimensions of the primary packaging.

Bubble-Free Filling

Bubble-free filling, the stoppering process and minimised overfill are all closely connected. For medical devices which require an exact injection volume, the precision will be higher if bubbles are minimised, however, in the case of ophthalmics, marketed products are known to present quite a large bubble (i.e. head space air). Any air in the syringe must be expelled before the injection can be administered, and this will result in loss of the drug substance. Even if there are no bubbles in the syringe, very small amounts of residual air may remain in the Luer bore and in the needle. If bubbles can be completely avoided, there will be no air to be removed so the overfill can be reduced, and less of the DP will be needed.

In order to achieve bubble-free filling, the stoppering process has to be adapted, and the plunger stopper must be set under quite a high level of vacuum. The stoppering process is driven by the product solution itself. If the solution is compatible with a high level of vacuum, the stopper setting is reasonably straightforward. It is always important to apply the vacuum, but this may be achieved with non-compressional stoppering or with a very short insertion tube.

Bubble-free filling may be crucial to reduce the risk of protein degradation in certain drugs. Denaturation of a protein-based product could start at the fluid-air interface, and the formation of aggregates must be avoided so that there is no risk of aggregates entering into the eye.

A further consideration is that during transportation, the syringe can be exposed to variations in pressure. Even with road transportation, changes in altitude during the journey cause changes in pressure (particularly in mountainous regions) and this can result in lower pressure outside the syringe than inside the syringe. If this happens, and the headspace or the bubble is too big, it may induce stopper movement during transportation, and result in loss of sterility of the product.

Similarly, the sterilisation process of the syringe surface placed into a blister closed with a lid is most commonly carried out with ethylene oxide (EO), and a vacuum is applied outside the syringe during the sterilisation process. The difference in pressure results in bubble expansion, with large bubbles expanding much more than small bubbles, potentially inducing stopper movement. This means that a final sterilisation which involves vacuum can be designed more easily if the headspace is smaller.

At present, although the bubble may be reduced in the syringe, air will generally remain in the syringe Luer bore. Air in the Luer bore could be avoided by applying a strong vacuum to the empty syringe prior to filling. Vaccum filling is now being implemented by swissfillon, which allows the residual air in the system to be reduced or removed. This will help to reduce loss of the DP and will be particularly valuable in the case of oxygen-sensitive products.

Stoppering

One of the challenges of using very small stoppers, which are necessary for 0.5 mL syringes, is that the stoppers must be correctly positioned and oriented during the transport and stoppering process on the manufacturing line in order to be correctly inserted into the syringes. The sorting of the stoppers in the bowl is very important, and therefore a high level of precision in the design of the bowl is needed to guarantee that the system runs well throughout the process. If there is a stopper which is not correctly aligned in the filling system, syringes can be lost or damaged. This means that wrongly positioned stoppers must be removed at the start of the transport system to the stoppering position (as they enter the swinger).

With small stoppers, the ratio between diameter and length means that the stoppers will be relatively longer than other stoppers. This, in turn, means that the centre of gravity of the stopper is usually higher than normal. The sorting board uses the position of the centre of gravity of the component to sort and orientate the stoppers, and to feed the stoppers into the machine, which can be much harder to achieve in this context.

The other challenge is that silicone oil-free stoppers are preferred for the ophthalmic market, in order to avoid subvisible particles and floaters in the eye, which means that silicone oil cannot be used on any of the filling machine

components. With standard plunger stoppers, there is "transport" silicone oil, and nearly all stoppers on the market have been covered with a very small quantity of silicone oil to avoid stickiness during processing. In the absence of silicone oil, the movement of the stopper in the bowl is very different, and the stoppers are not synchronised. The nature of these stopper complexities in DP manufacturing requires a high level of expertise and experience from the CDMO.

Sterilisation

The final sterilisation of the surface of the drug-filled syringe is very important for ophthalmic drugs. There are a number of options:

- Steam sterilisation is commonly used if the product is stable enough to be heated, but this is rarely the case for ophthalmic DPs as thermal sterilisation will destroy biologically derived substances.
- EO may be suitable in some applications, but any contamination with EO passing through the packaging may damage or destroy the product inside.
- Nitrogen dioxide (NO_2) is a relatively new technology that may be suitable in these applications, as NO_2 is known to be less aggressive than other sterilisation gases and the process can be carried out in relatively low temperature.

Although the final sterilisation is not part of swissfillon's process, the fact that sterilisation will subsequently be carried out has an impact on the DP manufacturing requirements, including the need for bubble-free filling and avoiding the use of silicone oil.

It is very important that swissfillon fully understands the final sterilisation requirements for a product, as this will affect the release testing and storage. If there is too much bioburden on a syringe when it is introduced into the steriliser, the system may not be able to achieve effective sterilisation. For this reason, the final inspection is performed in an ISO 7 cleanroom, in order to guarantee a class D minimum release environment.

Another specific requirement for ophthalmics relates to endotoxins. As mentioned prior, FDA guidance recommends that there should be no more than 0.2 EU/mL for ophthalmic viscosurgical devices. This has an impact on the DP manufacturing process because if the bioburden at the end of the compounding process is too high, it will result in a higher level of endotoxins due to cells killed during compounding releasing a large number of endotoxins. This must be kept under control as only bioburden (not endotoxins) is removed by sterile filters, so there is a risk that endotoxins will be found in the syringe.

ADVANTAGES THAT SWISSFILLON/TERUMO CAN OFFER TO MEET YOUR REQUIREMENTS

Taking into consideration the many complexities and specific requirements for ophthalmic DPs discussed thus far, a drug manufacturer can minimise risks by working with experts who have a proven track record and who are able to offer the latest technology. This will provide a much more streamlined solution than attempting to achieve each stage of the process in isolation.

Very few companies offer silicone oil-free systems, but such coating is one of Terumo's core technologies, and it has developed and applied a proprietary i-coating™ on the plunger stopper that allows for a consistent and predictable gliding force of the syringe. Terumo is confident that its advanced technologies can add value to its clients' ophthalmic projects.

A state-of-the-art filling environment has been developed by swissfillon that ensures maximum safety for ophthalmic applications. This was achieved by working from the outset with Optima (Schwäbisch Hall, Germany), a highly respected filling line manufacturer, in order to achieve exceptionally high specifications. The swissfillon technology involves a 100% automated filling process in which every glove intervention is documented, 100% tare and gross weighing to deliver high accuracy on extremely low filling volumes, and 100% stopper setting control to minimise bubbles. A speciality of swissfillon is that its filling line transports through syringe by syringe, providing exceptional accuracy and efficiency in the fill process. The company's aim is to become the global market leader in high-precision DP manufacturing, filling complex pharmaceuticals into next-generation containers and devices.

Implementing the Technology

The key principle of the swissfillon/Terumo collaboration is readiness. Working together, the companies will do all they can to respond to customers' requirements as quickly and effectively as possible. By forming relationships and working with machine makers, they are able to pre-validate or pre-design solutions, so they can be ready when a customer chooses to implement their technology.

Having multi-use and flexible filling equipment allows swissfillon to handle complex implementations. However, one of the most critical steps is the time taken to establish a process on the filling machine. This requires discussions on the best way to work together with the customer in order to have the solution on the machine in the shortest possible period of time.

Ideally, swissfillon would like customers to get in contact eight months before the filling is due to start, and Terumo should also be included in these initial discussions in order to consider the compatibility of the packaging that can be supplied. This would allow for the optimisation of process parts at the outset and set up of the initial templates, including the stoppering process.

The discussions should consider how the rubber components will be supplied,

Figure 2: swissfillon's rapid transfer port used for ophthalmic fill & finish.

for example in a transfer bag solution, or a double sterile bag solution. It is also necessary to consider whether the rapid transfer ports (RTPs) be 110 mm or 190 mm in port diameter. One of swissfillon's strengths is that it can accept components in either a 110 mm port bag or 190 mm port bag (Figure 2). 190 mm systems allow bags to be hooked up and disconnected several times. These points have to be agreed well in advance in order to assess whether it is necessary to customise either the filling machine or the packaging of the primary container. If the manufacturer's preferred solution isn't immediately available, it may take some time to develop and validate.

swissfillon/Terumo is the right DP manufactacturing partner for you if:

- **Streamlined communication** between partners is key
- **Time is critical** from your first inquiry to delivery
- **Maximum quality and security and minimal product loss** are must-have requirements
- **Bubble-free filling and precise plunger setting** are crucial
- **Innovative silicone oil-free syringes** could reduce the risks of your drug development

Figure 3: Together, swissfillon and Terumo offer a best-in-class solution for ophthalmic projects.

CONCLUSION

The close collaboration between swissfillon and Terumo has allowed the companies to tackle and solve the specific challenges related to ophthalmics and add value to customer projects.

There is a tendency for the industry to work in silos, which can slow down the manufacturing processes. However, once it can be demonstrated that a tiny detail in the design of a syringe can have a huge impact on the finish, then it becomes possible to optimise the overall value chain.

Time to market is often a key factor in the success of start-up companies developing biosimilars or entering the market with new DPs – and minimising time to market is one of the strengths of the swissfillon/Terumo collaboration. Early

discussions and collaboration between the drug manufacturer, the primary package manufacturer and the specialist CDMO is vital to support a project's timeline.

The companies are confident that the combination of Terumo and swissfillon will offer a best-in-class solution for ophthalmic projects (Figure 3). Their combined expertise and experience of using the technologies needed for this complex area enables them to provide support for other biologics entering the market, and offer reliable and stable solutions suitable for each product's specific requirements.

ABOUT THE COMPANIES

swissfillon is a CDMO for complex injectables, providing aseptic DP manufacturing (filling) services to pharmaceutical and biotech companies. It ensures the highest quality, security and fully cGMP compliant services for high value, complex and difficult to fill products. With its innovative, fully automated and highly flexible filling line, swissfillon provides manufacturing capacity for vials, syringes and cartridges for 1–200 L batch sizes, when the product is too complex for small (manual) DP manufacturing or when the larger manufacturers are fully utilised for large quantities.

Terumo Pharmaceutical Solutions is a global company which offers comprehensive product design and development services, as well as a portfolio of injection, infusion, and primary packaging solutions. Terumo is trusted for quality and precision and has decades of experience collaborating with pharmaceutical companies from the earliest phases of drug development to the latest stages of product commercialisation to optimise critical aspects of parenteral drug delivery.

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Katsuyuki Takeuchi is an Associate Product Manager at Terumo Pharmaceutical Solutions. With extensive knowledge in pharmaceutical science, he has worked in research and development for injectable drug products, such as IV solution bags and prefilled syringes, and contributed to launch various products onto the market. Using his experience, Mr Takeuchi currently has product management responsibilities for Terumo's polymer-based prefillable syringes platform.

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COMPARATIVE EXTRACTABLE STUDIES FOR INJECTABLES AND MEDICAL DEVICES ALIGNED WITH USP <1663> AND ISO 10993 GUIDELINES

Here, Matthias Bicker, PhD, Scientific Advisor, Michael Müller, Study Director, Marc Mittermüller, Study Director, Daniel Haines, PhD, Head of Pharma Services North America, and Uwe Rothhaar, PhD, Director, all of SCHOTT Pharma Services, discuss the regulatory requirements that need to be considered when designing an extractables and leachables study for a drug product or medical device. To illustrate the subject further, the authors provide two example studies, each following a different set of regulatory guidelines.

In order to conduct best practices for the safety assessment of materials used for pharmaceutical drug product packaging and medical devices, the most recent regulatory guidance needs to be considered. For chemical characterisation of components and materials, different regulatory guidelines focused on extractables have been established. United States Pharmacopeia (USP) <1663> provides a framework for an extractables assessment of pharmaceutical packaging and drug delivery systems.[1] The principles of this framework are recommended for pharmaceutical development, manufacturing applications and medical device components related to combination products. USP <1663> comprises scientific principles and best practices recommended for the manufacturer of drug substances and drug products as well as manufacturers of pharmaceutical and medical device packaging.

ISO 10993 addresses the evaluation of medical devices with respect to their biological safety. An important part of this framework is the new revision of ISO 10993-18,[2] focused on chemical characterisation of medical device materials within a risk management process. The scope of this new revised guideline is the identification and quantification of the chemical constituents of medical devices in a stepwise approach, including an estimation of the potential of the medical device to release chemical substances (extractables) and a measurement of released chemical substances (leachables). The new ISO 10993-18 revision emphasises a greater integration and harmonisation with ISO 10993-1 (a general framework for planning of biological evaluation and testing within a risk management process), ISO 10993-12 (recommendations for sample preparation and specific extraction conditions) and ISO 10993-17 (allowable limits for leachable substances).[3–5]

Further frameworks have been established by the Product Quality Research Institute (PQRI)[6,7] with general and specific recommendations for extractables and leachables (E&L), by the EMA with a guideline focused on "plastic immediate packaging materials" addressing the need for testing of the compatibility of the plastic material with the medicinal product by performing extraction studies,[8] and by USP <661>[9] among others. USP <661> is a further standard for plastics used to package

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medical devices, which will be substituted and expanded upon by USP <661.1> for plastic materials of construction and USP <661.2> for plastic packaging for pharmaceutical use. In addition to the implemented ICH Q3D standard for elemental impurities,[10] a new chapter for organic impurities, "ICH Q3E: Assessment and Control of Extractables and Leachables for Pharmaceuticals and Biologics", is currently under development.[11] Different levels of identification have been suggested for extractables studies, including "partial", "tentative", "confident" and "confirmed", with increasing certainty that the identification is correct.[12]

SCHOTT Pharma Services offers analytical services for extractables and leachables testing and related chemical characterisation of primary packaging and medical device components and materials.[13,14] These services are aligned with the requirements presented by customers and the most recent regulatory guidelines. To address the demands of E&L characterisation, this article covers the importance of the following systematic steps for conducting an effective extractables study.

PROCEDURE – HOW TO GATHER THE RIGHT INFORMATION TO SET UP AN EXTRACTABLES STUDY

The overall procedure to collect the underlying information for extractable studies typically comprises some or all of the following steps:

1. Clarification of the customer's request, product application (drug or medical product and associated packaging or device) and related requirements supported by scientific consulting.
2. Scientific advice concerning any relevant regulatory guidelines.
3. Support for analytical evaluation threshold (AET) calculation based on ICH M7,[15] USP <1663>,[1] ISO 10993-18[2] or PQRI[16] recommendations.
4. Recommendation of appropriate study design for drug product application, including a detailed study protocol and suitable extraction method (e.g. sealed vessel extraction with shaking incubation, reflux or Soxhlet extraction).
5. Extractables study, according to the recommendations from one or more of:
   - USP <1663>,[1] including exaggerated or simulated extraction conditions
   - ICH Q3D[10]
   - USP <232>[17]
   - PQRI[7,18]
   - ISO 10993-18 or 10993-12,[2,4] including exhaustive extraction or simulated extraction conditions.
6. Simulated in-use study (e.g. leachables from processing components) following current ISO 10993-18 recommendations.[2]
7. Accelerated leachables studies or bridging studies to fill the gap between extractables and leachables.
8. Collaboration with a toxicologist for alignment of organic and inorganic target compounds for a subsequent leachables study.

> "Secondary packaging components and components with indirect drug contact, such as labels, need to be taken into account as potential sources of chemical compounds that can migrate into the drug product."

The results of such an extractables study together with the toxicological assessment are the basis for the target list of substances to be considered in a subsequent leachables study.

COMPONENTS – WHAT NEEDS TO BE CHARACTERISED WITHIN AN EXTRACTABLES STUDY?

Extractables data need to be generated for all materials with direct or indirect drug contact, and should be separately generated for each individual component. Additionally, secondary packaging components and components with indirect drug contact, such as labels, need to be taken into account as potential sources of chemical compounds that can migrate into the drug product. Typical applications for extractables characterisation are primary packaging components made of polymer, glass or elastomer (rubber material), or secondary packaging materials, labels on polymer packaging and other manufacturing components used by the pharmaceutical industry.

Components that need to be considered include:

- Primary packaging components of container closure systems, such as:
  - Polymer syringe: plunger (rubber stopper), tip cap
  - Glass syringe: plunger (rubber stopper), needle shield
  - Glass cartridge: plunger (rubber stopper), rubber cap
  - Glass vial: rubber closure
  - Coated primary packaging components, such as siliconised components.
- Labels with glue and ink (particularly required for polymeric primary packaging).
- Secondary packaging materials, such as:
  - Nest
  - Tub
  - Cover sheet
  - Bag
  - Tray
  - Secondary packaging components of medical devices, for example the polymer adapter or plunger rod.
- Manufacturing components, such as:
  - Silicone tubing
  - Filters
  - Carboys.

As an example, different components of a sterile nest/tub packaging solution for glass vials are shown in Figure 1.

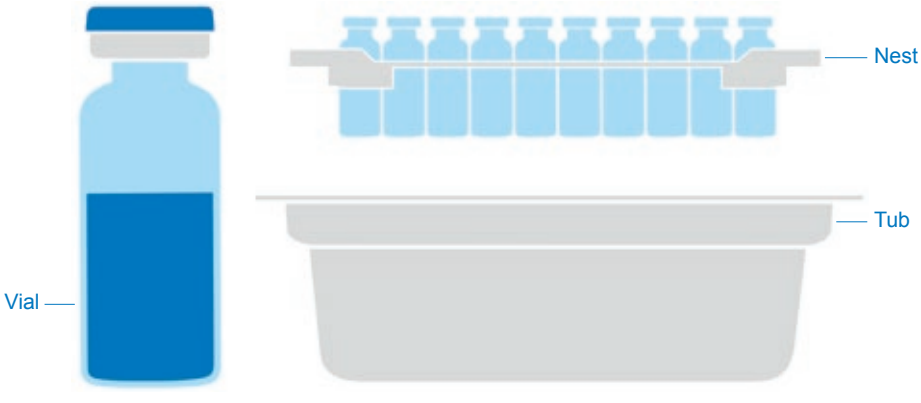

Figure 1: Components of a sterile ready-to-use packaging solution.

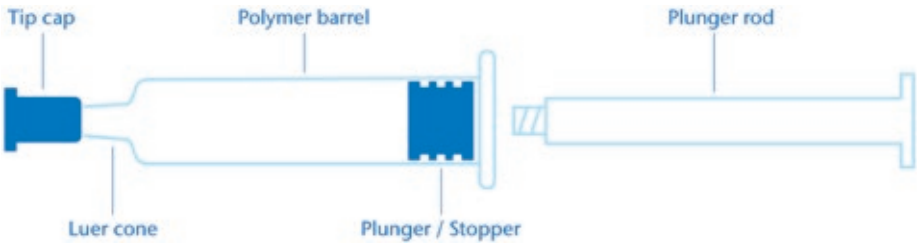

Figure 2: Polymer syringe system.

The next section presents an example of a comparative extractable study for injectables and medical devices aligned with USP <1663> and ISO 10993 guidelines. The study is focused on a polymer syringe system consisting of a polymer barrel, polymer tip cap and elastomeric plunger (Figure 2). An example with polymer and elastomer components was chosen for this comparison because specific extraction conditions were recommended in both guidelines that should be applied for these materials.

STUDY DESIGN – A SUITABLE ANALYTICAL PROCEDURE FOR AN EXTRACTABLES STUDY

The design used for an extractables study should be appropriate to identify organic and inorganic substances that are extracted when the components of a packaging system are exposed to suitable solvents, which are recommended by the regulatory guidance. The analytical methods used are:

- Gas chromatography – mass spectrometry (GC-MS)
  - Used for determination and screening of semi-volatile organic compounds (SVOCs)
  - Allows for the identification and quantification of low to medium molecular weight compounds, such as additives, catalysts, residual monomers and oligomers of polymers and rubbers, as well as semi-volatile plasticisers and processing agents.
- Headspace gas chromatography – mass spectrometry (HS-GC-MS)
  - Used for determination and screening of volatile organic compounds (VOCs)
  - Allows for the identification and quantification of low molecular weight leachables, such as residual monomers of polymers or elastomers, residual solvents[19,20] from component manufacturing and volatile oxidation and degradation products.
- Liquid chromatography – mass spectrometry (LC-MS) and ultraviolet detection (LC-UV)
  - Used for determination and screening of extractable and leachable non-volatile organic compounds (NVOCs)
  - Allows for the identification and quantification of organic compounds with high polarity and medium to high molecular weight compounds, such as antioxidants (Figure 3), fatty acids from polymer and rubber component manufacturing and non-volatile plasticisers and processing agents.
- High-resolution inductive coupled plasma mass spectrometry (HR-ICP-MS)
  - Used to quantify the amounts of extractable and leachable elemental impurities
  - Allows for the identification and qualification of elements of ICH Q3D classes 1–3 (summarised in Table 6).[10]
- Ion chromatography (IC)
  - Used to quantify the amounts of extractable and leachable target anions.
- Gravimetric non-volatile residue (NVR) analysis
  - Used to determine the amount of non-volatile residue of solvent solution after extraction
  - Allows for an assessment concerning the maximum total amount of non-volatile extractables and whether the extraction was exhaustive according to ISO 10993-12.[4]

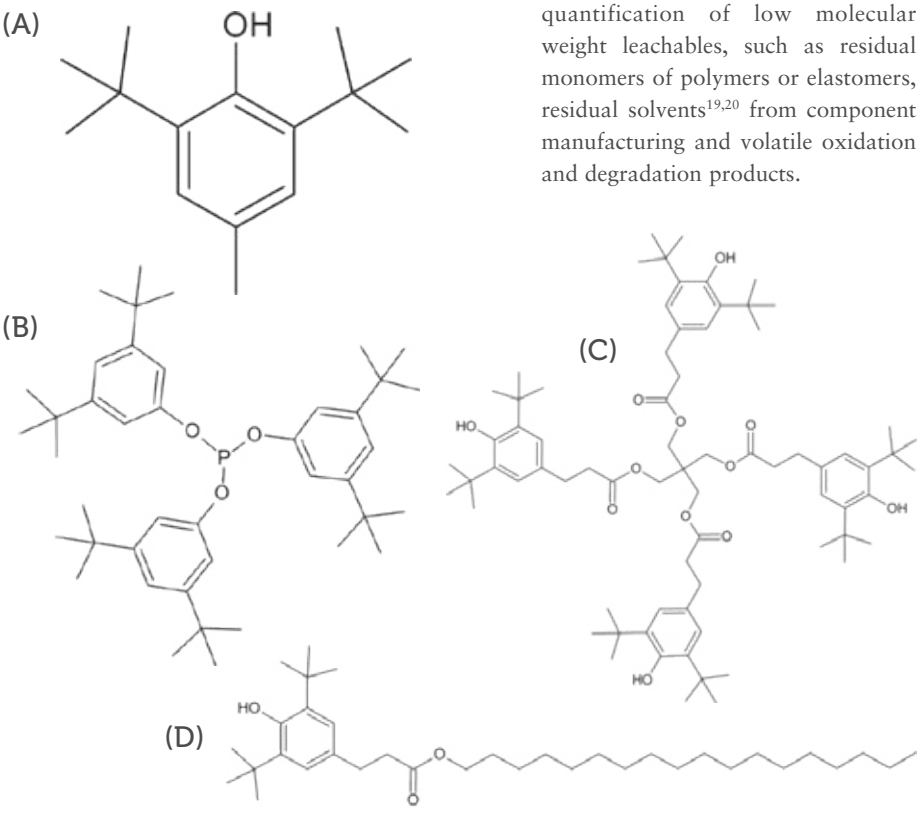

Figure 3: Typical antioxidants used as polymer addatives. (A) BHT, (B) Irgafos 168, (C) Irganox 1010 and (D) Irganox 1076.

Two examples of appropriate study designs for extractables studies conducted for polymer syringe components are illustrated in Table 1 and Table 2. The study design shown in Table 1 is aligned with current USP <1663> recommendations[1] and the one in Table 2 is aligned with current ISO 10993-18 and 10993-12 recommendations.[2,4]

The studies also each use different extraction techniques and methods. Study protocol A is based on a reflux extraction technique, while study protocol B is based on a sealed vessel extraction technique and an exhaustive extraction method. Results from a practical example of this study are shown in Box 1.

Analysis of VOCs by HS-GC-MS

- Incubation of neat sample material at 150°C for 45 minutes in sealed vessels
- Qualitative and semi-quantitative screening analysis of an aliquot of the respective gas phases for VOCs by HS-GC-MS

Analytical method	Neat material (*)	Solvent		
		IPA: Water (50:50)	Water (pH 5.2)	Water (pH 9.5)
Headspace GC-MS (VOCs)	X	–	–	–
GC-MS (SVOCs)	–	X	X	X
LC-MS and/or LC-UV (NVOCs)	–	X	X	X
HR-ICP-MS (elemental impurities)	–	–	X	–
IC (anions)	–	–	–	X

Table 1: Tests to be performed during study design A (aligned with USP <1663>). (*) – direct analysis of neat sample material during thermal extraction.

Analytical method	Neat material (*)	Solvent		
		n-Hexane	IPA	Ultrapure Water
Headspace GC-MS (VOCs)	X	–	–	–
NVR	–	X	X	X
GC-MS (SVOCs)	–	X	X	X
LC-MS and/or LC-UV (NVOCs)	–	X	X	X
HR-ICP-MS (elemental impurities)	–	–	–	X
IC (anions)	–	–	–	X

Table 2: Tests to be performed during study design B (aligned with ISO 10933). (*) – direct analysis of neat sample material during thermal extraction.

- Identification and semi-quantitative evaluation of substance signals using commercial and internal databases and suitable internal standards.

Extraction of SVOCs and NVOCs

Study protocol A:

- Reflux extraction of samples in 50:50 isopropyl alcohol (IPA) and water, water (pH 5.2) and water (pH 9.5).

Study protocol B:

- Exhaustive extraction conditions based on determination of NVR:
  - Evaporation of extract solutions from each extraction cycle to dryness for aliquots of each extract
  - Determination of NVR by gravimetric analysis of dry residue
  - Pooling of extracts from relevant extraction cycles for subsequent GC and LC analyses.
- Exhaustive extraction of samples in ultrapure water, IPA and n-hexane
- Multiple extraction cycles (incubation condition: 50°C, 72 hours, under agitation) performed, depending on the results of individual NVR determinations.

Analysis of SVOCs by GC-MS

- Liquid-liquid extraction of aqueous extracts with dichloromethane (DCM) at different pH values and subsequent pooling of organic phases, followed by concentration of extracts if necessary
- Qualitative and semi-quantitative screening analysis of prepared extracts SVOCs by GC-MS
- Identification and semi-quantitative evaluation of substance signals by using commercial and internal MS databases and suitable internal standards.

Analysis of NVOCs by LC-MS and/or LC-UV

- Liquid-liquid extraction of aqueous extracts with dichloromethane (DCM) at different pH values and subsequent pooling of organic phases, followed by concentration of extracts and reconstitution in isopropyl alcohol if necessary
- Target screening for typical polymer additives, and qualitative and semi-quantitative screening analysis of prepared extracts for NVOCs by LC-MS and/or LC-UV
- Identification and semi-quantitative evaluation of substance signals by using high-resolution, time-of-flight MS, internal databases and suitable internal standards.

Extraction of Inorganic Elemental Impurities and Anions

Study protocol A:

- Samples for HR-ICP-MS analysis reflux extracted in water (pH 5.2)
- Samples for IC analysis reflux extracted in water (pH 9.5).

Study protocol B:

- Pooling of extracts from relevant extraction cycles using ultrapure water for both HR-ICP-MS and IC analysis.

Analysis of Inorganic Elemental Impurities and Anions

- Analyses of resulting extracts by HR-ICP-MS for elemental impurities and reporting of up to 40 elemental impurities including all class 1–3 elements outlined in ICH Q3D and USP <232> guidelines.[10,17]
- Analyses of resulting extracts by IC for the following target anions: acetate, formate, bromide, chloride, fluoride, nitrate, phosphate and sulfate.

RATIONALE BEHIND THE STUDY PROTOCOLS

Study Design A – USP <1663>

Study design A and the respective extraction conditions are aligned with the USP <1663> guideline for "assessment of extractables associated with pharmaceutical packaging/delivery systems",[1] where the general framework of scientific principles and best practices for extractables studies is described. According to USP <1663>, extractable studies are required due to the

[Continued on Page 93...]

BOX 1: TEST RESULTS OF EXTRACTABLES STUDIES

A set of extractables studies for a commercial polymer syringe system were conducted using study protocols A and B. The syringe system under investigation comprises of a barrel made of polymer material and halobutyl rubber components (plunger, tip cap). Some selected results for antioxidants (polymer additives), non-volatile residues and concentrations of elemental impurities and anions in the following section are shown here (note: the peaks labelled with "IS" in the chromatograms belong to internal standard reference material for analysis – they were deliberately added and are not a syringe constituent).

HS-GC-MS

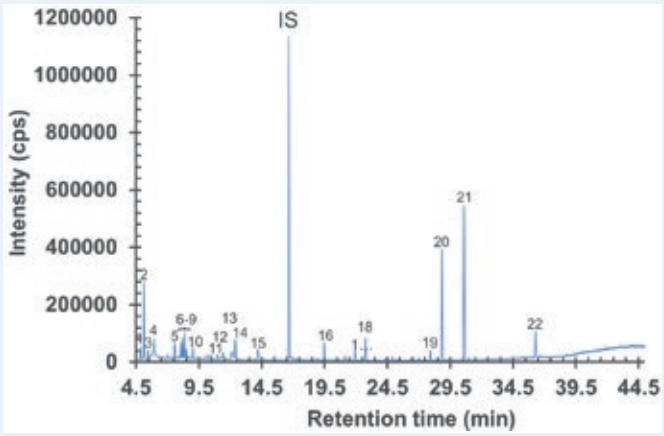

Figure 4: HS-GC-MS chromatogram of polymer syringe barrel component after incubation at 150 °C for 45 minutes.

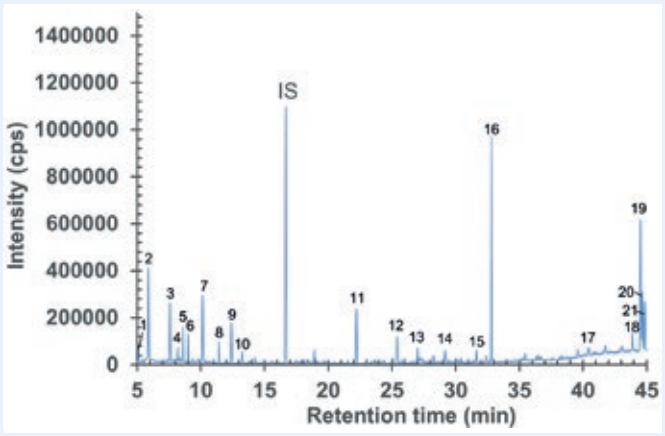

Figure 5: HS-GC-MS chromatogram of rubber stopper component after incubation at 150 °C for 45 minutes.

GC-MS

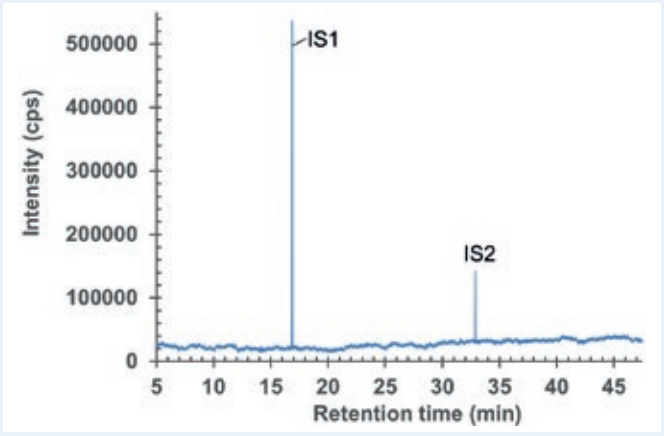

Figure 6: GC-MS chromatogram of polymer syringe barrel after extraction in water (pH 5.2).

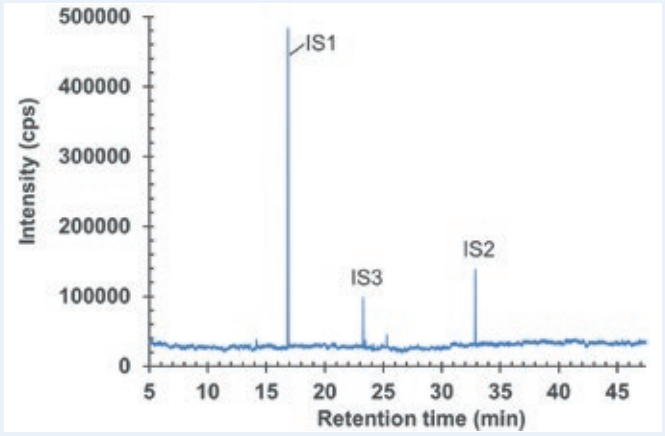

Figure 7: GC-MS chromatogram of polymer syringe barrel after extraction in water (pH 9.5).

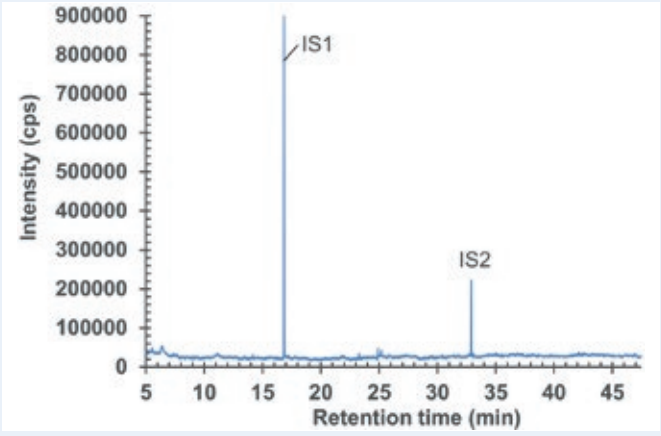

Figure 8: GC-MS Chromatogram of polymer syringe barrel after extraction in IPA/water (1:1).

BOX 1: TEST RESULTS OF EXTRACTABLES STUDIES, CONT'D

LC-MS and LC-UV

Antioxidant / degradation product	Polymer syringe barrel (Irradiation sterilised)			Halobutyl rubber tip cap (irradiation sterilised)			Halobutyl rubber stopper (irradiation sterilised)		
	Water pH 5.2	Water pH 9.5	IPA: Water (50:50)	Water pH 5.2	Water pH 9.5	IPA: Water (50:50)	Water pH 5.2	Water pH 9.5	IPA: Water (50:50)
BHT	< RL	< RL	< RL	< RL	< RL	5.4	< RL	< RL	5.7
BHT aldehyde	< RL	< RL	< RL	< RL	< RL	< RL	< RL	0.08	0.35
Irganox 1010	< RL	< RL	< RL	< RL	< RL	< RL	< RL	< RL	< RL
Irganox 1076	< RL	< RL	< RL	< RL	< RL	< RL	< RL	< RL	< RL
Irgafos 168	< RL	< RL	< RL	< RL	< RL	< RL	< RL	< RL	< RL
Irgafos 168 oxidised	< RL	< RL	< RL	< RL	< RL	< RL	< RL	< RL	< RL
	All amounts in (µg/unit)								

Table 3: LC-MS results of quantities of antioxidants found in components of a prefillable syringe system after extraction with aqueous and mixed solvents aligned with USP <1663>.[1] Reporting limit (RL) was within the range 0.05–1.0 µg/unit.

Antioxidant / degradation product	Polymer syringe barrel (Irradiation sterilised)			Halobutyl rubber tip cap (irradiation sterilised)			Halobutyl rubber stopper (irradiation sterilised)		
	Ultra pure water	IPA	Hexane	Ultra pure water	IPA	Hexane	Ultra pure water	IPA	Hexane
BHT	< RL	< RL	< RL	< RL	14	47	< RL	19	19
BHT aldehyde	< RL	< RL	19	0.06	0.49	1.5	0.06	0.67	1.2
Irganox 1010	< RL	< RL	393	< RL	< RL	0.22	< RL	< RL	< RL
Irganox 1076	< RL	< RL	< RL	< RL	< RL	0.09	< RL	0.03	0.04
Irgafos 168	< RL	< RL	< RL	< RL	< RL	< RL	< RL	< RL	< RL
Irgafos 168 oxidised	< RL	< RL	< RL	< RL	< RL	0.34	< RL	< RL	0.08
	All amounts in (µg/unit)								

Table 4: LC-MS results of amounts of antioxidants found in components of a prefillable syringe system after extraction with polar and non-polar solvents according to ISO 10993-18 and 10993-12. Reporting limit (RL) was within the range 0.02–1.2 µg/unit.

NVR

Extraction cycle no.	Polymer syringe barrel (Irradiation sterilised)		Halobutyl rubber tip cap (irradiation sterilised)		Halobutyl rubber stopper (irradiation sterilised)	
	IPA	Hexane	IPA	Hexane	IPA	Hexane
1	< 0.35	16	1.2	20	0.7	8.0
2	< 0.35	8.4	0.7	4.4	0.4	1.1
3	–	5.2	0.4	1.2	0.2	0.3
4	–	4.0	0.2	–	0.2	–
	All amounts in (µg/unit)					

Table 5: Results of gravimetric determination of NVR shown for up to four extraction loops. Extraction was conducted at 50 °C for 72 hours, in accordance with ISO 10993-12.[4]

BOX 1: TEST RESULTS OF EXTRACTABLES STUDIES, CONT'D

HR-IDP-MS

Classification ICH Q3D	Elements Tested	Classification ICH Q3D	Elements Tested
Class 1	As, Cd, Hg, Pb	**Class 4**	Ba, Cr, Cu, Li, Mo, Sb, Sn
Class 2	Co, Ni, V	**Other elements**	Al, B, Ca, Fe, K, Mg, Mn, Na, W, Zn
Class 3	Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se, Tl	**Additional**	Si, Bi, Ce, Hf, P, S, Ti, Zr

Table 6: Overview of elemental impurities listed in ICH Q3D and USP <232> by their classification[10,17] and additional elements tested for.

Elements	Classification according to ICH Q3D	Polymer syringe barrel (Irradiation sterilised)		Halobutyl rubber tip cap (irradiation sterilised)		Halobutyl rubber stopper (irradiation sterilised)	
		Water pH 5.2	Ultrapure water	Water pH 5.2	Ultrapure water	Water pH 5.2	Ultrapure water
As, Cd, Hg, Pb	class 1	< RL for all class 1 elements for all extracts of all components					
Co, Ni, V	class 2A	< RL for all class 2A elements for all extracts of all components					
Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se, Tl	class 2B	< RL for all class 2B elements for all extracts of all components					
Ba, Cr, Cu, Li, Mo, Sb, Sn	class 3	< RL for all class 3 elements for all extracts of all components					
Ca	–	< RL	< RL	**1.4**	**1.5**	**0.26**	**0.41**
Mg	elements	< RL	< RL	**18**	**17**	**2.6**	**2.1**
Al, B, Fe, K, Mn, Na, W, Zn		< RL for respective "other elements" for all extracts of all components					
Si	Additional (not classified in ICH Q3D)	< RL	< RL	< RL	**6.6**	< RL	< RL
Bi, Ce, Hf, P, S, Ti, Zr		< RL for respective additional elements for all extracts of all components					
		All amounts in (**µg/unit**)					

Table 7: Results of HR ICP-MS analyses for elemental impurities after extraction in water (pH 5.2) or in ultrapure water. Reporting limit (RL) for class 1–3 elements in the range of 0.003–0.33 µg/unit, for "other elements" of ICH Q3D in the range of 0.063–12 µg/unit and for additional elements in the range of 0.003–25 µg/unit.

IC

Extraction cycle no.	Polymer syringe barrel (Irradiation sterilised)		Halobutyl rubber tip cap (irradiation sterilised)		Halobutyl rubber stopper (irradiation sterilised)	
	Water pH 9.5	Ultrapure water	Water pH 9.5	Ultrapure water	Water pH 9.5	Ultrapure water
Acetate (CH_3COO^-)	< RL	< RL	**2.8**	**4.1**	< RL	< RL
Bromide (Br^-)	< RL	< RL	**6.5**	**6.2**	**2.4**	**2.6**
Chloride (Cl^-)	< RL	< RL	< RL	0.43	< RL	< RL
Fluoride (F^-)	< RL	< RL	< RL	< RL	< RL	< RL
Formate ($HCOO^-$)	< RL	**2.3**	**32**	**34**	< RL	**0.47**
Nitrate (NO_3^-)	< RL	< RL	**3.8**	**3.5**	**0.78**	< RL
Phosphate (PO_4^{3-})	< RL	< RL	< RL	< RL	< RL	< RL
Sulfate (SO_4^{2-})	< RL	< RL	< RL	< RL	< RL	< RL
	All amounts in (**µg/unit**)					

Table 8: Results of IC analyses for target anions after extraction in water (pH 9.5) or in ultrapure water.

[...Continued from Page 89]
potential exposure of patients to leachable substances that could migrate from the pharmaceutical packaging or delivery system into the drug product, therefor it is important to assess the safety risk to the patient and any other potential issues posed by leachables.

For a leachables assessment, it is required to "know the identities and the levels to which leachables will accumulate in the finished drug product over its shelf life". Since the primary and secondary packaging components are the "primary sources of potential leachables", performing an extractables study on these components is justified.

Depending on the chemical nature of the drug formulation and its route of administration, specific examples are given in USP <1663>. For a small-volume parenteral drug product application based on an aqueous formulation (e.g. a drug product dissolved in a formulation with a pH value of 6.5), extractions of rubber components with three different solvents are recommended "to reflect the chemical nature of the formulation":

- Aqueous acidic (pH 5.2)
- Aqueous alkaline (pH 9.5)
- Mixed aqueous and organic – IPA and water (50:50).

Study design A has been shown to be well suited for following all relevant USP <1663> guideline recommendations in numerous studies SCHOTT has conducted for its customers.

Study Design B – ISO 10993-18 and ISO 10993-12

Study design B is primarily based on the recommendations of the new ISO 10993-18 guideline, which outlines a chemical characterisation of medical device materials within a risk management process. A framework is specified in this guideline for "the identification and, if necessary, quantification of constituents of a medical device, allowing the identification of biological hazards and the estimation and control of biological risks from material constituents".[2]

For extractable studies, ISO 10993-18 is focused on the chemical characterisation procedure. Related to extraction conditions, ISO 10993-18 integrates and refers to ISO 10993-12.[4] For chemical characterisation of polymer components, an exhaustive extraction concept is recommended in ISO 10993-12. According to this guideline, the quantities of low molecular weight compounds (LMWCs) of polymers, such as additives, catalysts, residual monomers and oligomers, that can potentially migrate into the drug or medical product (and subsequently into the human body) should be determined, and an exhaustive extraction using both polar and non-polar solvents should be applied.

> "For material and extractables characterisation of polymeric components, all guidelines have many aspects in common. However, as can be seen by the approaches taken by study designs A and B, the guidelines partially differ in details of the procedures and extraction conditions they recommended."

An extraction is defined as exhaustive if the residues extracted by a subsequent extraction are below 10% of the amounts found after the first extraction. In the case of polymer components used in medical devices, it needs to be confirmed within the extractables study that the extraction was exhaustive. For this purpose, a gravimetric method is recommended. In study design B, the NVR is determined using a gravimetric method for confirmation that the extraction was exhaustive. Study protocol B has been established to fulfil the requirements of both ISO 10993-18 and ISO 10993-12.

DIFFERENCES BETWEEN ISO AND USP GUIDANCE AND PQRI RECOMMENDATIONS

For material and extractables characterisation of polymeric components, all guidelines have many aspects in common. However, as can be seen by the approaches taken by study designs A and B, the guidelines partially differ in details of the procedures and extraction conditions they recommended.

USP <1663> has a special focus on the chemical properties of the drug formulation (e.g. "many drug products are compositionally intermediate between polar and non-polar") and on the route of administration. For example, for simulation of a worst-case leachable profile, solvents should be applied for extraction that have a similar or greater propensity for extraction of substances than the drug formulation.[1]

As another example, according to ISO 10993-12, the quantities of LMWCs of polymers should be determined based on an exhaustive extraction method applied with both polar and non-polar solvents.[4] The strong focus on this exhaustive extraction method for polymer medical device components is only found in this guideline.

A hint for different concepts and recommendations depending on the applied regulatory guideline is also briefly mentioned in the new ISO 10993-18 guideline,[2] including a short statement that exaggerated conditions might be requested by some legal authorities like the US FDA as credible alternatives to the ISO recommendation of exhaustive extraction. For medical device applications, this topic is also addressed by the FDA,[22] which states that "a chemical analysis of the materials used in a device in its final finished form can be informative", "can be used to assess the toxicological risk of the chemicals that elute from devices" and "chemical analysis using techniques per ISO 10993-12 can also be helpful to evaluate long-exhaustive extraction term toxicity endpoints, such as potential carcinogens". On the other hand "chemical analysis is usually insufficient to identify all of the risks of the device in its final finished form, because it will not consider aspects of the finished device such as surface properties or device geometry that could affect the biological response in certain scenarios." Furthermore, "extraction solvents should be selected to optimise compatibility with the device materials and provide information on the types of chemicals that are likely to be extracted in clinical use."

As shown by the results data for LC-MS (Tables 3 and 4), the two study designs found significantly differing quantities of antioxidants (polymer and elastomer additives), which can be explained by the different extraction conditions and solvents. It is plausible that higher quantities of antioxidants were found in the non-polar hexane extracts, whereas very low quantities, sometimes even below the reporting limit, were found in the aqueous extracts due to their higher polarities.

> "It is a mandatory precondition for an appropriate extractables study design to review the drug product or medical device application and the route of administration in detail in order to align with the relevant regulatory requirements, which can vary by region, and to obtain a common understanding of the purpose of the study."

Nevertheless, the main purpose of an extractables study is the identification of potential leachables and both study designs met this goal, based on their respective regulatory frameworks.

Furthermore, the data for the HR-ICP-MS (Table 7) analyses showed comparable amounts of Ca and Mg found for the rubber components, even though aqueous solvents with different pH values and extraction conditions were used. Also, the data for IC analyses (Table 8) indicated that, for most anions, the extractable quantities were more or less comparable. These results indicate that similar quantities of the cations and anions were released for the aqueous solvents with different pH values and extraction conditions.

As a further example, according to PQRI recommendations for parenteral and ophthalmic drug products, extractables studies should be conducted with aqueous solvent solutions covering a very broad pH range between 2.5 and 9.5.[18] This is based on the rationale that most aqueous drug product applications will be covered within this broad pH range because only a few therapeutic products have pH values outside of this pH range.

As a consequence, it is a mandatory precondition for an appropriate extractables study design to review the drug product or medical device application and the route of administration in detail in order to align with the relevant regulatory requirements, which can vary by region, and to obtain a common understanding of the purpose of the study. The identification of potential leachables within a customised extractables study can provide the basis for a subsequent toxicological assessment. Based on the toxicological assessment of the extractable profiles, the target compounds for the subsequent leachables study can be specified.

For leachables studies, method development and validation is required before determination of leachables in order to meet the required AET. Relevant regulatory guidelines for leachable studies are:

- USP <1664>[21]
- USP <232>[17]
- USP <233>[23]
- ISO 10993-18[2]
- ISO 10993-17.[5]

CONCLUSION

A deep understanding of the most recent regulatory guidelines, in particular the USP <1663> guideline and the new ISO 10993-18 international standard,[1,2] is very important to give drug product-specific recommendations for an appropriate study design for extractables studies for pharmaceutical packaging, drug delivery systems and medical devices. Two different appropriate study designs, each primarily focused on one regulatory standard, and the applied analytical methods, have been described in detail, and example study results have been shown (Box 1) and the differences between them have been discussed.

SCHOTT Pharma Services provides analytical services, including extractables testing related to chemical characterisation of primary packaging and medical device components and materials. Such studies are designed with both customer requirements and the most recent regulatory guidelines in mind. Furthermore, SCHOTT provides leachables testing, including method

development and method validation, following ICH Q2 (R1) recommendations[24] and leachables characterisation based on USP <1664>, USP <232>, USP <233>, ICH Q3D and/or ISO 10993-18 and 10993-17 guideline recommendations.

SCHOTT Pharma Services' laboratories are ISO/IEC 17025 accredited and FDA registered. SCHOTT Pharma Services has more than 40 years' experience in analytical testing of pharmaceutical packaging containers. All quality relevant documents are electronically available, ensuring a hassle-free audit process.

ABOUT THE COMPANY

SCHOTT Pharma Services provides pharmaceutical analytical testing, focusing on drug formulation/container interaction studies (E&L, glass delamination), glass breakage root cause analysis (fractography), container reliability/suitability (strength testing), compendial verification testing according to USP/EP/JP/YBB/ISO/ASTM, and material identification testing. Composed of a seasoned team of chemists and physicists, SCHOTT Pharma Services offers insight and support for all development and commercial parenteral packaging challenges.

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