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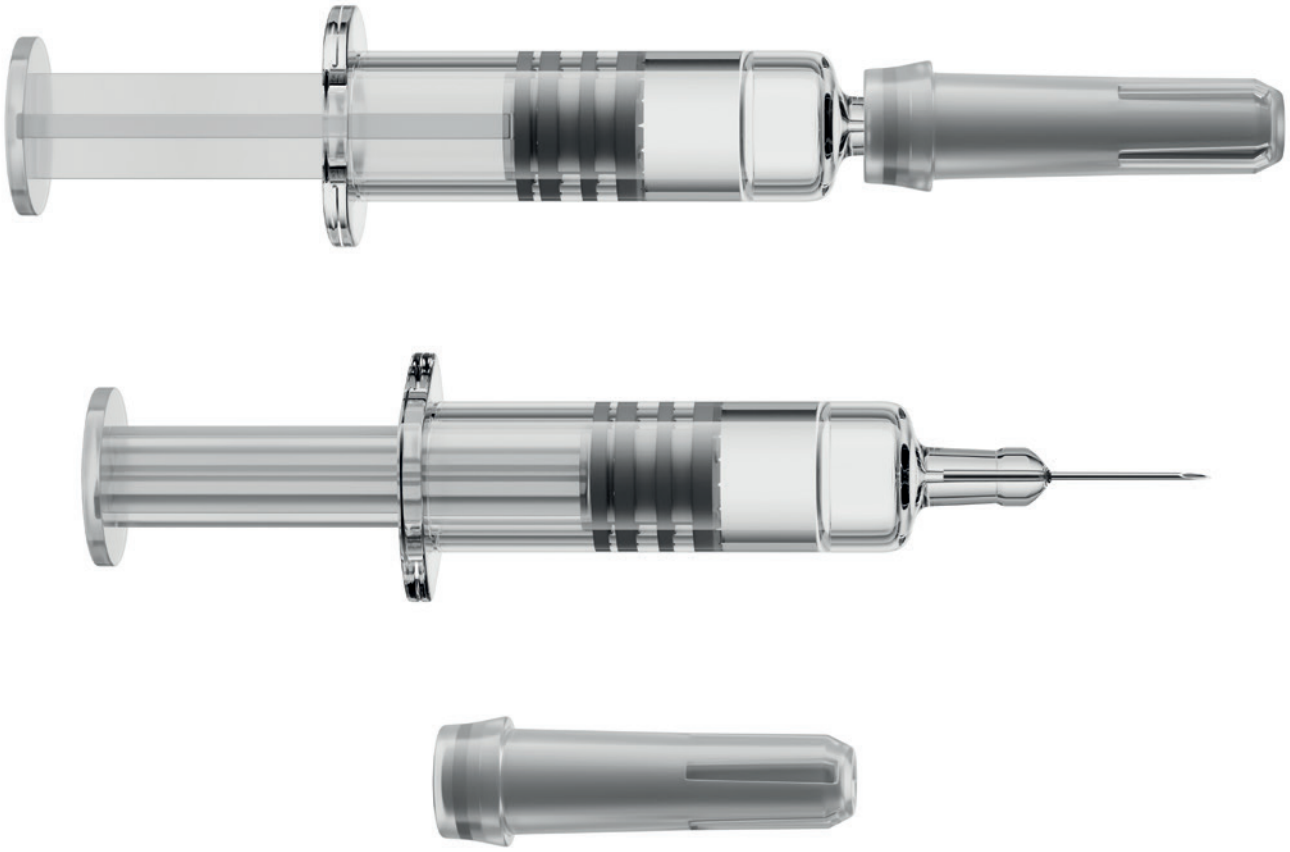

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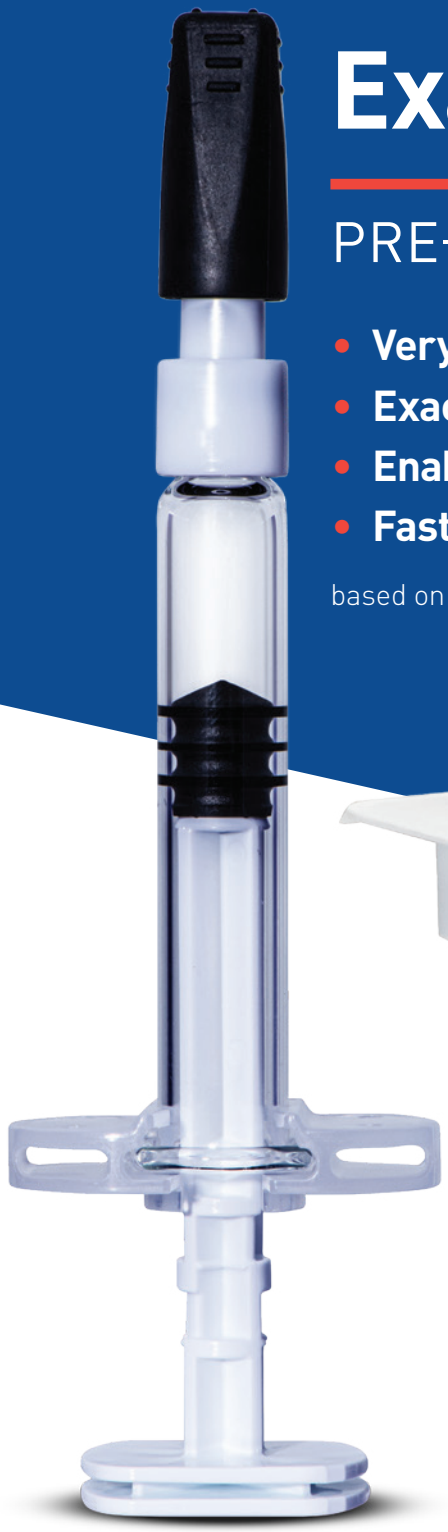

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ONdrugDelivery Issue N° 142, February 1st, 2023

PREFILLED SYRINGES & INJECTION DEVICES

This edition is one in the ONdrugDelivery series of publications. 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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Mar 2023	Ophthalmic Drug Delivery
Mar/Apr	Skin Drug Delivery: Dermal, Transdermal & Microneedles
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Feb 2024	Prefilled Syringes & Injection Devices
Mar	Ophthalmic Drug Delivery

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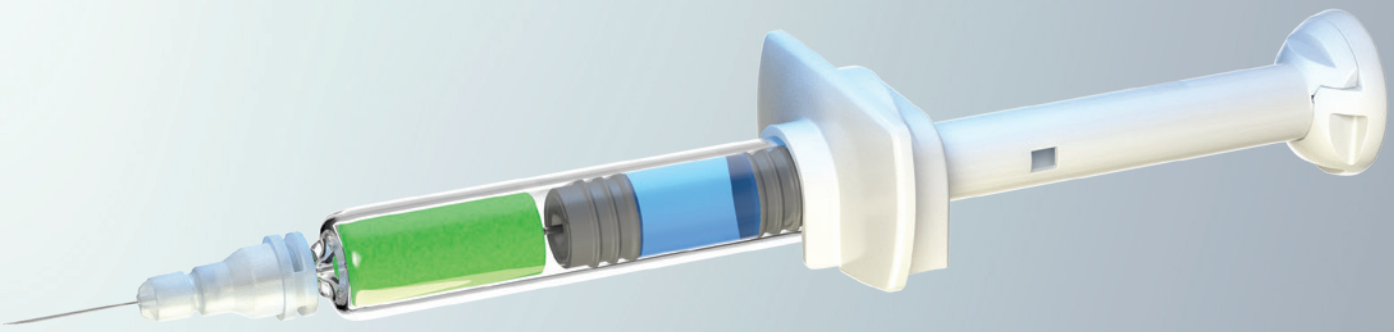

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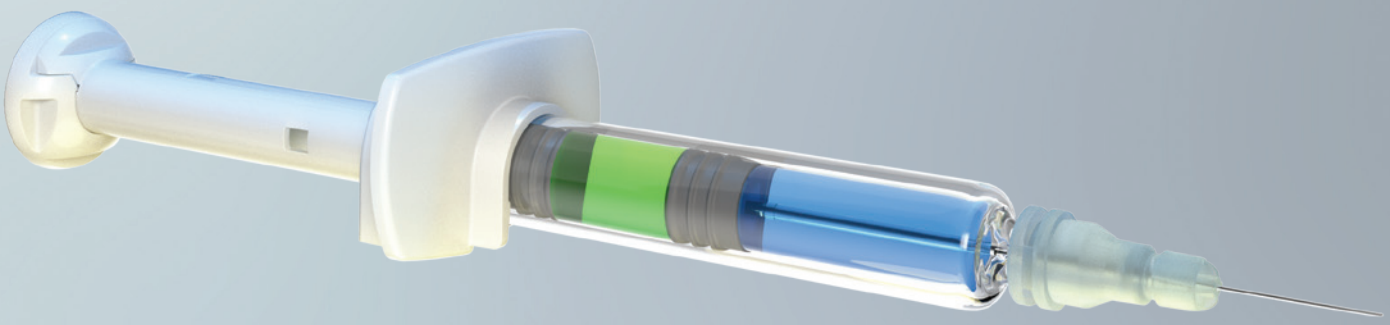

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OPPORTUNITIES FOR INNOVATION WITH BIOSIMILARS

Here, Iain Simpson, PhD, Commercial Director at Phillips-Medisize, and George Spooner, Chief of Staff at Oxford Medical Products, investigate the use of drug delivery systems that support self-administration of biologic drugs, and specifically biosimilars, for the treatment of chronic diseases. This article is based on research conducted by both authors as part of the MPhil in Therapeutic Sciences at the University of Cambridge (UK) and supported by Phillips-Medisize.

Biosimilars are biological medicines that closely resemble an already-approved biologic, referred to as the reference product. Their principal advantage is that they are usually priced much lower than the originator medicine, in some cases by more than 50%,[1] yet provide the same clinical benefits and safety. Europe has led the way with biosimilars of more than 16 different reference drugs available as of 2020. The US has lagged behind Europe with biosimilars approved for nine reference drugs but only six actually available in the market due to patent litigation and also the 12-year exclusivity period that the US allows for biologic drugs – longer than that for many other regions.

With more than 30 biologics losing exclusivity in the US between 2023 and 2028, and efforts being made in the US to address their historic slow uptake, we may see an acceleration in the approval of biosimilars. It has been estimated that the US biosimilars market will grow from US$9.48 billion (£7.76 billion) in 2022 to $100.75 billion by 2029 – an annual growth rate of 40.2%.[2]

The rise of the biologic drug has driven increased use of drug delivery devices that can better support subcutaneous self-administration of these drugs for chronic diseases. Although originally a source of differentiation, autoinjectors have now become a market expectation in many disease areas, so it is not surprising that biosimilar companies have frequently chosen to follow suit when entering the market. Even with a significant price advantage, only offering a biosimilar in a vial or prefilled syringe (PFS) would likely limit market uptake.

> "Autoinjectors have now become a market expectation in many disease areas."

Innovation through drug delivery technology has been a common defence mechanism for the originator biopharma companies against biosimilars. A good example of this is the Onpro® wearable pump for Neulasta® (pegfilgrastim) developed by Amgen, administered 24 hours or longer after chemotherapy to reduce the chance of infection due to a low white blood cell count. Normally this requires an additional visit to a clinician, but Onpro allows the device to be applied at the end of the last chemotherapy session and then the drug to be automatically delivered 27 hours later. In the US, this allows the prescribing clinician to claim a fee for administering the dose and the patient benefits from avoiding a further visit.

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Onpro was approved and launched in 2014 in the US and its share of the Neulasta market rapidly grew to 62% of the market by 2018, when the first biosimilar version of Neulasta was approved by the US FDA. Since then, five further biosimilars have been approved but none with a wearable pump to support delayed delivery. By 2021, data from Amgen[3] suggest these have gained around 37% of the Neulasta market but Onpro still commands 51% of the market and the originator Neulasta PFS a mere 12%. This suggests that the Onpro device has successfully protected 50% of a $3 billion US market. In Europe, the uptake of biosimilars that reference Neulasta has been much quicker – reaching 42% of the market in 2020, compared with only 29% in the US. Although Onpro is also approved in Europe, it appears to afford less of a commercial advantage, potentially due to different reimbursement processes.

Electronic autoinjectors have also entered the market for some of the lead drugs – AutoTouch® for Enbrel (etanercept, Amgen), ava® for Cimzia® (certolizumab pegol, UCB), BETACONNECT™ for Betaseron® (interferon beta-1b, Bayer), Rebismart® for Rebif® (interferon beta-1a, EMD Serono/Merck KGaA) and easypod® for Saizen® (somatropin, Merck KGaA) being the most notable examples. Published data show that these devices have been well received by patients and clinicians[4,5] and show some positive outcomes around adherence and efficacy outcomes,[6] although uptake has been limited. The reasons for their limited uptake are not fully clear in the published literature, but higher cost and trade-offs between the benefits and disadvantages that they offer users are likely confounding factors.

With a strong focus on price reduction and increasing competition amongst biosimilars for the same reference drug, biosimilar manufacturers have tended to focus on cost reduction through manufacturing efficiency rather than innovation around the drug and any associated delivery system. But there is some evidence their approach may change, in part to play the originators at their own game but also to seek differentiation from other biosimilars referencing the same biologic predicate.

In this article, we will look at two examples of where innovation with biosimilars has given some market advantage. We will then present the results of a research project conducted by George Spooner as part of a MPhil in Therapeutic Sciences at the University of Cambridge (UK) and supported by Phillips-Medisize. The aim of this work was firstly to understand the market dynamics for biosimilars in Europe and the US, and then to consider the opportunity biosimilars represent, for innovative drug delivery devices in general and, in particular, for the use of smart electronic autoinjectors. As described in previous work,[7] smart autoinjectors, such as the Aria device (Figure 1) being developed by Phillips Medisize, offer distinct advantages around:

Figure 1: The Aria device.

- Environmental sustainability.
- Connectivity – particularly around the ability to capture, reliably and in real time, medication-use data that can be used to provide better patient support directly through a companion app or through more targeted support by healthcare professionals or lay caregivers.
- Improved ease of use, and patient feedback that can reduce use errors and potentially improve adherence.
- Flexibility and performance to enable the device platform to be more easily adapted to a wide portfolio of drugs. (Although this is mainly a benefit for pharmaceutical companies, it can enable patient benefits around variable dosing and the administration of combination therapies.)

The scope of the interview-based research was therefore structured to gain insight around these topics.

EXAMPLES OF INNOVATION WITH BIOSIMILARS

Intravenous to Subcutaneous Switching of Infliximab

Remicade (infliximab) was the first TNFα inhibitor approved in the US for the treatment of Crohn's disease and subsequently for several other autoimmune disorders. It is delivered as an intravenous (IV) infusion in a clinic, which might be seen as a disadvantage compared with similar drugs such as Humira® (adalimumab, AbbVie) and Enbrel that can be self-administered. However, factors such as less-frequent administration and concerns around self administration for some patients meant it was well used, achieving sales in Europe in 2014 of around $2.3 billion.

In 2015, the first biosimilar versions of infliximab entered the market and, in 2020, Celltrion Healthcare (South Korea) gained approval for Remsima SC, a subcutaneous (SC) version of its infliximab biosimilar. Research in the UK suggests a saving for the UK NHS of around £40 million per annum in reduced administration costs for Remsima compared with an infliximab IV infusion.[8] Remsima now has over 50% of the EU market and it appears the SC version is set to grow its share of the market.

Code	Sex	Country	Stakeholders	Role	Compensated?
GBP1	M	UK	Payer	NICE TAC member	N
GBP2	M	UK	Payer	NICE TAC member	N
GBP3	M	UK	Payer	Health Economist and NICE advisor	N
GBP4	M	UK	Payer	NICE TAC member	N
GBHCP1	F	UK	HCP	NHS Rheumatologist	N
GBHCP2	M	UK	HCP	NHS Consultant	N
USP1	M	US	Payer	Pharmacy Director	Y
USP2	F	US	Payer	Pharmacy Director	Y
USP3	M	US	Payer	CMO at Commercial insurer	N
USP4	M	US	Payer	PBM Commercial Strategy Director	Y
USP5	M	US	Payer	Medicaid Drug Formulary Principal	Y
USHCP1	M	US	HCP	Rheumatologist	N
USHCP2	F	US	HCP	Rheumatology nurse	N
USHCP3	M	US	HCP	Rheumatologist	Y
USHCP4	M	US	HCP	Rheumatologist	Y
USHCP5	M	US	HCP	Gastroenterologist	Y
USHCP6	F	US	HCP	Rheumatology nurse practitioner	N
PC1	M	UK	Pharma company	Medical Director	N
PC2	M	Netherlands	Pharma company	Clinical Science Associate Director	N
REG	M	US	Regulator	Assistant Director FDA	N

Table 1: List of participants interviewed. TAC = technology appraisal committee, CMO = chief medical officer.

Autoinjector Innovation in the Delivery of Etanercept

Etanercept is used to treat several autoimmune diseases. The innovator version, Enbrel, is provided in the SureClick® autoinjector, or MyClic® pen, that require the user to press the device against the skin and then press a button to initiate the injection. Benepali™ was subsequently approved in 2016 as the first etanercept biosimilar and is also offered in an autoinjector. However, this device is a two-step device that eliminates the button and requires the user only to push the device against the skin to initiate injection.

In a preference study involving 149 nurses from Germany, France, Italy, Spain and the UK, 86% reported that their patients would prefer the Benepali autoinjector over the Enbrel SureClick®/MYCLICK® device on the basis of it being easier to use and being "button free". This is aligned with other user studies that suggest patients prefer two-step devices over button-actuated devices.[9] It is not clear from published data that the better-perceived device has had an impact in the growth of market share, but Benepali is the leading version of etanercept in the five leading European markets.

> "User studies suggest patients prefer two-step devices over button-actuated devices."

RESEARCH METHODOLOGY

Secondary research was conducted to understand potential drug candidates for delivery by autoinjector and market dynamics for biosimilars, including reimbursement, with a focus on the UK and US. Interviews were then conducted with three main healthcare stakeholders – healthcare professionals (HCPs), healthcare payers and pharmaceutical companies – to explore the opportunity for novel drug delivery technologies in the biosimilars sector, as summarised in Table 1.

Given the use of self-administered biologics in rheumatology, gastroenterology and dermatology, HCPs working in these areas were contacted and invited to take part in interviews. Healthcare payers are individuals who control market access of therapeutics: these include, in the UK, individuals on National Institute for Health and Care Excellence (NICE) technology appraisal committees; and, in the US, insurers and pharmacy benefit managers (PBMs). For the pharma companies stakeholder group, individuals involved in marketing, market access or drug delivery devices for companies engaged in the UK and/or US biosimilar markets were contacted. Suitable interviewees were identified through LinkedIn and academic directories, with "snowballing" used to ask interviewees for further individuals suitable for the study. Given the low recruitment of US stakeholders, recruiting agencies were used to identify and recruit additional payers and HCPs respectively. The individuals who received compensation or a financial incentive for their participation in the study are indicated in the right-hand column of Table 1.

The semi-structured interview guides were stakeholder specific and developed based on the preceding secondary research. Questions were open ended, non-leading and agnostic, inviting discussion surrounding biosimilar and drug delivery device (DDD) innovation, differences between bio-originators and biosimilars, and emerging DDD characteristics. Before each interview, interviewees received a participant information form outlining the purpose of the study, and data confidentiality and anonymity assurances. Interviewees could withdraw from the study at any point.

The interviews – mean length 49 mins – were all conducted by George Spooner, except for those with UK HCPs which were conducted by Phillips-Medisize due to university ethics guidelines. Interviews were conducted on Microsoft Teams or via a telephone call and digitally recorded.

Anonymised video/audio records were automatically transcribed by Rev.com, and the resultant transcripts checked for accuracy. The interviews were transcribed solely to ensure interview accuracy, with the data kept confidential. The data was analysed through thematic content analysis, with NVivo 12 used to facilitate the coding process. Analysis consisted of data familiarisation, open coding, theme searching, theme reviewing, theme defining and report production.[10]

Although meaningful results were achieved, several methodological limitations should be highlighted:

- The recruitment process may have introduced bias into the results.
- The sample size for the interviews was limited by the duration of the research project. Saturation was achieved in the UK payer and US HCP datasets, but not with the other stakeholder groups. Further work should seek to interview more individuals from these groups.
- Data only analysed by one individual with limited experience in qualitative analysis.

RESULTS

From the desk-based research, 16 suitable biosimilar targets for autoinjector delivery were identified, with the majority used in rheumatology and gastroenterology, as summarised in Table 2. The primary, interview-based research then identified cost savings as the principal uptake driver for biosimilars, but drivers for innovation, as well as some potential barriers for acceptance of biosimilars, were also identified.

Drug delivery technology was seen as important by HCPs, particularly in rheumatology where patients can have dexterity issues that affect their ability to manipulate a syringe.

Smart Autoinjectors

The introduction of an electronic autoinjector was not seen by payers as being particularly innovative in itself, but a reduction in dosing frequency or a change in administration route (e.g. from IV to SC) were seen as more significant. Payers wanted real-world evidence (RWE) of improved patient outcomes with the delivery device if they were to pay more for a biosimilar with the device. US payers generally viewed the release of the AutoTouch electronic autoinjector for Enbrel administration as a lifecycle management approach in the face of biosimilar, although some US HCPs strongly recommended the device because of the benefits they see it offers to patients.

Brand	INN	Area(s) of Medicine	Device Presentations	Key Patent Expiry	
				UK	US
Actemra	tocilizumab	Rheumatology	PFS; PFP	2017	2015
Benlysta	belimumab	Rheumatology	PFS; PFP	2026	2025
Cimzia	certolizumab pegol	Rheumatology; Gastroenterology	PFS; PFP; e-Device	2024	2024
Cosentyx	secukinumab	Rheumatology	PFS	2030	2029
Emgality	galcanezumab	Neurology	PFS; PFP	2031	2033
Enbrel	etanercept	Rheumatology	Vial; PFS; PFP; e-Device	2015*	2028**
Hemlibra	emicizumab	Haematology	Vial	2031	2027
Humira	adalimumab	Rheumatology; Gastroenterology	PFS; PFP	2018*	2016**
Orencia	abatacept	Rheumatology	PFS; PFP	2017	2019
Remicade[Y]	infliximab	Rheumatology; Gastroenterology	PFS; PFP (Remsima biosimilar)	2015*	2018*
Repatha	evolocumab	Endocrinology	PFS; PFP; wearable	2028	2029
Simponi	golimumab	Rheumatology; Gastroenterology	PFS, PFP	2025	2024
Takhzyro	lanadelumab	Immunology	Vial, PFS	2031	2032
Taltz	ixekizumab	Rheumatology	PFS; PFP	2031	2030
Trulicity	dulaglutide	Endocrinology	PFP	2029	2027
Xolair	omalizumab	Immunology	Vial; PFS	2017	2018

Table 2: Biosimilars candidates that could benefit from novel autoinjector technology. INN = international non-proprietary name, PFP: prefilled pen, e-Device = electronic autoinjector. *Biosimilars approved and launched. **Biosimilars approved but not launched. [Y]Remicade is administered IV.

"HCPs generally supported connected health, believing that knowledge of patient adherence trends could aid treatment decisions."

Sustainability

Environmental sustainability was considered by all stakeholders to be an increasingly important issue but not one that yet has that much influence on decision making by payers and HCPs. Payers were generally unwilling to pay more for environmentally friendlier devices but believed using less material could lead to cost savings. HCPs did not discuss the environmental impact of treatments with their patients, although some believed this could change as younger patients are diagnosed.

Connected Health

Based on current experience, payers were uncertain of the value of connected health systems and indicated they would only pay more if there was RWE of improved outcomes. US payers stated a connected device could facilitate value-based insurance design, whereby a patient's cost sharing is altered according to their adherence. HCPs generally supported connected health, believing that knowledge of patient adherence trends could aid treatment decisions. However, pharma companies recognised concerns with connected health systems around patient confidentiality and data security requirements, and generally deem these systems to be not critical in competing with bio-originators already offering these systems.

Adoption of Biosimilars

In both markets, payers control which drugs and delivery devices HCPs can prescribe and whether existing patients should be switched to a biosimilar. When deciding which biosimilars to pay for and prescribe, UK payers gave almost no consideration to factors not affecting cost effectiveness and UK HCPs had to prescribe the cheapest drug available. US payers considered a biosimilar's net price first, followed by its interchangeability status; an environmentally friendlier device conferred a slight advantage, but not connected health unless RWE of improved outcomes was available. US HCP preferences had some effect on which device was prescribed but only behind access and drug efficacy; they considered a device's usability and sustainability, and the availability of a connected health system, as advantages which would positively influence their device preferences. Whilst pharma companies saw drug delivery as a major source of differentiation in the biosimilars sector, a device which substantially raised the manufacturing cost would be problematic due to the inevitability of future price erosion.

Payers and HCPs did not expect patients to be switched between biosimilars for financial reasons regularly (i.e. annually), although most expected an initial switch from the branded drug to a biosimilar. Drug delivery devices were not perceived to impact these transitions since patients could be retrained on the new device. UK HCPs were confident about their ability to switch patients and supported pharmacy-level substitution of biosimilars. US HCPs were generally in favour of switching and substitution, provided there was supporting data.

Potential Barriers to Innovation

Barriers in both UK and US markets included HCP preference and experience, reluctance to switch, unknown biosimilar companies, and branded companies' defensive strategies. Several US-specific barriers were also found, including:

- Rebate "walls" implemented by the reference drug supplier to protect its market position
- Cost savings not being shared with payers
- Lack of administrative incentive and interchangeability.

For the UK, a lack of NICE appraisal for biosimilars was considered an issue. NICE has stated that guidance published for an originator molecule will apply to a biosimilar at the time it becomes available to the NHS so it does not automatically conduct a new appraisal. In general, this is a reasonable position to take, given the equivalence of the drugs, but cost savings associated with biosimilar use have the potential to increase accessibility. This is recognised and the arrival of adalimumab and etanercept biosimilars led NICE to conduct a new technology appraisal which found cost effectiveness in treating patients with moderate rheumatoid arthritis using these biologics[11] when previously only patients with severe disease have been eligible.[12] The use of novel drug delivery technologies would only be considered if it was felt this might impact outcomes that will improve cost effectiveness. For Remsima, NICE recognised the patient benefits but did not make a recommendation that favours this medicine over other intravenous forms of infliximab.[13]

In the UK as in many other markets, it is not permissible to switch from an originator drug to a biosimilar drug at the pharmacy without the agreement of the prescribing clinician. But in the UK, NICE guidance, an assessment of cost effectiveness, as well as clinical data that support the interchangeability of biosimilar drugs with their reference products, has driven the transition to biosimilars. The situation in the US is more complex, which partly explains the slower uptake of biosimilars in this market. However, US legislation does allow biosimilars that have been designated by the FDA as interchangeable to be substituted without the intervention of the prescribing HCP. This is clearly a potential advantage for the biosimilar provider, yet also creates a complication in looking to change to a more innovative device, at least until the FDA provides better guidance around this point. Present guidance seems to be confusing as it is in part encouraging innovation but also being unclear around the actual requirements to demonstrate equivalence between devices.[14] Unofficial feedback gained from the FDA suggests a change from a disposable to a smart reusable autoinjectors would not necessarily rule out interchangeability. However, further consultation with the agency would be required to determine this.

DISCUSSION

To be successful in the market, biosimilars need to be significantly cheaper than the branded drug and price competitive with other biosimilars. Whereas the former would seem an obvious requirement, in the US and some European markets the branded drug provider has used pricing and rebate strategies to make this more challenging.

Considering improved drug delivery devices for biosimilars, payers control the market in both the US and UK, and primarily see differentiation based on net price, and will only pay more for a biosimilar with

"The extent to which injectable biosimilar uptake is impeded in the US will be revealed in 2023 with the launch of multiple adalimumab biosimilars – their success will likely inform many companies' strategies in the future."

improved drug delivery technology if it shows RWE for improved clinical outcomes. Although evidence is emerging that smart delivery devices, potentially combined with a companion digital service, can improve adherence in real-world settings,[6] a pull through to better clinical outcomes is more difficult to demonstrate. At present, biosimilar companies are unlikely to consider it feasible or worthwhile to gather the evidence in a controlled study to try to make a claim for reimbursement. Provided it does not compromise price competitiveness, drug delivery technology and associated digital services can be a differentiator that can drive use of a particular biosimilar and these create a benefit for the pharma company.

Sustainability is likely to become an increasingly important differentiator and creates a significant opportunity for more environmentally friendly devices – a trend that generally favours reusable devices over conventional disposable devices.[15] The environmental benefits from a reusable device such as Aria would likely be realised for chronic biosimilar therapies as patients are unlikely to be changed regularly between biosimilars for non-clinical reasons, so the device should be used for its intended design life.

The NHS has taken a strong position on sustainability, with the aim of being the world's first net zero national health service by 2040. Other healthcare providers are also increasingly focused on this concern. A 2019 study estimated that 4.4% of the global carbon footprint is associated with healthcare.[16] Most of the leading global pharmaceutical companies have also set ambitious sustainability targets that include working with suppliers, including device companies, to reduce greenhouse gas emissions.

Fewer barriers exist to biosimilar uptake in the UK than the US, but benefits for advanced delivery devices are probably more likely to be recognised and valued in the US market, as has been seen for the Onpro device. Thus, whilst there may be more opportunity for biosimilars in the UK, there may be more opportunity for novel drug delivery technologies in the US. The extent to which injectable biosimilar uptake is impeded in the US will be revealed in 2023 with the launch of multiple adalimumab biosimilars – their success will likely inform many companies' strategies in the future.

CONCLUSIONS

Europe (including the UK) has already seen a rapid uptake in the use of biosimilars over the past 10 years and this trend is expected to continue, with price remaining the dominant driver. This will improve market access and likely accelerate the number of patients who will receive treatment with biologics.

In the US, with more than 30 biologics losing exclusivity during the rest of the 2020s, the opportunities for biosimilars are also set to increase dramatically. Although barriers to entry will continue to exist, increased efforts to address the disparity in drug pricing between the US and other markets are likely to support this trend.

In both markets, there is likely to be increasing competition between biosimilar companies to capture market share. Assuming equivalent pricing, the ability to differentiate must be driven by the commercial activities that support the introduction and use of specific biosimilars compared with competing drugs. In the same way that drug delivery technology has enabled differentiation in the innovative biologics market, it is likely to have an increasing role to play with biosimilars. A drive to more self-administration of medication potentially benefits patients and payers and can be facilitated by better drug delivery technology.

Sustainability will become an increasingly important consideration. Biosimilar pharma companies may conclude that their own approach to corporate social responsibility requires use of more sustainable devices, which in term may increase a trend towards reusable devices. Healthcare providers and payers are already demonstrating an ambition to reduce their own carbon footprint and may well start to apply pressure to their suppliers, including the pharma and devices industries, to support this. Our research has shown a strong interest from patients to be offered more sustainable treatments and this will also apply pressure to HCPs, providers and payers to respond to this.

With the ending of exclusivity for blockbuster biologics extending well into the 2030s, there is still a long runway for the launch of new biosimilars and the likelihood of changes in the market drivers that will favour more sustainable delivery devices. Furthermore, clearer evidence may well start to emerge around the value of more personalised devices and connected health in improving healthcare outcomes and efficiency – that will then drive interest in connected delivery devices. If progressive biosimilar companies seek to remain in the vanguard of the sector and achieve competitive advantage in crowded markets, they will do well to look beyond current drug delivery device technology and look to capitalise on the benefits offered by more innovative delivery solutions such as smart autoinjectors.

ABOUT THE COMPANY

Phillips-Medisize, a Molex company, helps clients get from concept to care quickly while reducing the inherent risks of any new product journey. The company acts as a singular resource for its clients, offering robust end-to-end capabilities, including drug delivery device platforms. For over 60 years, pharma, diagnostic and medtech companies have trusted Phillips-Medisize to deliver quality products that help people live healthier lives.

"In the same way that drug delivery technology has enabled differentiation in the innovative biologics market, it is likely to have an increasing role to play with biosimilars."

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ABOUT THE AUTHORS

Iain Simpson, PhD, is a Commercial Director at Phillips-Medisize, where he is part of a global team developing industry-leading solutions and platforms for drug delivery, digital medicine and connected health. He has a degree and PhD in Physics, both from University College London (UK), and an MBE in Technology Management from the Open University. Dr Simpson has published and presented at conferences on drug delivery, digital biomarkers, healthcare technology and technology licensing. He is an associate lecturer at the University of Cambridge (UK) in Bioscience Enterprise.

George Spooner studied for a MPhil in Therapeutic Sciences at the University of Cambridge (UK) and worked on a project with Phillips-Medisize for his dissertation. After completing his degree at Cambridge, he joined Oxford Medical Products as Chief of Staff.

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2023 EDITORIAL CALENDAR

Publication Month	Issue Topic
March	Ophthalmic Drug Delivery
March/ April	Skin Drug Delivery: Dermal, Transdermal & Microneedles
April	Pulmonary & Nasal Drug Delivery
April/May	Drug Delivery & Environmental Sustainability
May	Delivering Injectables: Devices & Formulations
May/June	Oral Drug Delivery
June	Connecting Drug Delivery
June/July	Industrialising Drug Delivery
September	Wearable Injectors
October	Prefilled Syringes & Injection Devices
October/ November	Drug Delivery & Environmental Sustainability
November	Pulmonary & Nasal Drug Delivery
December	Connecting Drug Delivery
December/ January	Skin Drug Delivery: Dermal, Transdermal & Microneedles

INTERVIEW

In this exclusive interview, Gabriel Zenker talks with ONdrugDelivery about Aptar Pharma's ambitions for the parenterals sector. Mr Zenker explains how Aptar, already a major player in the pulmonary, nasal and dermal markets, is undertaking a major expansion of its facilities, boosting the company's capacity, capabilities and technologies, to provide its extensive service and product offering to the exciting and growing injectables space.

GABRIEL ZENKER, APTAR PHARMA

Gabriel Zenker is President of Aptar Pharma's Injectables Division. Mr Zenker has been in the pharma and injectables space since 2005, having served as EMEA Sales and Marketing Director at BD Pharmaceutical Systems and Vice-President Sales at Stevanato Group prior to joining Aptar Pharma.

Q The majority of ONdrugDelivery's readers are no doubt very familiar with Aptar Pharma, but for those who might not be, please could you provide a brief overview of the company – first in general terms and then going on to focus on the company's offering in the area of injectables and how it fits into the broader Aptar Pharma segment?

A To begin with, Aptar Pharma is a global leader in devices. We already have a strong presence in the inhalable, nasal, ophthalmic and dermal sectors, and we are currently undertaking a major expansion and transformation of our injectables division. Aptar Pharma is a company with a strong focus on data and services, with some of its prior and recent acquisitions providing a strong demonstration of that focus, including working to provide more scientific and patient data in conjunction with our device capability. Building on that, the latest part of our expansion has been in the area of digital health, such as our recent acquisition of Voluntis, which adds digital to our device and data capabilities. We believe that there are clear points of intersection between the device and physical components on the one hand, and services and the digital aspects on the other. These are opportune sweet spots where Aptar can make a difference in the market and provide end-to-end solutions.

The injectables space has been a key area of investment for Aptar over the past few years. We've invested approximately US$180 million (£151 million) into our operations, resulting in a significant expansion of an existing plant in Granville (France) and leading towards building an additional plant next to the existing one (Figure 1), to further increase our elastomer component production capacity with a special focus on our film-coated PremiumCoat® solutions. This investment is also aimed at expanding Aptar Pharma's injectables operation in North America. Our facility in Congers (NY, US) will be a part of that, and we'll be developing our PremiumCoat® production capabilities and capacity to better serve the market locally.

Figure 1: Aptar Pharma's new Granville production facility.

"Aptar Pharma's injectables operations have gone beyond just increasing capacity, with investment in new technologies, sustainability and our people."

Furthermore, this transformation of Aptar Pharma's injectables operations have gone beyond just increasing capacity, with investment in new technologies, sustainability and our people. We're very committed to healthcare, very committed to pharma and our ambition is to shape the future of injectables together with our customers.

Q Looking towards the coming months and years, what are the major trends, significant innovations and key drivers for growth likely to be in the parenteral delivery space?

A First of all, I think there's been a very strong impact from covid-19. Looking at the situation now, I believe that covid-19 is becoming endemic and that there's a continuing market need and growth related to it. Beyond covid-19, some of the more high-value vaccines and treatments will require very specific solutions from the parenteral packaging sector to ensure that these sensitive doses are protected, remain efficient and are safe for patients.

I think the world overall was really impressed by how quickly the pharma industry was able to develop successful vaccines and manage the pandemic.

Furthermore, I think that investment in new drug technologies will continue and that we're going to see it with both large pharma companies and newer, smaller biotech start-ups. We are likely to see technologies such as mRNA (messenger RNA) picking up more traction and looking to address a wider range of diseases.

We're definitely seeing growth as we move past the pandemic, and we need to be ready. There are some definite learnings post-covid-19, a key one being security of supply. We've learned that having just one supplier can be risky and that having surge capacity available can prove critical for pandemic response.

However, capacity is not the only lever available – manufacturers must also consider more innovative manufacturing and supply models to be able to adapt and respond to emergency situations more quickly. This, of course, is coupled with the need to have the right technologies to deliver new and existing drugs in a safe and appropriate way. Though new trends are taking shape, we cannot know what the next healthcare challenge will be and we must be ready for the unexpected.

We must be proactive, we must be more open and we must make sure we have the right technologies ready to be delivered. We have to make sure we have the right supply chain and the right supplier base to really play our role, no matter what comes next.

Q What is Aptar Pharma's vision for itself within the injectables market?

A We've been investing in our capacity and capabilities, bringing in new manufacturing technologies that can raise the bar from a quality perspective. In parallel, we have been investing in the organisational, technical and commercial capabilities we need to be able to deploy this. It's our goal to be a first-choice solution provider for pharma, with our solutions able to deliver performances in line with, or even superior to, the gold standards currently on the market. We believe that we can be a trusted partner to lead our partners towards success. It's in our DNA to try harder – to make each of our relationships with our customers a commercial success.

> "It's our goal to be a first-choice solution provider for pharma, with our solutions able to deliver performances in line with, or even superior to, the gold standards currently on the market."

Figure 2: The expansion of Aptar Pharma's manufacturing capabilities will provide increased production of its PremiumCoat® product line and support the development of the North American market.

Our size and organisation is instrumental to providing the flexibility and proximity our customers need. This remains at the centre of our expansion programme with additional capacity and capabilities being built outside of Europe and closer to our customers.

Q Can you provide more details on what this expansion would involve and how these elements will strengthen the company's position in each area of its injectables offering?

A Our transformation started in France, with the upgrading of our two facilities in Normandy – Brécey and Granville. As part of our $180 million expansion plan, we have built an extension to our original factory, adding 30% to its capacity, which has been operational since 2021. We are also building a new factory right next to the historical plant.

A key focus of the expansion is to increase our rubber mixing capacity, while also implementing state-of-the-art manufacturing lines. This benefits our PremiumFill® and PremiumCoat® product lines and enables the deployment of surge capacity for all our components if needed.

We're also expanding in North America, with the implementation of moulding and trimming capabilities in our Congers facility, adding to the overall capacity for serving the American market. This puts us in a very strong position from a capacity perspective.

In addition to the trust of our customers, our expansion plan has been recognised by the French government and, as part of its Program of Investments for the Future, we received partial funding of €13 million for the building and expansion of our European facilities. This is further evidence that Aptar is a company worth investing in for shaping the future of injectables and to serve the healthcare industry.

Q So would you say that this expansion isn't just about volume, but also about upgrading Aptar's capabilities and technology?

A I agree, that's an important point to make – it's not just about volume. The digitalisation of our processes is a key pillar of our expansion that is essential for increasing the reliability and control of our processes.

In parallel to digitalisation, we are also implementing state-of-the-art robotisation as a way to increase the reproducibility of our processes while minimising the risk of contamination. With the same objective, we are increasing our cleanroom footprint to ensure that our operations meet the strictest cleanliness requirements.

We have taken the opportunity to upgrade our processes and technologies to ensure that we meet the quality requirements of our customers. As a major player for injectable delivery, our operations must be aligned with the expectations of the market

and we must anticipate the ever-increasing stringency of regulatory authorities.

Our expertise does not stop with rubber and closure component manufacturing for injectables. As part of improving the journey for our customers, we have service capabilities to support the drug development journey for our customers by providing additional data for derisking the choice of closure component and performing the analysis required for the regulatory validation of drug products.

Our history and proven track record ideally position us for offering this type of service, which may be essential for customers who do not necessarily have the resources and expertise they need available in-house. Our aim is to offer a complete value proposition and make our customers' drug development journeys with us as smooth, reliable and easy as possible.

Q Could you outline how the expansion of Aptar Pharma's injectables division fits within AptarGroup's broader position with respect to environmental sustainability?

A All of our Aptar Pharma sites are certified landfill-free, with our French and US sites using electricity produced from 100% renewable sources. Our new site in Granville includes improved water and waste management, as well as solar energy-generation for optimised energy efficiency. The new factory has obtained the Silver LEED Certification for sustainable manufacturing, and Aptar Group as a whole has received several accolades for its sustainability achievements. Our goal, all the way up to the corporate level, is to operate with care for the environment.

"Our aim is to offer a complete value proposition and make our customers' drug development journeys with us as smooth, reliable and easy as possible."

Q To wrap up, do you have any final thoughts on the topics we've discussed?

A To conclude, our objective is to transform the expectations of what an injectable partner can be, working very closely with our customers with agility and responsiveness. The core message I want to get across is that we try harder, and we will continue to try harder to make our customers' projects successful.

To learn more about Aptar Pharma's Injectables, visit: www.aptar.com/resources/aptar-pharma-expands-injectables-components-manufacturing-capabilities

ABOUT THE COMPANY

For pharma customers worldwide, Aptar Pharma is the go-to drug delivery expert, from formulation to patient, providing innovative drug delivery systems, components and active material 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 de-risk the development journey. With a strong focus on innovation, Aptar Digital Health is leading the way in developing digital health solutions to help improve the patient treatment experience. 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.

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Gabriel Zenker
President, Injectables Divison

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ANTICIPATING AND MITIGATING CHALLENGES IN THE COMMERCIALISATION OF PREFILLED SYRINGES & INJECTION DEVICES – A TECHNICAL DRUG PRODUCT PERSPECTIVE

Here Andrea Allmendinger, PhD, Chief Scientific Officer, and Hanns-Christian Mahler, PhD, Chief Enablement Officer, both at ten23 health, provide an insight into the challenges of integrated development of drug product and device design and fill-finish manufacturing operations.

Ready-to-use (RTU) delivery devices such as prefilled syringes (PFSs), autoinjectors, pens and large-volume injection devices are designed to facilitate administration for the end-user. This allows for self-administration, for example, in case of subcutaneously (SC) administered products, or increases patient safety, for example, for intravitreal (IVT) products administered by a healthcare professional.

The commercialisation of a combination product, such as a PFS or cartridge-based on-body injector (OBI), presents several key challenges during the technical development and manufacturing of the drug and drug/device combination product. This article provides a broad overview of most important challenges from a technical perspective and highlights the importance of integrated development of drug product and device design and fill-finish manufacturing operations.

PRODUCT CONFIGURATION

The selection of a suitable formulation for the API is essential to stabilise the product at the intended storage temperature over the desired shelf life. In particular, selection of the final dose, and therefore

> "The commercialisation of a combination product, such as a PFS or cartridge-based OBI, presents several key challenges during the technical development and manufacturing of the drug and drug/device combination product."

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concentration of the API, is key as it defines the fill volume of the final drug product. For ophthalmologic products applied to the vitreous humour, the maximum injection volume is currently believed to be 100 µL. For SC administered products, injection volumes have been traditionally considered as limited to volumes of 1 mL or less.

However, knowledge and experience in the clinical setting is increasing with regard to tolerability and usability, and SC administration has recently been facilitated by the development of highly concentrated formulations of greater than 50 mg/mL at injection volumes up to 1, 2 or sometimes 3 mL. The question of what the limit is for SC volumes remains open, but it is inspired by the recent commercialisation of 10 mL cartridge-based OBI device of FUROSCIX (furosemide – scPharmaceuticals, MA, US).

Besides molecular/biochemical product stability, one of the main technical challenges of highly concentrated formulations is the exponential increase in viscosity with increasing protein concentration. Notably, viscosity is dependent on temperature and shear rate, and subtle variations of protein concentration, even within specifications, can lead to drastic changes in viscosity. Viscosity is associated with both challenges during filling, but also an increase in the injection forces required to administer the product. The latter needs to be mitigated by device design to guarantee functionality and adequate injection time upon stress, stability and transport testing to maintain patient usability.

The variability of components also plays a major role in potential product liabilities and risks. For example, the variability of the inner diameter of the needle used for injection impacts injection forces significantly (by the power of 4, according to Hagen-Poiseuille's law).

PRIMARY PACKAGING CONTAINERS – RTU CONFIGURATIONS

Combination products are typically filled in RTU primary packaging containers, such as syringes or cartridges, preferably in nest/tub configurations. This means that the container is provided in prewashed and pre-sterilised configuration and ready for filling. However, this implies that device attributes must comply with final drug product requirements throughout the supply chain until the point of filling. This includes the performance of the device and safety relevant parameters, including the risk of potential contaminants, such as absence of micro-organisms (maintenance of sterility) or particles. In particular, novel containers, an increasing number of which have been entering the market lately, require a thorough and, sophisticated characterisation of the primary packaging container and product compatibility. Specifications of primary packaging material must be carefully designed and assessed with the final drug product quality requirements in mind.

"Novel containers, an increasing number of which have been entering the market lately, require a thorough and sophisticated characterisation of the primary packaging container and of product compatibility."

However, "traditional" glass containers, such as glass syringes, also require a thorough characterisation of material attributes impacting the injectability over the intended final product-use time and contaminants, such as particle load, must still be assessed (and minimised). In essence, the characterisation of the primary components, with the end quality in mind, is key.

Testing the primary packaging material's compatibility with the drug product solution and its stability is essential, even more so if novel containers are used. Characterisation should include extractables and leachables testing, container closure integrity and product quality including, for example, particle contamination. Stability testing of drug product filled into the primary containers includes a panel of biochemical and pharmacopeial endpoints that cover critical quality attributes (CQAs), including content and purity, and obligatory CQAs, such as (sub-visible and visible) particulates.

FILL-FINISH PROCESSES

The drug product manufacturing capabilities must be aligned with the requirements of the device partner and primary packaging supplier to ensure that the drug product will adhere to agreed parameters. The drug product manufacturer needs to be capable of reliably and consistently filling the related primary packaging containers (e.g. larger-volume cartridges, syringes or special containers), ideally offering RTU containers.

The filling process is especially challenging for highly viscous and low-volume products. The manufacturer should be able to handle a highly viscous product from the processing side, such as by choosing between different pumps, and be able to choose between weight or volume fill.

In general, overfills must be minimised as this is likely to result in significant cost savings. This is especially important for IVT products. Administration volumes of IVT products are in the range of 10–100 µL, which is often much less than the minimal volume that can be filled by most sterile facilities and contract manufacturing organisations. As a result, most products for IVT use are significantly overfilled. In addition, this also means that syringes for IVT use need to be manipulated by the final user, preferably a healthcare professional, by either expelling air or volume, which is also referred to as "downdosing". However, this carries a risk of variability in the volume administered.

Another challenge arises during (air) transport. The design of fill volume and allowable headspace with the chosen primary packaging is key as the transport conditions may lead to stopper movement, which may impact container integrity and, hence, potential loss of sterility. Therefore, a bubble-free plunger setting at the manufacturer facility allowing for minimal headspace, as well as the control of the plunger stopper position and stoppering under vacuum to allow reduced plunger compression (for example, for silicone-free container closure systems) is beneficial.

"The drug product manufacturing capabilities must be aligned with the requirements of the device partner and primary packaging supplier to ensure that the drug product will adhere to agreed parameters."

CONCLUSION

Joint and integrated development between product development – including formulation design – and selection of primary packaging container, device design and manufacturer is essential to transfer product knowledge, facilitate troubleshooting activities and enable successful commercialisation. Challenges and failure modes need to be appropriately assessed *a priori*, and appropriately mitigated and managed. This includes appropriate formulation development, manufacturing process design and holistic consideration of the interplay of the formulation and raw materials, primary packaging, fill process unit operations, usability and administration, as well as all their acceptance criteria and specifications, in order to yield a safe and efficacious final product.

ABOUT THE COMPANY

As a CDMO, ten23 health is appropriately positioned to anticipate and overcome the challenges that relate to sterile drug products, especially for SC or IVT use. The company offers integrated development of formulation services, analytical development and product characterisation, device selection and testing, drug product process design, product characterisation and failure mode assessments with its high-end capabilities in particulate characterisation and injection force and container closure integrity testing. ten23 health also provides fill and finish (sterile manufacturing) of complex and high-precision containers at its facility in Visp, Switzerland, including syringes, vials and cartridges, for both glass and novel containers (Figure 1).

Figure 1: ten23 health's facility in Visp, Switzerland.

ABOUT THE AUTHORS

Andrea Allmendinger, PhD, has been Chief Scientific Officer at ten23 health since November 2021. Dr Allmendinger is also Adjunct Professor and Group Leader at the University of Freiburg (Baden-Württemberg, Germany), researching novel parenteral drug formulations and device solutions to improve stability, usability and cost of goods. Between 2010 and 2021, she was Principal Scientist, Pharmaceutical Development at Roche, working on, *inter alia*, manufacturability and injectability of high-concentration formulations, syringe and high-volume drug/device combination products, particulates and surfactant strategy. Dr Allmendinger studied Pharmacy at the University of Heidelberg, Germany, and University College London, UK, and holds a PhD in Pharmaceutical Sciences from the University of Basel, Switzerland. She obtained the *venia legendi* (German Habilitation) from the University of Freiburg in 2021, and serves as Editor-In-Chief for the AAPS Open Journal.

Professor Hanns-Christian Mahler, PhD, is Chief Enablement Officer and Board Member at ten23 health. He previously led the Drug Product Services Business Unit at Lonza AG (2015–2021) and worked in various leadership roles, such as Head of Pharmaceutical Development & Supplies at Roche (2005–2015) and Merck KGaA (2000–2005). He has extensive expertise in formulation development, process development and validation, packaging/device development and integration, sterile manufacturing and regulatory submissions with numerous IND/IMPD and BLAs. Prof Mahler studied pharmacy at the University of Mainz, Germany, and holds a PhD in toxicology from the Institute of Pharmacy, University of Mainz, and pharmacist specialisation degrees in toxicology and ecology, and pharmaceutical technology. He also has qualifications in Business and Marketing (AKAD University, Germany). Prof Mahler obtained his *venia legendi* from the University of Frankfurt, Germany, in 2010 and is adjunct faculty member and lecturer at the universities of Frankfurt and Basel. He also serves as Editor for Pharmaceutical Research, Journal of Pharmaceutical Sciences, AAPS Open Journal and PDA Journal of Pharmaceutical Sciences and Technology.

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OWEN MUMFORD
Pharmaceutical Services

THE OPERATIONS PERSPECTIVE: BEST PRACTICES FROM 70 YEARS IN INJECTION DEVICE MANUFACTURING

Here, John Swift, Head of Supply Chain at Owen Mumford, looks at how the company has evolved over 70 years, discusses its latest disposable autoinjector, Aidaptus, and considers how it plans to actively reduce risk in its supply chain.

In 2022, as Owen Mumford celebrated its 70th birthday, the business reflected on its growth from a small, family-run business in Woodstock, near Oxford (UK), to a global medical device innovator. The industry has evolved dramatically during this period. Since the company pioneered the world's first plastic autoinjector (Autoject) in 1986,[1] the market for injection devices has grown, while welcoming increasingly sophisticated products.

It is expected that, in 2023 alone, the global injectable drug delivery devices market – comprising conventional injections, prefilled syringes, autoinjectors and pen-injectors – will grow by 9.0%, reaching a value of $43.54 billion (£35.8 billion).[2] During the same period, the global autoinjectors market is expected to expand at an even higher rate, 21.4%, reaching a valuation of $23.9 billion.[3] With 60% of drugs in the R&D pipeline designed for injectable delivery and a growing number of those for subcutaneous administration, it is likely that the industry will continue to see sustained growth in the coming years.[4]

With demand high and patients increasingly administering their own medication wherever possible, manufacturers of drug delivery devices must be able to keep up – reliably providing the required volumes, and meeting quality and regulatory standards while continuing to innovate.

> "Risk management begins at the design phase when deciding on manufacturing and assembly processes – both manual and automated."

SECURING SUPPLY RESILIENCE

A key aim of Owen Mumford's operations plan is to secure supply resilience, even while development programmes for other products are ongoing. Over the years, Owen Mumford's operations team has developed best practices to support product launches and growth, ensuring device excellence and optimally managing risk during industrialisation and capacity scale-up.

Risk management begins at the design phase when deciding on manufacturing and assembly processes – both manual and automated. Simplicity is paramount since it inherently reduces risk, but if there are residual risks during manufacturing, the company's process failure mode effects analysis (PFMEA) tracks and mitigates these. The team proactively assesses updates on a risk register to track changes and their potential impact and the likelihood of risks impacting project delivery timescales. This allows the team to take corrective action swiftly when needed, to manage risk appropriately and ensure continuity of supply.

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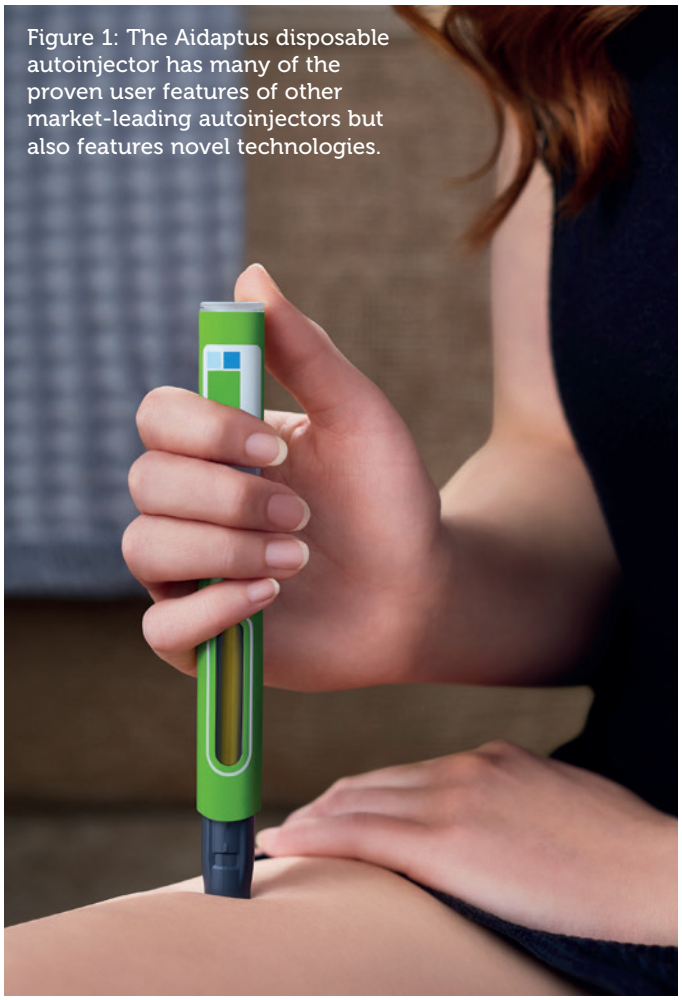

Figure 1: The Aidaptus disposable autoinjector has many of the proven user features of other market-leading autoinjectors but also features novel technologies.

Alongside this, Owen Mumford has a specific initiative to monitor supply chain vulnerability. Brexit and the global pandemic highlighted risk areas that needed addressing to protect continuity of supply, prompting this new initiative, which supports ongoing supplier management. The company has developed a "virtual factory management" concept, with key performance indicators that enable early detection of vulnerabilities caused by key suppliers' performance, capability or strategies. To manage suppliers effectively, the company has made sure there are clear roles, responsibilities and governance, an optimal meeting cadence, triggers and escalation procedures. The teams audit and work alongside suppliers, making it easier to check that appropriate systems, equipment, methods and skill sets are in place to deliver to the agreed level of quality.

With so many factors to monitor for supply security, the creation of centres of excellence is invaluable so that each focuses on a particular area of operations, whether this is moulding, assembly, automation or another key function. The company's approach is to clearly define the skills and tools needed for each individual centre and then create a focused training programme that allows staff to learn continually and upskill. This, in turn, supports staff retention, contributing to a reduced risk profile. Through dedicated centres of excellence, operations teams can develop and implement best practices across all key areas and employ individuals with a variety of backgrounds and experience levels. In fact, they can support risk management in multiple ways, through improved planning and awareness of potential issues or by providing key skill and competency coverage in times of planned or unplanned leave.

Owen Mumford's upcoming new production facility in Oxfordshire, UK, will become a centre of excellence for automation and assembly, manufacturing the company's latest medical devices and supporting its global commercial and sustainability strategy. The building itself is designed with excellence in mind and will be certified by the Building Research Establishment Environmental Assessment Method, the world's leading sustainability assessment method. This certification recognises the highest levels of environmental, social and economic sustainability performance, not only protecting natural resources during the building process but also enhancing the wellbeing of associates who will be located there.

INNOVATION, INNOVATION, INNOVATION

While continuing to provide its existing products, Owen Mumford is constantly looking ahead and designing new devices, always with the aim of improving the patient experience while maintaining ease of use. Its latest innovation, the Aidaptus disposable autoinjector, has many of the proven user features of other market-leading autoinjectors but also features novel technologies (Figure 1). These technologies help provide flexibility for pharmaceutical companies during their drug development and lifecycle management.

As well as accommodating both 1 and 2.25 mL syringes in the base form, Aidaptus's novel auto-adjust plunger technology can dynamically adjust to different fill volumes with no change parts. The plunger automatically adjusts to the required stopper position during final assembly of the device with no requirement for special equipment. Essentially, this means that the same device can be used irrespective of formulation changes. This has advantages in reducing work such as additional verification testing, human factors studies and regulatory documentation. Therefore, it can help to reduce risk for the company's pharma partners as well as reduce time to market in combination product development.

For Aidaptus, Owen Mumford has chosen to collaborate with Stevanato Group (Padua, Italy) with the aim that the combined resources, expertise and manufacturing capabilities of both companies will help to reduce complexity, minimise supply-chain risk

Figure 2: For Owen Mumford, the new assembly equipment will be installed at its new state-of-the-art facility in the UK, which is due for completion in 2023.

and simplify final assembly for pharma customers. Both parties are currently making investments in building the capacity for Aidaptus scale-up, and equipment will be installed at both companies' production sites. For Owen Mumford, the new assembly equipment will be installed at its new state-of-the-art facility in the UK, which is due for completion in 2023 (Figure 2). This approach to dual sourcing options is another example of how the company is actively planning to reduce risk in its supply chain.

ABOUT THE COMPANY

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.

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ABOUT THE AUTHOR

John Swift is Head of Supply Chain at Owen Mumford. He is an experienced operations programme manager with a successful track record working throughout the supply chain, covering procurement, supplier management, invention, development and manufacture, as well as promotion, sales and distribution. He is experienced in applying and adapting skills across both large corporations – such as Abbott, Abbvie and Tyco – and small and medium-sized enterprises, and has worked in multiple industries, including medical device, aerospace and defence, rail, chemical, automotive and printing.

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Owen Mumford Pharmaceutical Services

1952–2022 INTO THE FUTURE... WITH CONFIDENCE AND CONSCIENCE

ACCELERATING NOVEL THERAPIES TO THE CLINIC – CUSTOM SOLUTIONS

In this article, Asmita Khanolkar, a Senior Director at SMC Ltd, discusses the key offerings necessary to accelerate "speed to clinic" for custom manufacturing solutions.

Pharmaceutical trends today are shifting towards targeted therapies, precision medicine and personalised treatment for smaller patient populations. With the growth of novel therapeutics, "speed to clinic" is more critical than ever. These novel therapeutics target a more specific indication, resulting in a smaller potential market. The overall revenue projection, along with available clinical study patients, are reduced – as seen in markets for oncology.

The formulations involved are more complex biotherapeutics, and large yet fragile molecules pose many unknowns and uncertainties throughout development. Bioavailability and immunogenicity are often not well understood, which means multiple iterations for therapy optimisation. In addition, delivery of these formulations is difficult, as they are often non-Newtonian or high viscosities and require custom high-pressure primary drug containers and devices. This requires flexibility to support adaptive and flexible sterile manufacturing towards an integrated approach for a path from development to small-batch manufacturing and commercialisation that can save time to clinic.

PHARMA SUPPLY CHAIN

The pharma supply chain still overwhelmingly represents the legacy needs of large-scale launches of blockbuster drugs with more "off-the-shelf" delivery options. In contrast, novel therapeutics often require customised delivery solutions for more targeted therapies. This gap or lack of alignment can increase the time required for development of novel therapeutics.

> "Novel therapeutics often require customised delivery solutions for more targeted therapies."

The unique combination of skills and expertise of the SMC Group (SMC Ltd, Oval Medical Technologies and Cambridge Pharma) aligns with the need for delivery customisation and results in reduced time to clinic for challenging novel therapeutics. With the combined offerings of SMC, Oval Medical and Cambridge Pharma, a portfolio of integrated services is provided – from the exploratory, preclinical stage through to clinical development and registration – to help accelerate the combination product development process from early stages onwards.

This includes formulation characterisation, drug product compounding, drug scale-up, innovative drug delivery device autoinjector platforms, animal testing, human factors studies, clinical sterile fill-finish and commercial

> "Speed to clinic is more critical than ever for novel therapeutics due to potentially reduced market sizes."

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Figure 1: Integrated manufacturing from early research to commercial launch.

manufacturing (Figure 1). Speed to clinic is more critical than ever for novel therapeutics due to potentially reduced market sizes, which impacts both return on investment and available clinical study patients – but, more importantly, the need to bring critical solutions to patients faster.

The following are the key offerings necessary to accelerate speed to clinic for custom manufacturing solutions:

- Vertically integrated development and manufacturing services to iterate quickly and cost effectively and avoid lengthy delays later in the development cycle.
- Enabling drug delivery solutions that can help early characterisation of formulations for optimised delivery of novel therapies.
- Small-batch manufacturing flexibility from clinical trials to commercial scale-up
- State-of-the art facility for GMP fill-finish with flexibility to handle legacy and customised delivery solutions for novel therapies.
- Specialised isolator equipment and filling experience to optimise fill-finish while maintaining container closure integrity (CCI) for challenging formulations.
- Experience providing solutions for challenging formulations including high viscosity, suspension and non-Newtonian fluids.
- Dedicated process development laboratory for process engineering solutions.
- Analytical laboratory solutions for test-method development and stability studies.
- Broad expertise across multiple facets of regulatory, clinical and commercial strategy.

SMALL-BATCH MANUFACTURING

Small-batch manufacturing requires flexible filling processes and innovative equipment that can handle a range of primary drug containers, including prefilled syringes and custom-designed vials and cartridges. Fast, flexible fill-finish isolator-based filling suites including qualified person (QP) release set-up is needed for handling small batch sizes ranging from 100 units to 10,000 units.

In contrast to dedicated high-volume lines, small-batch manufacturing requires flexibility for changeovers. However, due to the complexity of these formulations, there may be conflicting requirements for specialised equipment. Thus, the need for innovation through single-use systems, automation, non-contact processing, robotic inspection and CCI testing (Figure 2).

Novel therapies, including biotherapeutics, have special manufacturing needs and may need special processes developed for drug compounding, scale-up and fill-finish processes. Different pump technologies and fill methodologies can help tailor filling suitable to the drug. Depending on the application, peristaltic pumps for use with sensitive products like biotherapeutics and contact-free or single-use applications, for example, versus rotary piston pumps and special heads, which are suited to highly viscous formulations. Separately, optimisation of aseptic drug filling, stability, storage and delivery profiles for custom devices while maintaining CCI requires significant process mapping steps. In addition, quality control (QC) and analytical test methods for biotherapeutics need significant development (Figure 3).

Adaptive manufacturing is a strategy that supports customisable processes and adjustments as the process is developed and unknowns of novel formulations are revealed. A true adaptive manufacturing process can enable adjustments to improve quality at each step as the process is developed from lab scale to GMP scale. For custom primary drug containers,

Figure 2: Small-batch sterile manufacturing.

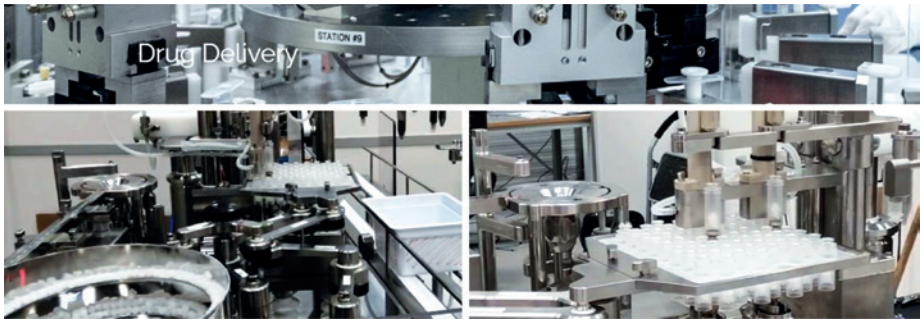

Figure 3: Speciality processes.

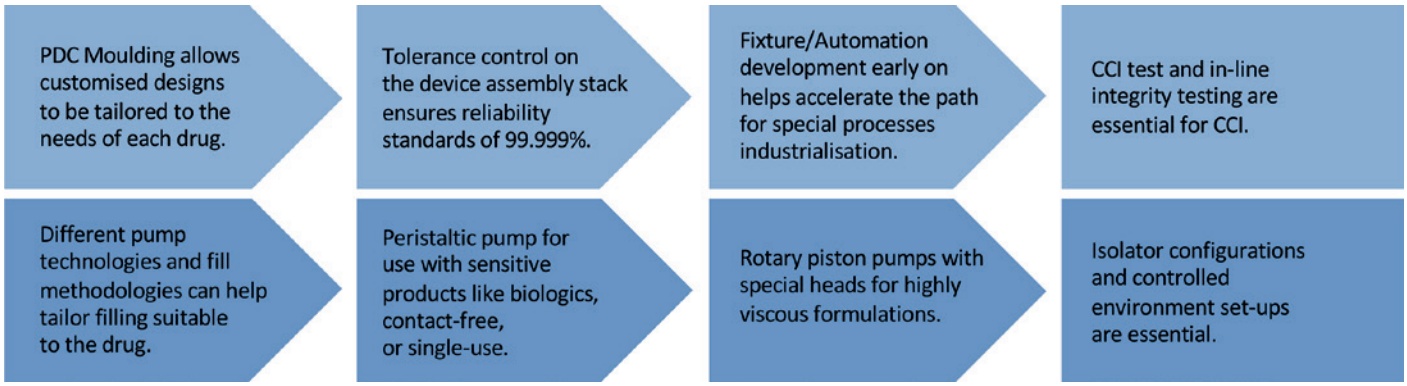

Figure 4: True adaptive manufacturing from start to finish.

mould design and tolerances can be adjusted to meet the needs of the drug. Flexible isolator configurations and controlled environment set-ups are essential for developing GMP similar processes from the beginning (Figure 4).

BROAD TECHNICAL EXPERTISE

Alongside the GMP manufacturing facility, process engineering laboratory and analytical laboratory capabilities allow the experienced scientific team to carry out process development work, analytical method transfer and validation, QC release and stability testing and, if required, QP certification to clinic. This type of process development work requires a holistic cross-functional approach and broad expertise looking at various facets of development and streamlining.

It is time consuming and challenging when engaging with multiple different suppliers and many items are missed at process hand-offs and interfaces. A single source partner with in-house expertise to support novel drug development from pre-clinical to commercialisation eliminates any fragmented approach and streamlines development. Process engineering and development information is leveraged for clinical production to eliminate risks early on, which reduces time to clinic (Figure 5).

CUSTOM IS THE NEW NORMAL

Novel formulations require characterisation for various aspects of drug filling, storage and delivery. Early characterisation at the start of a project eliminates lengthy delays at later stages in the programme (Figure 6).

STATE-OF-THE-ART FACILITY

The regulatory requirements landscape for GMP facilities is stringent and newer facilities have to meet the latest requirements for compliance as well as sustainability. Cambridge Pharma has state-of-the-art facilities with optimised material and people flow. Two filling suites are available for flexible small-batch manufacturing, including a clinical isolator line and a commercial semi-automated isolator line.

> "Continuing trends from hospital to home treatment have changed the clinical trials landscape."

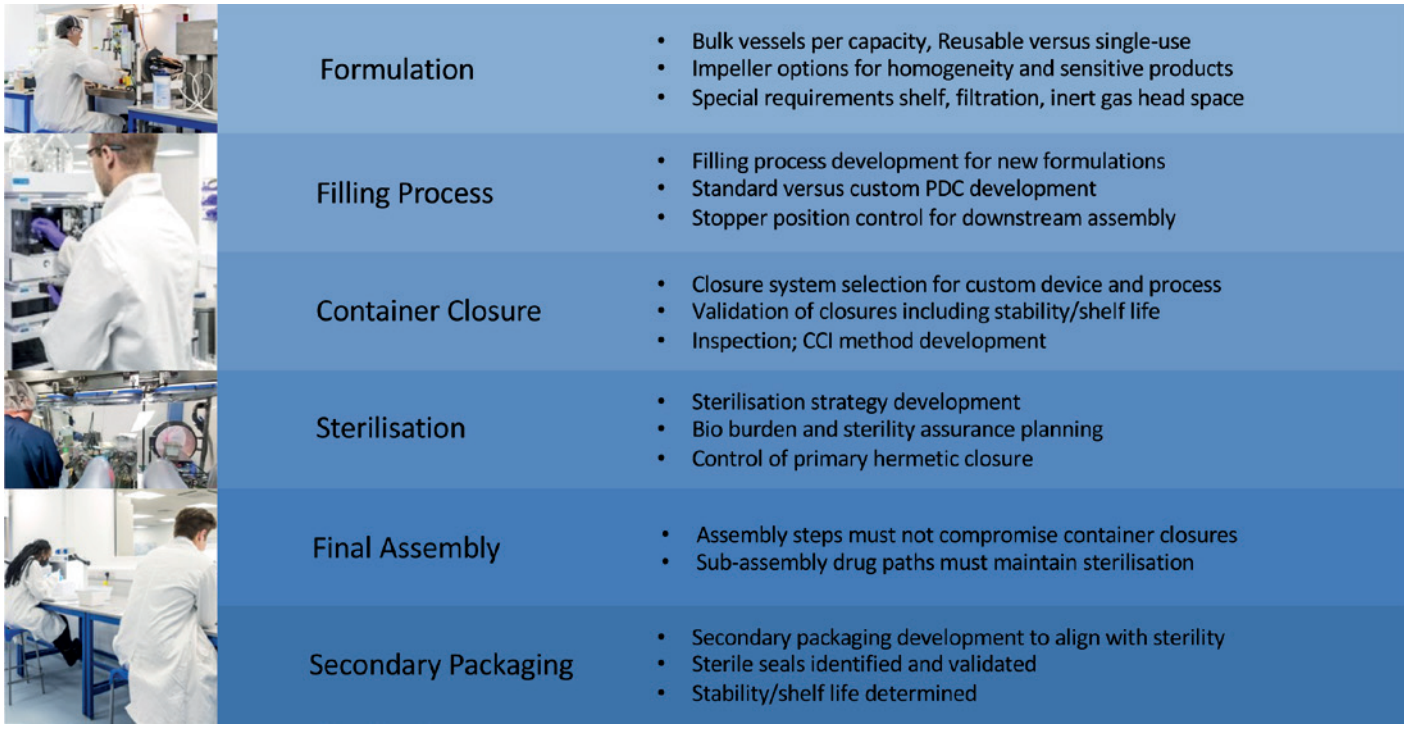

Figure 5: Streamlined process development interfaces.

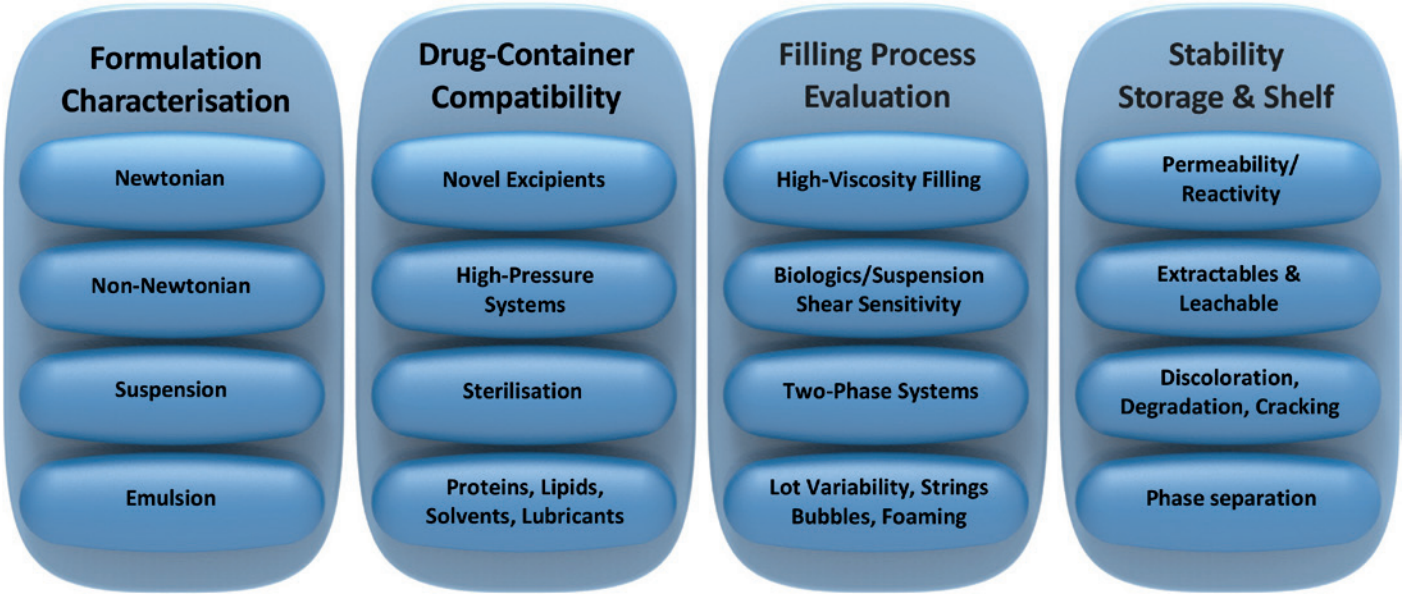

Figure 6: New drug formulation considerations.

Not only do the suites have innovative cleanroom control systems, enabling real-time monitoring and energy-efficient heating, ventilation and air conditioning systems, but they are also controlled separately so the suites can be operated independently.

NEW LANDSCAPE FOR CLINICAL TRIALS AND REGULATORY PATHWAY

Continuing trends from hospital to home treatment have changed the clinical trials landscape. This is driving the industry to focus more on the self-administration of therapies and the need for devices in clinical studies earlier in the cycle. The cost of therapy is also lower when delivered at home rather than in a hospital setting, which puts additional importance on speed to market. New regulatory pathways allow faster avenues for breakthrough therapies and emergency use. This means less time to commercially scale and a shorter development cycle.

In summary, as a single-source supply partner with small-batch manufacturing capabilities, SMC can substantially improve speed to market and de-risk programmes. A state-of-the-art facility with innovative equipment and systems provides the specialised systems needed for novel therapies. In addition to a GMP facility, a process development and analytical lab provides an adaptive manufacturing model and increases speed to clinic.

ABOUT THE COMPANY

The SMC Group comprises SMC, Oval Medical Technologies and Cambridge Pharma. The group provides end-to-end integrated services for clinical and commercial manufacturing of combination products for drug delivery.

SMC, with more than 35 years of experience, provides product services from initial concept through to the final packaged device, including programme management, design and development, product manufacturing, clinical/commercial manufacturing, electronics integration and global supply chain management. SMC has global GMP manufacturing sites in the US, the UK, Costa Rica and India.

Oval Medical Technologies specialises in the development of patient-centric autoinjectors that meet the most challenging requirements arising from diverse patient groups and novel drug formulations. Oval's technology platforms can be customised to deliver a wide range of drug formulations, including fragile molecules and biologics for both subcutaneous and intramuscular injection with high viscosities and large volumes. Oval's patented primary drug container technology provides the design freedom to create truly optimised devices for patient benefits.

Cambridge Pharma specialises in pharmaceutical services, sterile fill-finish batches for a range of presentations, including its own primary containers, as well as syringes, cartridges and vials with the highest standard of quality to ensure sterility assurance. It can work with a wide variety of formulations including small molecules, proteins, peptides and biologics. Its flexible, broad service offers clients development of the fill-finish process including CCI method development and testing, analytical methods for QC release and stability testing. The company provides fast and flexible services to meet clinical and commercial critical deadlines.

ABOUT THE AUTHOR

Asmita Khanolkar has a master's degree in Materials Science & Engineering from Worcester Polytechnic Institute in Worcester (MA, US). With more than 25 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, drug-device and device-biologic combination products for drug delivery, biotech, biotherapeutics 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 lifecycle management.

ONdrugDELIVERY

2023/24 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
March 2023	Ophthalmic Drug Delivery	Feb 23, 2023
Mar/Apr	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Mar 2, 2023
April	Pulmonary & Nasal Drug Delivery	Mar 9, 2023
Apr/May	Drug Delivery & Environmental Sustainability	Mar 16, 2023
May	Delivering Injectables: Devices & Formulations	Apr 6, 2023
May/Jun	Oral Drug Delivery	Apr 20, 2023
June	Connecting Drug Delivery	May 4, 2023
Jun/Jul	Industrialising Drug Delivery	May 18, 2023
September	Wearable Injectors	Aug 3, 2023
October	Prefilled Syringes & Injection Devices	Sept 7, 2023
Oct/Nov	Drug Delivery & Environmental Sustainability	Sept 21, 2023
November	Pulmonary & Nasal Drug Delivery	Oct 2, 2023
December	Connecting Drug Delivery	Nov 7, 2023
Dec/Jan 2024	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Nov 21, 2023
February	Prefilled Syringes & Injection Devices	Dec 28, 2023

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TRAININGS: 19-20 OCTOBER 2023
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REDUCE PHARMA DEVELOPMENT TIME THROUGH LARGE-VOLUME SUBCUTANEOUS DELIVERY WITH THE ENFUSE®

Here, Mehul Desai, PharmD, Vice-President of Medical Affairs at Enable Injections, discusses how the company's enFuse® delivery system provides a flexible alternative for subcutaneous administration of high-volume therapeutics.

Subcutaneous (SC) drug development presents several challenges, and these challenges are amplified when trying to achieve a low-volume formulation. Intravenous (IV) administration has a bioavailability of 100%, but the bioavailability for SC monoclonal antibody drugs is 60%–80%.[1] This means the dose is typically higher for SC delivery than for IV delivery to achieve therapeutic efficacy.

Unfortunately, there is a common and inaccurate belief that SC drug delivery should not exceed a volume of 3 mL per dose.[2] Several well-known drugs are available subcutaneously at volumes >3 mL, including, but not limited to, trastuzumab,[3] rituximab,[4] daratumumab[5] and pertuzumab/trastuzumab.[6] Despite these therapies being co-formulated with a permeation enhancer (hyaluronidase), they are still administered at quite large volumes, ranging from 5–15 mL and delivered over several minutes.[3–6] With current innovations, it is unnecessary for manufacturers to continue attempting to overcome physiochemical challenges to achieve a small volume (<3 mL) for SC delivery. Formulation challenges can be expensive and time consuming, delaying convenient life-saving treatments for patients.

> "With current innovations, it is unnecessary for manufacturers to continue attempting to overcome physiochemical challenges to achieve a small volume (<3 mL) for SC delivery."

The process for storing a drug for SC delivery is multifaceted and involves several steps. The container that the drug is stored in can vary and requires substantial testing, but most often, biologic drugs are manufactured and stored in glass vials. From beginning to end, this testing is expensive and can take several months; therefore, the chosen SC delivery method can impact time to market, development costs and even commercial uptake. The value of reaching the market faster with a flexible drug delivery format is an obvious benefit and even more pronounced when considering the evolving competitive landscape and limited patent life of a molecule.

While the drug is the foundation of treatment, the delivery method of the drug is critical for patient preference, as some methods of SC delivery allow for self-administration at home. Various methods exist for delivering drugs subcutaneously,

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> "Larger volumes are administered by infusion pumps or OBDS, like the enFuse®, and allow flexibility for administration at home or in the clinic."

and they commonly include prefilled syringes, autoinjectors, infusion pumps and, more recently, on-body delivery systems (OBDS). However, larger volumes are administered by infusion pumps or OBDS, like the enFuse®, and allow flexibility for administration at home or in the clinic.

These methods vary in complexity of development due to certain requirements with container and formulation stability. This article focuses on the impact of formulation changes and container closure systems on development time, as well as touching on patient preference.

ORIGINAL CONTAINER CLOSURE CHALLENGES WITH OBDS

Few OBDS possess the ability to use an original container closure. For OBDS that require a change in container closure to deliver the drug, drug compatibility and stability must be tested with the primary packaging material, which is often a vial or a prefilled cartridge. If the drug manufacturer chooses an OBDS that does not use the original container closure, then the drug will likely be stored in a prefilled cartridge, which qualifies as new primary packaging material. As a result, stability and compatibility testing must be performed for OBDS that store the drug within a cartridge.

Stability and compatibility testing can take several months to complete. Some tests that must be done include, but are not limited to, compendia assessment, critical quality attributes, biocompatibility testing, container closure integrity, extractables/leachables testing and particle analysis. These tests on the new primary packaging material with an OBDS that does not use the original container closure may lead to additional costs and development time, potentially prolonging the launch of the combination product.

FORMULATION CHALLENGES

High-concentration formulations are sought after by drug manufacturers for SC drug delivery. They are pursued because a higher concentration formulation can lead to a reduced total drug volume, which can potentially be administered via an autoinjector. Unfortunately, this is not always possible due to the complexity of biologic drug formulations. Several elements must be considered when concentrating biologic drugs, including but not limited to, stability, subvisible particles, viscosity, pH, osmolality and tonicity.

Ideally, a stable formulation with low viscosity and less protein aggregation is desirable; unfortunately, high-concentration formulations tend to have a high viscosity and risk of protein-protein interactions. The process of concentrating an IV dose to a small volume SC dose with proper stability and viscosity can take many months or years, depending on the molecule. Formulation choices impact many processes, including stability, manufacturability and administration.

With large-volume SC delivery, the development and formulation process could be less strenuous, depending on the situation. If a manufacturer must concentrate a high-volume IV dose to a 3 mL SC dose, the development and formulation process is likely to be more challenging and time consuming than concentrating the same dose down to 15 mL. This enables the possibility of a low-concentration, high-volume formulation, which is likely to have lower viscosity and protein-protein interactions.

IMPROVEMENTS IN LARGE-VOLUME SC DRUG DELIVERY DEVELOPMENT

Enable Injections' novel enFuse® drug delivery system delivers high-volume therapeutics through SC administration, offering a more flexible alternative to IV administration and SC options, such as an infusion pump.

The enFuse® is designed to be a discreet, lightweight and simple device that allows patients to self-administer their medication when and where it is needed. The enFuse® could alleviate the challenges pharma companies face when considering large SC delivery options by accommodating a range of drug viscosities and volumes while using the original container closure. The original container closure and the high-volume capacity could reduce development time for pharma when converting drugs from IV to SC or from SC with a pump to SC with an OBDS.

Original Container Closure

The enFuse® platform allows the manufacturer to use the original container closure, allowing the potential to leverage historical data and potentially reduce time to market. Because the enFuse® uses the original container closure and does not require switching configurations to a prefilled cartridge, manufacturers can maintain their procedures and processes with the same standard vial. Depending upon the situation, by choosing large-volume SC delivery with enFuse®, drug manufacturers may be able to forgo additional validation studies, stability testing and the associated costs and time needed by other wearable injectors requiring a configuration change (Figure 1).

Figure 1: The enFuse® is a novel, wearable drug delivery system that can deliver large volumes of large- and small-molecule therapeutics from 5–25 mL.

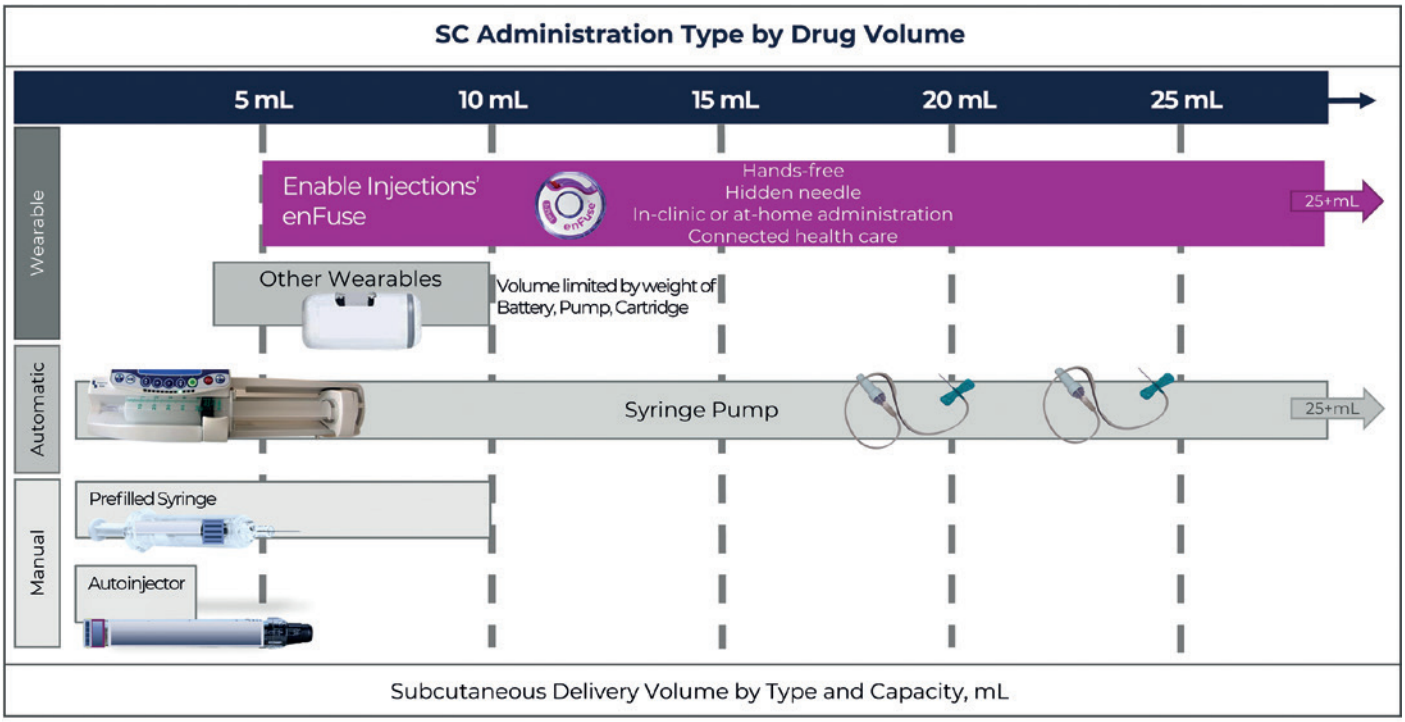

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Figure 2: Overview of SC drug delivery system technology by delivery volume capacity, by type of administration for manual systems and wearable systems.

Range of Volume and Patient Preference

The ability to handle volumes up to 25 mL at a range of viscosities in a single device can alleviate concerns around the formulation and stability. This is because concentrating a large IV drug volume down to 10 mL or less for SC administration can be a challenge even with a permeation enhancer. In addition, the volume can impact the number of devices needed to administer the required dose (Figure 2).

Most wearable injectors can only accommodate 3.5–10 mL, and for larger volumes, the technology becomes burdensome because two or more devices must be worn. The recent example with SC Ultomiris (ravulizumab) (Alexion Pharmaceuticals, MA, US) approved for paroxysmal nocturnal haemoglobinuria (PNH) is an example of this. Ultomiris was approved as a once-weekly treatment using West Pharmaceutical Services' (PA, US) SmartDose platform, specifically the SmartDose 3.5 mL OBDS. With its 3.5 mL capacity and the total weekly dose for patients >40 kg of 490 mg (7 mL), two SmartDose devices must be used per dose every week.[7]

In contrast, the enFuse® allows administration for a range of volumes, from 5–25 mL, with a single device. In the situation that a dose increase would be needed, for example, from 10–20 mL, the enFuse® would still only require a single device and no change would be necessary. Unfortunately, other wearable injectors would require multiple devices. Using a high-volume OBDS, such as the enFuse®, may allow a direct conversion from an IV to a SC formulation, eliminating the task of upconcentrating.

> "The enFuse® allows administration for a range of volumes, from 5–25 mL, with a single device."

When it comes to wearing multiple enFuse® devices or using an infusion pump, a recent study demonstrated patient preference for wearing multiple enFuse® devices rather than using an infusion pump at a mean administration volume >50 mL using SC immunoglobulin.[8] The main reasons that patients preferred the enFuse® included ease of use, more mobility during infusion, less time to set up the devices and less pain at the injection site.[8] The number of devices used per weekly dose ranged from two to five devices, with one patient administering almost 100 mL subcutaneously; additionally, a maximum of four devices could be used simultaneously (Figure 3).[8]

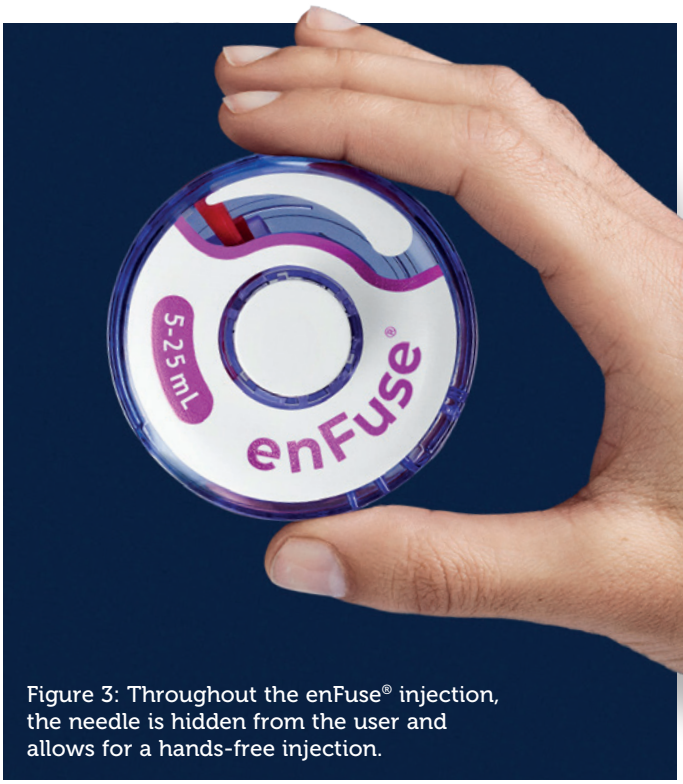

Figure 3: Throughout the enFuse® injection, the needle is hidden from the user and allows for a hands-free injection.

CONCLUSION: REDUCE PHARMA DEVELOPMENT TIME WITH THE ENFUSE®

Innovative large-volume SC delivery methods, such as the enFuse®, can accommodate various scenarios when it comes to drug development and commercialisation, for example, converting directly from IV to SC without major formulation changes. The ability to administer 5–25 mL in a single device at home or in the clinic with an original container closure has the potential to provide manufacturers with development time savings, patient preference and a faster time to market over other OBDS.

ABOUT THE COMPANY

Enable Injections is a global healthcare innovation company developing and manufacturing drug delivery systems designed to improve the patient experience. Enable's body-worn enFuse® delivers high-volume pharmaceutical and biologic therapeutics via SC administration, with the aim of improving convenience, supporting superior outcomes and advancing healthcare system economics.

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ABOUT THE AUTHOR

Mehul Desai, PharmD, MBA, serves as Vice-President of Medical Affairs at Enable Injections. His experience includes development and execution of tactical plans, driving strategic direction through KOL insights, supporting clinical trial execution and contributing to business development activities across various therapeutic areas. His background includes being the Associate Medical Director for the haematology franchise at argenx. Prior to this, his experience included field medical assignments in rare disease for hematology at argenx, haematology/nephrology at Alexion, and nephrology/neurology at Mallinckrodt Pharmaceuticals. Mehul Desai holds a bachelor's degree in Biochemistry and Business Foundations from Indiana University (Bloomington, IN, US); a PharmD from Purdue University (West Lafayette, IN, US); and an MBA in Pharmaceutical and Healthcare Business from the University of the Sciences (Philadelphia, PA, US). He also completed a post-doctoral fellowship in Medical Affairs at Johnson & Johnson.

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LOW-COMPLEXITY, EASY-TO-USE WEARABLE INJECTION PLATFORM

In this article, Jesper Roested, Chief Executive Officer of Subcuject, discusses the increasing prevalence of biologics formulated for large-volume injections in drug development and how wearable devices, including Subcuject's own offering, may be a better solution for delivering these drugs than scaled-up conventional autoinjectors.

PUSHING AUTOINJECTORS ABOVE 1 ML

During recent years, drug development pipelines have come to include biologics for subcutaneous delivery in volumes above 1 mL. This development has been driven by factors including a push towards at-home use and increased convenience. Previously, the general consensus was that 1 mL could be delivered quickly, but anything above 1 mL would require a slow injection. As such, autoinjectors were limited to 1 mL until the first 2.25 mL autoinjector was launched in 2020.

Single-use, handheld autoinjectors have now become a successful method for administering biologics up to 2.25 mL, and a variety of autoinjectors are available from a large number of suppliers. A number of 5 mL handheld autoinjectors are now also in development, responding to market needs for increasing demand for higher volume delivery.

Delivering volumes larger than 2 mL in a conventional handheld autoinjector may require a permeation enhancer, as well as either very fast injection or for the injector to be held steady for an extended period of time. It has been claimed that patients can hold a handheld autoinjector in place for 60–70 seconds.[1,2] However, there may be a risk of premature removal, resulting in wet injections, if the hold time is increased. As such, scaling up the size of conventional handheld autoinjectors may not be the ideal solution for larger-volume injections.

> "Scaling up the size of conventional handheld autoinjectors may not be the ideal solution for larger volume injections."

The field of larger-volume wearable injectors was established in 2016 with the launch of Repatha (evolocumab, Amgen, CA, US) in the Pushtronex 3.5 mL wearable injector. Since then, other drugs formulated for wearable injectors have entered the drug development pipeline. It is expected that a number of new drugs, currently in clinical trials, will be approved as combination products in wearable injectors over the next few years.

Wearable injectors were developed to eliminate the need to hold an autoinjector steady when delivering larger-volume drugs

> "To address the challenges of conventional autoinjectors and electromechanical wearable injectors, Subcuject has developed a platform of wearable injection devices based on osmosis (salt and water) and a spring-driven injector."

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without permeation enhancers, enabling much slower injection. It is a technical challenge to generate a slow release of energy from traditional drug delivery device power sources, such as springs. As such, many of the wearable injectors currently in development are based on electromechanical solutions where energy release is electronically controlled, resulting in complex devices that also may be less acceptable for disposal after single use.

SUBCUJECT'S WEARABLE AUTOINJECTOR PLATFORM

To address the challenges of conventional autoinjectors and electromechanical wearable injectors, Subcuject has developed a platform of wearable injection devices based on osmosis (salt and water) and a spring-driven injector (Figure 1). The devices share the same user interface, are easy to use and are intended as prefilled single-use devices. Both are characterised by low technical complexity. Furthermore, both devices use standard primary packaging in the form of a glass cartridge with a standard septum and a conventional rubber compound for the plunger.

In its current configuration, the osmotic wearable injector holds up to 5 mL and could be adapted to hold 10 mL or more, with an injection rate of around 1 mL per minute. The benefit of an osmotic actuator is that energy is generated over time – no slowdown is needed. Furthermore, as the device platform does not include any electronics, it is better suited for disposal after single use than an electromechanical device.

In its current configuration, the spring-driven wearable injector holds 3 mL and can be adapted to hold more than 5 mL. When attached to the skin, longer holding time is not an issue. It is intended for medium flow rates below 5 mL/minute. The configuration with the needle inside of the housing and subsequent needle retraction means that the user will never see the needle in the intended use case.

The 5 mL osmotic wearable bolus injector (Figure 2) has the following features:

- Prefilled
- Single use
- Small size
- Makes no noise
- Uses a glass cartridge and standard primary packaging components

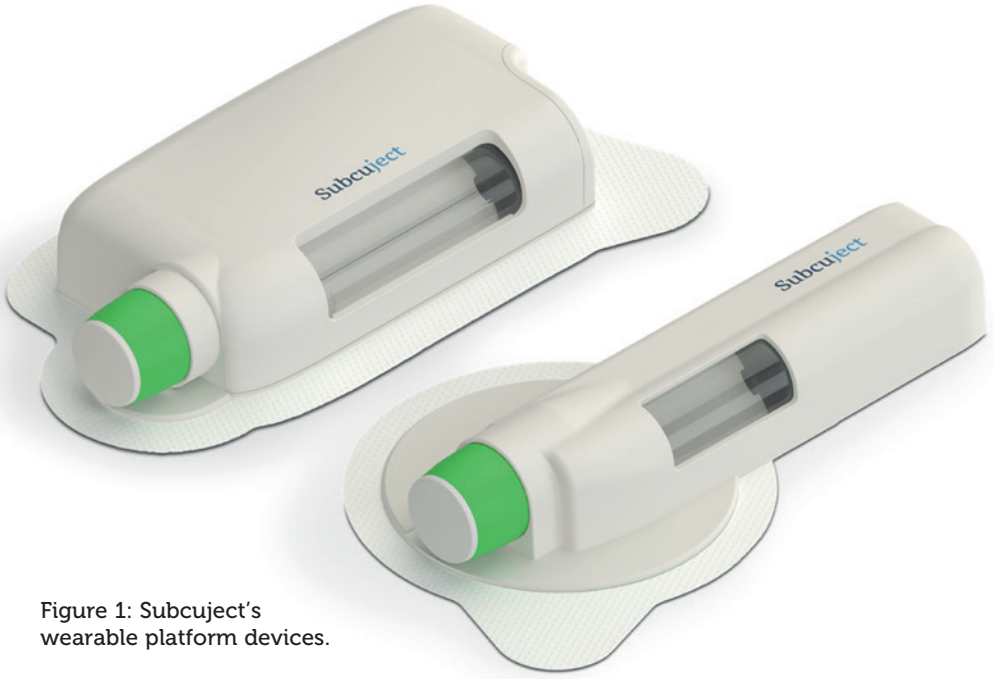

Figure 1: Subcuject's wearable platform devices.

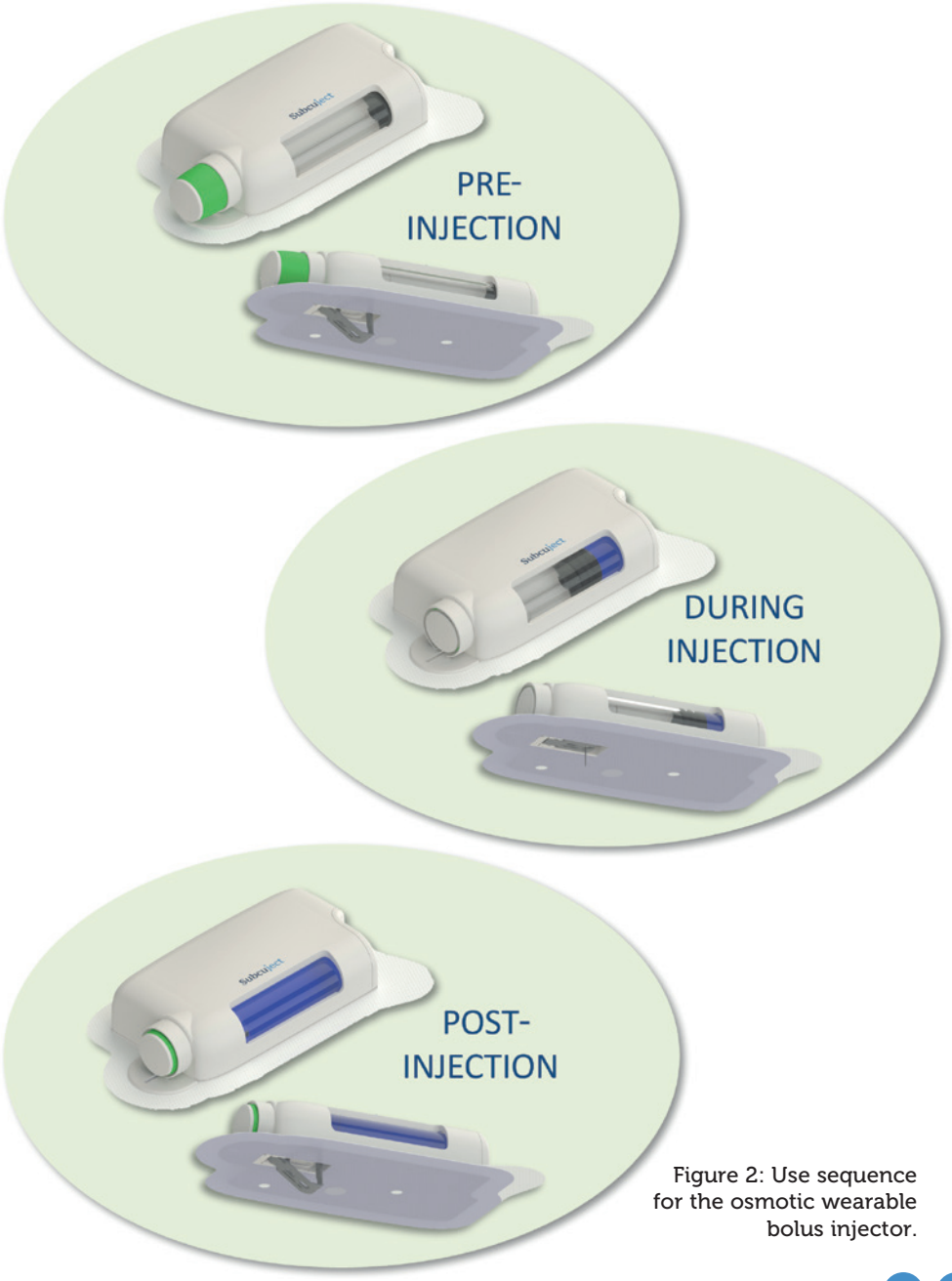

Figure 2: Use sequence for the osmotic wearable bolus injector.

- One button activation
- Visual, audible and tactile end-of-dose confirmation
- Automatic needle retraction
- No electronic components.

The 3 mL spring-driven wearable injector (Figure 3) has the following features:

- Prefilled
- Single use
- Small size
- Uses a glass cartridge and standard primary packaging components
- One button activation
- Visual, audible and tactile end-of-dose confirmation
- Automatic needle retraction
- No electronic components.

Subcuject has a partnership with LTS Lohmann (Rheinland-Pfalz, Germany) for the development and commercialisation of these wearable platform devices. LTS is a leading pharmaceutical technology company that develops and manufactures innovative drug delivery systems, such as transdermal datches, oral thin films and micro-array patches.

ABOUT THE COMPANY

Founded in 2017, Denmark-based Subcuject is a privately held technology development company focused on developing an innovative and proprietary device platform for wearable bolus injection, the Subcuject WBI. The founder of Subcuject, Claus Schmidt Moeller, is the inventor of multiple innovative injection devices, including a number of the injection pens from Novo Nordisk. The Subcuject board of directors includes substantial drug delivery industry expertise, including Paul Jansen (ex-Sanofi and Eli Lilly) and Lars Guldbaek Karlsen (ex-Novo Nordisk).

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"Subcuject has a partnership with LTS Lohmann Therapie-Systeme AG for the development and commercialisation of these wearable platform devices."

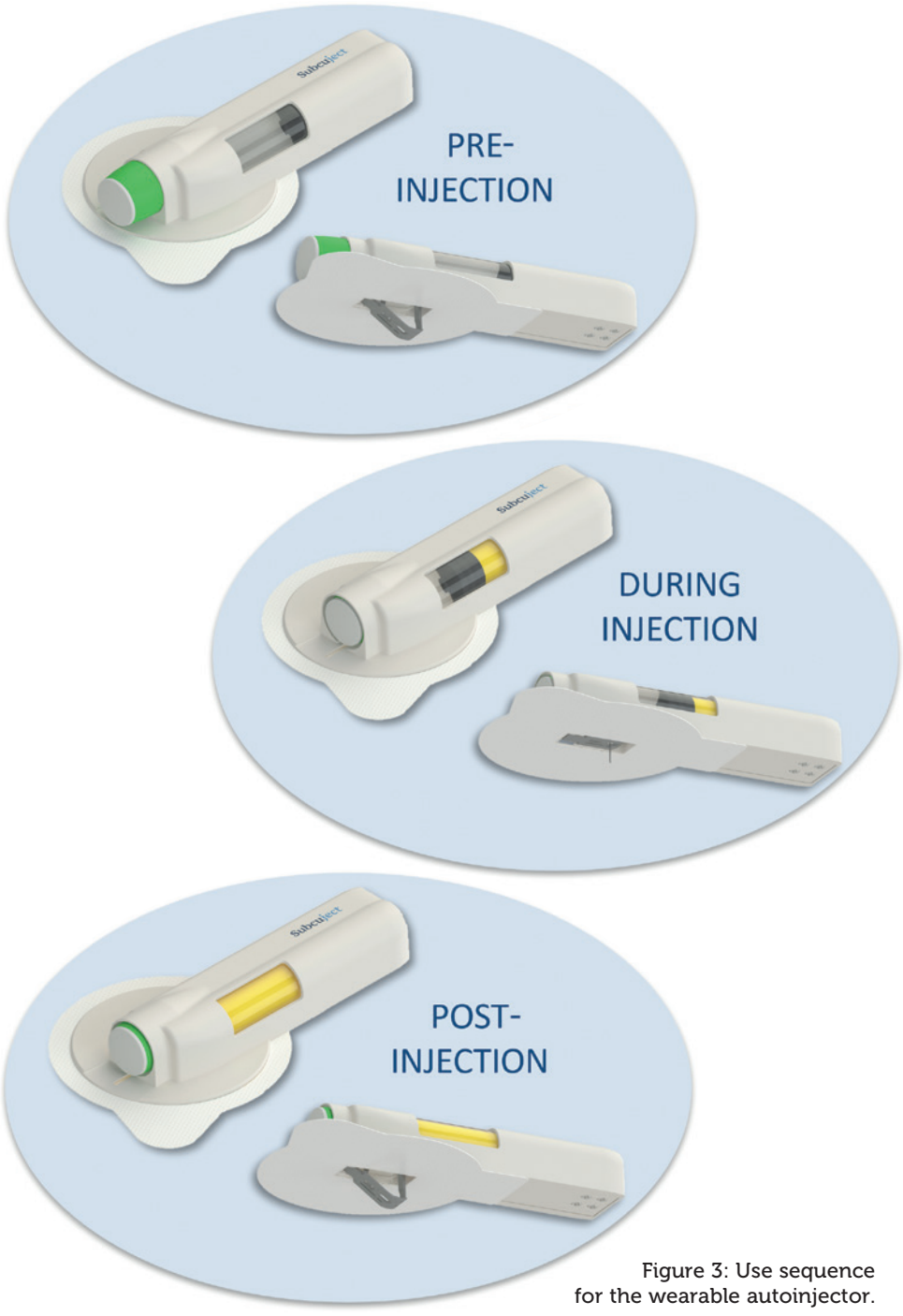

Figure 3: Use sequence for the wearable autoinjector.

ABOUT THE AUTHOR

Jesper Roested, Chief Executive Officer of Subcuject, holds an MSc in Medical Electronics and Physics and has 25 years of business experience. Mr Roested has primarily held business development and management roles in the life science industries, including several years as a partner in a venture capital fund, specialised in medtech. Furthermore, Mr Roested previously worked as a Management Consultant at McKinsey & Co.

ENABLING DRUG DEVELOPMENT THROUGH DRUG DELIVERY MANUFACTURING

In this article, Andrei Yosef, PhD, General Manager Pharmaceutical Solutions at Eitan Medical, looks at the role of manufacturing in the development of drug delivery devices and highlights the benefits of the company's Sorrel device, which enables pharma companies to experiment during clinical trials to ensure that drugs produced are safe and cost-effective.

The past few years have seen growing recognition of the need for patient-centric drug delivery devices that support effective administration of new biologic medications with large molecules. This has inspired significant investment in this area by global pharma players.

The covid-19 pandemic has also highlighted the urgency of moving the point of care from the hospital to the home. Particularly in the case of biologic-based treatments, the preference has clearly become self-administration from home.

As a result, pharmaceutical companies are increasingly turning to wearable drug delivery devices as the preferred method for bringing new medications to market. This has placed the burden of responsibility on device manufacturers to respond with robust and reliable devices that are also easy-to-use and able to support digital connectivity.

> "Pharmaceutical companies are increasingly turning to wearable drug delivery devices as the preferred method for bringing new medications to market."

Eitan Medical has been at the forefront of these changes. The Sorrel™ drug delivery platform is a solution for pharma partners that facilitates the transition to safe and reliable self-administration at home.

The key to developing the optimal solution has been to understand and address pharma partners' needs, which often centre around flexibility – both of the device itself and the manufacturing capabilities of the device developer.

EMBRACING FLEXIBILITY

With the advancement of pharmaceutical technologies and investments in research and development, pharmaceutical companies are developing more complex large-molecule biological drugs, increasing the molecular weight and the volume of medication to be infused.

Drugs currently under development require subcutaneous delivery at higher volumes – 10–25 mL and even higher. Due to the physical properties of biologics, including their higher viscosity, these medications cannot be concentrated into a smaller dose to fit the capacity limitations of delivery devices currently on the market.

Combination drug delivery devices, including prefilled syringes (PFSs), autoinjectors and pen injectors, are generally favoured by pharmaceutical companies due to their flexibility, ease-of-use and

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"The flexibility provided by the Sorrel device, coupled with its compatibility with any primary container, makes Eitan Medical an attractive partner for pharmaceutical companies."

reduced risk of patient error and injury. However, most of the devices currently available on the market are designed for small-volume drugs and can only deliver between 1 and 2 mL at a time – far below the required volume for newer large-molecule biological drugs.

Eitan Medical's Sorrel platform solution (Figure 1) is compatible with both vials and cartridges in a wide variety of volumes, ranging from 3 mL up to 50 mL. This allows pharmaceutical companies to develop drugs for self-administration in higher volumes. The flexibility in volume size that the Sorrel device offers is crucial for allowing pharma companies to experiment with drug volume, molecule size and viscosity during clinical trials, ensuring the drugs produced are as safe, clinically sound and cost-effective as possible.

Figure 1: Eitan Medical's Sorrel wearable drug delivery platform.

The flexibility provided by the Sorrel device, coupled with its compatibility with any primary container, makes Eitan Medical an attractive partner for pharmaceutical companies. While cartridges and PFSs are predominantly used for smaller-volume infusions (up to 2 mL), drug developers tend to prefer using vials as the primary container when it comes to larger volumes.

The ability of the Sorrel device to easily change between vials and cartridges has become a key asset for pharmaceutical companies, allowing them to directly integrate the device into their packaging line and reduce disruptions during the development and production processes. The devices currently on the market require pharma companies to change the primary packaging; when using Sorrel, no change is needed, saving time and money and reducing risk for pharma companies.

HEADING HOME

The recent experience of the covid-19 pandemic has resulted in a paradigm shift in terms of the way we think about care delivery, putting patient experiences and expectations at the forefront. At the height of the pandemic, the fear of contracting the virus led many to avoid hospitals and medical centres altogether. At the same time, hospitals became overloaded while caring for critically ill patients. This made home-based care a strong preference and, in many cases, a necessity.

Pharmaceutical industry recognition of at-home care trends and the recent awareness and acceptance from other parts of the healthcare ecosystem should add up to a compelling case for on-body wearable injectors. However, pharma companies still face barriers when bringing home-based solutions to market. To develop drugs that can be delivered at home, pharmaceutical companies need devices that offer high quality, ease of use and leverage connectivity. Medical device manufacturers need to recognise these needs and help support drug development by pharmaceutical companies.

"Connected devices ensure the safe and secure administration of medication, proofing of errors and troubleshooting of problems."

Sorrel is an intuitive, independently operated device that reduces the need for patients to regularly visit infusion clinics, enabling them to minimise disruption to their lives while still receiving the treatments they need. Patients can simply attach a band-aid-like wearable drug delivery device to their body, turn it on and go about their day while receiving their treatment. Sorrel is single-use and fully disposable, creating an easy end-to-end experience for the patient.

REDUCING RISK

Medical device companies are also embracing connectivity opportunities in the Medical Internet of Things (MIoT) industry. Connected devices ensure the safe and secure administration of medication, proofing of errors and troubleshooting of problems. When patients are away from the direct care of a physician or nurse, connectivity expands this presence and ensures continuing quality of care.

Additional benefits of Sorrel are its prefilled and preloaded cartridge and vial configuration options. The Sorrel device is purposefully designed so that pharma companies can supply a fully prepared device requiring minimal steps by the patient to initiate administration. This minimises risk of patient errors and ensures high-quality care throughout usage of the device.

However, as with any patient-facing device, scalability to meet demand is crucial for success. As the popularity of new drugs grows and they eventually become available on the market, pharma companies will require a device partner that can match demand with supply. Setting up in-house manufacturing capabilities is the best way to achieve this.

SCALING UP

When planning a manufacturing facility, high quality and high capacity cannot be an afterthought. These factors must be prioritised and initialised on day one of the development and planning.

The focus on high quality and high capacity must also be an essential part of the final design of the device. Drug delivery device manufacturers need to have the end-user in mind at every stage of development to ensure that the device offers the highest quality treatment to patients and the greatest value to pharma.

Automation should be a precursive requirement to the device manufacturing infrastructure. Even if device manufacture is not initially automated, it is a vital factor in achieving scalability and ensuring that, as demand for a drug grows, the production of the administering device can match it. The thoughts and requirements on how to scale up manufacturing and fully test the disposable device should start from day one and be a part of the device requirements.

Eitan Medical has incorporated these concepts into its thinking when designing the manufacturing facilities at its headquarters (Figure 2). Sorrel is a simply designed, yet highly sophisticated device that does not compromise on quality. With in-house manufacturing capabilities, Eitan Medical maintains complete oversight of its independent manufacturing lines and cleanrooms. The recent addition of semi-automated lines is configured to scale as Eitan Medical expands globally and receives increased demand from its pharma partners.

The company has ensured that its research and development, engineering and mass production teams have all been key participants in the discussion and development process from initial conception through to final production. The teams provide essential inputs, requirements and design features, and are all looking to the future of full automation.

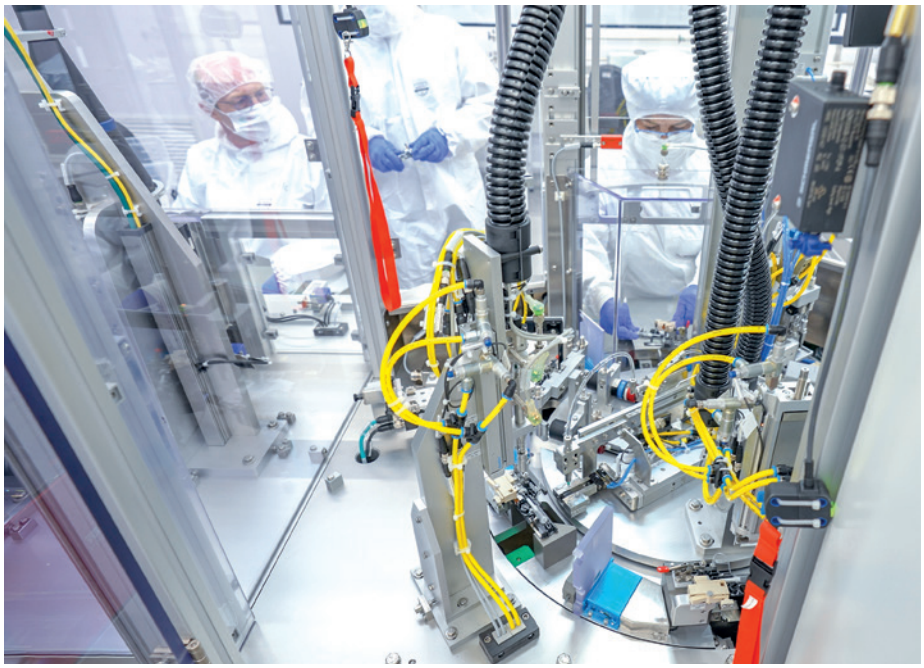

Figure 2: Eitan Medical's on-site manufacturing facilities.

Having all teams close to the manufacturing facility allows for rapid implementation of new features and innovations directly into manufacturing lines with minimal delays. This grants more control over the processes, facilitating quality assurance – a critical issue for pharma companies.

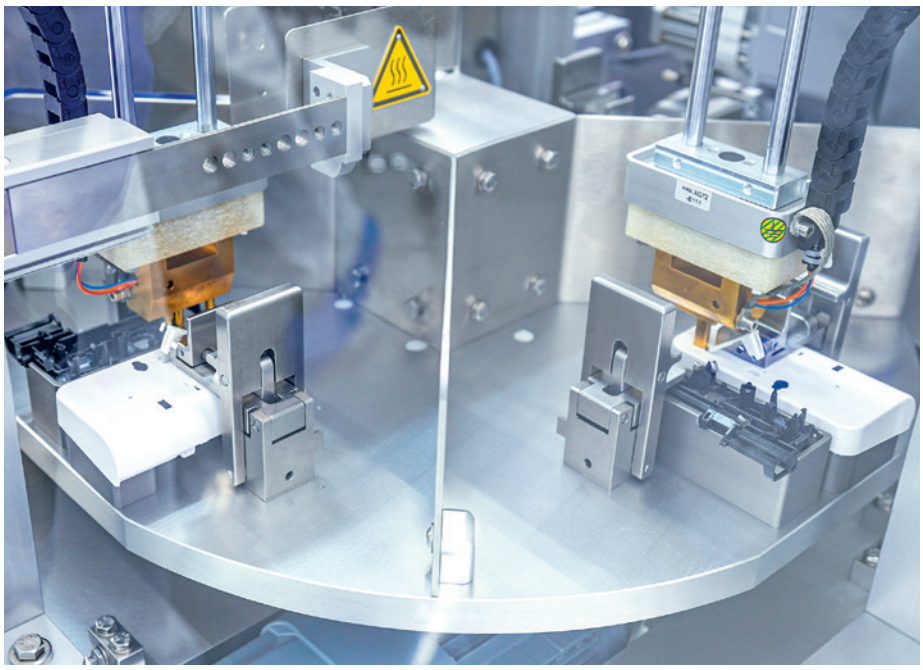

Figure 3: Eitan Medical's separate testing stations.

SHAPING MANUFACTURING TO MEET PHARMA DEMAND

Developing in-house manufacturing capabilities has also allowed Eitan Medical to dedicate manufacturing lines for specific pharma partners, allowing for flexibility to cater to each pharma partner's needs. If requested, Eitan Medical can integrate customised tools and fixtures into production to suit the needs of specific drug manufacturers or end-users. Having multiple cleanrooms has also enabled the fulfilment of multiple customer orders simultaneously, ensuring that the company can collaborate with several pharma companies at any one time.

Uniquely, each single-use device is fully tested for function without affecting the device performance with the end user. Testing for reliability without affecting the product required unique tooling and processes, which was deemed critical to ensure quality and reliability.

The assembly lines in the manufacturing facility contain separate testing stations (Figure 3), which are fully automated and operate seamlessly. These testing stations provide clear data on device performance, including key performance indicators and certified key performance indicators, which would not otherwise be obtainable for testing a single-use device.

Finally, by integrating semi- and fully automated functions (Figure 4) into the manufacturing lines, Eitan Medical has been able to limit the risks of human

error during production – an especially important issue for medical devices that must perform for every patient and for every treatment.

Demand is growing from pharmaceutical companies for a solution that is patient-centric, innovative and suited to the latest drug development trends. As this demand grows, the ability to scale up production and tailor Sorrel to pharma partners' needs will become increasingly valuable and ensure that Eitan Medical can act as a trusted partner with the highest quality devices and development services.

ABOUT THE COMPANY

Eitan Medical is re-imagining drug delivery, with reliable innovations that put patients at the centre of care. Patient safety and care are only the starting point, as Eitan Medical goes beyond, delivering connected, intuitive drug delivery and infusion solutions that are designed to improve patient and clinician quality of life across the continuum of care, including hospital, ambulatory and homecare environments.

Figure 4: Eitan Medical's semi-automatic manufacturing lines.

For over a decade, Eitan Medical has provided safe, intuitive and flexible solutions that meet evolving drug delivery needs. Eitan Medical's product lines include the Sapphire™ infusion platform, which provides connected infusion therapy systems in hospital and ambulatory settings; the Sorrel™ wearable drug delivery platform, a patient-centric on-body injector for delivery of biologic treatments; and Avoset™ infusion pump, connected infusion systems for the homecare market.

ABOUT THE AUTHOR

Andrei Yosef, PhD, is General Manager of Pharmaceutical Solutions at Eitan Medical. He is a recognised expert in drug delivery device technology and high-end development processes, having served in several executive positions at the company and as Chief Executive Officer and Founder of C-Wide. Dr Yosef holds a PhD in Biomedical Engineering and an MA in Mechanical Engineering, both from the Technion – Israel Institute of Technology.

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to bring to market tailored, smart drug delivery and infusion solutions across the continuum of care - from the hospital to the home.

"We believe in developing tailored solutions to meet the needs of our pharmaceutical partners, with a platform of software-controlled and highly versatile smart infusion pumps and wearable injectors"

Dr. Andrei Yosef, General Manager, Pharmaceutical Solutions at Eitan Medical

Contact our business development team to explore partnership opportunities:
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INTERVIEW

In this exclusive interview, Mathias Romacker, Fran DeGrazio and Paul Jansen, all Kymanox Executive Advisors, sit down with ONdrugDelivery's Publisher, Guy Furness, to discuss what has driven Kymanox's rapid rise in the drug delivery space and what makes the consulting company's model so successful, as well as to share their expertise on a variety of topics in an illuminating discussion, including connectivity, how large and small drug developers engage with consultancies, 5 mL autoinjectors and the interface between drug primary packaging and delivery devices.

MATHIAS ROMACKER

Mathias Romacker is a Kymanox Executive Advisor with more than 30 years of experience in the field of injectable drug delivery devices. He brings a deep understanding of prefilled syringes, handheld injection devices and on-body wearable devices, having been involved in multiple successful combination product launches. Mr Romacker was a co-chair for the PDA Universe of Pre-filled Syringes and Injection Devices in 2013, 2017, 2019 and 2022, and received the PDA Edward Smith Packaging Science Award in 2018 for his contributions over the years.

FRAN DEGRAZIO

Fran DeGrazio is a Kymanox Executive Advisor with over 35 years of experience in the life sciences industry. She has extensive expertise in sterile drug product systems, including vial container closure systems and prefillable syringes for combination products. Ms DeGrazio has published numerous technical articles and book chapters, and was a recipient of the PDA Packaging Science Award in 2021, the Philadelphia Business Journal 2018 Healthcare Innovators of the Greater Philadelphia Region Award and the Healthcare Businesswoman's Association Luminary Award for West Pharmaceutical Services in 2017.

PAUL JANSEN

Paul Jansen is a Kymanox Executive Advisor with over 35 years of experience as a professional engineer in drug device development. He has extensive experience in the design, development, manufacturing and lifecycle management of medical devices and has successfully led teams that have launched several award-winning devices, including Sanofi's Lantus SoloStar, the world's most popular insulin pen injector. Mr Jansen is a longstanding member of the International Organization for Standardization (ISO), serving as Working Group Convenor and Expert on many working groups responsible for standards related to injection devices.

Q Can you please tell our readers what first attracted you to Kymanox – your route to joining as a KEA and what you bring forward from your previous roles and experiences?

MR I spent the first half of my career on the supplier side with BD and Gerresheimer, and the second half with pharma, working for Amgen and Pfizer. After I left Pfizer, I did a little bit of freelancing, after which I joined Kymanox in 2022.

I've been in touch with Kymanox for a long time now and, as someone whose career 'grew up' alongside combination products, I couldn't help but be intrigued by Kymanox's success. Before I joined, I also heard about them from their clients, who consistently told me how their co-operation with Kymanox was really beneficial. As one of my colleagues put it, Kymanox is almost like a pharma company without a product – it's a fully end-to-end service provider. I find it a very interesting model, so I was keen to be a part of it, both to see the business grow and, obviously, to provide my expertise.

I can provide assistance and insights on a variety of topics relevant to my experience. My expertise is mostly focused on the front-end, particularly around combination products – I can look at a device and drug portfolios and see how to really maximise the impact of actually bringing them together as a combination product.

FDG Initially, Kymanox was just a company that I had seen start to grow and flourish in the

"You get real solutions and real experts – highly talented, highly competent individuals across a wide range of areas that can really dig down into problems and come up with solutions."

combination product space over the last few years. However, after I retired in 2022, they reached out to me and asked if there was potential for me to bring my experience and expertise to their customers, to see if we could reach a balance that would satisfy both my needs and theirs. That's essentially what I see the KEA as – a group of highly seasoned experts with a wealth of knowledge and experience with a lot still to offer the industry. I enjoy taking opportunities to share my knowledge, so was pleased to accept Kymanox's offer.

As for what I specifically bring to the table, I was at West Pharmaceutical Services for close to 39 years in a myriad of technical and R&D roles, as well as working in the quality and regulatory departments. I've had a hand in a lot of different areas, which means that I've developed a significant understanding of the market and pharma customers and their needs. Sharing that knowledge with Kymanox as a KEA is a great fit for me.

PJ My current relationship with Kymanox started with a request during the early days of the covid-19 pandemic. They reached out to me looking for specific information to help one of their clients. This was a really good way to get to know Kymanox better; I had interacted with them previously, but there's nothing better than actually working together – I realised then that they were in a unique space.

If you wanted to, you could make a long list of competitors but, as Mathias said, the fully end-to-end nature of the business, combined with with really high-quality talent, isn't something easy to find anywhere else. There are a lot of agencies out there that claim to be able to do everything Kymanox does but, truthfully, in my experience from when I worked at Sanofi and Lilly, such organisations often come in and they ask you, as the client, what's wrong? They ask you, what you would do to fix it? Then they package up your answers, and that's what you pay for.

That's not the case with Kymanox. Here you get real solutions and real experts – highly talented, highly competent individuals across a wide range of areas that can really dig down into problems and come up with solutions. That's what makes Kymanox unique to me.

Regarding my background, I retired from Sanofi in 2017, which meant that I'd had a few years of retirement before covid-19 hit. What I was looking for were unique experiences; both opportunities where I could grow and where I could help other people learn and benefit from what I've picked up over the years. That's what Kymanox offered me.

I've had a long tenure; I've been very fortunate in that I've been able to work with two large pharma companies and, at the same time, I've interacted with a lot of people through my work at the ISO. Many of the standards that come out of Technical Committee 84 are those relating to drug-device combination products, from autoinjectors to pens to on-body wearable injectors. I've been able to meet not only the people in the companies I've worked with and their suppliers, but with a wide variety of people from across the industry. This experience has given me a somewhat unique perspective that allows me to add real value and help solve problems.

Q **Kymanox has seen rapid growth over the past few years. Why does its unique model work so well, and what advantages does Kymanox offer that pharma companies couldn't get if they kept everything in-house? Are factors in the current state of the market also driving this growth?**

PJ There are a lot of factors but, to really get to the heart of the matter, I think the key factor at play is that, in reality, when an employee at a big pharma company, for example, tells their leadership the certain way a thing should be done, they often just aren't listened to. Instead, the leadership decides to hire a consulting company but, as I said before, those companies are often just repackaging the ideas and concepts that weren't being listened to in the first place.

What you're missing with some traditional consulting companies is any real innovation, any new ideas. They might offer a new set of eyes, but if they are only repackaging ideas that are already there – the only difference is that they're coming from someone who the CEO listens to better, for whatever reason. It's a bizarre syndrome, but I've seen it play out over and over again, and I'm sure that Fran and Mathias have too. It's just how the big corporate world works.

So it all comes back to what I said before; Kymanox can listen to what the customer's problems are and then turn to their own group of talented people who aren't afraid to give their own ideas and perspectives, building and expanding on what employees are saying rather than just repackaging it. That's what makes the model unique.

KYMANOX EXECUTIVE ADVISORS

A key part of Kymanox's model is the employment of the Kymanox Executive Advisors (KEAs) – a group of prestigious, seasoned and well-respected industry professionals with a wealth of diverse experience from across the pharmaceutical industry. Together, the KEAs have over a century of experience in building businesses, enhancing capabilities and bringing products from inception through commercialisation in the pharmaceutical, biotechnology, and medical device industries. With their collective knowledge and expertise, the KEAs are able to provide guidance and strategic thinking, foster valuable relationships and identify additional resources to help your project be successful, particularly in the areas of combination products, connected devices and pharmaceutical manufacturing.

Kymanox currently has five KEAs. In addition to Fran DeGrazio, Mathias Romacker and Paul Jansen, interviewed here, Kymanox Founder and Chief Executive Officer Stephen Perry, and the company's Chief Innovation officer, Evan Edwards, are both also KEAs.

The other part of it is demonstrated by the three of us that you're talking to right now – we all have a unique set of experiences, and we have a lot of them, and that provides credibility, which is what the customer really wants. Kymanox has been so successful because they can say, "We've got people who have done this before and who know how this is done."

FDG I concur one hundred percent with what Paul just said. I think there's a unique benefit to the Kymanox model.

To answer the part of the question about market factors, it's the growth of combination products, which is clearly the direction that the industry is going. This is driven by the need for more at-home administration, more self-administration. With biologics in particular, there are additional challenges in delivering those types of products.

Kymanox has a wealth of experience in these areas, as well as talented people they can leverage or reach out to. So, if there's a certain type of specialised talent that's needed, which there often is, we as KEAs, as well as Kymanox staff more broadly, may know certain people with that specific expertise. They know who to reach out to, who they can then bring in and gain access to that certain specialised talent as needed.

MR Firstly, I'd like to say that what Paul was saying about the big pharma experience made me smile because it sounded all too familiar. I think Paul and Fran have answered the question very well, but maybe one aspect we haven't discussed yet is that, when you look at smaller biotech organisations, they usually have a really good, innovative molecule but, at best, they have maybe one or two people who have any real knowledge when it comes to combination products. That means that there's a huge void in their understanding regarding topics like quality management systems, design history files, design controls – all the detail that you have to get right to successfully bring a product to market.

I understand that, for many of them, the business model is essentially to get the molecule ready and then get bought-up by one of the big pharma companies who will then go on to commercialise it. Yet, with current trends, I think it's a mistake to neglect the device side of the puzzle. Smaller biotech companies can really benefit from bringing in the expertise to develop their molecule as a combination product.

> "Kymanox's clients, both current and future, know that they need to get the strategy right and to understand what's actually going on out in the market, including from a regulatory and a technical standpoint. That's what the KEAs can bring to the party."

Kymanox can really offer a lot of value here because, to be serious about developing a combination product, a company must bring in a lot of expertise – which traditionally meant a lot of new employees. However, these companies often want to stay lean and mean, and bringing all that expertise in-house would be a huge expense.

Furthermore, when you're talking about combination product development, you don't need all of that expertise all the way through the process – there are going to be peaks and valleys where such people spend some time incredibly busy but at other times they'll have very little to do. Based on conversations I've had over the years, my feeling is that there's a genuine need within that class of company to outsource this type of expertise, which is where Kymanox comes in.

PJ Another aspect with small companies is that they don't know what they don't know, and Kymanox can add a lot of value there. There is a real benefit for companies from engaging with the combination product conversation sooner rather than later – many of them still come to the conversation far too late. One of the benefits of working with some of the smaller companies is that you tend – not always, but often – to be able to get involved a little bit earlier.

As Mathias said, smaller companies aren't in a position to hire all the necessary people – they're running with limited cash and they need to be able to move quickly if something goes wrong in their clinical trials; they don't want to have to lay off a whole bunch of people. Kymanox knows how to work from end-to-end, so we can be brought in when needed, for any part of the development programme, or even the whole thing.

Q **What value and insights can you deliver to Kymanox clients, both existing and prospective, as a KEA?**

FDG Part of our role is to understand and think more strategically – Kymanox's clients, both current and future, know that they need to get the strategy right and to understand what's actually going on out in the market, including from a regulatory and a technical standpoint. That's what the KEAs can bring to the party. Certainly, my specific expertise includes strategy, planning and execution in a lot of different areas, including quality and regulatory coupled with technical aspects. So, I can bring some unique experiences to bear.

One of the things that I'm most proud of, personally, is that I've always tried to look at everything from the pharmaceutical side – even looking from the outside in, you need to understand what challenges the pharmaceutical client needs to meet and how to get their product to the end patient. From that perspective, I think that there's a unique combination of experience, knowledge and outlook that I can bring to the table.

When I started at West, it was a much smaller organisation. Being a part of growing the company and able to influence the industry has been a great learning experience for sure. And now it's something that I can bring to others as a KEA.

MR A key to success when developing a combination product is understanding that you need to answer important questions early. For example, if you pick your concentration and your injectable volume, it could be the difference between a handheld injector or a wearable injector. However, doing so has proven to be difficult for the industry, as the internal structure at pharma companies is often complicated. So, while I wouldn't say it's treated as an afterthought, making these decisions is definitely not seen as core activity within drug companies.

With that in mind, I think what we can do from the consultant side is to help these companies to better understand their drug portfolios and what device technology they may need. We don't live in an insulated world – there's so much innovation

"Kymanox has a very thorough understanding of the novel and emerging technologies, and I think it would be very beneficial for our pharma clients to make use of it, combined with a full picture of their drug portfolios."

happening right now and it should be of interest to anyone who really wants to understand their drug portfolio.

Let's take an example, maybe you have some blockbusters that are on the decline but still delivering good value. You need to ask yourself how you can make sure that, five to ten years down the road, you have the right device technologies in-house to maximise the value of those assets. Obviously, this can be a very difficult conversation. Sometimes there may be an easy business case for a single asset that's likely to be high value down the road, which means that there's a temptation to grab some innovative technology and focus on that single asset. However, it should be the needs of the whole portfolio that drive such decisions.

Kymanox has a very thorough understanding of the novel and emerging technologies, and I think it would be very beneficial for our pharma clients to make use of it, combined with a full picture of their drug portfolios. I remember from my pharma years that conversations between the drug development and commercial teams can be difficult. However, if you have a structured approach across the full portfolio, which, realistically, you probably need an outside partner to facilitate, it can yield results in the way you categorise and look at new technologies in the device area.

PJ I completely agree that strategic thinking is the critical element that we, as senior leaders and former senior executives of our organisations, can provide for any existing or prospective customers. If you total it up, we've got more than 100 years of experience between us, which is a lot of years in this business.

Reflecting on my early days in the industry, I had the good fortune of working in the diabetes sector. I was involved with the very first pen injectors way back in the in the mid-1990s. We were like a maverick band of engineers from Eli Lilly, Novo Nordisk and, in those days, Hooks – which is now Sanofi – that were putting these ideas together. Looking at how the industry has evolved in regard to injections since then, I feel both incredibly old, because I've been there since the beginning, and incredibly lucky, because I've been part of that evolution all the way through, including the establishment of the standard.

I remember when ISO 11608 was first – and finally – published, we all looked at each other from those three companies and, while we knew that we'd use it, we wondered if anyone else would. Today, it's the document that's been adopted by regulatory agencies around the world. I still get phone calls from people who, because I was part of writing it, want to ask me what this or that part really means. So, I think my perspective on the standards side of things is somewhere I can add true value.

Another thing to mention, aside from the understanding of the strategy and technical side of things you get from actually having been in the thick of development projects from the beginning to the end, I've learned a lot of lessons from hard experience. In fact, there's a lecture I give at Northeastern University as part of a bioengineering course there, which is entirely focused on what mistakes I made and what I learned from them – the things that didn't work out. You don't often learn a lot from the things that went well; you learn a lot more from the things that went badly, and so those are what I tend to reflect on. Importantly, I can share those lessons with other people so that they don't make the same mistakes.

The last thing to mention is that I had the good fortune of being able to develop and commercialise the SoloStar pen, which has been widely successful and for many years was, and probably still is, considered to be the gold standard for pen injectors. Along with that came my desire to get involved in managing patents and intellectual property, which led me to create and oversee a patent department at Sanofi that started with seven patent families and, 10 years later, had more than 1,300. We were a patenting machine! And that's an experience that I learned a lot from. Not just about patents themselves, but also about the litigation aspects and strategic elements of how to manage patent portfolios. In my experience, companies both big and small still don't fully appreciate the value such an understanding can bring them.

Q **Something that I find interesting about expertise is that you can instinctively know that something will or won't work with certainty before you necessarily have the words to explain why. In your roles as KEAs, is this something you experience often and how do you handle it when dealing with clients?**

PJ Our opinions aren't entirely black or white and I think that we're generally very good at justifying why we feel the way we do. We might know it first in our gut, but I think if we sit back and think about it, we've had enough of these things go wrong or go right that we know what's going to work and what's likely not to work.

I'll give you a real example. I often have people come to me with a new pen injector, on-body wearable injector or other kind of device who say, "We've got this new device and we want to go into diabetes". My advice to them is almost one hundred percent consistent: don't. Don't go after diabetes with a new device, there's far too much competition there so go somewhere else. And nearly every time I have to take them through the very laborious rationale, but they just don't want to hear it, because diabetes is such a huge market. I understand where they're coming from, but it's the wrong approach and I have to convince them to trust me.

MR One thing I want to point out is that, of course, you're not always right. For instance, 10 years ago I predicted that on-body wearable injectors would be a major thing by 2023. I expected a lot of product launches by now. But, while this class is clearly emerging,

"Being able to always put your instinct and the reason behind it into words so that someone else can understand it effectively is a skill, and I think we've all got that."

we only have a few out there, nowhere near as many as I predicted. The point being, you're not always going be right with your gut feeling.

FDG Although you have a gut instinct, there's always a reason why. Being able to always put your instinct and the reason behind it into words so that someone else can understand it effectively is a skill, and I think we've all got that.

PJ Another example is connectivity. I couldn't count the number of times that the three of us collectively have been asked, "Should we go with a connected solution, yes, or no?" My view is always yes, you should be making provision for connectivity. You may not want to put it into your device right away, but you do need to make sure you can accommodate it.

That said, before you do anything, you should figure out what you're going to do with all the data you plan to generate. We've got all kinds of people making connected devices and it's still a mystery to me how patients are really benefiting. We're increasing the cost of the device and we're generating a whole bunch of numbers, but what's the real added value? There are a few who really benefit but, for most of these solutions, most people don't just yet, primarily because the devices we're making are far too complicated. We're not making it easy enough for patients yet, there are too many steps added and there's too much going on.

That's my view on connectivity – it's emerging and it's going to be important, but as an industry we're not getting it right just yet. I think it's a sector where the three of us can give good insights and good advice, and somewhere Kymanox can add a lot of value. We have experts who know the software and the hardware, the ins-and-outs of whether you use Bluetooth or NFC or other types of solutions.

Q **As you mentioned before, a big part of the value the Kymanox model can offer is the variety of your experience. Therefore, I've got a question for each of you individually that focuses on your particular areas of expertise. Starting with you, Mathias, what is the right time for pharma companies to look at selecting a drug delivery technology during the lifecycle of a drug product? Additionally, how can drug delivery technology be adapted to maximise the value of such assets?**

MR For pipeline projects the answer is as early as possible in development – there's no such thing as "too soon". Drug developers are beginning to take this advice on board and consider delivery technologies sooner. Big pharma have definitely changed their game in this respect over the past few years, by which I mean delivery device technology is no longer an afterthought. In some cases, it means they've adopted a single device platform and stick to it for everything, even as drug delivery technology evolves.

After a product is an inline product, once it's launched, it's a different story. Then you're getting into lifecycle management strategies.

As we discussed earlier, it's difficult for smaller companies who don't have any device expertise in-house. They know the properties of their molecule, they know the target indication and, at some point, they may figure out that self-injection is the way to go. Once they've figured that out, they need to consider the details, including injection frequency, therapy duration and several others. You can imagine that they may be inclined to kick that can down the road, but they shouldn't.

In fact, if you wait too long to consider the device, you can jeopardise the filing date. You can't launch as a combination product if the device isn't ready. Many smaller companies want to partner with or be bought by one of the big players to commercialise their drug. Imagine you're in talks with a big pharma company and everything's looking good, the molecule is good, the clinical work is good, but then it comes out that you've not done any work on the device part of the combination product – that could really harm the conversation.

This is one of the sweet spots where Kymanox can really help, especially for those companies that only have one or two employees that are device savvy. We can help to get their projects moving ahead – put the quality management system in place, the device design controls, you name it.

Q **To follow on from that, is there ever a time where you would advise a smaller company not to go too far with looking into the combination of their molecule with the device? My thinking is that, when it comes to being incorporated into a large pharma company, they might have a particular way of doing things or their own preferred suppliers.**

> "Every company, whether they're big pharma, small biotech or a start-up – whatever size they are – the number one priority is always to get the product to market."

MR My take is, if you're a small biotech, you probably don't want to go with a device that's at all experimental. For example, if your molecule is designed to be a single fixed dose in a handheld device, go with a prefilled syringe – go with what's established, reliable and accepted.

Following on with that example, you're filling your product in a prefilled syringe, you're generating stability data, etc. You probably want to partner with a company on the device side that has done this before, one that has several customers and products on the market. Then let's say you're having talks further down the road with a big pharma partner and that partner has a different take on it. That's when you want to have a conversation about potentially taking the molecule in a different direction, but up until that point I would strongly recommend to move forward with something that's proven, potentially with an established device partner.

PJ I agree with Mathias. It's really a risk question; every company, whether they're big pharma, small biotech or a start-up – whatever size they are – the number one priority is always to get the product to market. As Mathias said, if you introduce a new, unproven technology, you'll increase the risk.

Take Sanofi as an example with Dupixent (dupilumab). It was launched in a prefilled syringe because a prefilled syringe was the fastest way to get to market. Now, the autoinjector is following behind it. That's a much more convenient way for users to take it, particularly in some of the newer indications that are coming along. It's a great example of prioritising speed to market. Enbrel (etanercept) from Amgen did exactly the same thing – prefilled syringe then an autoinjector. So, I think I'd expand on your point about using proven technology by saying

what you want is always the fastest way to market with the lowest risk. That's what I'd advise.

Q My next question is for Paul, on the topic of the recent emergence of 5 mL autoinjectors. What are your thoughts about these larger volume devices?

PJ At a PDA conference last year, a speaker in the closing session said that the delineation between an autoinjector and an on-body wearable was now 5 mL. When I heard that, I thought to myself, this can't be true. 5 mL of liquid in the subcutaneous cavity is a huge volume.

The response to that is usually that the people trying to inject these large volumes say that they're going to use a Halozyme-type solution [Enhanze, recombinant human hyaluronidase PH20 enzyme, rHuPH20, which locally degrades hyaluronan in the subcutaneous space temporarily removing a barrier to fluid flow] and it's going to dissipate into the subcutaneous cavity quicker. That is a solution, and there may be some others. And Halozyme loses its patent soon, so others will be able to copy it. But you're still trying to get 5 mL of liquid out through a fairly thin needle into the subcutaneous space. The injection doesn't go any faster even if you increase the speed at which it dissipates into the subcutaneous tissue – it still has to get out of the container in your autoinjector and into the patient. And that means that the user has to hold this autoinjector against their skin for a long period.

Some of the companies developing 5 mL devices say they can do the full injection 30 seconds, others say 60 seconds, and a couple have said that it's probably going to be more than a minute. Try holding something against your skin for a minute and then just imagine putting a needle on the end of it; I promise you that you're going to get a lot of incomplete injections – the problem with an autoinjector is that once you start it, you can't stop it, although some do claim ability to pause it.

I'm told that there are pharma companies demanding 5 mL, but that doesn't include any I've spoken to about it. I think 2 mL is about the right volume and, maybe, under the right circumstances, you can stretch to 3 mL.

FDG I really see this as a case of technology-driven thinking. People ask, "Can we do it?" first and then develop it from a technical standpoint. Once they've developed the product, they need to find a place for it, so they've targeted it as an alternative to on-body wearables.

> "People don't commonly think about stoppers and vials as a potential part of a combination product, but many of those are packaged in kits with reconstitution systems or vial adapters. Well, that's a combination product and the vial is a part of it."

PJ That's a really good way of putting it, Fran – it's technology-driven rather than patient-driven. I think that's probably what's actually happening. I did some of the studies in this area myself when I was at Sanofi, and we found that people do tell you that, given the choice of holding something against their skin versus sticking something on, they prefer to hold. But what isn't clear in those studies, at least in the ones I've seen and was involved with, is the amount of time they're willing to hold. They aren't comparing sticking on against holding for a full minute or more.

MR Talking of the voice of the customer, I also recall market research where the choice was between sticking the device on and getting two injections, say two of 2.5 mL each. The result was consistently 50-50. So, there's already an autoinjector-based alternative to on-body wearables.

One argument you could possibly make for 5 mL is, if the system is cartridge based, which I believe one is. In that case, it's just your maximum fill volume that's 5 mL, which means you can fit all the fill volumes that you have in your portfolio into this single device platform. You'd have to accept having a larger, and therefore less favourable device as a trade-off.

PJ That's an interesting thought, Mathias, especially from a sustainability perspective. Once, we never imagined that a cartridge-based autoinjector platform would be possible because of potential mix-ups and creating extra steps for the patient. But now that sustainability and climate change are really taking root in the industry, I think the sustainability angle of a single cartridge-based system for a whole portfolio will become increasingly relevant. And there's a very elegant programme that Novo Nordisk has put in place for recovering pens in Europe and the UK, which could also play into this idea. For certain, sustainability is going to become a bigger topic as time goes on.

Q Lastly, a question for you, Fran – can you tell us your thoughts about the risks and issues involved with companies thinking about the device without putting much thought into the packaging?

FDG This is actually a favourite topic of mine because, as you know, when you talk about a combination product, you're bringing together the device and the drug – in its primary packaging. And, as Mathias emphasised, you want to bring those two pieces together as early as possible. However, in large companies, the delivery device and drug packaging side are frequently treated as almost separate organisations. You have engineers in delivery, and you have scientists in drug formulation, so it's critical that those aspects be brought together as early as possible.

When you talk about packaging, it's not only the chemical side of it that's a concern – how the container interacts with the drug – but also how that package is going to work with whatever delivery device it is going to be paired with it. People don't commonly think about stoppers and vials as a potential part of a combination product, but many of those are packaged in kits with reconstitution systems or vial adapters. Well, that's a combination product and the vial is a part of it.

All these pieces very much marry together, and they each need to be thoroughly considered – the drug, the package and the delivery device – because the whole combination product is only as strong as its weakest link. You really need to understand these things both as individual elements and as part of the system as a whole. In my experience, most challenges occur where these things interface with each other, so that's one of the primary things that you need to be aware of.

Q To wrap up, I want to look to the year ahead. What do you think 2023 will bring and what will you be doing as a KEA in the coming year?

PJ I'm going to continue to spread the word about Kymanox. That will include at conferences, now that they are back to being in-person events – you can't do this kind of work virtually, you have to do it face-to-face.

There is going to be a lot of activity in the combination product space. My prediction for 2023 is there will be noteworthy advances made in three areas: on-body wearable injectors, connectivity and sustainability.

FDG I concur with Paul, and I think he picked out the right three areas. I think on-body will continue to grow, and digital and sustainability certainly will.

Sustainability really started in and has been driven by Europe more than anywhere else so far. But these things go global, and sustainability is becoming a real hot topic globally.

MR On sustainability, I learned recently that some fund managers are now putting together their portfolios according to sustainability goals, which could have a significant effect on the industry in 2023 and beyond.

As for what I'll be doing, as Paul already said, face-to-face events are back, so I'll be on the conference circuit. Another thing that I'll be doing is serving on the board of directors with PDA for another year. Many of us will get together at the PDA Universe of Prefilled Syringes & Injection Devices in Gothenburg in October.

It's going to be a great year, there are many positive developments happening, and I'm looking forward to it.

ABOUT THE COMPANY

Kymanox is a life sciences professional services organisation that offers engineering, scientific and compliance support to companies exclusively in the biotechnology, pharmaceutical, medical device and combination product industries throughout the product lifecycle from early development to postmarket.

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BEING PREPARED FOR PHARMA INNOVATION IS KEY IN 2023

In this article, Victoria Morgan, Marketing Director, Global Biologics, and Ana Marques Kuschel, PhD, Principal, Scientific Affairs, Europe, both of West Pharmaceutical Services, discuss three recent innovations that West has introduced to help pharma companies adapt to the evolving pharma landscape. They highlight how these technical solutions enable West's partners to respond to specific market-driven challenges, from pandemic-driven pressures on fill-finish productivity to the underlying shift towards biologics and the accelerated growth of home-based treatment.

For such a heavily regulated industry, where safety and the mitigation of risk are paramount, those on the outside could be forgiven for thinking that pharma is not an environment conducive to fast-paced innovation.

However, in reality, innovation has always been at the sector's core – you only have to look at the fact that around 50 new, US FDA-approved drugs are consistently delivered each year,[1] and further evidence can be found in the whiplash speed with which the industry collectively responded to the demand for covid-19 vaccines.

Behind every one of those successful drugs is an effective drug-delivery platform, supported by a resilient and innovative partner that has both the competence and determination to keep pace with the ever-evolving macro, regulatory and patient landscape.

ANSWERING UNMET NEEDS IN INJECTABLE DRUG PACKAGING

Throughout the covid-19 pandemic, indeed throughout its 100-year history, West has continued to innovate by delivering products that demonstrate better quality, greater strength and more environmentally sustainable designs.

In response to the challenges posed by the pandemic and the existing industry hurdles, West partnered with Corning Incorporated to deliver innovation in drug containment and delivery system solutions. A significant milestone in this collaboration was recently achieved with West's introduction of the ReadyPack System™ with Corning Valor® Glass at Pharmapack Europe.

The new ReadyPack System offering includes Valor ready-to-use (RTU) vials with SG EZ-fill® technology. Valor Glass's unique aluminosilicate composition and chemically strengthened surface has been developed to deliver superior chemical durability and physical integrity. This, combined with the exterior coating, which can improve throughput efficiency and reduce particle contamination in robust processing environments, improves both the drug manufacturer's and the end user's confidence in the product. Valor Glass therefore represents a significant development in primary packaging materials.

As the pharmaceutical and biotech industries broaden their drug offerings, they must manage more complexity and mitigate risk in the drug development process. Valor RTU vials with SG EZ-fill® technology respond to a demand for flexible manufacturing, increased speed to market, improved glass quality and reduced risk. Combining these qualities with the ReadyPack™ System creates a complete packaging system that allows companies to maximise their time and resources to get

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a drug to market quickly and safely – and provides a proven vial containment solution that scales from research and development to commercial manufacturing.

Valor® Glass vials undergo an ion exchange strengthening process during production that results in improved load-bearing qualities and helps prevent the formation of cracks. The compressive stress imparted on the glass surface during this process also exceeds the tensile stress levels observed during freeze-thaw processes, such as lyophilisation. Indeed, laboratory tests conducted between -100°C and room temperature using aggressive 15% mannitol with 50% fill volumes have shown that Valor® Glass demonstrates a dramatically lower potential for breakage compared with traditional borosilicate glass vials.[2]

Valor® Glass eliminates the risk of delamination, which can be costly if discovered too late, through the material's boron-free composition. In the absence of boron, the vial possesses a uniform surface chemistry that does not feature boron-rich heterogeneities, eliminating a factor that can increase the likelihood of delamination.

Furthermore, because it has a chemically strengthened surface that is engineered with higher internal energy compared with conventional glass vials, Valor® Glass offers enhanced protection against cracking. In typical borosilicate vials, surface flaws can develop into more substantial cracks under subsequent loads experienced during processing and downstream distribution. In the case of Valor® Glass, relatively minor surface flaws are contained within the outermost compression layer, leading to an intact vial with improved breakage resistance. More severe damage that can cause cracking in conventional vials is instead converted into complete breakage by Valor® Glass, thereby rendering the container unusable.

Valor® Glass also features an exterior coating with a low coefficient of friction, which has been shown to protect against scratching and reduce peak particle counts on commercial filling lines by 96%.[2] Combined with its highly consistent dimensional geometry and chemical strengthening, this presents production line managers with the ability to operate equipment at higher speeds (Figure 1).

In tests at a set filling-line speed of 350 vials per minute (VPM), Valor® Glass is shown to be highly efficient, registering an overall equipment effectiveness (OEE) rate in excess of 80% compared with

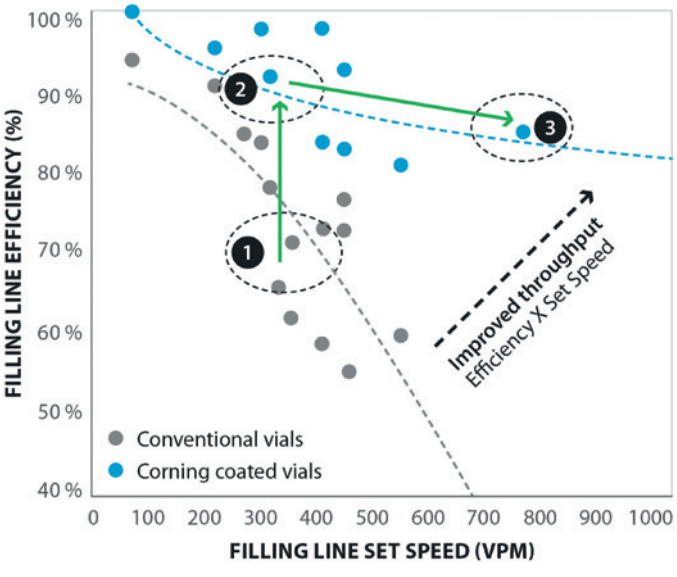

Figure 2: Line speed versus efficiency.

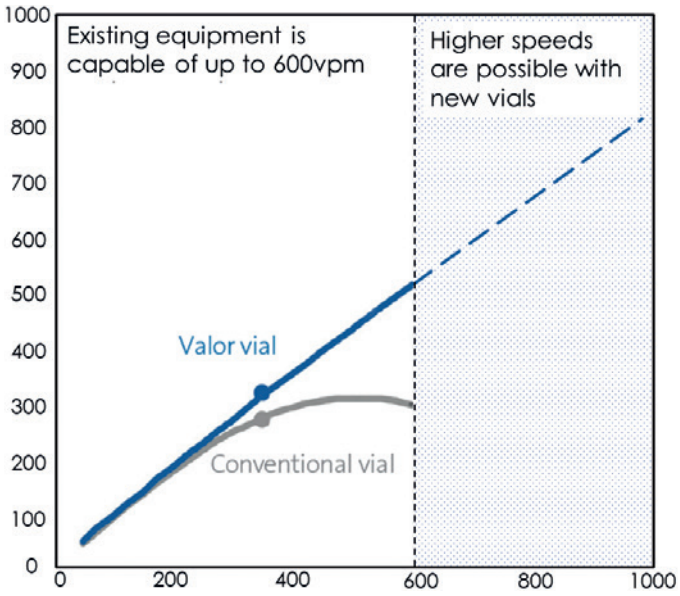

Figure 1: Effective throughput versus filling-line set speed.

60% for conventional vials (Figure 2). Furthermore, this OEE rate can be maintained at a line speed of 750 VPM, meaning that the door is open to demonstrable reductions in filling costs on a per-unit basis.[3]

PROTECTING LARGER VOLUME, SENSITIVE MOLECULES

Vials are, of course, not the only primary packaging platform where changing trends are creating new challenges in terms of drug protection. In recent years, the industry has witnessed a sustained shift of treatment location from hospital to home, driven by patient demand for greater convenience, which has led to increasing recognition of the value of autoinjectors for delivery across multiple therapy areas.

In tandem with the growing market share of biologic formulations, where higher volumes may be required to deliver the desired effect, and the emergence of results from human factors studies showing patient tolerance for an extended injection duration of approximately 15 seconds,[4] the door has been opened to the self-administration of a wider range of biologic therapies via subcutaneous injection for applications that would previously have required multiple injections or intravenous delivery within a clinical setting.

One of the challenges associated with this growing opportunity, however, is compatibility with glass primary packaging options – most notably that some sensitive biologic drug formulations become unstable when exposed to silicone oil. Siliconised glass syringes can also pose a risk to the supply chain and the patient, with challenges around aggregation, contamination and breakage. For some formulations, there is also a requirement to expand the potential drug volume delivered via autoinjectors from the typical dose of 1 mL up to 2.25 mL and even 5 mL.

The question, therefore, is how to protect the integrity of a highly valuable, yet sensitive, biologic formulation at a 2.25 mL volume in a non-glass-based container without compromising the cleanliness and robustness required of the primary packaging.

One answer can be found in the Daikyo Crystal Zenith® (CZ) component portfolio, which includes a 2.25 mL insert needle (IN) prefillable syringe (PFS) system (Figure 3). CZ is a cyclic olefin polymer (COP) that presents a sterile containment system for silicone-oil-sensitive drug formulations. The elastomeric plunger used

Figure 3: The Daikyo Crystal Zenith® component portfolio protects modern biologics from filling to patient injection.

in the CZ PFS system is coated with an inert FluroTec® barrier film, which reduces the risk of leachables from the elastomer and prevents absorption of the drug formulation. By supporting syringe functionality, the film also avoids the need for additional silicone oil to be used, dramatically reducing exposure to a key source of protein aggregation. Indeed, studies conducted by West on a randomised selection of syringe samples detected no silicone oil, down to 1 ppm, extracted from the assembled syringe.

In further evidence of CZ's credentials for safeguarding formulation integrity, the precision injection-moulding process used to engineer CZ polymer PFSs facilitates a four-log reduction in endotoxin levels while enabling needles to be attached free of tungsten or glue, which are additional possible sources of drug contamination.

Break-test data recorded during tests carried out by West also demonstrate how CZ mitigates against the risk of breakage. This is not only an important consideration in relation to the fill-finish process, where breakages result in costly downtime, but also in transportation environments and for the activation of the autoinjector itself, where higher forces can be required to deliver larger volume or high-viscosity injections.

LARGE-VOLUME ON-BODY DELIVERY SYSTEMS

One consequence of the sustained shift of treatment from hospital to home is the evolution of on-body delivery systems (OBDSs). Today, OBDS platforms can deliver higher volumes of medicines that traditionally would have been administered intravenously via an infusion at a clinic under the supervision of a healthcare professional (HCP).

West's SmartDose® OBDS platform helps to provide patients with confidence in their therapy while reducing or preventing the need for frequent visits to infusion centres. Additionally, by using the FluroTec® film-laminated 5-10 mL cartridge plunger, patients can, for the first time, self-administer more than 1 mL, which would have historically been via multiple injections or administered intravenously.

Not only that, but there is also a great deal of evidence to suggest that supporting self-management delivers many patient benefits, including an increase in overall wellbeing, improved mental health, better clinical outcomes and smarter, more cost-effective use of healthcare services.[5] Such innovation has implications for the wider ecosystem too, including pharma, payers, HCPs and regulatory bodies in terms of adherence, symptom management and, of course, cost.

> "Transitioning infusion therapies from hospitals or clinics to at-home care could result in a cost saving of up to 70% for both patients and HCPs."

From a pharma perspective, OBDS platforms can play a key enabling role in delivering on the patient experience and safety, regimen efficacy and adherence priorities. And, as advances in therapeutic proteins, biologics and monoclonal antibodies (mAbs) deliver improved treatments for diseases such as cardiovascular disease and cancer, then the scope for OBDS platforms grows too.

There are other benefits, too. For companies working on lifecycle management, the FluroTec® film-laminated 5-10 mL cartridge plunger opens up a previously untapped market and, together with the compatible stopper, drug manufacturers can simplify their lifecycle management by selecting one platform with multiple delivery options.

With the increase in patient engagement derived from at-home care comes better outcomes, and the net effect is often a lower total cost of care – a key driver for payers. Transitioning infusion therapies from hospitals or clinics to at-home care could result in a cost saving of up to 70%[6] for both patients and HCPs, demonstrating the value OBDSs bring to the payer community.

ADDRESSING THE IMPLICATIONS OF EU GMP ANNEX I

Irrespective of where drugs are administered and the packaging used to contain them, maintaining sterility and avoiding product contamination are critical to patient safety, and pharmaceutical companies face new regulatory challenges in this area. The EU GMP Annex I: Manufacture of Sterile Medicinal Products was first published in 1971 with a major revision finalised in August 2022. The review process was a collaborative effort with the WHO and the Pharmaceutical Inspection Co-operation Scheme (PIC/S).

The latest iteration aims to correct inaccuracies and clarify ambiguities, as well as align the guideline with international requirements. The new version of EU GMP Annex 1 focuses on the need for a holistic contamination control strategy, with an expectation for a formal document that reflects the site-wide strategy for minimising contamination, such as particulates, microbes and pyrogens, throughout the whole sterile manufacturing process. Another focus is a guidance for the usage of new technologies, such as restricted access barrier systems (RABSs) and isolators. In addition, greater attention has been given to an in-depth understanding of container closure integrity (CCI) and container closure integrity testing (CCIT). Finally, the current revision embraces the philosophy of a holistic risk management system – the expected benefit being that there will be fewer deviations in manufacturing and improved supply chain integrity.

As always, with increased market opportunity comes greater oversight, and the evolving regulatory landscape does require pharma and biotech companies to partner with a true expert who can help them navigate the drug/delivery interface development path successfully. West has a full-service portfolio of expertise – including device development, containment systems, regulatory

support, analytical testing, combination product manufacturing and fill-finish solutions – to enable partners to develop devices faster, more safely and with less risk, while ensuring the end product is reliable and usable.

CONCLUSION

Today, with greater market focus on sensitive, high-value biologics and advanced therapies extending their reach into several therapeutic areas, including the treatment of chronic conditions, innovation and quality remain the bywords for the pharma supply chain. West has risen to that challenge, delivering a vial technology with demonstrably superior chemical durability and physical integrity to aid patient safety, while simultaneously enabling seismic improvements in operational efficiency.

The company's advancements in OBDS technology have enabled larger volumes to be administered subcutaneously, over a longer period and in a non-clinical setting, by ensuring user requirements are at the heart of the patient experience. The consequence of this innovation can be felt right across the pharmaceutical ecosystem. For patients, disruption to daily life is limited, with growing evidence that outcomes are improved via the patient-driven care route.[6] For payers, there is the potential of a very real cost saving. For HCPs, this technology can offer reduced treatment times and workload. Lastly, pharma partners now have an opportunity to develop more complex therapies, with higher volume capacities than have been possible before.

Finally, with the advent of changes to EU GMP Annex 1, West is continuing to develop innovative responses to help its pharma partners prepare for what lies ahead – in recent years, the only constant has been change, and 2023 promises to be no different.

ABOUT THE COMPANY

West Pharmaceutical Services is a leading provider of innovative, high-quality injectable solutions and services. As a trusted partner to established and emerging drug developers, West helps ensure the safe, effective containment and delivery of life-saving and life-enhancing medicines for patients. With approximately 10,000 team members across 50 sites worldwide, West helps support customers by delivering over 45 billion components and devices each year.

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ABOUT THE AUTHORS

Victoria Morgan has been in the pharmaceutical industry for more than 25 years. She has extensive sales and marketing experience across primary and secondary care and the area of injectable drug delivery products, including primary packaging and combination products for vials, prefilled syringe systems, cartridges and devices. Ms Morgan spent more than 17 years in global sales roles followed by five years as Marketing Director, Global Biologics, at West, where she has responsibility for strategy development and implementation.

Ana Marques Kuschel, PhD, provides technical support relating to West's packaging components and delivery systems for injectable drugs and healthcare products, as well as bridging scientific information through industry outreach. Previously, she was Manager Material Development, where she worked on the development of new rubber formulations. Ms Marques Kuschel holds a PhD in Macromolecular Chemistry and is an active member of the ISO TC 76 and PDA Packaging Science groups.

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1. No silicone oil or other lubricants are applied for syringe functionality. Silicone oil is used as a process aid in elastomer manufacturing. Studies detected no silicone oil down to 1ppm extracted from the assembled syringe in 10 samples. West Report #:1116-STR
2. https://www.westpharma.com/products/quality-enhancements/films-and-coatings/flurotec-barrier-film

gerresheimer

SILICONE-OIL-FREE PREFILLED SYRINGE SYSTEMS – GUIDANCE FOR SELECTING THE APPROPRIATE PACKAGING MATERIALS AND FOR SILICONISATION

Here, Bernd Zeiss, Head of Global Technical Support at Gerresheimer, addresses the influence of silicone oil on syringe systems and highlights the advantages and possibilities of novel silicone-oil-free prefillable syringes, both for glass and for plastic syringes.

The degree of siliconisation is just one of many aspects for consideration when selecting the right primary packaging material. Prefilled syringes (PFSs) are usually siliconised on the inside to allow the plunger stopper to glide.[1] Vials can also be siliconised on the inside to improve emptying.

VIAL OR SYRINGE

PFSs offer a number of advantages over traditional vials, which include considerably less effort required to prepare for injection and a reduced risk of application errors by specialist personnel or patients. The residual volume (dead volume) is also much lower for PFSs than for vials, even if disposable syringes – which have a low residual volume – are filled. Vials are always "overfilled" with a certain amount of drug to ensure complete withdrawal of the specified dose. One of the disadvantages of PFSs over vials, however, is that comparatively more materials come into contact with the liquid drug during storage. Besides glass and the elastomer stopper, these materials also include silicone oil as a lubricant for the stopper, usually another elastomer for the cap and possibly traces of tungsten, which can interact with the drug.[2]

Tungsten pins are used in glass syringe production to define the bore in the cone (Figure 1). Some advantages and

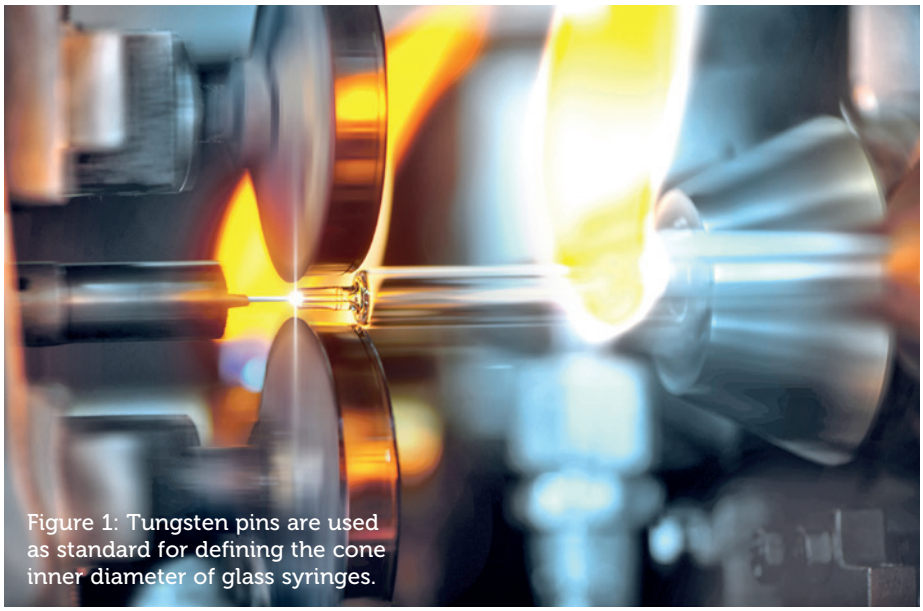

Figure 1: Tungsten pins are used as standard for defining the cone inner diameter of glass syringes.

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Prefilled Glass Syringe	Advantage	Filled Glass Vial, Closed	Advantage
Total cost for container			
Low overfilling, low residual volume	+	High overfilling, high residual volume	–
Higher costs for packaging materials	–	Lower costs for packaging materials	+
User-friendliness			
Single dose	+	Single or multiple dose	±
Few steps through to injection	+	Many steps in injection preparation	–
Low risk of incorrect dosing	+	Higher risk of error for correct dosing	–
No other components needed (needle syringe) at point-of-care, except for: push-on cannulas for Luer syringes	+	Disposable components necessary at the point of care: Plastic single-use syringe Cannula for filling Injection cannula	–
Contact materials			
Contact with the drug during storage: Glass Elastomer stopper Elastomer cap Tungsten (extractables) Silicone oil (glide agent) Needle adhesive, Stainless steel	–	Contact with the drug during storage: Glass Elastomer stopper	+
Special applications			
High-viscosity drugs, low volumes	+	High-viscosity drugs	–
Lyophilisation: reconstitution complex	–	Lyophilisation: reconstitution simple	+
Autoinjectors are simple to use for at-home use	+	Training necessary, especially for the uninitiated	–
OVERALL ADVANTAGE	**7+ 3–**		**3+ 6–**

Table 1: Overview of some advantages of PFSs versus vials. The advantages for PFSs predominate. Case-by-case considerations are necessary for selecting the appropriate packaging material.

disadvantages of PFSs and vials are listed in Table 1. Novel stoppers have also eliminated the need for silicone oil in glass syringes, which is particularly important for sensitive formulations and in ophthalmology (Figure 2).

WEIGHING UP THE ADVANTAGES OF GLASS AND COP

Silicone-oil-free PFSs are not fundamentally new; they have long been available as cyclic olefin polymer (COP) plastic syringes from various suppliers.[3] The advantages of plastic syringes are their resistance to breakage, absence of adhesive in the case of needle syringes and their very tight manufacturing tolerances.

Figure 2: Vial, closed with rubber stopper and crimp cap. Syringe closed with needle shield and stopper, with plunger rod and "backstop".

	Advantage of Glass	Advantage of COP	Remarks
Risk of breakage during filling	±	±	Line clearance after glass breakage during filling is expensive but rare
Risk of breakage at the point of care	±	±	Possible, but rare with small volume syringes. Breaking force minimised in advance during development
Luerlock integrated	–	+	Slipping of the thread and detachment impossible with COP
Tungsten	–	+	Alternative pin materials available today, no tungsten in COP injection moulding
Adhesive	–	+	COP syringe free of adhesive
Silicone oil	±	±	COP syringes silicone oil free, long available
Gas and especially oxygen barrier	+	–	Glass unsurpassed
Extractables	+	–	Low for glass and known, inorganic
pH shift	–	+	No pH shift with COP
Experience	+	–	Experience with glass in the pharmaceutical industry is extensive, also for filling lines
Costs	+	–	COP more expensive than glass
Design freedom	–	+	Injection moulding allows diverse designs
Tool	+	–	Free moulding needs no special, expensive injection moulding tools
Tolerances	–	+	Glass with wider tolerances through free moulding
Scratch resistance	+	–	Plastic sensitive, however scratches do not affect the breaking force
Sterilisation of the packaging material	±	±	Glass: EtO COP: gamma, steam
Terminal sterilisation	±	±	Glass: steam, EtO, other methods COP: steam, gamma, other methods
OVERALL ADVANTAGE	6+ 6–	6+ 6–	

COP = Cyclic Olefin Polymer EtO = Ethylene Oxide

Table 2: Advantages of glass versus COP as primary packaging material for syringes and vials. Case-by-case considerations of the advantages of the syringe material must be given depending on the formulation and the field of application.

Disadvantages include the inferior barrier against gases and the specific plastic-extractables profiles as compared with conventional Type-1 glass. Table 2 provides an overview of the most important criteria.

"The emergence of silicone-oil-free, adhesive-free and tungsten-free plastic syringes around 10 years ago was a challenge for glass syringe manufacturers, who had previously only competed among themselves."

The emergence of silicone-oil-free, adhesive-free and tungsten-free plastic syringes around 10 years ago was a challenge for glass syringe manufacturers, who had previously only competed among themselves. This challenge was accepted and glass syringes have been significantly improved by many technical innovations as a result:

- Complex camera technology combined with special software allows extremely precise dimensional controls.
- Cosmetic defects that can cause glass breakage can be detected and minimised by special cameras and scanning algorithms.
- Design adjustments, such as small round finger flanges, further reduce the risk of breakage, e.g. for autoinjector applications.

Risks are minimised during product development, validation and quality control well before the market launch:

- Tungsten pins can be replaced by ceramics or other materials, which means that tungsten-free syringes are available today.
- Needle adhesives, with their narrow extractables profile, are now a reliably assessable risk for pharmaceutical companies. Special dry-needle systems can always be used as an alternative.
- Luer lock adapters on glass syringes have been optimised in terms of their twist-off and pull-off forces – see the Tamper Evident Luer Lock Closure (TELC) syringe (Figure 3).
- Silicone-oil-free prefillable glass syringes are now also an option. Special plunger

stopper materials display good gliding properties and ensure container closure integrity (CCI) during storage, which is a key concern. Ultimately, the emergence of plastic syringes has improved glass syringes. Glass still has a market share well in excess of 90% compared with plastic syringes for small injection volumes primarily for intramuscular or subcutaneous use.

ADVANTAGES OF SILICONE-OIL-FREE SYRINGES

Glass has been well investigated as a material for injectables and is widely used in vials, PFSs, cartridges (mainly insulin) and ampoules.[4] Additional siliconisation is often straightforward, both for the drug during storage and for the patient, who still takes a small amount of silicone oil onboard with each injection. Until recently, only plastic PFSs were available, but this is now changing with the advent of glass PFSs. Although silicone-oil-free syringes do not serve a mass market and classic glass syringe systems continue to be siliconised, there are still a number of interesting fields of application for silicone-oil-free glass syringes – primarily in ophthalmology and the biopharma sector. Table 3 compares the advantages and disadvantages of silicone-oil-free syringe systems.

Figure 3: Ophthalmology 0.5 mL syringe with Luer lock adapter, BOS or silicone-oil-free, ready-to-fill format, various elastomer components and dose mark available. Gerresheimer syringe with TELC.

	Advantage for Silicone-Oil-Free Syringes	Advantage for Siliconised Syringes	Remarks
Drug			
Particle load in accordance with USP / Ph. Eur.	+	–	Silicone droplets contribute significantly to the total particle load
Interaction of silicone oil with the drug	+	–	Silicone oil can interact with drug constituents in a variety of ways
Inertisation of the polar glass surface	–	+	pH shift, delamination, protein adsorption on glass hitherto unknown for siliconised syringes
Silicone oil is also injected	+	–	Adverse reaction in the patient, if applicable
Functionality			
Break-loose and gliding force	–	+	Lack of gliding layer increases forces, greater scattering
Constant break-loose and gliding force after storage	?	?	Possibly advantages of silicone-oil-free systems in the autoinjector, lower aging effect assumed**
Proven and familiar rubber stoppers	–	+	Possibly advantages over new types of materials in the approval process
F&F process	–	+	Special moulding sets and process adaptation in F&F necessary
Integrity of the CCI system	–	±	Lack of siliconisation may increase risk of leakage
Filling level meniscus	–	+	Concave meniscus in silicone-oil-free syringes – larger air bubble
OVERALL ADVANTAGE	3+ 6–	5+ 3–	

*F&F = Fill and Finish ** Further studies pending*

Table 3: Some comparative advantages of siliconised and silicone-oil-free glass PFSs. Case-by-case considerations of the advantages of the siliconised or silicone-oil-free syringe system must be given depending on the formulation and the field of application.

Ophthalmology

In ophthalmology, silicone-oil-free means, above all, a significantly lower number of particles. Injection into the eye is subject to strict total permissible particle count requirements in accordance with USP <789> and Ph. Eur. 2.9.19. The most important applications for PFSs are cataract surgery and intravitreal injections.

Cataract surgery involves removing the clouded lens. To prevent the remaining outer lens epithelium of the lens capsule from collapsing during removal, the resulting cavity is briefly in shape with a hyaluronic acid-based fluid prior to insertion of the artificial lens. PFSs are generally used to achieve this.

Injections into the vitreous body – intravitreal injections – have to be performed repeatedly depending on the clinical picture, especially in cases of wet macular degeneration with vascular endothelial growth factor (VEGF) inhibitors. This may lead to the accumulation of particles in the vitreous body and, therefore, in the field of vision.

Baked-on silicone (BOS) for PFSs[5] for such purposes is now state of the art to meet stringent regulatory requirements and, ultimately, minimise impairment of vision due to the accumulation of silicone droplets in the eye. Here, it is important that the maximum particle counts specified in USP/Ph. Eur. refer to the filled PFS, with the particles from the glass container, the stopper, the manufacturing process and the drug itself also contributing (Table 4). The fewer the particles coming from the container itself, the more likely it is that the USP or Ph. Eur. conditions are met.

Biopharma: Antibodies and mRNA Stability in PFSs

The requirements are less clear in the biopharma sector. The advantages of silicone-oil-free or siliconised systems depend on the specific API and its formulation. Monoclonal antibodies can be sensitive to silicone oil in their formulations,[6] so silicone-oil-free syringe systems may be beneficial in these cases.

Injections at intervals of a few weeks do not lead to a significant accumulation of silicone oil in the tissue; in addition, silicone oil is harmless to the patients themselves and is considered inert and non-allergenic. Only in the case of more frequent injections, such as with insulin, could a silicone-oil-free injection offer advantages in reducing silicone oil deposition under the skin, which may be cosmetically relevant.

USP <789> Test on Particle Count	Light Obscuration		Microscopic Method		
	Diameter		Diameter		
Size of particles	≥10 µm	≥25 µm	≥10 µm	≥25 µm	≥50 µm
Number allowed per mL	50	5	50	5	5

Table 4: USP <789> and Ph. Eur. 2.9.19 prescribe maximum values for subvisible particles in ophthalmic applications. Depending on the measurement method, particles ≥50 µm can also be detected.

If formulations are sensitive to silicone oil, silicone-oil-free syringe systems are recommended. Sensitive drugs may also be sensitive to oxygen, shock or shear forces during injection through the needle and leachables from the elastomers.

Despite some advantages, silicone-oil-free plastic syringes have failed to become widely accepted on the market, which could be due to the poorer oxygen barrier of COP compared with glass. Formulations are generally designed to be stored in syringes before being administered and must remain stable throughout. This is researched in extensive stability and spiking studies before a drug goes on the market.[7,8] Suppliers of PFSs offer a wide range of glass and COP test samples, such as for pharmaceutical R&D purposes, and can help customers find the best PFS for their specific requirements.

In some cases, liquid formulations react to silicone oil[9] and may therefore be less well suited for siliconised PFSs. This appears especially true for the new mRNA formulations that need to be combined with specific additives.[10]

The lipid nanoparticles (LNPs) used to introduce mRNA into cells could possibly be impaired by silicone oil. Besides LNPs, which are the vectors for introducing the mRNA into the cell, many other additives (excipients) are also needed in the formulation to stabilise the active substance. These are mainly pegylated or ionisable lipids, phospholipids, cholesterol, various buffers and salts.

Today, the new mRNA formulations are mostly stored frozen in silicone-oil-free vials for stabilisation prior to injection. However, pharmacists aim to improve upon this by formulating drugs that can be stored as an unrefrigerated lyophilisate or, ideally, as a liquid formulation that remains stable at room temperature or under refrigeration (4–8°C) and thus could be made available in a PFS. This would significantly simplify handling, as with other classic vaccines, such as those administered in doctors' offices.

Whether silicone oil, like oxygen, has a destabilising effect on mRNA drugs still needs further investigation. What is certain is that the lower the number of materials in contact with the drug, the lower the risk of failure in stability studies.

Figure 4: Gx Biopharma syringe Gx RTF 1 mL long needle syringe, low silicone level or silicone-oil-free, specified tungsten level, low specified extractables (elastomers), adaptation to autoinjectors, elastomer components possible.

"The lower the number of materials in contact with the drug, the lower the risk of failure in stability studies."

Even though silicone oil is inert and does not directly impair the drug, the silicone layer applied as a lubricating coating can cause further problems.

Some liquid formulations dissolve the lubricating coating so that the break-loose and gliding forces deteriorate after some time.[11] This is especially the case for autoinjectors, which empty the installed syringe with a specific spring force. This can lead to the undesired failure of the system after a certain period in storage. Pharmaceutical companies should not underestimate this risk, which will be investigated in the aforementioned stability studies prior to market approval. Silicone-oil-free syringe systems work without a coating that may be susceptible to change over time (Figure 4).

INVESTIGATIONS AT GERRESHEIMER

Gerresheimer has recently tested various silicone-oil-free syringe systems.[12] Various systems have been initially evaluated in pre-studies. In addition to well-known providers whose products are already marketed,[13,14] other providers were also considered. Extensive studies have demonstrated the suitability of the syringe systems that were investigated. The most important aspects of the investigations were particle load, CCI and functionality in terms of break-loose and gliding forces, including after storage. The stoppers should be freely available and also suitable for glass and COP syringes. The silicone-oil-free syringe systems on the market today are mainly available for COP syringes; in addition, the stopper and syringe body are only available from the providers as a fixed system. As a result of the diverse requirements for a syringe system, fixed combinations of stopper and syringe tend to be undesirable. The more flexibly a pharmacist can choose a stopper, the better they can respond to any difficulties in stability testing. The technical aspect of the fill-finish process should also be considered. Depending on the characteristics of the stopper, the setting tube method, vacuum setting or particular combinations of these may be considered. Without silicone oil, setting the stopper becomes even more complex.

Container Closure Integrity

Silicone oil performs two roles in a PFS – sealing and ensuring sliding while emptying. Integrity and integrity measurements represent a complex topic[15] because different techniques can be deployed depending on the requirements – from testing in a dye bath (ISO 11040-4, Annex H) to sensitive helium leakage testing and beyond. All systems investigated met the basic requirements for PFSs – integrity testing in accordance with ISO 11040-4, Annex H was passed in all cases. Helium leakage tests were also carried out together with the stopper manufacturers, proving the integrity of the systems. Integrity tests with pharmaceutical formulations are pending, as they must be specifically drug-related.[16]

Particle Tests

The particle loads of the silicone oil-free syringe systems were determined in accordance with USP <788>/<789> and Ph. Eur. 2.9.19. Like many methods, the light obscuration particle count procedure is harmonised between the USP and Ph. Eur. USP <789> uses the same method, but with

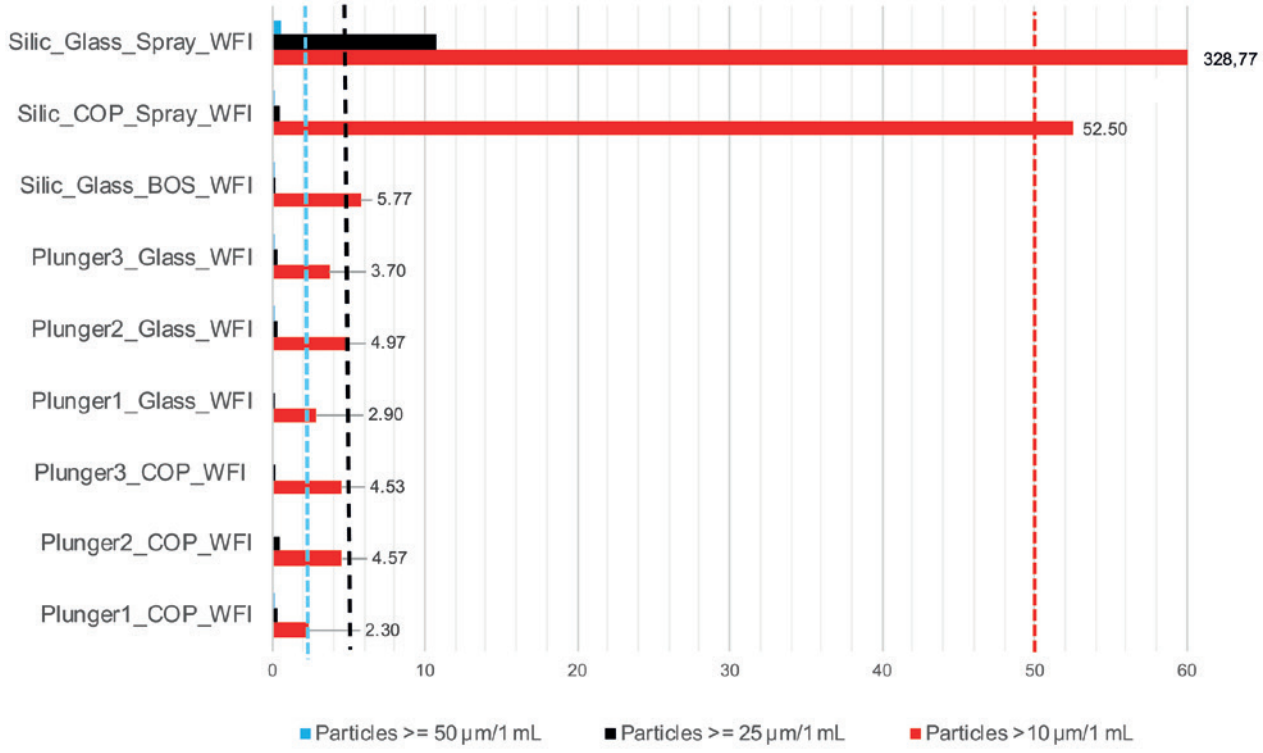

Figure 5: Particle measurements of silicone-oil-free 1 mL long syringes compared with siliconised (Silic) systems in accordance with USP <789>. Dashed = limits for three particle classes in accordance with USP <789>. Spray = spray siliconised, BOS; each with modern coated stoppers; COP/glass = syringe body material. Plungers 1–3 = silicone-oil-free syringe systems with various special stoppers. WFI = syringes filled with water for injection.

stricter particle limits, as shown in Table 4. For all silicone-oil-free syringe systems – glass or COP – and all stoppers investigated, the maximum particle values were significantly below the total permissible particles per container. The required values were also achieved for the established BOS syringes, and familiar, existing plunger stoppers can also be used. Further reduction in particle count is reaching its limits. Silicone-oil-free systems with specialised plunger stoppers have been developed to offer patients a PFS qualitatively improved in terms of particle load as well as the drug itself.

Figure 5 shows the particle measurement results for various siliconised and silicone-oil-free 1-mL-long syringe systems with limits in accordance with USP <789>. BOS syringes and non-siliconised syringes with novel stoppers (Plungers 1–3) are well within the non-critical range for intravitreal applications for all particle classes. Clear differences between the syringe body materials, (i.e. glass or COP) are not identifiable with silicone-oil-free systems. These syringes are suitable for ophthalmic applications.

Spray-siliconised syringes are generally not used for ophthalmic applications because the limits of 5 and 50 particles for the ≥10 µm and ≥25 µm size classes, respectively, are exceeded. A comparative measurement is included in Figure 5. Among the spray-siliconised syringes, it is noticeable that the COP syringes have significantly fewer particles in the ≥10 µm size class (52.5 versus 328.77 particles). The higher viscosity oil (12,500 cSt) used in the COP syringe bonds better to the glass and releases fewer particles that can be detected in the test liquid than the 1,000 cSt silicone oil classically used in glass syringes. This result may be of interest for non-ophthalmic applications.

Break-Loose and Gliding Forces

Silicone-oil-free syringe systems face special challenges in the absence of a lubricant coating. Integrity must not be impaired but, at the same time, the break-loose and gliding forces must be ensured. Higher gliding forces can be generally expected without silicone oil than with classic siliconised syringes. Measurements at Gerresheimer were made with different stoppers in 1 mL long syringes three days after filling and stoppering, after three months of storage and after three and six months of accelerated ageing. Glass and COP syringes were investigated. Further data on 0.5 mL glass and COP syringes is also available or being acquired.

The results show good and fully acceptable break-loose and gliding forces for the silicone-oil-free syringe systems investigated (Figure 6). In particular, two systems showed very good results with hardly any changes during the storage period.

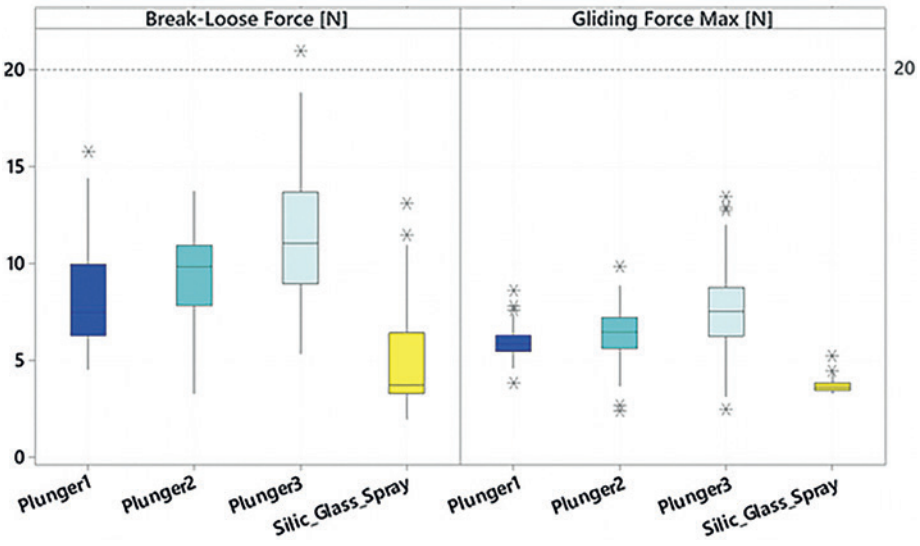

Figure 6: Break-loose and gliding forces of silicone-oil-free syringes compared with spray-siliconised syringes. Extrusion force 270 mm/min. Plungers 1–3: Three special stoppers from different manufacturers in unsiliconised syringes. Silic_Glass Spray: 0.5 mg silicone oil, coated stopper; 1 mL long 27 G needle syringe with standard ID, filled with WFI. Measurement times each with N = 160: summed [T0 (three days after filling), T1 three months, T1 acc (three months accelerated ageing in accordance with ICH), T2 acc (six months accel. ageing in accordance with ICH), T2 (six months)].

OUTLOOK

Eliminating silicone oil expands the options for PFSs and will become increasingly important in the future. Besides ophthalmic and biotech applications, which primarily use 0.5 mL and 1 mL long syringes, 1, 2.25 and 3 mL syringes can also be used. The corresponding stoppers are available or are under development. Fill-and-finish (F&F) equipment manufacturers will add processability for silicone-oil-free syringe systems to their machines, and contract manufacturing organisations (CMOs) will gather experience in the filling process. Innovations in F&F will also generally require some time prior to implementation in the market because of the large number of interfaces that must mutually harmonise – from the successful development of a liquid drug, to the syringe manufacturer, to the stopper and machine manufacturer, through to the CMO.

ABOUT THE COMPANY

Gerresheimer is a major drug delivery device and primary packaging company. Its products include insulin pens, inhalers, PFSs, pharma plastic containers and glass ampoules, vials and cartridges. Gerresheimer Bünde is its centre of excellence for glass PFSs and cartridges.

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ABOUT THE AUTHOR

Bernd Zeiss graduated from the University of Göttingen, Germany, and is a biologist by education. After several years working as a biostatistician, in lab automation and in pharma sales, he is currently a member of the Gerresheimer Business Development Team. Mr Zeiss works in the Gerresheimer Centre of Excellence for PFSs as Head of Technical Support, Gx® Solutions and Syringe Systems. His main areas of work are technical customer support with regard to syringe systems as well as investigating possible interactions between syringe components and drug substance.

MITSUBISHI GAS CHEMICAL

OXYCAPT: SUPERIOR PRIMARY CONTAINERS FOR BIOLOGICS AND GENE AND CELL THERAPIES

In this article, Yasuaki Yoshimura, Researcher, and Tomohiro Suzuki, Associate General Manager, both of Mitsubishi Gas Chemical, review the advantages that OXYCAPT, the company's multilayer material for vials, offers to biologics and gene and cell therapies, and discuss the results of recent tests into low temperature storage and dimethyl sulfoxide resistance.

OXYCAPT™ is a multilayer plastic vial developed by Mitsubishi Gas Chemical (MGC) that offers a number of advantageous qualities as a primary drug container (Figure 1). MGC continuously conducts tests to confirm OXYCAPT's excellent properties, including:

- Excellent oxygen and ultraviolet (UV) light barrier
- Strong water vapour barrier
- Very low extractables
- High pH stability
- Low protein adsorption and aggregation
- High transparency
- High break resistance
- Easy disposability
- Lightweight material.

Figure 1: OXYCAPT multilayer plastic vial.

OXYCAPT OVERVIEW

OXYCAPT consists of three layers – the drug contact layer and the outer layer are made of cyclic-olefin polymer (COP), and the oxygen barrier layer is made of MGC's novel polyester (Figure 2). One variety of OXYCAPT, OXYCAPT-P, provides an excellent oxygen barrier. For example, the oxygen barrier of an OXYCAPT-P vial is about 20 times better than that of a COP monolayer vial (Figure 3).

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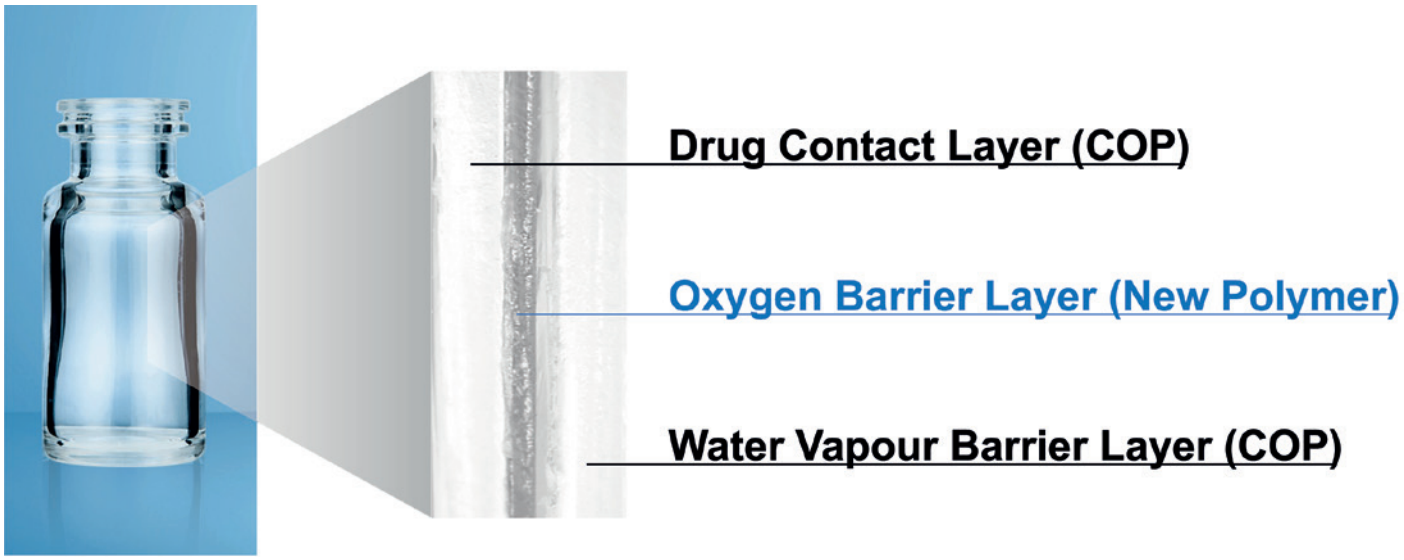


Figure 2: Multilayer structure of OXYCAPT.

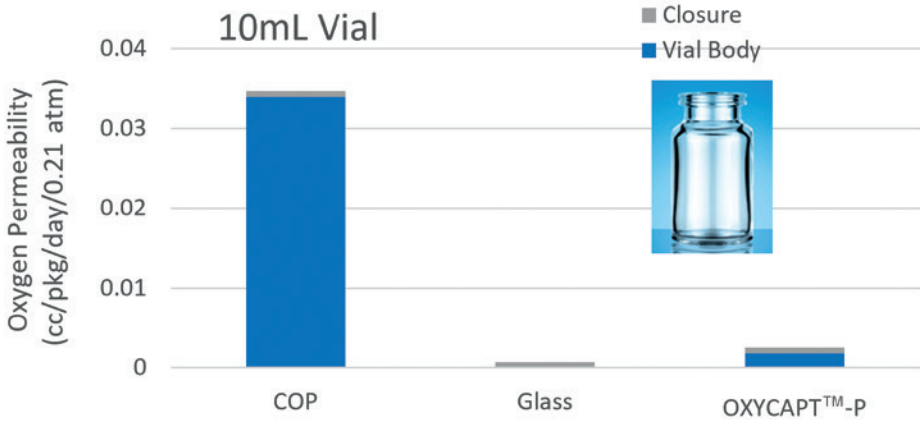


Figure 3: Oxygen permeability comparison of a typical COP, glass and OXYCAPT-P.

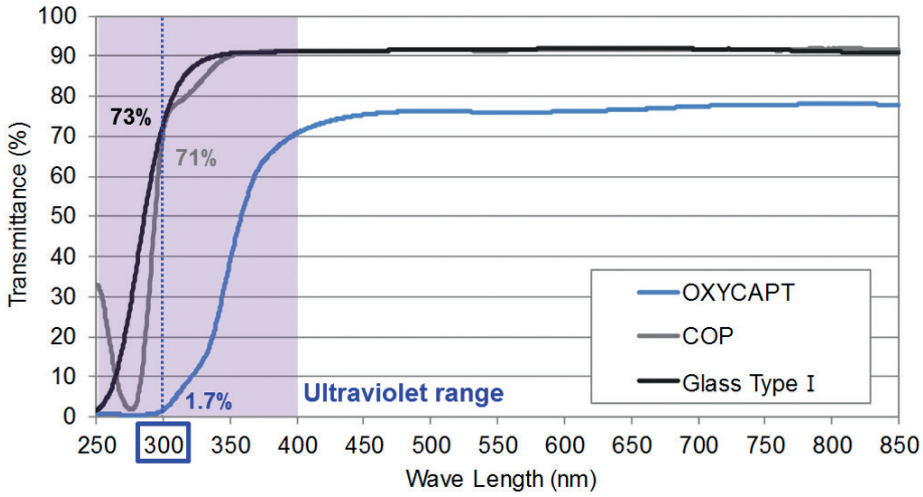


Figure 4: UV light transmittance comparison of a typical COP, Type 1 glass and OXYCAPT.

"The oxygen barrier of an OXYCAPT-P vial is about 20 times better than that of a COP monolayer vial."

MGC recently obtained a report on the environmental impact of glass and plastic containers for medical use from a Japanese research company. The report shows that plastic containers for medical use are much more environmentally friendly compared with glass containers. For example, the carbon footprint, nitrogen oxides (NO_x) emissions, sulfur oxides (SO_x) emissions and water consumption associated with plastic containers for medical use are several times smaller than those of their glass equivalents.

Furthermore, OXYCAPT provides an excellent UV barrier. While about 70% of 300 nm UV light transmits through glass and COP, only 1.7% transmits through OXYCAPT (Figure 4). MGC has confirmed that this feature contributes to the stability of biologics.

While OXYCAPT cannot reach the performance of glass with respect to acting as a water vapour barrier, its properties are similar to those of COP, which has been used for injectable drugs for a long time. This means that OXYCAPT easily meets the requirements of a water vapour barrier set out by the International Council for Harmonisation (ICH) guidelines.

Studies have shown an extremely low level of extractables from OXYCAPT. One study was conducted to confirm the levels of volatile, semi-volatile and non-volatile impurities from OXYCAPT. Water and four solutions (50% ethanol, sodium chloride, sodium hydroxide and phosphoric acid) were selected and impurities were measured by gas chromatography mass spectrometry (GC-MS) and liquid chromatography-UV spectroscopy-mass spectrometry (LC-UV-MS) after 70 days at 40°C. Compared with the control,

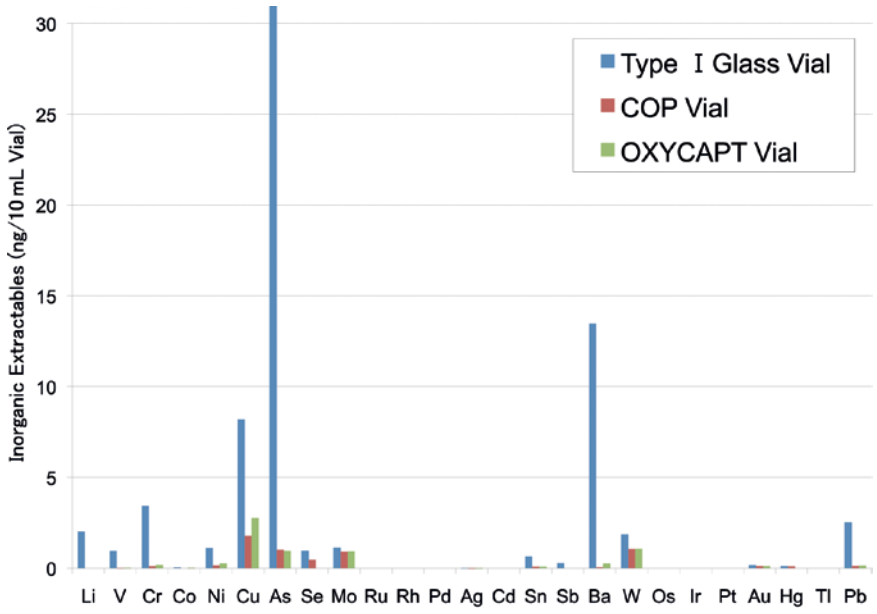


Figure 5: Comparison of inorganic extractables found in COP, Type 1 glass and OXYCAPT.

ISO Vial	Height (mm)	Outer Diameter of Body (mm)	Outer Diameter of Crown (mm)	Inner Diameter of Crown (mm)	Option
2R (2 mL)	35	16	13	7	Bulk or RTU
6R (6 mL)	40	22	20	12.6	Bulk or RTU
10R (10 mL)	45	24	20	12.6	Bulk or RTU
20R (20 mL)	55	30	20	12.6	Bulk or RTU

Table 1: MGC's OXYCAPT product portfolio.

impurities were not detected in the OXYCAPT containers. A second study confirmed that inorganic extractables levels from OXYCAPT were similar to those from COP, which is well known for being an extremely pure polymer with a better extractables profile than Type 1 glass (Figure 5). Lower levels of inorganic extractables are known to contribute to better pH stability in drug products.

The OXYCAPT vial is produced by co-injection moulding technology. MGC has also developed inspection methods for testing the oxygen barrier layer. All the containers are fully inspected by state-of-the-art inspection machinery.

MGC can offer bulk vials and ready-to-use (RTU) vials, with its RTU products provided in standard nest and tub formats. The nest and tub are mainly sterilised using gamma rays. There are 2, 6, 10 and 20 mL variants for vials (Table 1). MGC is willing to provide samples for initial testing free of charge.

Each polymer meets the requirements of US Pharmacopeia (USP) regulations USP<661>, USP<87> and USP<88>, as well as those of the European Pharmacopoeia, and has been filed in the US FDA's drug master file (DMF). The vials are also compliant with each pharmacopoeia and have been filed in the DMF.

> "OXYCAPT is well suited to emergency adrenaline, which is well known as an oxygen-sensitive drug."

The primary target market for OXCAPT is the therapeutic application of biologics. As mentioned in ICH Q5C (Stability of Biotechnological/Biological Products), oxidation is one of the causes of protein instability. As such, the oxygen and UV barrier properties of OXYCAPT will definitely contribute to the stability of biologics stored within. Additionally, MGC believes that OXYCAPT is well suited to emergency adrenaline (epinephrine), which is well known as an oxygen-sensitive drug. Furthermore, some drug developers have recently started evaluating the OXYCAPT vials for their gene and cell therapies; the RTU vial is sterilised by gamma radiation, making it ideal for protein-based drugs.

OXYCAPT AT VERY LOW TEMPERATURES

To verify the suitability of OXYCAPT for drugs stored at very low temperatures, MGC carried out studies using OXYCAPT vials. As customers often ask about the durability of OXYCAPT at low temperatures, MGC conducted quick defrosting and dropping tests. Firstly, the vials were stored in a freezer at -80°C for one day. After being removed from the freezer, the frozen vials were immediately dipped into hot water (40°C) for 15 minutes. No breakage, leakage or layer separation was detected in any of the vials (Figure 6).

A further test was conducted where the vials were stored in a freezer at -80°C for one-week, six-month and 24-month periods. After being removed from the freezer, the vials were immediately dropped

Figure 6: No breakage, leakage or layer separation was found after the quick defrosting test (-80°C to 40°C).

onto a steel plate from a height of 1.5 m. No breakage or leakage was detected in any of the vials for any length of time in cold storage.

The same dropping test was conducted using OXYCAPT and COP monolayer vials that had been stored at approximately -180°C, as regenerative medicines such as gene and cell therapies are often preserved in liquid nitrogen gas-phase freezers. After being removed from the liquid nitrogen gas-phase freezer, the vials were immediately dropped to a steel plate from a height of 1.5 m. Although eight of the COP-monolayer vials were broken (Figure 7), no breakage or leakage was detected in any of the OXYCAPT vials (Table 2). For clarification, as it was considered obvious that glass vials would shatter as a result of these tests and present a safety risk to the experimenters, glass was excluded from the test.

DMSO RESISTANCE

Dimethyl sulfoxide (DMSO) is often used as a cryoprotectant for gene and call therapies because it has been demonstrated that it can prevent the intracellular freezing that causes cell death. As MGC is often asked by customers about OXYCAPT's DMSO resistance, the company conducted some related studies. OXYCAPT 10R vials with polytetrafluoroethylene (PTFE) stoppers were filled with 10 mL of 10% or 20% by weight DMSO solutions and stored at 40°C for 70 days. Then, volatile impurities were measured by headspace gas chromatography/mass spectrometry (HS-GC/MS) and gas chromatography/mass spectrometry (GC/MS) while non-volatile impurities were measured by ultra-high performance liquid chromatography/ion trap Fourier transform mas spectrometry (UHPLC/IT-FT-MS). No impurities derived from OXYCAPT vials were detected in the either the 10% or 20% by weight DMSO solutions (Table 3).

Figure 7: Broken COP vial after drop test following storage at -180°C.

	OXYCAPT Vial	COP Monolayer Vial
Breakage	0/20	8/20
Leakage*	0/20	8/20

** Dropped vials were stored at room temperature until the frozen water was defrosted and then leakage was observed.*

Table 2: Breakage and leakage from COP and OXYCAPT vials stored at -180°C.

CONCLUSION

These latest results have contributed to MGC's ongoing studies verifying OXYCAPT's superior properties for biologics and gene and cell therapies. In addition to the advantages of COP, such as a strong water vapour barrier, high break resistance, very low extractables and low protein adsorption, OXYCAPT also provides a strong oxygen and UV barrier. MGC believes that OXYCAPT offers a multitude of benefits to the rapidly growing field of biologics and gene and cell therapies.

ABOUT THE COMPANY

Mitsubishi Gas Chemical is a major chemical products manufacturer, operating across a wide range of fields, from basic chemicals to fine chemicals and functional materials. In 2012, MGC established a new division as a centre for continually creating new businesses. In the field of drug delivery, the company has developed the OXYCAPT plastic vial and syringe as an alternative to glass containers.

Analytical Method		Target Materials	OXYCAPT-P Vial		Type I Glass Vial
			10wt% DMSO aq.	20wt% DMSO aq.	20wt% DMSO aq.
HS-GC/MS		Volatile impurities	ND from vial*	ND from vial*	ND from vial*
GC/MS			ND	ND	ND
UHPLC/IT-FT-MS	Positive mode	Non-volatile impurities	ND from vial*	ND from vial*	ND from vial*
	Negative mode		ND	ND	ND

** Two kinds of impurities were detected from both OXYCAPT and Type 1 glass. As the impurities were of the same kind, it is believed that these were derived from the closures.*

Table 3: DMSO resistance of OXYCAPT.

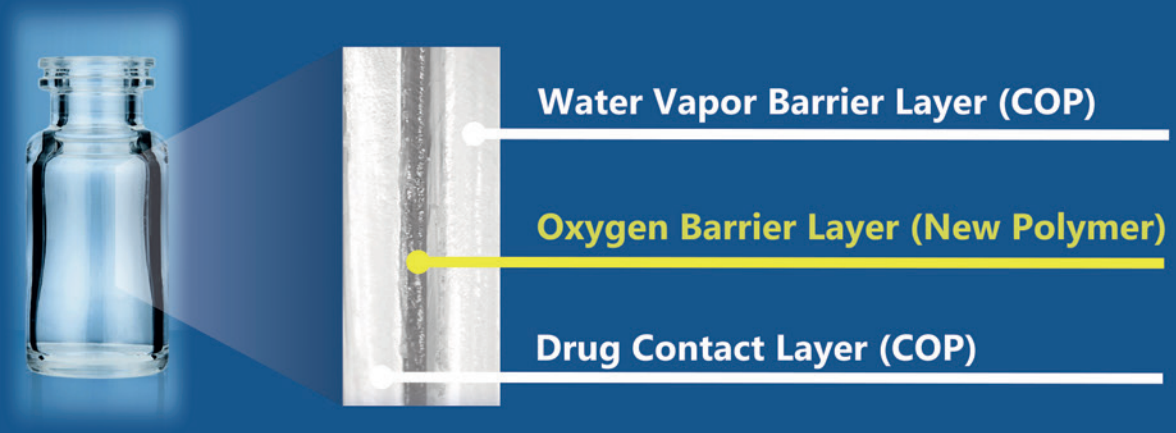
ABOUT THE AUTHORS

Yasuaki Yoshimura is a researcher at MGC, having joined the company in 2011. Until 2021, he was in charge of developing novel transparent resins with high heat resistance and excellent optical properties, after which he became a member of the OXYCAPT development team. Since joining the OXYCAPT team, Mr Yoshimura has been in charge of designing and synthesising the resins used for the middle layer of OXYCAPT containers, making prototypes of containers and developing new grades of OXYCAPT.

Tomohiro Suzuki graduated from Waseda University (Japan) in 1997 and joined MGC in 1998. He belonged to the Oxygen Absorbers Division until 2011, after which he was transferred to the Advanced Business Development Division in 2012 to be a member of the OXYCAPT development team. Since then, he has been in charge of marketing for the OXYCAPT vial and syringe. His current position is Associate General Manager.

OXYCAPT™ Multilayer Plastic Vial

Multilayer Structure



- Excellent Oxygen Barrier
- High Water Vapor Barrier
- Very Low Extractables
- Low Protein Adsorption
- Excellent Ultraviolet Barrier
- High Break Resistance
- High pH Stability
- Gamma-sterilized Vial
- For Biologics & Regenerative Medicine
- Customizable

2, 6, 10, 20mL Vial

Nest & Tub for Vial

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ENGINEERING ADVANCES IN NEEDLE GEOMETRY TO ACCOMMODATE VISCOUS BIOLOGICS

In this article, Silvia Gallina, Product Management Team Member for Syringe Platform at Stevanato Group, discusses the challenges faced in administering highly viscous biologics to patients via subcutaneous injection, and how Stevanato Group's new special thin-wall needles are able to tackle them.

In many ways, drug delivery can be regarded as a science of managing variables. The variables in question might be influenced by, for example, evolving market requirements, advances in technological capabilities or the emergence of breakthrough treatments. Alternatively, the status quo might be challenged by the continual push to innovate around patient needs, whether in terms of maximising therapeutic benefit, reducing exposure to risk or providing a better drug delivery experience overall.

One area where such challenges have given rise to new and evolving variables is in the parenteral delivery of biologics and the associated requirement to handle high-viscosity formulations. Another example can be seen in the healthcare industry's transition towards increased levels of drug self-administration in the home rather than in traditional clinical settings. At the intersection of these two examples, further challenges have arisen in the effort to deliver viscous biologics via patient-controlled injection devices.

This article reflects on these trends, exploring the questions they pose in relation to drug delivery and the associated issues that can arise for patients. It then goes on to explain how Stevanato Group is supporting pharma companies in responding to these challenges, specifically focusing on the development of a special thin-wall needle that fulfils the growing need for managing the delivery of viscous injectable formulations within autoinjector devices.

RESPONDING TO THE GROWTH OF THE BIOLOGICS MARKET

The biologics market is expected to continue to grow in the coming years. Differing market projections vary in the extent of this growth, but there is general acceptance that sales of biologic compounds will outstrip those of small molecules in the near future, possibly by as much as US$120 billion (£101 billion) by 2027.[1]

Digging deeper, monoclonal antibodies are expected to make up the most significant share of biologic sales, while high-growth areas include gene therapies and gene-modified cell therapies. Biosimilars are also forecast to register sustained double-digit growth as exclusivity arrangements end, triggering a rise in competition, demand and uptake over time.

> "Due to the complex structure of biologics, their physical and chemical stability is a constant concern due to the sensitivity of their formulations, with stimuli such as temperature posing a risk to their structural integrity."

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Looking at the properties of these drugs, there continue to be limitations when it comes to administration. Due to the complex structure of biologics, their physical and chemical stability is a constant concern due to the sensitivity of their formulations, with stimuli such as temperature posing a risk to their structural integrity. They are also susceptible to degradation through processes such as aggregation and denaturation.

Taken together, these characteristics have historically made parenteral administration via injection or intravenous (IV) infusion the preferred delivery methods to maximise the bioavailability of biologics. Parenteral delivery does not come without compromises, however. For the patient, there is the need to rely on a healthcare professional (HCP) to administer IV infusions, which can necessitate visiting a clinic, with the associated personal burden for patients and caregivers, particularly where frequent dosing is required.

Self-administration via subcutaneous (SC) injection, including the use of autoinjectors, provides an alternative solution here. However, injection opportunities are limited by the volume of drug acceptable to the patient, which is generally acknowledged to be between 1 and 2 mL, although more recently this ceiling has been increased to around 3 mL.

At a fundamental level, maintaining SC injection volumes within these thresholds may require reformulation, resulting in the creation of high-concentration formulations. However, with increasing concentrations come increasing levels of viscosity, which can have implications for injection force – and therefore injection time – unless the gauge of the needle is increased. As such, a proper evaluation of the container must be performed from the earliest stages of drug development in order to meet injection time requirements, while also keeping focus on the overall patient experience.

LIMITING INJECTION FORCE AND TIME — OPTIMISING THE PATIENT EXPERIENCE

Many factors contribute to the overall sensation of pain associated with an injection, from the location on the body to the injecting action and the nature of the formulation, including make-up and volume. While it is not possible to manipulate and resolve all these variables, certain key elements can be addressed to help limit pain, including the thickness of the needle wall.

Figure 1: The enlarged internal channel diameter of sTW needles enables a smooth delivery of highly viscous biologic solutions without the need for higher gauge needles.

"With a thinner wall, the internal diameter and volume of the needle chamber are increased to allow the formulation to flow more easily without increasing the needle's overall diameter."

With a thinner wall, the internal diameter and volume of the needle chamber are increased to allow the formulation to flow more easily without increasing the needle's overall diameter. This means that the required glide force and injection time can be reduced for viscous formulations without necessitating the selection of a higher gauge needle, and thereby reducing the pain experienced by the patient.

This has clear benefits for the patient experience, which can encourage improved adherence. It also helps address potential mechanical challenges associated with autoinjector devices, where higher break-loose and glide forces can lead to an increased risk of breakage and, therefore, drug wastage.

Stevanato Group, due to the intimacy of its pharma relationships and its deep understanding of patient needs, is always evaluating how progress can be realised in relation to technical challenges such as this through advances in design, engineering and chemical science. As a result, Stevanato Group has developed a special thin-wall (sTW) needle that optimises the delivery of viscous biologics without requiring the use of higher gauge needles (Figure 1), thereby satisfying autoinjector device requirements and enhancing the patient experience.

Available in 27G and 29G, the 0.5 inch needles with five-bevel tips are manufactured from AISI 304 stainless steel and have been designed to meet the requirements of Stevanato Group's high-performance Nexa® and Alba® container platforms in terms of dimensional performance, cosmetics, penetration and breakage. sTW needles are currently applicable to 1 mL long and 2.25 mL syringe formats, with the main target being autoinjector-based biologics.

THE CORRELATION BETWEEN NEEDLE DIAMETER AND GLIDE FORCE

To analyse the comparative performance of the sTW needles against standard thin-wall (TW) needles, a series of in-house tests was undertaken by Stevanato Group. These studies were designed to gather data on the quality attributes of sTW needles and the characteristics they display in combination with rigid needle shields (RNSs) and when deployed within an EZ-fill® configuration.

The tests were carried out by trained personnel according to approved methodologies and with a statistically valid number of randomised samples. Performance was verified after three and six months based on accelerated and real-time conditions according to ASTM F-1980 and ICH Q1A guidelines. Tests on breakage, elasticity, flexural strength and glycerine colouring were performed in accordance with ISO 9626 and Korean Pharmacopeia standards.

For the EZ-fill® syringes incorporating the sTW needles, this included testing for needle axiality, hooks needle and cosmetics. Furthermore, performance remained within Nexa® specifications for the sTW after the three- and six-month storage periods. It can therefore be concluded that an enlarged channel diameter, as provided by sTW needles, does not impact performance in terms of cosmetics or mechanical resistance.

Subsequent testing was carried out to analyse sTW syringe glide force reduction when a highly viscous solution is present. This was achieved by filling 1 mL long syringes 27G TW and 27G sTW with different solutions: 1 cP and 15 cP glycerol solutions. Syringes were then tested for glide

force at a consistent rate of 100 mm per minute and 250 mm per minute to simulate the speed observed during manual and autoinjector injections respectively.

As shown in Figures 2 and 3, in every case, the sTW needle registered a lower glide force than the counterpart standard TW needle. Furthermore, it could be seen that the reduction in glide force became more significant as the viscosity of the solution increased – a 3 N glide force reduction with the 15 cP solution through a sTW needle (Figure 2). Additionally, the effect is also more significant at higher plunger stroke speeds – a 6 N glide force reduction with the 15 cP solution through a sTW needle at 250 mm/min (Figure 3).

AN UNCOMPROMISING APPROACH TO THE MANAGEMENT OF VARIABLES IN DRUG DELIVERY

As these tests show, the sTW needle for the Nexa® and Alba® container platforms, using both 1 mL long and 2.25 mL syringe formats, can reduce the glide force for highly viscous solutions. As such, sTW needles avoid the need to move to a higher needle gauge to accommodate biologic formulations, which would have a detrimental effect on the patient experience.

As the biologics segment continues to grow in size and influence, and pharma companies look to deliver these life-changing drugs via patient-friendly devices and in patient-centric settings, new challenges will continue to arise. Managing all the variables at play can sometimes be a case of balance and compromise, but, as the development of the sTW needle shows, sometimes it is a challenge that can be answered directly through engineering expertise and innovative thinking.

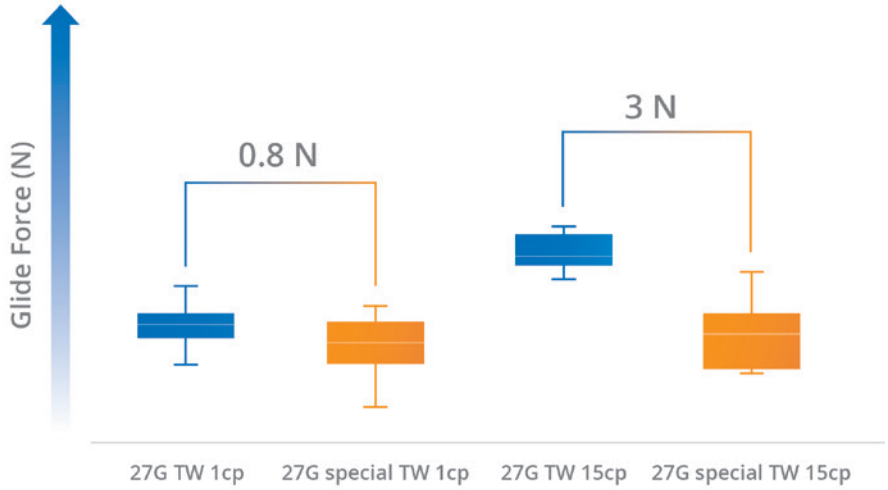

Figure 2: Glide force of 1 mL long Nexa® syringe with 27G TW and 27G sTW ½" needle filled with 1 cP and 15 cP solutions at 100 mm/min.

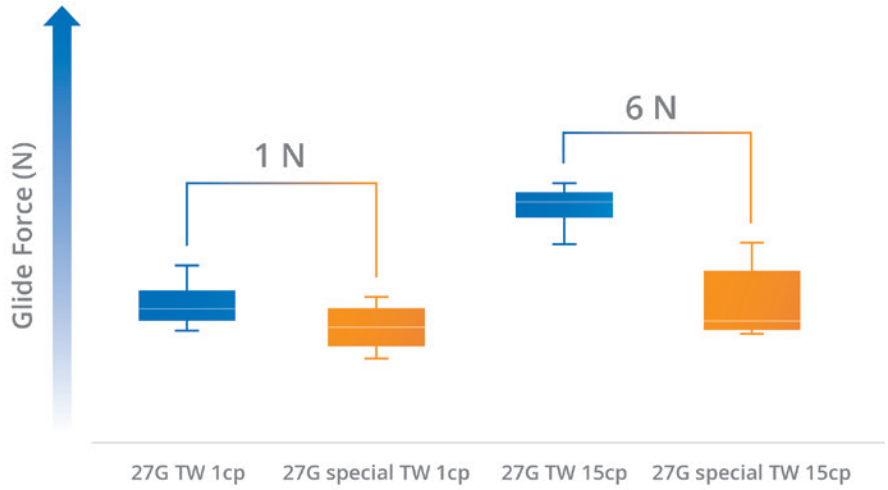

Figure 3: Glide force of 1 mL long Nexa® syringe with 27G TW and 27G sTW ½" needle filled with 1 cP and 15 cP solutions at 250 mm/min.

ABOUT THE COMPANY

Founded in 1949, Stevanato Group is a leading global provider of drug containment, drug delivery and diagnostic solutions to the pharmaceutical, biotechnology and life sciences industries. Stevanato Group delivers an integrated, end-to-end portfolio of products, processes and services that address customer needs across the entire drug life cycle at each of the development, clinical and commercial stages. Stevanato Group's core capabilities in scientific research and development, its commitment to technical innovation and its engineering excellence are central to its ability to offer value-added solutions to clients.

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Regular wall

Thin wall

Special Thin wall

Needle inner diameter increases reducing wall thickness

Its enlarged internal channel diameter has been designed for high-viscous biologic solutions without the need for bigger needles. This 27G ½" Special Thin-Wall needle thereby satisfies the auto-injector device requirements whilst enhancing the patient experience.

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Pro-Tects – A NOVEL SOLUTION TO THE CHALLENGE OF BIOLOGIC INSTABILITY

In this article, Shane Smith, PhD, Chief Executive Officer, Eoin Scanlan, PhD, Chief Scientific Officer, and Paula Colavita, PhD, Chief Technology Officer, all at Glycome BioPharma, discusses the difficulty inherent in developing parenteral biologic products due to the challenge of creating a stable formulation in the face of surface-mediated protein aggregation and introduces Pro-Tects – Glycome's patented surface-treatment technology platform that offers a solution to this critical issue without introducing further development challenges.

Biologic therapeutics are one of the fastest growing and most exciting areas in the modern pharmaceutical industry. This category of medicines is made up of large protein molecules, including monoclonal antibodies, and shows great promise in several disease areas, particularly oncology and autoimmune diseases. However, developing, formulating and delivering biologics is far from a trivial task, and several challenges remain to be overcome.

At present, the most common delivery method for biologics is the parenteral route; biologics are inherently delicate molecules, and so parenteral delivery is a natural choice to ensure that they are delivered intact. Specifically, many biologic developers are looking to prefilled syringes (PFSs) as the delivery device of choice, as they are convenient, avoid the need for manual filling required by vials and enable drug developers to design for at-home delivery – another major trend in the pharmaceutical industry.

However, PFSs are not without their own design challenges. Biologic drugs tend to either be large-volume or highly viscous – or both – when formulated for parenteral delivery. However, biologics are frequently subject to protein aggregation when formulated in this way, especially in glass syringes coated with silicone oil for lubricity. The challenge of developing a biologic formulation that remains stable is a critical concern for the pharmaceutical industry; solving it could be a key to unlocking the enormous potential of biologics.

> "Stabilisation issues have been known to result in project delays of over a year, with approximately 60% of respondents to a survey by Informa Pharma Intelligence reporting that such issues lead to significant delays, or even outright failure, of projects."

THE CHALLENGE OF STABILITY

The struggle to stabilise biologic formulations for parenteral delivery is a consistent factor in drug development project delays and setbacks. Stabilisation issues have been known to result in project delays of over a year, with approximately 60% of respondents to a survey by Informa Pharma Intelligence (London, UK) reporting that such issues lead to significant delays, or even outright failure, of projects.[1]

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The simple fact is that the longer a biologic drug development programme continues, it becomes increasingly expensive and decreasingly competitive, making these delays a major concern for the industry. Getting to market quickly can be a significant factor in the success of a project, especially if a competitor might get there first. The order in which products enter the market matters, with analysis data suggesting that the first and second products to enter the market typically obtain 70% of the overall market share between them.[2]

Therefore, it is evident that a solution to biologic stability for PFSs will be necessary to accelerate development timelines and achieve a desirable return on investment, as well as mitigate the potential safety concerns associated with protein aggregation.[3] The evidence suggests that one of the most significant causes of instability of biologics is surface-mediated aggregation – the interaction between the container materials, such as the silicone oil used in glass syringes, and the drug molecules.[4–6] As such, technologies looking to solve the stability problem focus on preventing these interactions.

One of the proposed solutions to the problem of stability is to circumvent the need for silicone oil by switching to cyclic-olefin polymer (COP) syringes.[7] There has been some uptake of COP PFSs, but there is hesitancy in the industry when it comes to switching away from glass. Glass is a well understood material, and the conservative nature of the pharmaceutical industry leads it to prefer working with the established over the new, especially where patient safety is concerned. This is true for plastic syringes, which may lead to aggregate generation when put under mechanical stress.[8]

To continue working with established glass syringes, other biologic drug developers are turning to alternative formulation technologies, such as adding surfactants. This is also not an ideal solution, as biologic formulations are already highly complex, and many are pushing the boundaries of acceptable volume and viscosity for parenteral delivery. As such, surfactants and similar technologies are challenging to work with and may result in their own development delays, ultimately failing to solve the problem at hand, simply replacing one cause for delay with another.[4]

> "Glycome BioPharma's technology enables a swifter time to market for drug development, increasing product competitiveness, and counteracts protein aggregation, improving compliance with safety and efficacy standards."

This leaves an urgent and unmet need for a stabilising technology that works with glass and is simple to implement, working with existing pharmaceutical practices and not contributing to further formulation complexity and production delays. As an expert in the field, Glycome BioPharma has met this need with its patented first-generation stabilisation platform for parenteral devices – Pro-Tects.

PRO-TECTS – THE GLYCOME BIOPHARMA SOLUTION

Glycome BioPharma has developed the patented Pro-Tects technology platform to provide intrinsic stabilisation to biologics in parenteral containers. Pro-Tects is a surface treatment for glass and olefin polymer parenteral containers that solves the problem of stabilising biologic molecules by preventing surface-mediated aggregation of the proteins.[4]

The Pro-Tects technology mitigates protein aggregation by denying the proteins sites where they can anchor to the surface of the syringe. The technology works by covalently binding immobilised sugars to the container-surface interface, thus blocking the protein aggregation mechanism and mitigating the traditional issues with using sugars as a stabilising agent.[4] Tests by Glycome BioPharma have demonstrated that this method is hugely successful at reducing aggregation and boosting the stability of biologics in containers using the Pro-Tects platform.

Glycome BioPharma drew the inspiration for using sugars to stabilise biologic drugs from the glycocalyx – the extracellular region of the cell membrane. The glycocalyx is a gel-like mesh containing glycoproteins and glycolipids that contribute to the steric repulsion that prevents undesirable objects from entering the cell. By basing its technology off this naturally occurring barrier, Glycome BioPharma has created a system that effectively and reliably mitigates the ability of proteins to aggregate by interacting with the container surface.

In offering a reliable way to stabilise parenteral biologic formulations, Pro-Tects alleviates the burden of complex formulation on drug development programmes. Glycome BioPharma's technology enables a swifter time to market for drug development, increasing product competitiveness, and counteracts protein aggregation, improving compliance with safety and efficacy standards.[9]

PRO-TECTS COMPARISON WITH UNTREATED GLASS

To establish the efficacy of the Pro-Tects solution, Glycome BioPharma conducted a series of tests that compared glass treated with Pro-Tects technology with regular, commercially available glass, including in glass syringes. The results demonstrated that the use of Pro-Tects overwhelmingly reduced protein aggregation at the container-surface interface and confirmed Pro-Tects's value in contributing to biologic formulation stability.

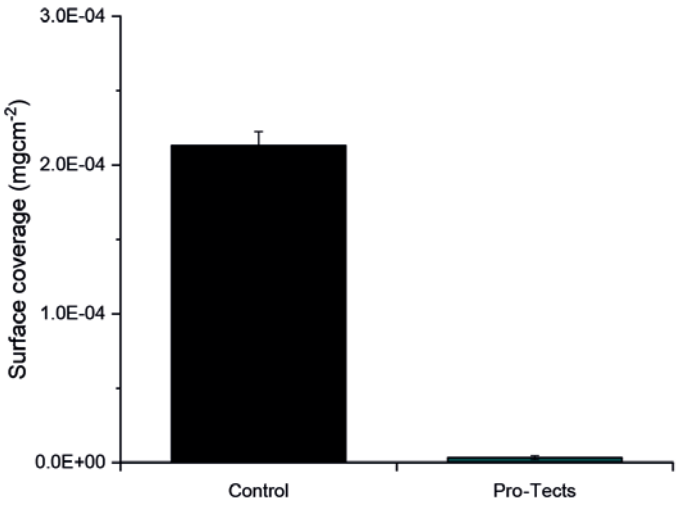

Figure 1: Type I borosilicate glass coupons, untreated (control) and functionalised with Pro-Tects, exposed to a 2 mg/mL solution of BSA-FITC. The amount of protein adsorbed on the surface of each coupon was measured by photoluminescence and normalised by the surface area exposed to it.

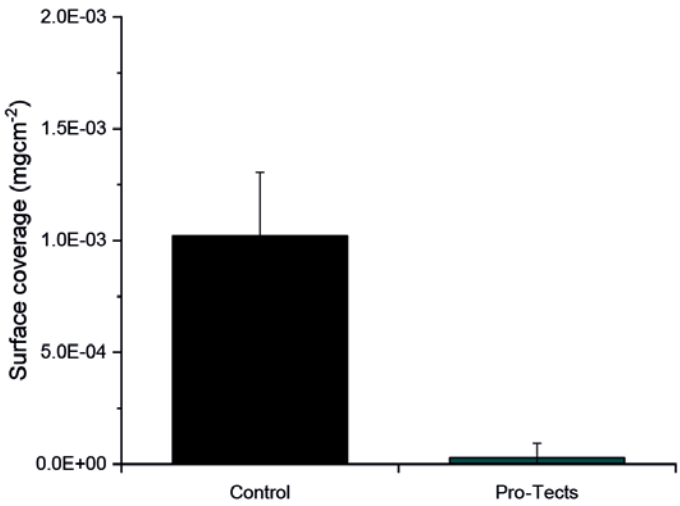

Figure 2: Type I borosilicate glass syringes, untreated (control) and functionalised with Pro-Tects, exposed to a 2 mg/mL solution of BSA-FITC. The amount of protein adsorbed on the surface of each syringe was measured by photoluminescence and normalised by the surface area exposed to it.

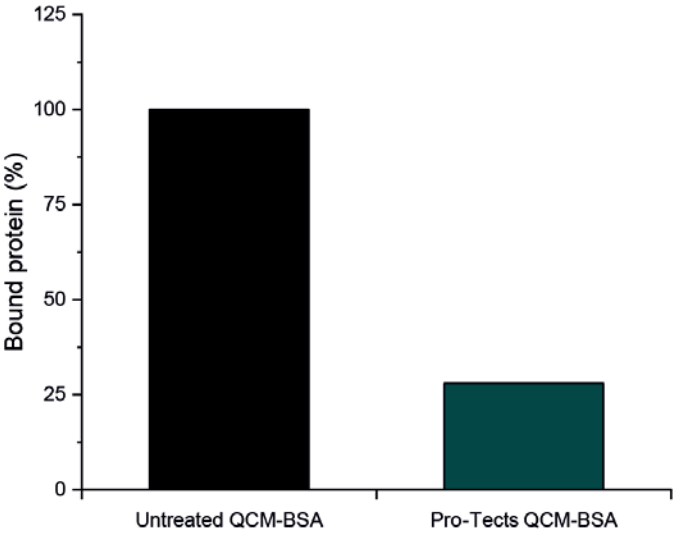

Figure 3: Type I borosilicate glass QCM sensors, untreated (control) and functionalised with Pro-Tects, were exposed to a 2 mg/mL solution of BSA. The binding of protein mass at the surface was measured and reported here as the amount of protein bound to the surface as a percentage, with the mass bound to the control assumed to be 100%.

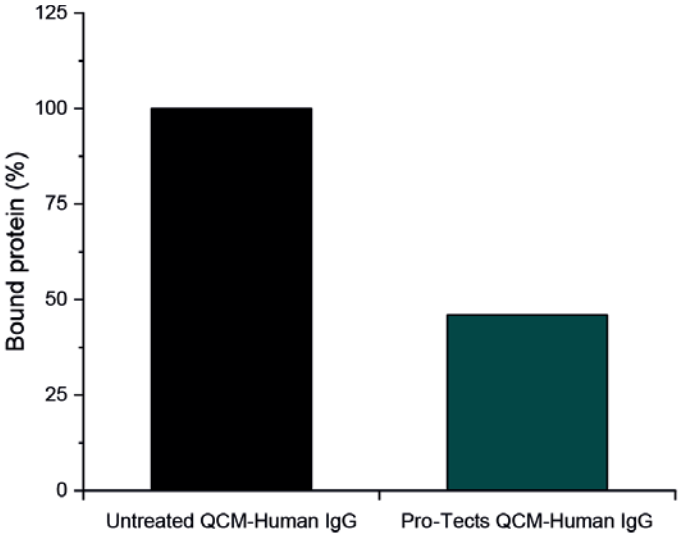

Figure 4: Type I borosilicate glass QCM sensors, untreated (control) and functionalised with Pro-Tects, were exposed to a 2 mg/mL solution of Human IgG. The binding of protein mass at the surface was measured and reported here as the amount of protein bound to the surface as a percentage, with the mass bound to the control assumed to be 100%.

BSA Protein Rejection on Glass Coupons

First, Glycome BioPharma compared the level of protein adsorption and aggregation of a model protein – bovine serum albumin conjugated with fluorescein isothiocyanate (BSA-FITC) – in untreated glass coupons with those treated with the Pro-Tects platform. Both the Pro-Tects-treated and untreated glass coupons were exposed to a solution of 2 mg/mL BSA-FITC. The glass coupons functionalised with Pro-Tects achieved an almost quantitative reduction in adsorbed protein, with the coated glass demonstrating a protein rejection of 98% (Figure 1).

BSA Protein Rejection on Glass Syringes

Next, Glycome BioPharma performed a similar test with commercially available glass syringes. As with the glass coupons, the syringes treated with Pro-Tects achieved an almost quantitative reduction in protein adsorption of the model BSA-FITC protein compared with those of untreated glass after contact with a 2 mg/mL BSA-FITC solution. In the case of syringes, the Pro-Tects-treated glass demonstrated a protein rejection of 97% (Figure 2).

Protein Rejection on Glass QCM Sensors

To further investigate the ability of the Pro-Tects platform to mitigate protein adsorption, Glycome BioPharma used quartz crystal microbalance (QCM) technology. QCM is an extremely sensitive mass balance that is able to detect changes in mass per unit area on a nanogram to microgram scale by monitoring changes in frequency as the quartz oscillates under an applied voltage.

Using Type I borosilicate glass QCM sensors, Glycome BioPharma was able to compare the mass of both Pro-Tects-treated and untreated glass after contact with a 2 mg/mL solution of BSA to determine the mass of protein that had adsorbed to the glass. As anticipated, the glass treated with Pro-Tects showed a

"Pro-Tects has no detrimental effect on syringe glide force and remains robust under a variety of adverse environmental stresses, including temperature, pH and sterilisation."

significant reduction in mass compared with the untreated glass. In this test, the Pro-Tects-treated glass achieved a final protein rejection of 72% (Figure 3).

A subsequent test investigated the mass of Type I borosilicate glass QCM sensors after contact with a solution of 2 mg/mL human immunoglobin G (IgG). As with BSA, glass treated with Pro-Tects demonstrated a significant decrease in bound IgG compared with untreated glass. For the IgG test, the Pro-Tects-treated glass achieved a final protein rejection of 54% (Figure 4).

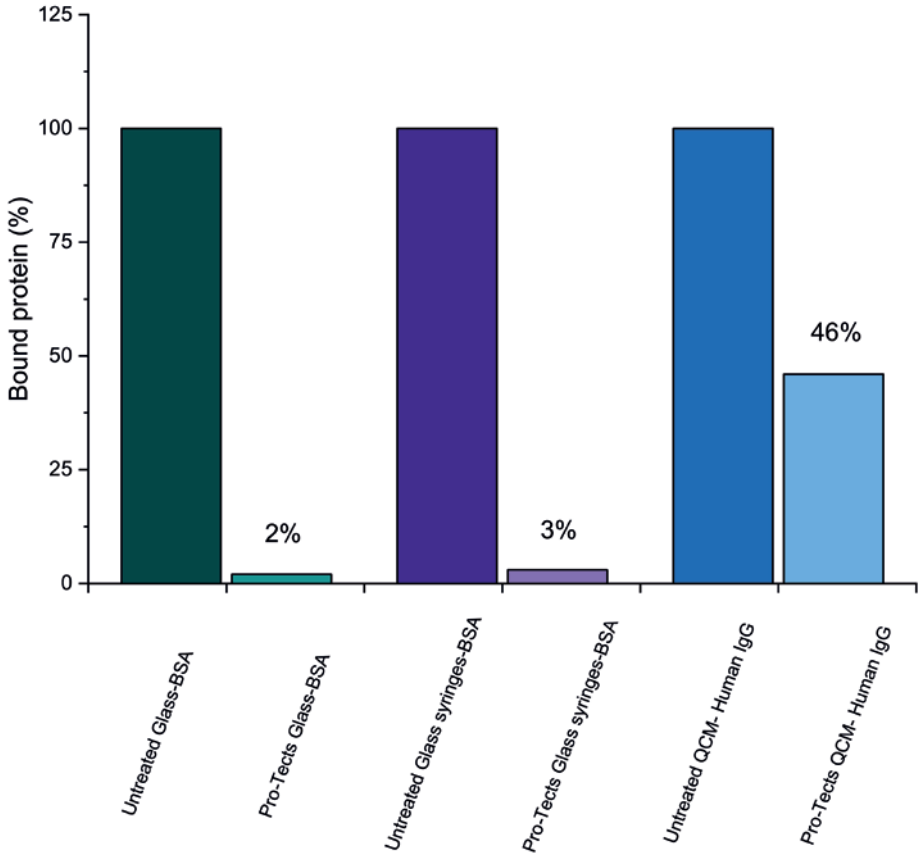

Figure 5: Type I borosilicate glass coupons and syringes, untreated (control) and functionalised with Pro-Tects, exposed to a solution of BSA-FITC alongside Type I borosilicate glass QCM sensors, untreated (control) and functionalised with Pro-Tects, exposed to a solution of Human IgG. The binding of protein mass at the surface was measured and reported here as the amount of protein bound to the surface as a percentage, with the mass bound to the control assumed to be 100%.

CONCLUSION

Surface-mediated aggregation of proteins is a critical factor when it comes to the stability of biologics. Stability is one of the critical challenges in biologic drug development, potentially creating additional risk both to drug efficacy and project timelines, leading biologics that struggle with stability to become less competitive. Therefore, any biologic development project looking to gain an edge needs an answer to the challenge of stability.

Glycome BioPharma has provided this answer with its patented Pro-Tects technology platform, an immobilised sugar treatment for glass syringes. As discussed in this article, Pro-Tects has demonstrated a significant reduction in bound proteins in both FITC and QCM sensor testing (Figure 5). Furthermore, according to Glycome BioPharma's internal data, Pro-Tects has no detrimental effect on syringe glide force and remains robust under a variety of adverse environmental stresses, including temperature, pH and sterilisation, which will be discussed in a future article.

Partnering with Glycome BioPharma will enable biopharmaceutical developers to accelerate and de-risk their drug development projects by implementing this exciting and novel technology, with no need to transition away from established and readily available glass syringes, or take on the formulation challenge of including surfactants and thereby increasing risk to their project from another angle. The Pro-Tects technology platform offers a reliable way to tackle the challenge of biologic stability without introducing additional production challenges, improving compliance with safety and efficacy and smoothing the way to market.

ABOUT THE COMPANY

Glycome BioPharma is a medical technology company that provides disruptive solutions to major challenges based on glycotechnology. Entrepreneurship and passion is the foundation for everything the company does and it aims to create technologies that will make a global impact. Glycome BioPharma creates value through strategic alliances, and identifying opportunities by following a need led innovation approach.

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ABOUT THE AUTHORS

Shane Smith, PhD, is an experienced innovator in medical technologies with a 10-year track record of business success and entrepreneurship. He earned his Master's in Medical Bio-Business and a PhD in Medical Sciences from University of Aberdeen. After his post-graduate studies, Dr Smith worked in a number of small-to-large-sized biotech companies, working his way up to a C-level position at BioCyto (Cork, Ireland). He is a director of PanEuro Venture Partners and sits on a number of high-growth company boards.

Professor Eoin Scanlan, PhD, is an accomplished organic and medicinal chemist with over 80 publications in international peer-reviewed journals. He leads an international research team in Trinity College Dublin (Ireland) with a focus on biomolecular synthesis, including peptides, proteins and glycoconjugates towards the development of novel therapeutics, diagnostics and biomaterials. Prof Scanlan is a PhD graduate of the University of St Andrews (UK) and completed his postdoctoral work at the University of Oxford (UK).

Professor Paula Colavita, PhD, has unique experience in the design and development of advanced functional materials. She is the author of over 80 publications in international journals and co-inventor of two patents and leads a research team at Trinity College Dublin (Ireland), whose activities focus on understanding and achieving control of interfacial processes and reactions. Prof Colavita completed her PhD at the University of South Carolina (US) and carried out postdoctoral research work at the University of Wisconsin-Madison (US).

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Formulation integrity

Reduced Risk of Immunogenicity

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Durability & Dimensional Consistency

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PERFORMANCE BENEFITS

Flexibility
Pro-Tects' drug contact surfaces can be customized to reduce burden of formulation development.

Inert Contact Surface
Pro-Tects offers the stabilising properties of natural glycans and does not involve use of leachable coatings or inorganic modifiers.

Stability & Shelf Life
Patented Pro-Tects barrier coating system enhances stability of biotherapeutics across a range of storage conditions (pH, temperature) thus assuring biotherapeutics efficacy and shelf-life.

Durability & Dimensional Consistency
Protects and preserves high value contents; offers higher dosing accuracy and better consistency with auto-injectors.

Formulation integrity
Pro-Tects reduces protein losses at the container wall hence maintaining biotherapeutic concentration and pre-filled formulation performance descriptors.

Reduced Risk of Immunogenicity
Protein aggregation triggered by interfacial stresses is a leading cause of adverse immune effects. Pro-Tects reduces protein aggregation, leading to reduced risk of adverse immune response.

CONGRUENCE
MEDICAL SOLUTIONS, LLC

NEXT-GENERATION AUTOINJECTOR PLATFORM FOR HIGH-DOSE DRUGS

In this article, Richard Whelton, Head of Business Strategy and Marketing at Congruence Medical Solutions, introduces the new Congruence Autoinjector, a next-generation disposable autoinjector platform, which leverages a compressed-gas power source and has significant advantages over currently available legacy devices, including the ability to deliver higher viscosity and larger volume drugs, easier customisation and enhanced usability that addresses well-known user errors.

Autoinjector devices have evolved significantly since their introduction in the 1980s to address the needs of patient self-injection.[1] However, fundamentally different delivery needs have emerged beyond what legacy autoinjector technologies are able to address. Of particular importance is the trend, primarily within biologics, towards high-dose formulations (above 250 mg), which tend to be highly viscous (50 cP+) and/or larger volume (2 mL+).

> "Current delivery approaches... for high-dose formulations can introduce compromises to the patient experience and/or pharma operations."

HIGH-FORCE DELIVERY TODAY HAS KEY TRADE-OFFS

Legacy, spring-based autoinjectors became prevalent when delivery was focused on small-volume, low-viscosity (water-like) drugs. To deliver larger volumes and/or higher viscosities, as is often required for high-dose formulations, springs need to be larger and bulky, meaning the autoinjector becomes bigger and noisier, with higher actuation and recoil forces. Insufficient force from springs can result in long injection-hold times and/or a compromise on needle size (lower gauge). Options with stronger springs have also been explored but with non-standard primary containers.

A new device category – wearable injectors – has emerged to address some of these issues. But the move away from the standard autoinjector format is a significant trade-off, given its generally high patient acceptance and the simplicity it offers to pharma operations. Overall, both current delivery approaches (larger autoinjectors and wearable injectors) for high-dose formulations can introduce compromises to the patient experience and or pharma operations.

Another approach is to use alternative power sources that can deliver higher forces in a standard autoinjector format – but here, too, key trade-offs have previously been made. For example, electromechanical autoinjectors come with high cost and sustainability concerns, causing them to be typically limited to reusable versions for chronic treatments requiring many injections. This means moving away from disposable devices, which are more convenient from a user standpoint, as well as impacting pharmaceutical operations' end-product support. Compressed gas power sources have also been introduced

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but have included drawbacks such as high actuation forces, reliability issues and the use of gases with poor sustainability profiles. A potential source of these issues is the use of gas containers and gas sources originally developed for applications outside drug delivery.

WELL KNOWN YET UNADDRESSED USER ERRORS

Beyond the energy source to power an autoinjector for high-dose drugs, there are also user errors that are currently unaddressed by legacy technologies, and which are potentially more impactful and/or common with high-dose drugs. For example, a well-known user error is premature removal from the skin before dose completion,[2] which can be caused by:

- Lack of clarity regarding end of dose
- Fatigue due to long hold times
- Patient startled by sounds at injection start or other accidental causes
- A painful injection site.

Currently, the injection cannot be paused once started, so this error typically results in expensive drugs being lost and the dose not being completed, which can affect clinical outcomes. Pharma companies may also have to bear the cost of replacing the lost or missed dose. The impact is greater for high-dose formulations, as they tend to be less frequently administered, more expensive and may involve longer hold times.

Another user error is when patients forget to let a drug warm up before injection. The colder temperature effectively increases the drug viscosity, which can jam legacy autoinjectors, which do not inherently have sufficient force to overcome the higher viscosity. The effective result with high-dose formulations is the waste of an expensive dose, as well as potential treatment delay due to the next dose not necessarily being on hand.

> "There is a compelling need for a next-generation autoinjector platform that extends the capability of autoinjectors beyond what is possible with legacy technologies."

The standard user-error mitigation approach with legacy autoinjectors has been the use of indicators and patient training. However, it is known that these alone are insufficient, and a better approach would be innovative autoinjector designs that reduce or eliminate the negative consequences of these errors altogether.[2] This would not only potentially reduce costs and improve treatment adherence but also enhance the patient experience by providing peace of mind.

Overall, there is a compelling need for a next-generation autoinjector platform that extends the capability of autoinjectors beyond what is possible with legacy technologies. What is needed is a true platform, designed to be suitable for the full range of current and future drugs – both standard and high-dose formulations – and that enhances usability and better meets key pharma needs throughout development and production, rather than forcing compromises.

CONGRUENCE'S APPROACH TO SOLVING UNMET AND EMERGING NEEDS

Congruence Medical Solutions designed the Congruence Autoinjector to be a next-generation platform, addressing key need-based criteria (Figure 1):

- **High force capability** – enabling drug delivery in situations where there is a large volume, high viscosity, cold temperature, fine injection needle or a combination of these factors.
- **Enhanced usability** – has the look and feel of widely used 1 mL disposable autoinjectors, while also addressing additional usability needs, especially for high-dose drugs.
- **Greater versatility** – suitable not just for high viscosity and large volume but also "standard" formulations to address a broad range of therapies in one platform.
- **Easier customisation** – for faster, low-risk device development.
- **Uses standard primary containers** – including glass prefilled syringes (PFSs).
- **Sustainability aligned**.

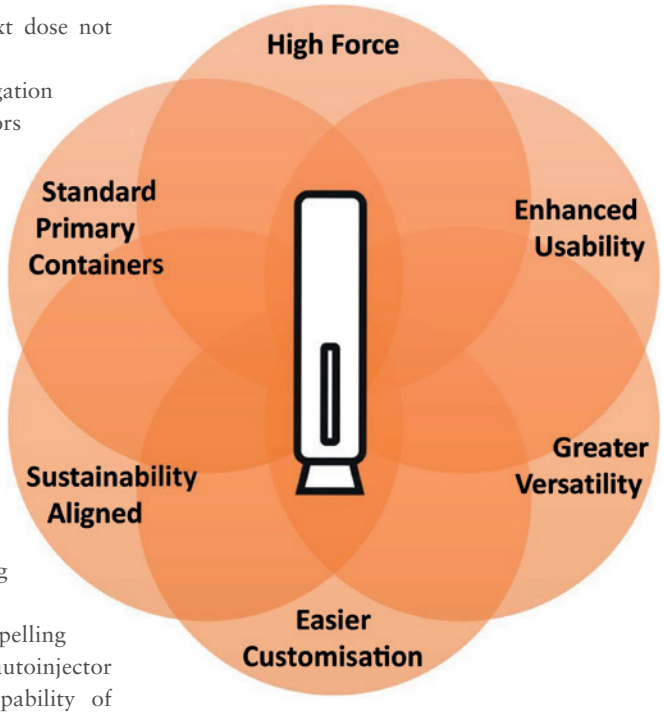

Figure 1: Key criteria for next-generation autoinjector.

The team at Congruence has decades of drug delivery device experience, but the company itself is a new autoinjector player. Therefore, as the team set out to find the optimal way to solve the unmet and emerging needs, it was unburdened by pre-existing technology or design, and avoided attempting to force legacy technology into a novel solution.

A pivotal decision point was the power-source selection, as it has a significant influence on the capabilities and size of an autoinjector (Figure 2). Ultimately, the company chose to proceed with compressed gas. This power source enables high injection forces for injecting drugs in standard primary containers without the impact shock observed in spring-based systems at the start of injection, as well as enabling easier customisation and assembly and a more compact device format with quieter delivery.[3]

When using compressed gas as a power source, there are other options to consider, such as gas type and gas-container design. To mitigate environmental and sustainability concerns, the Congruence Autoinjector uses an inert gas. The device also uses a customised, proprietary gas container to provide the flexibility to include novel usability features that address the issue of gas leakage, thereby minimising the actuation force and other potential issues. The proprietary compressed gas source, combined with the proprietary autoinjector

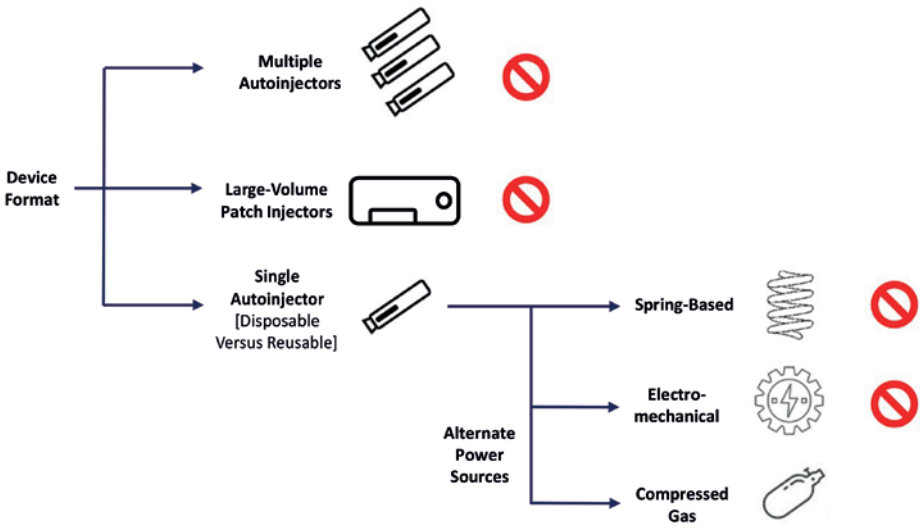

Figure 2: Key choices in injector design.

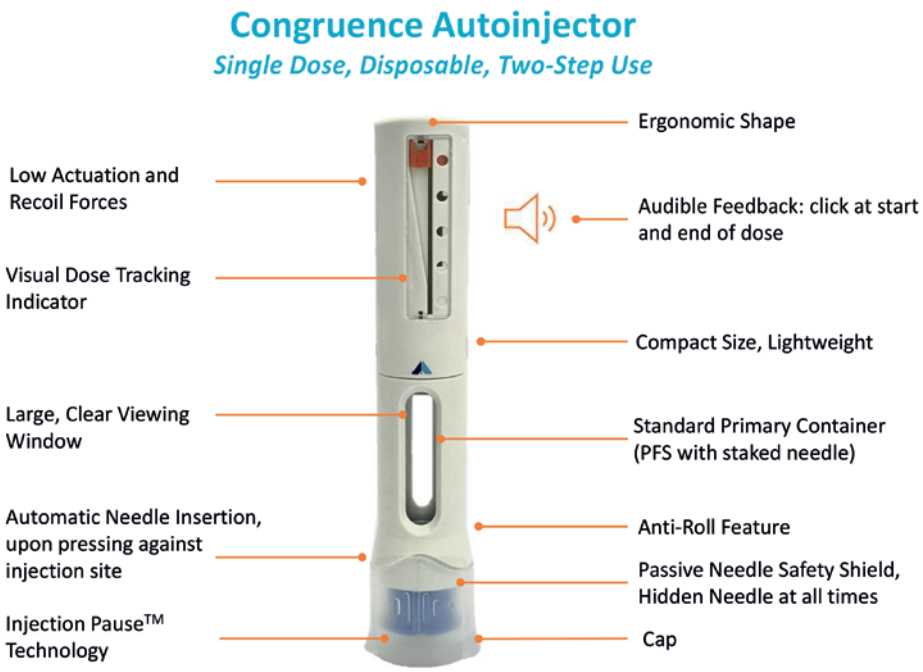

Figure 3: Congruence Autoinjector overview.

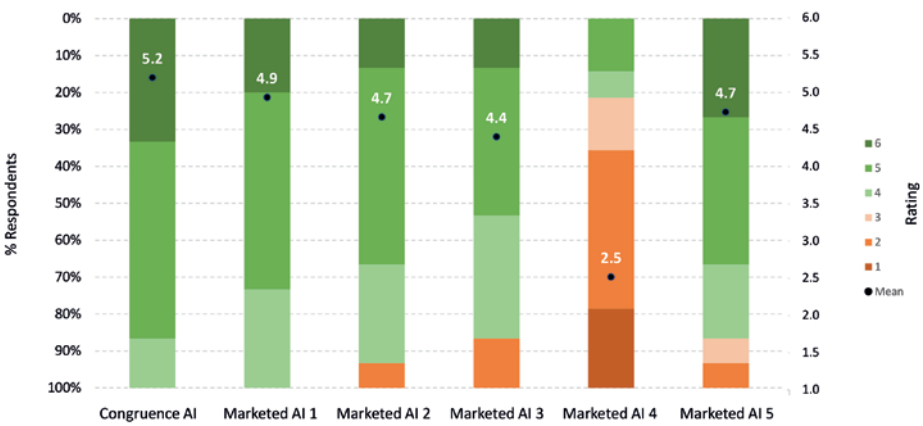

Figure 4: Acceptability of Congruence Autoinjector 2.25 mL form factor and mock-ups of marketed large-volume autoinjectors (6 = completely acceptable; 1= completely unacceptable) (n=15).

design, allows for further customisation opportunities that are not possible with currently available autoinjectors.

In terms of the core usability and functionality of the Congruence Autoinjector, the team chose to include base features aligned with what is typically expected in currently available autoinjectors as a minimum (Figure 3). It is a two-step autoinjector, requiring the user to simply remove the cap, place on the skin and push down to activate automatic needle insertion. There are standard visual and audible indicators across the start, progression and end of dose, including a large, clear drug viewing window. The needle is hidden at all times, and at the end of the dose a proprietary passive needle-safety shield deploys and locks.

HIGH INJECTION FORCE CAPABILITY IN A COMPACT SIZE

The Congruence Autoinjector can deliver a range of injection forces, from low to very high, and is readily adjustable. It is capable of rapid drug delivery even in situations with a large drug volume, high viscosity, cold temperature, fine injection needle or a combination of these factors. As an example, one embodiment of the Congruence Autoinjector has been shown to deliver 2.25 mL of 100 cP solution in 15 seconds from a glass PFS for biologics (SCHOTT's syriQ BioPure®) with a 27G staked needle.

Crucially, the Congruence Autoinjector can deliver high forces while incorporating standard primary drug containers, including glass syringes. Therefore, pharma companies do not need to deal with the arduous and expensive process of validating and using novel primary containers. Furthermore, the proprietary compressed gas source design enables very low, imperceptible actuation (3N) and recoil forces, as confirmed in a Congruence user study.[4]

In comparison with many large-volume and high-viscosity autoinjectors, the Congruence Autoinjector has an ergonomic shape and compact size. With a 2.25 mL PFS incorporated, the dimensions for one embodiment are 14.1 cm height and 2.4 cm width – which is the same or smaller than most conventional, commercially available 1 mL autoinjectors, and likely smaller than most 2.25–5 mL autoinjectors incorporating legacy technologies. A Congruence user study showed the 2.25 mL Congruence Autoinjector form factor was well accepted

by patients and healthcare professionals (HCPs) – equivalent to commercially available 1 mL autoinjectors (Figure 4).[4] It is therefore suitable for injections using either a 2.25 mL PFS or 1 mL long PFS.

The compact size also aligns with sustainability objectives – it results in fewer device materials, lower transportation weight, smaller packaging and a reduced cold-chain footprint. Sustainability can be further enhanced through manufacturing and material strategies.

Table 1 indicates one reason why the Congruence Autoinjector is so compact. It shows the relationship between syringe size (or, more specifically, syringe cross-section) and delivery force required. For larger drug volumes, larger syringe sizes are needed, which in turn results in higher injection forces. For a spring-based autoinjector, this would mean different, larger springs are progressively required, whereas for the Congruence Autoinjector, the same compressed gas source provides an increased injection force as syringe cross-section increases.

	1 mL	2.25 mL	10 mL
Syringe cross-section (mm^2)	31	58	165
100 cP injection force (N)	35	70	194
Compressed spring source			
Force (N) from 200 psi compressed gas source	 **43**	 **80**	 **227**

Table 1: Force (N) from 200 psi (example) compressed gas source by syringe size.

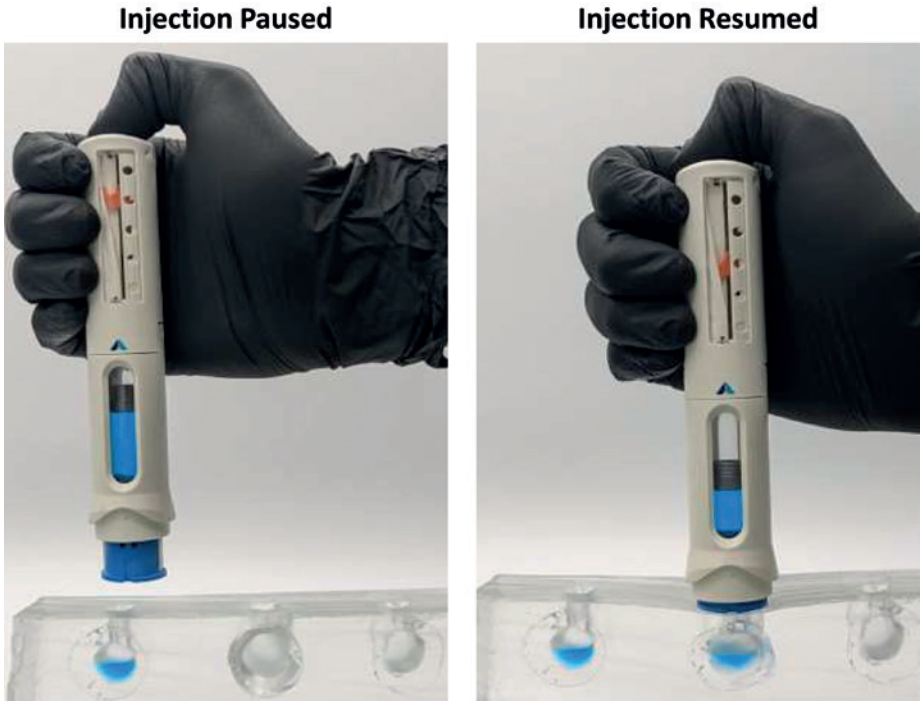

Figure 5. Congruence Injection Pause™ technology and novel visual dose progress indicator address premature removal from skin, increasing potential for full-dose delivery.

NOVEL FEATURES ENHANCE USABILITY

The Congruence Autoinjector truly addresses key user errors, including premature removal from skin before dose completion – both its potential impact and frequency – as well as cold-drug injections.

The unique Injection Pause™ feature and a novel Visual Dose Progress Indicator work in combination to mitigate the impact of premature removal (Figure 5). The Injection Pause™ feature pauses the injection if the device is removed from the skin before dose completion, ensuring that no drug is lost. The visual dose progress indicator shows the amount of dose remaining, enabling patients to have a more informed conversation with their HCP. They can also continue the dose to completion if desired, as the Injection Pause™ feature allows needle reinsertion and injection resumption. The needle always remains hidden, and the passive needle-safety shield locks only once the full dose is delivered.

Reduced incidence of premature removal and incomplete dosing is addressed in several ways, alongside mitigation of cold-drug injection. The visual dose progress indicator ensures that the user knows how far an injection has progressed, which is even more crucial with cold drugs as the injection time can change, the quiet injection reduces the potential for patients to be startled or concerned, and the high injection force reduces the chance of the device jamming due to cold-drug injection.

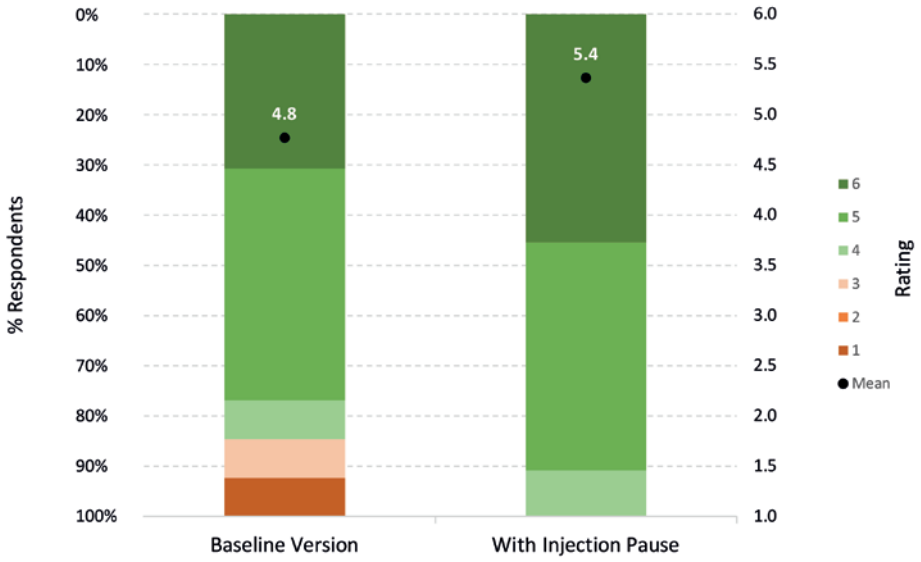

Figure 6: Acceptability of Congruence Autoinjector – with and without Injection Pause™ technology (6 = completely acceptable; 1= completely unacceptable) (n=15).

In an initial Congruence user study, these novel features were well received by patients and HCPs (Figure 6).[4] Any concerns regarding reinsertion with the same needle are mitigated by the fact that there are examples of other approved therapies involving needle reinsertion.[5,6] Furthermore, any perception of risk (valid or otherwise) was viewed by participants as being outweighed by the significant benefits – especially the extra confidence that the full dose would be received at the right time, as well as an overall better injection experience. The potential to reduce drug (and device) waste was also seen as sustainability aligned and reducing the cost burden on pharma companies to replace lost doses.

SINGLE PLATFORM WITH GREATER VERSATILITY

An ideal self-injection device platform should accommodate a wide range of drug-specific requirements, such as drug formulation changes during development, if a drug has different dosing options or if a pharma company wants to leverage the device across a drug portfolio.

The Congruence Autoinjector platform addresses a broad range of possible viscosity and volume requirements, as well as minimising customisation time and cost, including for parameters such as:

- Drug viscosity: 100+ cP
- Syringe size and type: ISO 11040 compliant standard glass syringes – 1 mL long, 2.25 mL and 5 mL; plus different fill volumes (design is agnostic to fill volume). Cartridges also possible for 5 mL+
- Target injection time: typically <15s
- Standard needle gauges
- Same form factor for 1 mL and 2.25 mL is possible.

The combination of proprietary power source and specific autoinjector design is key to enabling the range and speed of these customisations. In addition, the autoinjector can be adapted to accommodate different external look and feel options.

> "The Congruence Autoinjector platform addresses a broad range of possible viscosity and volume requirements, as well as minimising customisation time and cost."

Property	Congruence Autoinjector Specification
Key needs addressed	Viscous, large volume
Device type	Autoinjector
User profile	Caregivers, patients, HCPs
Administration route	Subcutaneous, intramuscular
Primary container format	1 mL long, 2.25 mL or 5 mL standard prefillable syringe; drug cartridge option possible
Primary container material	Glass or polymer
Usage	Single dose; disposable
Dosage type	Fixed
Dose volume	0.3–2.25 mL (5 mL or higher if required)
Viscosity	100+ cP
Injection time	Customisable (typically <15 s)
Priming & dose setting	N/A
Needle attachment	Pre-attached (staked-in)
Needle safety	Integrated, passive needle shield
Injection feedback	Audible & visual indicators, drug viewing window
Premature removal safety	Injection Pause™ technology

Table 2: Congruence Autoinjector specifications summary.

LOOKING TO THE FUTURE

The Congruence Autoinjector platform marks a significant update for the autoinjector category, with an ability to address the delivery needs of the full range of current and future drugs, including high-dose formulations (Table 2). Congruence plans to continue to work with its customers to meet their specific needs with customised versions of the device that will enable patients to receive critical therapies.

ABOUT THE COMPANY

The purpose of Congruence Medical Solutions is to optimise the potential of injectable drugs that have emerging and hard-to-address delivery needs. It does this by designing, developing and supplying innovative, flexible drug delivery device platforms, in partnership with multiple pharma customers who trust its domain expertise and responsive, innovative approach. The company's growing portfolio addresses compelling problems, including microlitre dosing, viscous drug delivery, multi-dosing, variable dosing and minimising drug waste.

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ABOUT THE AUTHOR

Richard Whelton leads strategy and marketing at Congruence Medical Solutions. He has two decades of experience in medical technology, devices and life sciences, and is passionate about improving human health through innovative solutions. Over his career, he has held multiple roles in strategy, innovation and marketing, including a decade at Becton Dickinson & Co, where he developed and commercialised a variety of drug delivery products, including self-injection and infusion devices. Mr Whelton holds an MBA from The Wharton School at the University of Pennsylvania (US) and a Master's degree in Biochemistry from the University of Oxford (UK).

ENABLING LARGE-VOLUME, HIGH-DOSE SUBCUTANEOUS AUTOINJECTIONS WITH CARTRIDGE-BASED TECHNOLOGIES

Here, Michael McGowan, Senior Director of Market Intelligence at SHL Medical, examines the emerging interest in autoinjectors that are capable of delivering higher injection volumes into the subcutaneous space and considers the potential benefits of SHL Medical's cartridge-based 3 and 5 mL Maggie® autoinjectors.

An examination of the clinical pipeline reveals the extent to which oncology, in particular immuno-oncology, features heavily in the biotech industry's research and development focus. With groundbreaking advances in the understanding of cancer, new therapies and molecules currently account for around 39% of the industry's development pipeline.[1] Traditionally delivered via intravenous infusion within a hospital setting, molecules used for oncology indications have historically been well outside the scope for autoinjectors or other subcutaneous drug delivery devices. However, with the advent of injection site absorption enhancers and other formulation innovations, the pharmaceutical industry's interest in more practical and patient-centric administration for oncology drugs has grown.

Recent years have seen the launch of a number of oncology treatments formulated for subcutaneous administration in a variety of injection volumes, ranging from 5 mL to around 20 mL. Within the drug delivery field, on-body devices for higher-volume subcutaneous drugs have generated a great deal of interest in recent years and a number of different models and concepts have been well presented and promoted by device companies. However, to date, the number of commercially available drugs in such devices remains low, suggesting that pharmaceutical companies have still not fully embraced the concept of on-body devices for higher-volume injections.

"Recent years have seen the launch of a number of oncology treatments formulated for subcutaneous administration in a variety of injection volumes, ranging from 5 mL to around 20 mL."

THE RISE OF THE AUTOINJECTOR AND THE TREND TOWARDS HIGHER VOLUMES

Since the mid-2000s, the number of drugs commercially available in single-use autoinjectors has risen considerably. While it is difficult to be exact on the number of marketed drugs in autoinjectors, it is now thought to be well in excess of 90 brands, with global sales close to 300 million units.[2] This growth has occurred mainly due to the rise of chronic conditions associated with changing demographics and the advent of biologics to treat conditions such as Type 2 diabetes, rheumatoid arthritis, psoriasis, atopic dermatitis and, more recently, obesity. The development of these highly effective biologics in conjunction with autoinjectors has seen long-term treatment shift from a clinical setting into patients' homes.

To date, the overwhelming majority of the drugs commercialised in autoinjectors have injection volumes of 1 mL or less and use a prefilled syringe (PFS) with staked

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needle as the primary container for the drug. Over the past few years, a number of drugs with higher injection volumes have reached the market in autoinjectors that are designed around 2.25 mL PFSs. Treating atopic dermatitis, high cholesterol and other chronic medical conditions, these drugs and devices are showing that higher-volume subcutaneous injections with autoinjectors are possible in a home setting. As handheld single-use autoinjectors continue to gain traction in new therapy areas, the perception of the higher volume potential of the subcutaneous space also continues to evolve.

DEVELOPING CARTRIDGE-BASED SOLUTIONS IN A PREDOMINANTLY PFS-BASED AUTOINJECTOR MARKET

Since the company's creation more than 30 years ago, SHL Medical has been at the forefront of autoinjector innovation and industrialisation on a large scale. Based on experience in developing and commercialising projects, SHL Medical understands that each device project is unique and requires a tight collaboration between the device supplier and the drug company – whether the project is based on a platform technology, such as SHL Medical's Molly®, or on highly customised and bespoke designs.

Responding to specific customer needs has led SHL Medical to develop autoinjector designs that not only accommodate PFSs with staked needles but also cartridges. Well-known and trusted as a primary container within the pharmaceutical industry, cartridges have a number of properties that are well adapted to the needs of sensitive biologic molecules, such as baked silicone, absence of tungsten and limited contact materials.[4–8] As the drug/primary container contact area increases with higher volumes, these properties may become more significant. Through innovative device technology working in tandem with primary container system design, SHL Medical is looking to drive forward the evolution of the large-volume, high-dose autoinjector market segment.

SHL MEDICAL'S MAGGIE® – A TWO-STEP CARTRIDGE-BASED AUTOINJECTOR FOR LARGER VOLUMES

The use of cartridges as the primary drug container requires a highly innovative solution to facilitate an end-user experience that is equivalent to that of a two-step autoinjector built around a PFS with staked needle. The result is SHL Medical's Maggie® autoinjector, which is designed to accommodate a standard 3 mL cartridge as the drug primary container. The Maggie device incorporates a cannula unit (Figure 1) featuring SHL Medical's Needle Isolation Technology (NIT®). NIT offers the added flexibility of a wide range of needle lengths and gauges not readily available in PFSs with staked needles.

SHL MEDICAL'S NIT® TECHNOLOGY

SHL Medical's NIT enables cartridges to be used as the primary container in a simple two-step autoinjector. The NIT unit consists of a sterile self-contained cannula with patient and non-patient ends. As the needle cap is removed, the non-patient end moves backwards to pierce the cartridge septum and open the drug fluid path (Figure 2). The patient end of the needle remains hidden at all times by a sliding needle cover, which also serves to activate the autoinjector when pushed against the injection site.

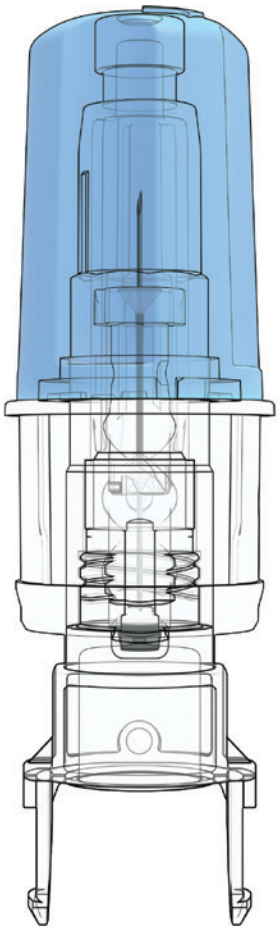

Figure 1: A close-up image of SHL Medical's proprietary NIT technology. The NIT subassembly is a sterile unit that houses the needle within the cartridge-based Maggie autoinjector.

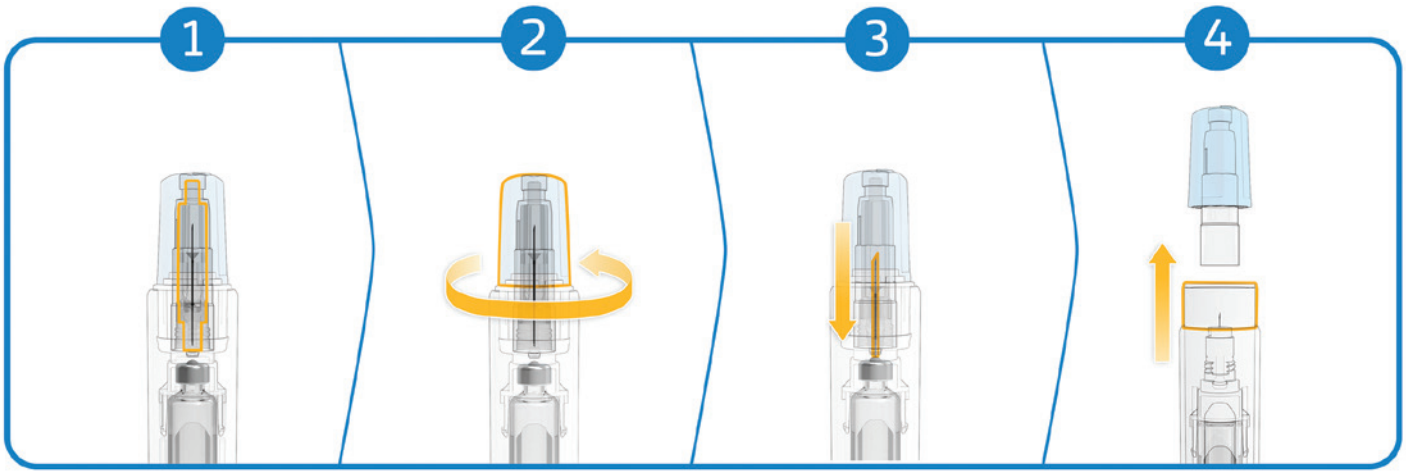

Figure 2: An overview of the NIT mechanism: 1. The closed system. 2. Twist off the needle cap. 3. The non-patient end of the cannula moves backwards to pierce the cartridge septum and open the fluid path. 4. Remove the needle cap to ready the device for injection by pushing against the skin.

"The NIT – created with end user safety and convenience considerations in mind – eliminates the need for patients to manually attach the needle to the cartridge prior to injection."

THE "SPACE BETWEEN" – CARTRIDGE BIOBURDEN VERIFICATION

The NIT – created with end user safety and convenience considerations in mind – eliminates the need for patients to manually attach the needle to the cartridge prior to injection. This simplifies the whole injection process while underscoring the interconnected importance of patient safety and convenience. Traditionally, some cartridge-based injection systems recommend swabbing the cartridge septum as a precaution, with the aim of reducing the surface bioburden prior to injection. In the case of NIT, its end-user-friendly architecture results in a septum that is neither visible nor accessible prior to the use of the Maggie autoinjector.

Nevertheless, as any drug product may be susceptible to bacterial contamination when the septum is pierced, SHL Medical sought to understand this question fully by conducting a multi-phase bioburden study using NIT. For the device-specific verification phase of the study, autoinjector devices assembled at SHL's facilities in Deerfield Beach (FL, US) for performance qualification (PQ) and process validation (PV) activities were subjected to bioburden testing. None of the PQ or PV samples showed any evidence of microbial growth.

These results provide industry evidence of contaminant-free dose delivery using the market-proven, cartridge-based NIT.[3] Devices integrating the NIT cannula system have already enjoyed considerable commercial success on the market, recording end-user sales of several tens of millions since launch in 2017.[1] Hence, bioburden and the "space between" should not be a concern in the manufacturing of cartridge-based combination products in Maggie devices.

PRIMARY CONTAINER OPTIONS – PFS OR CARTRIDGE

Originally developed decades ago for heparins and vaccines, the PFS has demonstrated itself to be a very successful and highly versatile primary container for the storage and the injection of complex biologic medicines. The integration of PFSs with staked needles into autoinjectors has enabled pharmaceutical companies to develop drug brands that are both clinically and practically efficacious and easy for patients to use.

However, despite the success of PFSs as a primary container for biologics, the stability of protein-based molecules or complex monoclonal antibodies in PFSs with staked needles can still present challenges. It has been widely documented that the presence of silicone oil for lubricating the glass barrel and the presence of tungsten residues from the manufacturing process can potentially pose stability issues for PFS-based combination products.[4–6] Other contact materials, such as the adhesive used to bond the staked needle to the barrel and the needle itself, also need to be taken into consideration. In general, when considering biologics, cartridges may present some stability advantages as a primary container overall, as they have fewer materials in direct contact with the drug.

The siliconisation of the primary container is particularly important, as silicone oil-water and air-water interfaces can give rise to protein aggregation and particle formation in the drug product.[4] Baking the silicone using high temperatures has been shown to reduce silicone migration and protein aggregation efficiently, while maintaining the functionality of the injection system.[7] As reported by Funke *et al*, baking silicone on parenteral containers is a challenging process that may require temperatures in excess of 300°C to obtain uniform silicone layers.[8] Considering the need to preserve the bonding force between the staked needle and the glass barrel, it would not be desirable to expose a PFS to such temperatures. However, cartridges, which do not have a staked needle, are well suited to undergo such a process as a way to reduce protein aggregation and particle formation.

MAGGIE 3 AND 5 ML – HIGHER-VOLUME AUTOINJECTORS FOR EMERGING NEEDS

Since the approval and commercial availability of the first drugs with a 2 mL fill volume in SHL Medical's Molly 2.25 mL autoinjectors, the self-injection of higher volumes has become a reality. As the perception of large-volume subcutaneous injections evolves, the cartridge-based

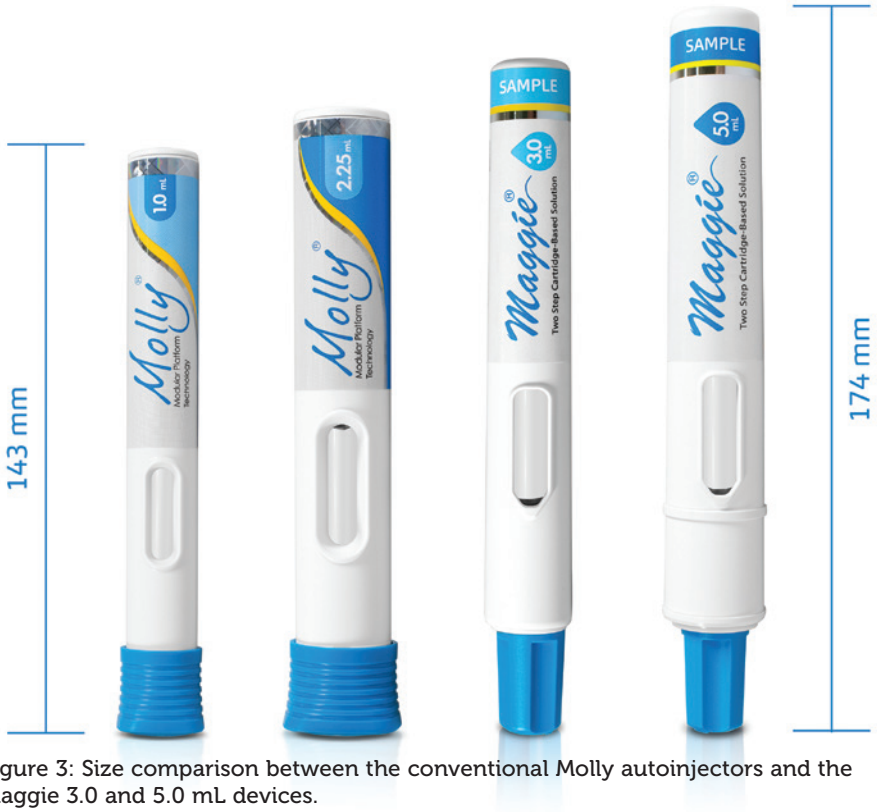

Figure 3: Size comparison between the conventional Molly autoinjectors and the Maggie 3.0 and 5.0 mL devices.

Maggie 3.0 mL has further extended the potential fill volumes for SHL Medical autoinjectors up to 3 mL.

Enabling higher dose delivery and the possibility of less frequent injections, Maggie 3.0 mL provides potential benefits and delivery solutions for both patients and the biotech industry alike. As studies continue to generate more data to suggest that even larger volumes of drug may be administered subcutaneously,[9,10] the extension of the Maggie range continues with the introduction of the Maggie 5.0 mL autoinjector.

The compact design and optimised dimensions of the Maggie 5.0 mL (Figure 3) give rise to a device that is not significantly larger than other successful and widely used SHL Medical autoinjectors. With its simple two-step activation, Maggie 5.0 mL integrates SHL Medical's NIT cannulas and the breadth of possible needle gauge and length options that this technology opens up.

SUPPORTING THE FUTURE OF LARGE-VOLUME, HIGH-DOSE DRUG DELIVERY

With the development of 5 mL cartridge autoinjectors well underway, SHL's Maggie device aims to support therapy areas that will one day require higher injection volumes, including the emerging trend towards subcutaneous drugs in the oncology market. As the product development process gathers pace, the use of autoinjectors for volumes up to 5 mL, and possibly higher, will require deeper clinical investigation to better understand the influence of injection variables, such as time, volume, viscosity and injection depth. As the conundrums of this new subcutaneous drug delivery area are unravelled, SHL Medical will continue to investigate and explore the intrinsic advantages of cartridge-based technologies while working with its partners around the world to address longstanding questions in large-volume, high-dose drug delivery.

ABOUT THE COMPANY

SHL Medical is a solutions provider in the design, development and manufacturing of advanced drug delivery devices, such as autoinjectors and pen injectors. The company 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 Medical 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 injection systems that can accommodate large-volume and high-viscosity formulations – and connected device technologies for next-generation healthcare.

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Michael McGowan is Senior Director of Market Intelligence at SHL Medical, responsible for the research and analysis of market trends and business strategies. Mr McGowan has over 30 years of experience in the medical industry with a focus on international sales and marketing management in the drug delivery market.

windgapmedical

PATIENT-CENTRIC DESIGN CAN BE A FASTER PATH TO MARKET

Here, Brent Buchine, PhD, Chief Executive Officer at Windgap Medical, considers a faster path to market for automated and easy-to-use reconstitution devices through simplification of the delivery systems.

Focusing on the patient and the delivery device system in Phase I clinical trials can speed up and simplify every phase that follows.

A drug is only as effective as its delivery system. Often what drives the necessary innovation of complex drug delivery devices are the challenges created by formulations. But this can be at the expense of a greater burden on the patients who depend on them.

IS COMPLEX DRUG DELIVERY MORE COMPLICATED THAN IT NEEDS TO BE?

Complex, multicomponent injectables (powder and diluent) offer effective therapies across clinical conditions from cancer to Crohn's disease. However, when the drug administration process is also complex, it creates additional barriers to patient adherence, which may, in turn, have a negative impact on patient outcomes.

While the number and specific steps required for successful drug administration varies greatly for each complex formulation, most delivery systems have four critical administration protocols: kit preparation, dosage steps, a timed mixing window and injection considerations (Table 1).

Consider Alkermes' Vivitrol (naltrexone), a US FDA-approved prescription injectable therapy for opioid and alcohol dependence. Proven effective when administered regularly, Vivitrol has eight different pieces within its mixing kit – one dose requires 16 steps.[1]

> "Technological advances in drug delivery devices can improve quality, reduce cost and increase safety, access and adherence to many complex medications."

Alternatively, some injectable suspensions require up to 10 steps for their assembly, mixing and administration processes, have specific mixing instructions and must be administered at a 90-degree angle.

A FASTER PATH TO MARKET – RIGHT FROM THE BEGINNING

Technological advances in drug delivery devices can improve quality, reduce cost and increase safety, access and adherence to many complex medications.

Historically, drug manufacturers have focused on developing the API before considering how best to deliver and administer it. Taking clinical and human

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Prepare	Dose	Mix	Inject
1. Remove from refrigeration. 2. Bring up to room temperature. 3. Open all internal packages. 4. Sterilise as needed.	5. Prepare syringes and/or reconstitution vials (may have multiple steps). 6. Combine required components.	7. Mix contents for the required time and in the required manner, until the appropriate suspension is achieved. There may be very specific instructions (e.g. "swirl the product gently" or "shake for at least 45 seconds" and multiple sub-steps).	8. Select and attach the appropriate needle for the injection site. 9. Prepare the injection site. 10. Administer the entire contents of the medication. 11. Activate the needle sheath and dispose appropriately.

Table 1: Example of complex drug delivery administration.

factors studies into consideration sooner can ease delays in regulatory approval and design reconfiguration.

For example, it is not uncommon for pharmaceutical companies to develop lyophilised (freeze-dried) formulations to get through their clinical trials and then reformulate a more user friendly liquid version of the product for commercial sale. This process adds years and increased risk to their programme as they innovate, engineer and test different drug delivery methods.

When innovative device design and human-factors engineering are considered as early as Phase I, drug delivery technology can be tailored to the unique characteristics of the drug and the unique needs of the patient. By taking the lyophilised product all the way through approval to market, pharmaceutical companies can create a differentiated device – and a competitive advantage – without the time, expense and testing required for reformulation.

As processes are increasingly automated across industries, replacing manual device assembly and administration processes with automated assembly improves accuracy, efficacy and adherence while reducing costs and chances for patient or HCP error.

Complex drug formulations and devices have high hidden costs along the entire value chain, from development and clinical trials to manufacturing and patient support. Paving a faster path to market is essential to getting better profits on the bottom line, and in getting better products into patients' hands.

THE RISE OF PATIENT CENTRIC, NEXT-GENERATION AUTOINJECTORS

Lyophilisation, a freeze-drying technique for drugs and biologicals, offers many benefits for pharmaceutical companies and patients alike. Compared with liquid solutions, lyophilised drugs offer increased stability, temperature resilience and increased shelf life, virtually eliminating dependence on cold-chain logistics – even for notoriously unstable, large-molecule biologics.

In addition to these benefits, lyophilised drugs have paved the way for the rapid growth of depot injections. These extended-release medication formulations enable long-acting drug dosing, allowing patients to reduce a daily regimen of medication to a bi-weekly, monthly or longer interval with a single injection.

While they are designed to improve patient compliance and outcomes, depot formulations, like biologic formulations, are notoriously challenging to mix. The lyophilised drug "powder" must be stored separately and then dissolved or suspended in a liquid carrier just prior to administration. The process requires a substantial amount of time and medical training – and even with training, these complicated, multi-step processes introduce or increase the possibility of human error and environmental impact, which can result in an incorrect dose, a reduction in a drug's effectiveness or worse.

Figure 1: The ANDIPen® reduces the number of steps to two simple user operations: twist and inject. *(Windgap Medical's products are not commercially available or currently approved anywhere around the globe.)*

Figure 2: Windgap's side-by-side primary drug container with mixing and delivery hub.

Next-generation autoinjectors, such as the device technologies behind Windgap Medical's compact ANDIPen® (Figure 1) and its large-volume, dual chamber (LVDC) autoinjector (Figure 2), create an "instant solution" for pharmaceutical companies seeking a simple, stable and swift way to reconstitute lyophilised drugs.

Each of these two wet/dry dual-chamber autoinjector platforms automates rehydration and administration, simplifies complex reconstitution steps and allows the user to administer a dose in seconds.

As the FDA pushes for generic complex drugs, drug makers and device platform providers continue to develop new and adapted drug delivery systems to lower the cost of these medications while meeting the changing needs of the industry and the real-life needs of patients (Box 1).

EFFECTIVE DRUG-DEVICE COMBINATIONS START WITH PATIENTS

Injectable formulations are the fastest-growing segment in the pharmaceutical industry. According to Precedence Research, the global injectable drug delivery market reached US$561 billion (£462 billion) in 2021 and is expected to surpass $1,224 billion by 2030.[3]

The FDA defines these complex drug-device combinations as devices in which the drug constituent is preloaded into a device specifically designed for the product. In real-life applications, these drug-device combinations are designed specifically for something else entirely – the patient. In the case of injections, drug-device combination products may simplify the regimen from an intravenous or a multi-component kit (as described above) to a patient-friendly self-injection.

Many current drug delivery solutions include special features designed to ease self-dosing, promote active lifestyles and support digital health monitoring. For instance, an abundance of personalised patient adherence data has been able to drive technological advancement across the pharma industry, such as electronic pillboxes, smart bottles that provide reminders to patients and smart caps for insulin injection pens.

> "As technological advances allow complex drug formulations to become more effective and available, it is more important than ever to simplify the drug delivery process for patients in real life."

In-depth behavioural research is the backbone of human-centred design, and it is essential to understanding how patients use devices and identifying what is working and what is not. Studies show that, in the US, 40%–70% of patients are noncompliant with their drug regimens.[4] Poor adherence to treatment protocols leads to inadequate treatment and adverse drug effects, negatively impacting patient outcomes.

In developing drug delivery devices, companies must examine three factors:[5]

- **Desirability**: How easy is the device to use? Will patients want to use it?
- **Feasibility**: How reliably can the device function as expected?
- **Viability**: Will there be a demand? Will it be reimbursed?

For injectables, early conversations with patients can address drug delivery options, such as multiple dosing, alternative dose volumes or therapeutic regimens.

Patients always benefit from simplified administration to promote adherence, stronger outcomes and faster access to better products. No matter how well a complex drug formulation performs in trials, the most effective formulations are accurately dosed, adequately mixed, easily administered and readily available.

As technological advances allow complex drug formulations to become more effective and available, it is more important than ever to simplify the drug delivery process for patients in real life.

ONE STEP CLOSER TO INCREASED SELF-ADMINISTRATION

The modern autoinjector was invented in the mid-1970s to accelerate the administration and treatment of life-threatening allergic reactions. Primarily consisting of two steps – cap removal and injection – these liquid autoinjectors set the standard for best practice in single-dose design and usage. Windgap's ANDIPen does exactly this by reducing the number of steps to two simple user operations: twist and inject. This is a first for dual chamber autoinjectors.

The ANDIPen addresses significant yet unmet user needs within a competitive market by increasing portability, ease of use and shelf life for the medications it administers.

Capitalising on the success of its ANDIPen drug delivery platform and with funding from the National Institutes of Health, Windgap began developing a 5 mL wet-dry, LVDC device to quickly and completely mix larger-volume doses for biologics, large molecule and lyophilised medications.

The novelty of this device comes from its innovative primary drug container (PDC) configuration. Windgap's PDC architecture uses two standard, off-the-shelf, single-chamber cartridges nested side by side, which are connected with Windgap's novel proprietary mixing and delivery needle hub. Internal studies have shown that this method of reciprocated mixing has

BOX 1: WHAT QUALIFIES AS A "COMPLEX"?

With biologics and insoluble APIs on the rise, the FDA now defines complex in the following ways:[2]

- **Complex APIs**, such as peptides and polymeric compounds
- **Complex routes of delivery**, such as locally acting formulations, suspensions, and gels
- **Complex dosage forms and formulations**, such as implantables and transdermals
- **Complex drug-device combination products**, such as autoinjectors, where the drug is preloaded in a product-specific device or is cross-labelled for use with a specific device in which the device design affects delivery to the site of action or drug absorption.

> "This method of reciprocated mixing has decreased the mixing time for difficult-to-mix drugs from hours to seconds, increasing the rate of dissolution by an astounding 98%."

decreased the mixing time for difficult-to-mix drugs from hours to seconds, increasing the rate of dissolution by an astounding 98% compared with conventional shaking and swirling methods.

This customisable technology eliminates several steps in the complex drug delivery playbook while improving dosing accuracy, efficiency and stability (Table 2).

The advent of the autoinjector has not only opened the door for simplified drug delivery but also opened up the possibilities for more drugs to be self-administered, making it easier for patients to integrate necessary medications into their daily lives.

Any simplification or reduction of steps is a win for patients, and the more simplicity the industry can inject into the earlier stages of drug and device development, the faster everyone can benefit from better adherence and ideal patient outcomes.

As the injectables market continues to skyrocket, the demand for simple, automated and easy-to-use reconstitution devices will continue to rise in tandem. Windgap's technology platforms continue to rise to the challenge, with innovative pharmaceutical solutions built from the beginning with patients in mind.

ABOUT THE COMPANY

Windgap Medical offers autoinjector platforms that simplify, automate and accelerate the delivery of difficult-to-mix drugs, freeing patients, families and potential treatments from the limitations of current medical delivery technology. With an innovative design, development and manufacturing process, Windgap's "instant solutions" create a new frontier for partners seeking to harness its wet-dry drug delivery technology and an increased speed to market. Its first product is for the administration of adrenaline (epinephrine) for anaphylaxis, with additional products under development in a variety of markets. Windgap Medical is an emerging, privately held pharmaceutical company in the Greater Boston area.

Prepare	Dose	Mix	Inject
No preparation needed.	An accurate dose is pre-measured in the device.	Mix with the press of a button or twist of a cap.	Remove the safety cap and inject.

Table 2: Injecting simplicity into complex drug delivery.

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ABOUT THE AUTHOR

Brent Buchine, PhD, has worked in advanced R&D and innovation for over 20 years. In addition to being a serial entrepreneur, he has authored multiple peer-reviewed publications, received over 150 citations and filed dozens of patents based on his inventions. As Chief Executive Officer of Windgap Medical, he oversees corporate strategy, business development and an assertive drug development pipeline across several treatment areas.

windgapmedical

Injecting Simplicity

Into Complex Drug Delivery Devices

At Windgap Medical, we create autoinjector platforms that simplify, automate, and accelerate the delivery of difficult-to-mix drugs. Our proven, patient-centric technologies free patients and potential cures from the limitations of current device technology.

Large-Volume Dual-Chamber Autoinjector

DRUG DELIVERY AT THE PRESS OF A BUTTON

The instant solution for high-viscosity, difficult-to-mix, large-molecule injections of up to 5 ml.

Compact Dual-Chamber Autoinjector

TWICE THE SHELF LIFE. HALF THE SIZE.

Thermally stable drug delivery platform offering automatic mixing and rapid dissolution for <.3ml delivered doses.

Find out how Windgap designs, develops, and manufactures instant solutions at **windgapmedical.com**

AN INTUITIVE ALL-IN-ONE AUTOINJECTOR: EMBEDDED MIXING AND INJECTION TECHNOLOGIES TO SIMPLIFY DAY-TO-DAY LIFE

In this article, Benjamin Morel, Innovation and Intellectual Property Manager, and Gladys Corrons-Bouis, Business Development Director, both at EVEON, discuss the challenges faced by the injectable drug delivery industry and present EVEON's solution – the INTUITY® Ject MX platform.

Over the past few years, the pharmaceutical industry has faced a rapid shift in the preferred delivery route for its products, with the injectable route becoming increasingly prevalent in the development pipeline. According to the US FDA, 40% of new drugs approved are injectable products, with a great proportion of those targeting subcutaneous and intramuscular routes. In 2022, seven out of the top ten selling drugs were injectables, compared with one in 2003 and five in 2010. Consequently, the pharmaceutical industry has begun adopting new strategies and putting the patient first to improve treatment adherence and boost product sales. It now takes more than a promising molecule and a validated therapeutic target to gain traction in the market.

These trends come in tandem with a global increase in the incidence of chronic diseases, which has become one of the greatest global health threats of the 21st century. Worldwide, they caused 42 million deaths in 2019. Chronic diseases require chronic treatments, and important follow-up work by healthcare workers. As such, improving the patient experience for chronic injectable treatments is now a critical challenge to address.

> "Improving the patient experience for chronic injectable treatments is now a critical challenge to address."

CHALLENGES FOR THE INJECTABLES INDUSTRY

New Drugs in the Pipeline

The injectable drug delivery market is forecast to experience double-digit growth between 10% and 15%.[1] It is a complex industry involving multiple interconnected partners, each of them able to solve or create challenges for the others. These players include drug developers, primary packaging companies and device companies. One of the key drivers impacting all of them is the aforementioned paradigm shift in the drug development pipeline that is shaping the future needs of the industry.

Biologics are having a major impact on market trends – they represent over double the value of the small molecule market and will continue to strongly support the global injectables market.[2–4] However, a key challenge associated with biologics is their formulation and storage, meaning that about one-third of the market will come to involve lyophilised

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> "The pharmaceutical industry currently faces a major unmet need – offering to patients an intuitive, easy-to-use autoinjector that enables automatic reconstitution, mixing and injection."

products.[1] For example, highly concentrated antibody formulations are often designed as lyophilised product, as liquid formulations frequently fail to pass stability tests.[5]

Due to the need for a diluent and a reconstitution step, lyophilised products present additional complexity prior to administration. Furthermore, reconstituting highly concentrated formulations can take several minutes due to the physical properties of the lyophilised cake.[6] Therefore, it is necessary to find appropriate devices that facilitate easy reconstitution and injection of viscous lyophilised drug products.

New long-acting injectables (LAIs), or "depot-injection formulations", are currently of high interest due to their potential in increasing patient adherence to treatments. LAIs have been used in the field of antipsychotic, antiviral and addiction treatments. Over the past few decades, LAI formulations have proven their worth as safe and effective products and are now true game changers in the field of controlled-release delivery. However, ensuring their stability and homogeneity over time remains a great challenge. Most LAI formulations are water-insoluble, which requires drug delivery solutions that can handle their viscosity and ensure that they are properly mixed in order to avoid clog formation during injection.

Devices and Product Lifecycle Management Strategies

Product lifecycle management involves finding ways to maximise the value of the product and retain market share as patent expiry or market exclusivity rights approach expiration. Offering a new device solution that will enhance the patient experience is a key strategy for lifecycle management, which is currently gaining interest in the pharmaceutical industry.

From a device perspective, two key drivers can be outlined to explain future changes related to improving the patient experience within the injectables industry:

- The switch from hospital settings to at-home treatment is a key trend that received a boost from the covid-19 pandemic.[7] Accordingly, there is a need to develop solutions that will fit with patients' daily lives. In so doing, the medical device can become a key element for treatment adherence.
- The second important driver is digitalisation. Digital devices can provide injection guidance, dose confirmation and reminders, among other benefits. Additionally, digitalised devices offer an enhanced way to monitor patient adherence and maintain the link between patients and healthcare professionals.

INTUITY® JECT MX – SIMPLIFING PATIENTS' DAILY LIVES

The pharmaceutical industry currently faces a major unmet need – offering to patients an intuitive, easy-to-use autoinjector that enables automatic mixing, dosing and injection. As of today, there is no state-of-the-art solution that is able to provide a full answer to this unmet need.

Figure 1: EVEON's INTUITY® Ject MX platform.

Scan me, watch the video!

EVEON's core expertise is focused on drug preparation, including precise drug mixing and dosing. As such, the company's INTUITY® Mix platform has been designed to overcome the challenges presented by difficult-to-mix drugs, including:

- Liquid-to-liquid mixing: pooling of multiple doses, emulsion preparation, dilution.
- Liquid-to-solid mixing: lyophilised drug reconstitution, suspension preparation, powder dispersion.

To achieve this, EVEON developed a range of patented micropumps, dedicated to complex drug mixing. Recent developments regarding the company's micropump technology were discussed in a previous ONdrugDelivery article,[8] showcasing its strong mixing properties – even in its silicon-free version – to better comply with the constraints associated with delivering biologics. EVEON's latest optimisation enables the preservation of mechanical properties while avoiding clog formation and particle aggregation due to the presence of silicon oil.

EVEON's micropump is perfectly suited to handle high pressure (up to 10 bar), which enables strong mixing properties for lyophilised cake dissolution and powder dispersion in a highly viscous oil phase. However, while developing its expertise in drug mixing, EVEON found that new challenges arose regarding the need for an all-in-one autoinjector capable of full-automatic drug mixing, dosing and drug injection.

EVEON has developed INTUITY® Ject MX, which is shown above in Figure 1, with more information available in the video on EVEON's YouTube channel (scan QR code). INTUITY® Ject MX is an all-in-one autoinjector platform integrating the company's core mixing technologies. It is compatible with a broad range of standard primary containers, including vials, cartridges and syringes. Developments have been made to mix from two or more containers and to make the platform adaptable to multiple combinations of standard primary packaging

Suspension in aqueous phase	
Suspension viscosity	60 cP
Suspension volume	1.5 mL

Performances	INTUITY® Ject MX	Manual mixing & injection
Mixing time	90 s	25 min
Mixing quality	Standardised no/few foaming no clogging	User-dependent
Mixing stability *Maximal time between mixing and injection*	3 min	3 min
Injection time	12 s	18 s
Product loss	5%	10%

Suspension in oil phase	
Suspension viscosity	500 cP
Suspension volume	2 mL

Performances	INTUITY® Ject MX	Manual mixing & injection
Mixing time	7 min	50 min
Mixing quality	Standardised no/few foaming no clogging	User-dependent
Mixing stability *Maximal time between mixing and injection*	6 min	3 min
Injection time	15 s	20 s
Product loss	5%	10%

Figure 2: INTUITY® Ject MX performances regarding mixing and injection of LAIs for different viscosities and solvent type.

types and sizes. Automatic mixing from cartridge to cartridge, vial to cartridge or syringe to cartridge are new possible options, opening new opportunities and providing flexibility to the industry.

Figure 2 provides a snapshot of the range of viscosities INTUITY® Ject MX is capable of handling, as well as data on its mixing and injection performance. Its key technical benefits include the reduction of preparation time, improvement of homogeneity and stability after mixing, and a reduction in clog formation compared with manual extemporaneous drug preparation. Figure 2 also shows performance data for suspension preparation, with stability time increased by two for oil-phase suspensions.

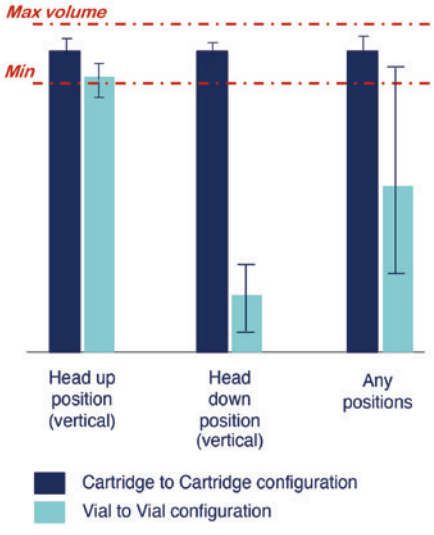
The INTUITY® Ject MX autoinjector platform relies on two side-by-side standard primary containers (vials or cartridges) and a custom fluidic cassette dedicated to receiving those two containers upon device activation. Many possibilities are available, from fully disposable devices with embedded drug containers to reusable devices with disposable fluidic cassettes and drug containers. The platform's modularity enables it to be adapted for various patient needs and also presents a possible answer to the need for increasing the sustainability of medical devices. Indeed, the covid-19 pandemic exposed several drawbacks of disposable medical devices. Finding alternatives to limit medical waste by using a two-part device with a reusable injector and single-use fluidic cassette could be a solution for improving sustainability in future years.

In the platform's fully automatic configuration, a single user action initiates the electronic activation and fluidic connection between the containers and the fluidic cassette. Then the device automatically starts mixing the powdered drug and the diluent and informs the patient when it is ready for injection. A motorised micropump with embedded software controls the number of back-and-forth movements, enabling perfect drug mixing. Furthermore, the injection can be triggered and controlled by the device to avoid unsuitable injections.

Studies have demonstrated that INTUITY® Ject MX enables both highly precise final concentrations after mixing and delivered dose volumes (Figure 3). Additionally, the fluidic cassette is fully customisable according to the primary drug containers used and factors such as the drug sensitivity to shear stress, homogeneity, preparation time and dead volume reduction.

INTUITY® Ject MX performance data demonstrate that the platform is able to mix and deliver a drug product regardless of orientation when using a two-cartridge configuration with no impact from the sticking effect of the cartridge stoppers. This enables new opportunities for use in emergency situations or for specific populations, such as children, disabled or the elderly, with fully automatic delivery from a single user action (Figure 3).

Additional key benefits are a drastic reduction in the number of steps required during product preparation, dosing and injection while also ensuring patient safety and standardised drug administration. INTUITY® Ject MX reduces the number of steps in a standard use scenario from about 20 steps to 5–8 steps, depending on the global level of automation required for the final application.



Lyophilised drug	
Product viscosity	**10 cP**
Volume to be injected	**1 mL**

Performances	Intuity® Ject MX
Mixing time	**5 s**
Dose *accuracy*	**± 4.3%**
Injected volume *accuracy*	**± 1.1%**
Injection time	**6 s**

Figure 3: Use case of INTUITY® Ject MX for Lyo reconstitution.

Figure 4: EVEON's digital companion for INTUITY® Ject MX.

Finally, digital functionality has also been developed, enabling EVEON to offer a digital companion alongside the device (Figure 4). The companion provides dose-mixing monitoring, injection monitoring, injection reminders and an injection timer.

CONCLUSION

The INTUITY® Ject MX platform opens new opportunities for the pharmaceutical industry, offering a fully automatic autoinjector that enables drug mixing, dosing and injection in the same handheld device. INTUITY® Ject MX has both standard essential features and nice-to-have functionality that can be fine-tuned to each drug.

Figure 5 showcases the key benefits for both the pharmaceutical industry and patients. Positioned as an expert in drug preparation and having the right set of combined expertise in fluid physics, mechatronics and software, EVEON is the partner of choice for developing an advanced custom drug delivery device.

"The INTUITY® Ject MX platform opens new opportunities for the pharmaceutical industry, offering a fully automatic autoinjector that enables drug mixing, dosing and injection in the same handheld device."

ABOUT THE COMPANY

EVEON designs and develops custom devices for the preparation and delivery of advanced therapeutic treatments, providing solutions that improve patient compliance and therapeutic performance. EVEON has built its expertise over the past decades in drug preparation, from lyophilised drug reconstitution to complex suspension preparation. EVEON is certified under ISO-13485:2016 and integrates the IEC 62304 standard for medical device software. EVEON has received several Pharmapack awards in the Best Innovation Exhibitor category for its developments in 2016, 2017 and 2021.

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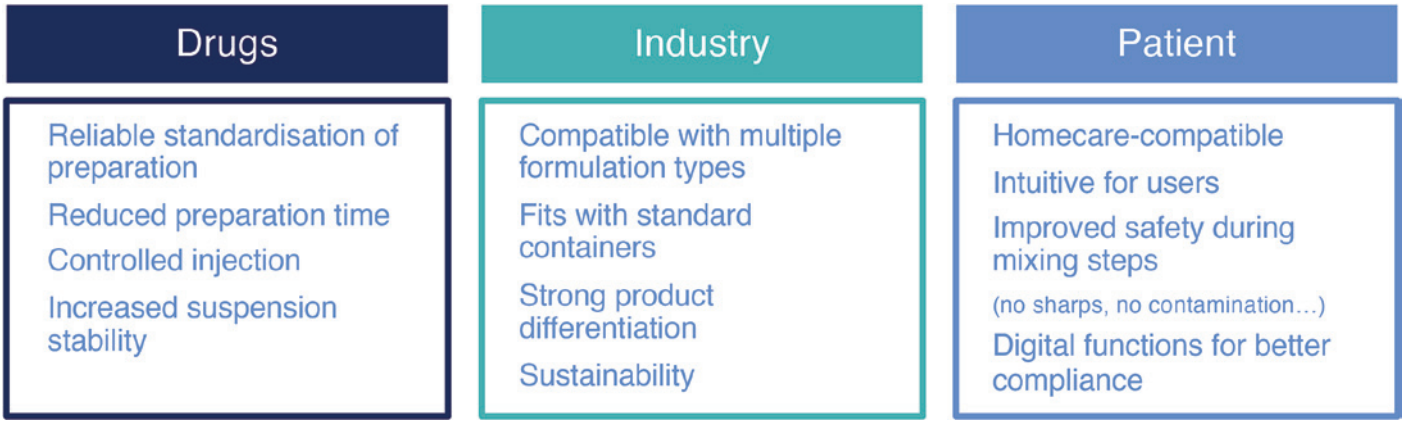

Figure 5: Key benefits of INTUITY® Ject MX.

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ABOUT THE AUTHORS

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, Mr Morel 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.

Gladys Corrons-Bouis is Business Development Director at EVEON. She started her career in the pharmaceutical industry in regulatory affairs and market access for orphan drugs. In 2007, she joined CEA to help with the maturation and licensing-out of CEA's portfolio of drug candidates. She then participated in the creation of Avenium Consuting in 2009 and became a partner in this intellectual property strategy and business intelligence consulting firm. For 10 years, Ms Corrons-Bouis helped start-ups, small to medium enterprises, and big pharma companies, to define their industrial property strategy and consolidate their technology portfolio. Ms Corrons-Bouis also contributed to the structuring of consulting activity and solution selling within Becton Dickinson's Preanalytical Systems division. Since 2019, she has been developing EVEON's commercial activity by forging key co-development partnerships with pharmaceutical companies. Ms Corrons-Bouis holds a Pharm D and a degree in Regulatory Affairs and Market Access.

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THE FUTURE OF PREPARATION
& DELIVERY SOLUTIONS

PRODUCT SHOWCASE: New Requirements for Injection Devices Make Advanced Testing Solutions Necessary

Zwick / Roell

With a drastic increase in administered vaccine doses in recent years, as well as the growing demand for biopharmaceuticals, needle-based injection systems with different injection volumes are becoming increasingly important. From disposable and prefilled syringes (PFSs) with active and passive safety systems to pens, autoinjectors and on-body delivery systems (OBDSs), there is currently a wide range of medical devices available.

"All injection products are subject to strict use and hygiene requirements and must be carefully and critically examined in accordance with corresponding standard requirements."

Figure 1: Testing system for multiple tests on autoinjectors.

These products are extremely important regarding patient treatment and must therefore adhere to high quality standards. Another reason for the increase in injectable products is the growing trend of patient at-home drug self-administration – an application which requires injection devices that are safe and easy to handle.

All injection products are subject to strict use and hygiene requirements and must be carefully and critically examined in accordance with corresponding standard requirements.

Intelligent test methods from ZwickRoell guarantee that the above-mentioned medical devices meet their intended purpose. ZwickRoell testing systems feature a high level of modularity, the option to choose between partial and full automation, and compliance with corresponding standards and several US FDA requirements.

TESTING SYSTEMS FOR AUTOINJECTORS

The latest FDA and ISO 11608-5 requirements specify autoinjector cap removal testing that is dependent on how it is described in the patient instructions for use (IFU) guidance. Most recently, this applies to cap removal before injection,

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"Daily checks for all implemented sensors include the load cell, laser sensors, microphone, scale and optical measuring system."

which now often occurs in an upward motion. With its latest expansion stage, ZwickRoell offers a multifunctional testing system that can perform every required test on one autoinjector (Figure 1).

This also includes the removal of injector caps in both a downward motion and upward motion for any autoinjector currently on the market. A further improvement included in the new expansion stage is the measurement of injection-defining results using a high-resolution optical measuring system. Both injection depth and injection time are optically measured and documented using new accuracy and resolution standards.

In addition, the system offers various unique benefits, for example, reliable installation of injector-specific interchangeable parts. The poka-yoke method is a multi-part safety concept. This includes clear coding and verification of interchangeable parts using a 2D scanner and checking if the interchangeable parts are correct and in place. If this is not the case, the test sequence cannot be started.

Daily checks for all implemented sensors include the load cell, laser sensors, microphone, scale and optical measuring system. Typically, these check tests are performed daily, before the testing machine is used or when a product is changed. The results provide assurance that the sensors being used are functioning properly.

A universal cap gripper allows for the removal of different types of injector caps. Reliable weight measurement results are guaranteed by avoiding antistatic influences on the scale.

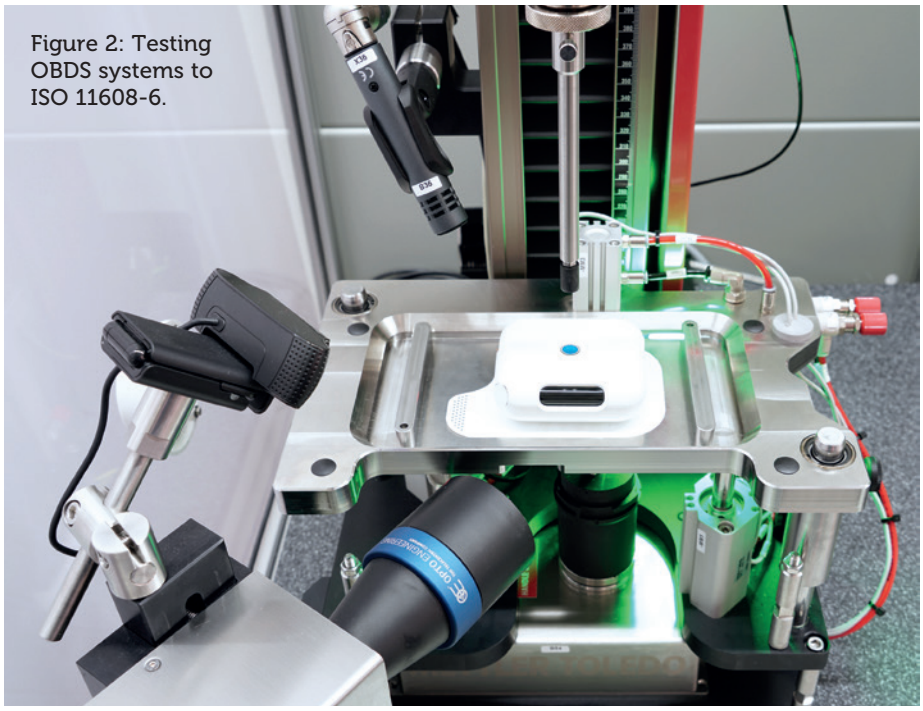


Figure 2: Testing OBDS systems to ISO 11608-6.

"Optical measurement of the injection results and video recordings of the injection process are recorded by a single camera system integrated in the testXpert III testing software."

Optical measurement of the injection results and video recordings of the injection process are recorded by a single camera system integrated in the testXpert III testing software. Convenient expansion options are offered through fully automated feeding of specimens using robotic systems.

Another testing system – a combination testing machine for autoinjectors and PFSs (with or without a needle shield) – provides flexibility with a small footprint.

This system offers a high level of flexibility through tool-free expansion of testing options for tests on PFSs with or without a needle safety device. Typical results include breakaway force, glide force or injection volume.

TESTING OF OBDS TO ISO 11608-6

The ISO 11608-6 standard describes testing of an OBDS. For higher drug volumes and/or longer administration times, autoinjectors offer an additional injection method. For this application, the ZwickRoell testing system provides a wide range of testing options: testing of the actuation force, injection time, injection volume and needle/cannula length (Figure 2).

Additional features include recording of optical and acoustic signals of the OBDS. Furthermore, adhesive forces of the application surfaces can be determined in the upper test area. The high flexibility of this testing machine and the ability to implement specific customer requirements means additional test requirements can also be integrated for different OBDS types.

REQUIREMENTS ACCORDING TO FDA 21 CFR PART 11

The software is undoubtedly crucial for reliable test results. The testXpert III testing software guarantees optimised operating processes and seamless documentation. It covers every requirement related to injection-system testing. In addition, it fulfils requirements according to FDA 21 CFR Part 11. ZwickRoell deeply integrated these FDA requirements in the testXpert testing software more than a decade ago. Features are data integrity (data manipulation is not possible), user management with different access rights and lightweight directory access protocol (LDAP) access and audit trails included for test parameters.

In addition, ZwickRoell offers various qualification services. These include design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and on-site services to perform these tests. A fully executed DQ, IQ, OQ service for an autoinjector testing system includes approximately 300 pages. This service is unique to ZwickRoell. Figure 3 shows ZwickRoell's universal syringe holder for various tests according to ISO 11040.

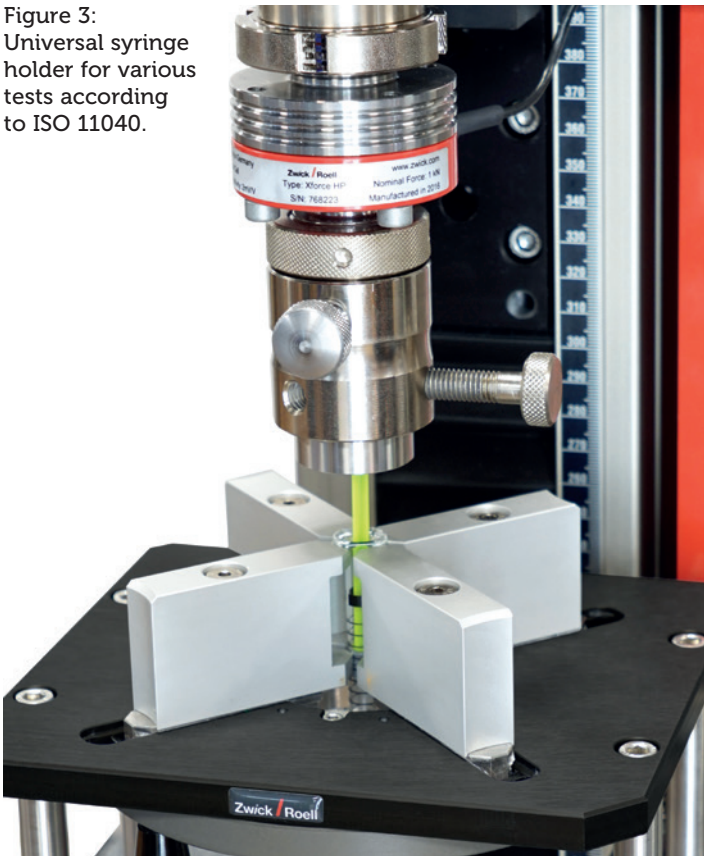
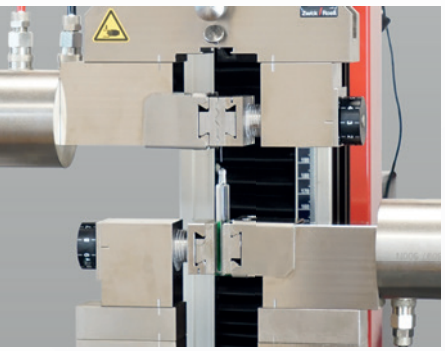
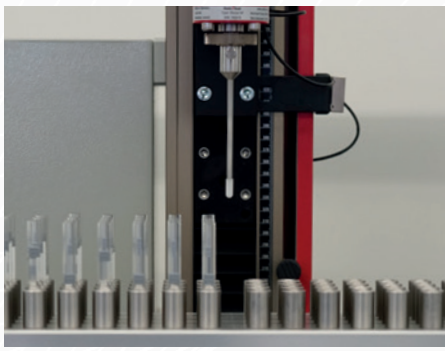
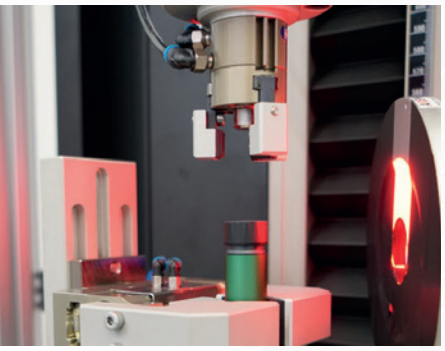
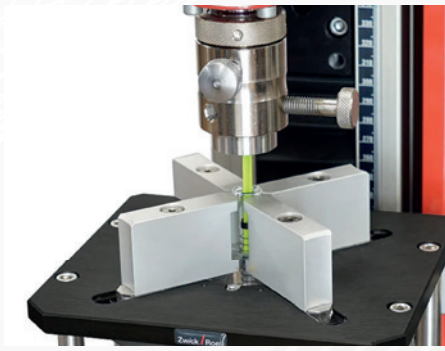


Figure 3: Universal syringe holder for various tests according to ISO 11040.

Testing systems

for the medical and pharmaceutical industry



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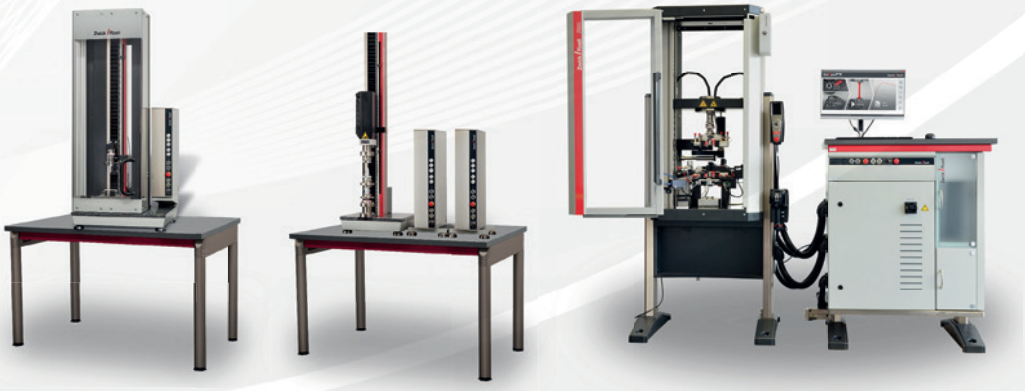

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EXTRACTABLES/LEACHABLES TESTING CONSIDERATIONS FOR SINGLE-USE SYSTEMS

Here, Sandi Schaible, Senior Director of Analytical Chemistry and Regulatory Toxicology at WuXi AppTec, discusses testing considerations for extractables and leachables along with the regulatory environment for single-use systems.

Traditionally, drugs are manufactured in large stainless-steel containers. These containers pose two main hurdles to drug manufacturers. First, the stainless-steel systems have to be thoroughly cleaned after each batch, with testing required to ensure that the container is free of contaminants. While such containers are reusable, the cleaning process requires significant time and resources. Furthermore, because the containers are made of stainless steel, manufacturers do not have the flexibility to change the size of the drug batch on a case-by-case basis.

Single-use systems (SUSs) eliminate the need for arduous cleaning processes and validation testing. Moreover, they can also allow for scaling batch sizes, require a much smaller footprint in the manufacturing facility and reduce cost.

> "Single-use systems eliminate the need for arduous cleaning processes and validation testing."

DESIGNING EXTRACTABLES SCANS IN THE ABSENCE OF REGULATORY REQUIREMENTS

Regulatory requirements have yet to catch up to the rising use of SUSs, however. Most regulatory bodies ask to see extractables/leachables (E/L) data as a part of the submission process, but there is not a uniform requirement for how that testing should be done or what it should include. China already requires E/L testing for SUSs. Likewise, the EMA and International Council on Harmonization have begun to expect E/L testing data for SUSs.

In the absence of formal regulations, the BioPhorum Operations Group (BPOG) published the first standardised extractables protocol in 2014. The BPOG protocol, as it is commonly referred to, is based on the extraction capabilities of various solvents over recommended time periods. That protocol was revised in 2020, removing some extraction solvents and paring down the extraction timepoints.

The US Pharmacopeia (USP) recently issued two new chapters (665/1665) on production equipment and patient safety for polymeric components and systems used in biomanufacturing. The new USP chapters provide information for assessing risk and a standardised testing procedure. USP <665> discusses the characterisation of plastic components and systems used to manufacture biopharmaceutical drug substances and biopharmaceutical and pharmaceutical drug products. USP <1665> discusses the selection and qualifications of plastic components and systems used to manufacture APIs, biopharmaceutical drug substances and biopharmaceutical and pharmaceutical drug products.

Even though E/L studies on SUSs are not explicitly required by regulatory bodies, they are still essential for drug development and safety/toxicological risk assessments. Moreover, the new USP chapters also give regulatory bodies a test method to point

> "When evaluating which SUS components to test, careful consideration should be given to how the SUS will interact with the final drug product."

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to as they request the data they would like to see. In the absence of clear guidance for E/L studies on SUSs, the following section covers some factors to consider regarding study design.

DETERMINING WHICH SUS COMPONENT TO TEST

It is not the expectation that every component in a SUS needs to be tested. There are multiple methods to determine which components should be tested. When evaluating which SUS components to test, careful consideration should be given to how the SUS will interact with the final drug product. Factors to consider include:

- **Proximity to the final drug product:** When SUSs are used upstream in the manufacturing process, there may be opportunities for leachables to be filtered out or diluted downstream in the final drug product and thus may not be considered a high risk for leachables. However, SUSs used downstream may have a much higher risk of the leachables reaching the final product.
- **Contact duration:** Extractables study design should also factor in the amount of time that the drug product is in contact with the SUS component. Longer durations can result in more opportunities for leachables to migrate out and at a higher concentration.
- **Temperature:** Higher temperatures during the manufacturing process should be considered when evaluating if a SUS component might be at higher risk. These conditions can create more opportunities for leachables to release from the plastic of the SUS and into the final drug product.
- **Contact surface area:** The greater the surface area of the SUS that is in contact with the drug product, the more opportunity for leachables to make their way into the final drug product.
- **Type of plastic:** Most single-use plastics are made from several materials. That said, softer plastics generally have more potential for leachables in greater quantities than more rigid plastics.

"A drug product's clinical use is also an important consideration for E/L testing."

"A drug that will only be used once may have a higher threshold for leachables than a drug that will be administered on a daily basis for a prolonged period of time."

CONSIDER CLINICAL USE CASE

A drug product's clinical use is also an important consideration for E/L testing. For example, final drug products that are used for neonates are more likely to have a much lower permitted daily exposure for leachable chemical compounds than ones used in adults.

Frequency of use also matters. A drug that will only be used once may have a higher threshold for leachables than a drug that will be administered on a daily basis for a prolonged period of time. Toxicologists must consider the potential for leachables to accumulate in a patient's body.

The potential benefit of the drug product versus the potential risk should also be considered. In some cases, such as a drug developed in response to a public health emergency or to treat a rare disease, a higher threshold may be tolerated because of the potential benefit of the drug.

COMPLETE CHEMICAL CHARACTERISATION IS CRITICAL

In the absence of comprehensive regulatory requirements, complete chemical characterisation is still an essential part of the process because of the role it plays in a safety assessment/toxicological risk assessment. Complete E/L testing identifies all chemicals within a SUS. Unidentified chemicals must be considered carcinogenic or genotoxic; therefore, when unknowns are present, it is virtually impossible for the toxicologist to accurately assess safety or risk. Simply put, unknowns are unacceptable.

Given the way the regulatory environment is evolving, manufacturers should consider laboratory testing partners that offer a commitment to complete chemical characterisation as a default for extractables scans, have an existing database of compounds and expert scientists who can identify new compounds.

A FINAL WORD

SUSs are rising in popularity for drug manufacturers, but regulatory bodies have not kept pace with definitive requirements for E/L testing. In the absence of such guidance, drug manufacturers should still conduct robust testing, striving for complete chemical identification and characterisation.

ABOUT THE COMPANY

As a global company with operations across Asia, Europe and North America, WuXi AppTec provides a broad portfolio of R&D and manufacturing services that enables the global pharmaceutical and healthcare industry to advance discoveries and deliver groundbreaking treatments to patients. Through its unique business models, WuXi AppTec's integrated, end-to-end services include chemistry and drug development contract research, development and manufacturing organisation (CRDMO) services, biology discovery, preclinical testing and clinical research services, cell and gene therapies contract testing, development and manufacturing organisation (CTDMO) services, helping customers improve the productivity of advancing healthcare products through cost-effective and efficient solutions. WuXi AppTec received an AA environmental, social and governance (ESG) rating from MSCI in 2021, and its open-access platform is enabling more than 5,800 collaborators from over 30 countries to improve the company's health of those in need, and to realise the company's vision that "every drug can be made and every disease can be treated".

ABOUT THE AUTHOR

Sandi Schaible is the Senior Director of Analytical Chemistry and Regulatory Toxicology at WuXi AppTec, located in St Paul, MN, specialising in extractables and leachables studies. She is a US delegate and international delegate for ISO 10993 part 18 in chemical characterisation, and also a US delegate for ISO 10993 part 13 and the particulates committee (TIR42).

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A TALE OF TWO SPRINGS

Here, Sebastian Block, Development & Application Engineer, and Drew Jelgerhuis, Business Development Manager, Medical, both at Scherdel Medtec, introduce two types of springs and highlight their important role in drug delivery devices.

With apologies to Charles Dickens and all literary lovers, Scherdel has stolen from the title of his best-selling novel. There are many lessons to learn from that classic story (A Tale of Two Cities), but one of the main moral lessons is that "things are not always as they seem". To stretch that lesson to springs may be deemed a road too far, but let's try anyway.

Springs are rarely seen and often underestimated for their value. They seem easy to make and unimportant. In reality, they serve a very important role in drug delivery devices. So, the lesson is: springs are not always recognised for their value. They seem insignificant but are actually a very key component. This article focuses on two very important spring types: the constant force spring and the power spring – a tale of two springs!

Despite its unimposing form, the constant force spring has an important function. The spring is often used for a triggering mechanism or as a drive spring to push a plunger dispensing medication. The main feature of a constant force spring is to produce high and constant rotational force in a small space (Figure 1).

> "The spring is often used for a triggering mechanism or as a drive spring to push as a plunger dispensing medication."

There are many options for the production processes and multiple choices of suitable material. These need to be defined early in the development phase. Scherdel's development team works closely with the customer's device development team to optimise the spring design.

The first design step is to choose a suitable material according to the customer's needs and requirements. Most commonly

Figure 1: Constant force and power springs.

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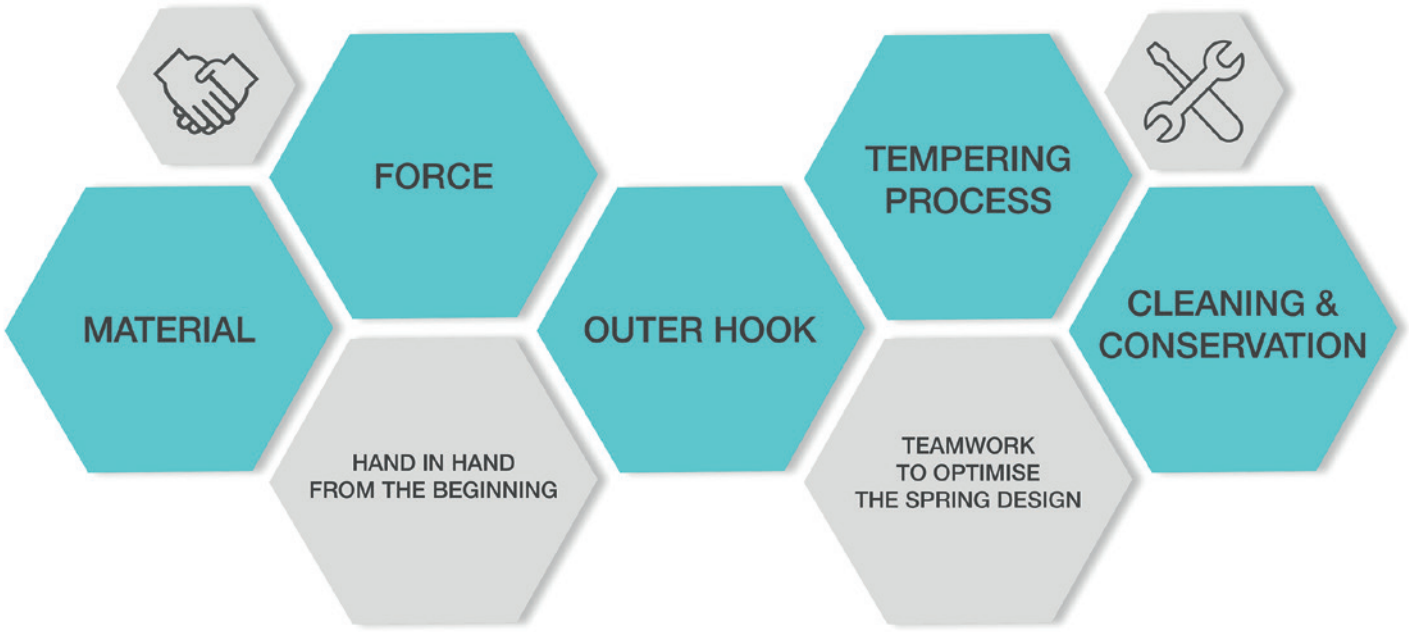

Figure 2: Critical characteristics and Scherdel Medtec advantages.

austenitic stainless steel AISI 301 or EN 10088-3 X10CrNi18-8 (1.4310) with a high tensile strength (almost 2000 N/mm²) is used for a constant force spring.

Scherdel agrees a special supply contract with the material supplier including the material composition, the state of microstructure and the surface characteristics of the material. Additionally, the geometric characteristics, such as thickness and width, the mechanical and technological characteristics, such as tensile strength, yield strength or modulus of elasticity, as well as the medical requirements (for example, to avoid contamination) are defined.

The production of material includes processes such as milling, heat treatment up to 1,200°C (2,200°F), levelling and slitting, and edge conditioning. The milling process, consisting of several loops, is necessary to achieve the desired thickness and tensile strength. This process is especially expansive (material will be rolled with the 20-roll rolling mill machine) and alternates with the heat treatment process. Subsequently, the material is available with the right thickness on a wide range of coils. The slitting process creates strip widths to match customer specifications. The material supplier coils the strips after edge conditioning. The coiled material from the supplier with the specified thickness and width is unwound from the coiler and formed on the winding machine.

"The material width and especially the thickness and tensile strength have a big impact on the force."

The material width and especially the thickness and tensile strength have a big impact on the force. (For example, for a constant force spring and thickness with a diameter and width of 20 mm: thickness 0.1 mm, force approximately 1.4 N; thickness 0.2 mm, force approximately 11.2 N.) The force can also be adjusted with the spring diameter on the winding machine. That is also very important to compensate for the tolerances of the material characteristics. Additionally, the shape of the outer hook has a big influence on the behaviour of the characteristic line and can also be adjusted on the machine. Special stamping and cutting tools on the machine are necessary and available in Scherdel's tool shop.

The tempering process is a follow-up process to improve the stress and reduce the stress peaks. The right choice of temperature and time have a significant influence on the forming of the chromium oxide layer for the stainless steel and are also very important as a corrosion protection layer.

For cleaning and conservation, there are also many options, including injection flood washing, ultrasonic cleaning, a vacuum drying process and conservation in Scherdel's washing machine. Scherdel can also use a cleanroom. The choice of the preservative must be agreed with the customer. For medical technology projects, Universal Oil for Food Processing Technology is often used (Figure 2).

"In contrast to the constant force spring, the power spring has two hooks – one inside and one outside."

Across all production processes for the constant force spring – such as forming, heat treatment, cleaning and conservation – the diameter of the spring body, the behaviour within the working range and the spring force can change; the smaller the spring body diameter, the larger the force.

In contrast to the constant force spring, the power spring has two hooks – one inside and one outside. Very often, there is a housing with support for the outer hook and a shaft for the inner hook. In the same procedure used for the constant force spring, the material characteristics are defined by the material supplier.

There is a distinction between three types of power springs. At Scherdel, the types are known as normal, straight material and a cross-curved power spring.

The cross-curved power spring is produced in the first step in the same way as a constant force spring. This spring has the greatest power potential.

The constant force spring with two hooks is wound in the opposite direction,

ideally in the customer's assembly housing. This is the best delivery form for the power spring.

In the development phase, the constant force spring diameter and the shaft diameter are determined to achieve the force or torque and geometrical characteristics. The geometry of the outer hook can have a significantly positive influence in achieving the right power and optimal behaviour of the characteristic line within the working range. Thus, this power spring plays a significant role in achieving a higher constant force for highly viscous drugs in medical devices.

Scherdel has much expertise in the development and manufacturing of constant force and power springs, and the company has a global reach with its engineering and production processes. This tale of two springs reveals the importance and value of these spring types in drug delivery devices and how material, thickness, width, heat treating, milling, hook design and integration into the device are all so important yet often undervalued. Scherdel can optimise the value of these important components by working with the customer's development team from the initial device concept.

ABOUT THE AUTHORS

Sebastian Block is a Development & Application Engineer for Scherdel SFS in Seifhennersdorf (Germany), and holds a university degree from the Technical University Berlin (Graduate Eng) and a degree for executive and administrative technical classes of service in the state of Saxony, Germany. As well as freelance experience in engineering, Mr Block has been a project manager in the field of development for constant force, power and spiral springs within the Scherdel Group for 11 years.

Drew Jelgerhuis is the Business Development Manager, Medical, for Scherdel Medtec North America. With over 15 years of business development experience in the medical device sector, Mr Jelgerhuis leads the North American Medtec team growth in co-operation with the other global Medtec leaders. Mr Jelgerhuis holds a BS in Mechanical Engineering from Dordt University (IA, US) with a minor in Business Administration. He enjoys solving technical problems for customers by providing solutions for their medical device component requirements. When he is not working you can find him on his stand-up paddle board on Lake Michigan.

ABOUT THE COMPANY

Scherdel Medtec, is part of the Scherdel Group. With about 5,800 employees at 32 locations worldwide, the Scherdel Group is a family-owned, leading company in the field of metal forming, with core competence in the production of engineering springs, stamping parts and assemblies for the pharmaceutical market as well as vehicle components.

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