PREFILLED SYRINGES & INJECTION DEVICES

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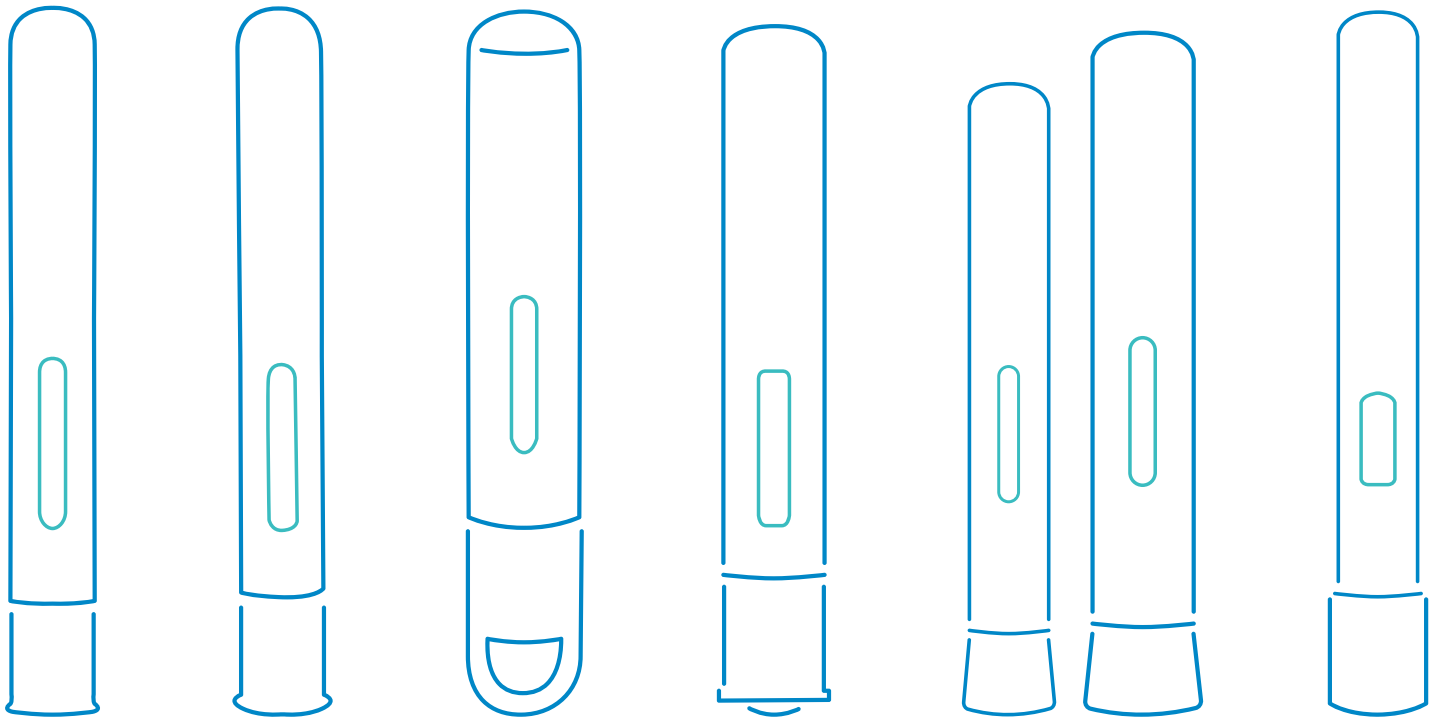

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Contents

ONdrugDelivery Issue N° 125, October 5th, 2021

PREFILLED SYRINGES & INJECTION DEVICES

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

EDITORIAL CALENDAR

Oct/Nov 2021	Drug Delivery & Environmental Sustainability
Nov	Pulmonary & Nasal Drug Delivery
Dec	Connecting Drug Delivery
Jan 2022	Skin Drug Delivery: Dermal, Transdermal & Microneedles
Feb	Prefilled Syringes & Injection Devices
Mar	Ophthalmic Drug Delivery
Mar/Apr	Drug Delivery & Environmental Sustainability
Apr	Pulmonary & Nasal Drug Delivery
May	Injectable Drug Delivery: Formulations & Devices
Jun	Connecting Drug Delivery
Jul	Novel Oral Delivery Systems
Aug	Industrialising Drug Delivery
Sep	Wearable Injectors
Oct	Prefilled Syringes & Injection Devices

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Cover image: a selection of combination products using SHL Medical's Molly modular platform device technology (see this issue, page 8). Reproduced with kind permission.

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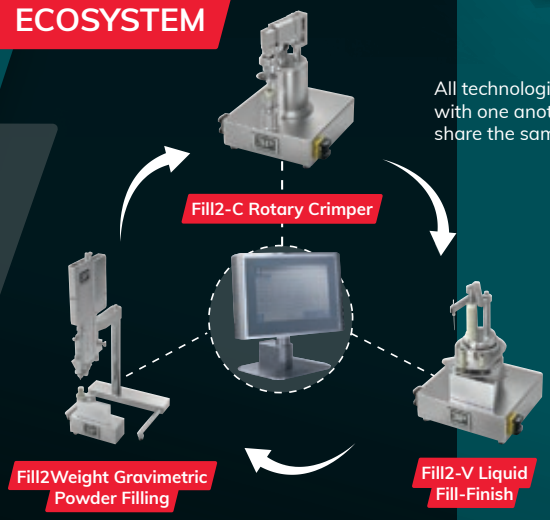

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CREATING TIMELESS DEVICE TECHNOLOGIES

In this article, Andrew Moore, Global Head of Product Management, and Gene Rhode Fuensalida Pantig, RPh, Resident Molecular Biologist and Pharmacist, both of SHL Medical, discuss the importance of a sound strategy for product lifecycle management.

The pandemic has led to unforeseen changes to the current disease landscape and, as a result, the increasing value of adopting either hospital- or home-based treatments can be seen. The data show telemedicine in the form of hybrid virtual/in-person care models are increasingly favoured by patients. This uptake can be seen even in chronic diseases – fields of interest in the self-injection space, such as rheumatology and endocrinology. Likewise, the injectable drug delivery market is expected to rise at a compound annual growth rate (CAGR) of 12.9% to reach US$1.251 trillion (£915 billion) by 2027. Although more of a correlation, these factors highlight the importance and urgency of home-based treatment and care, whenever possible.[1,2,3]

Viewing these staggering numbers in the context of the pandemic, the concepts of speed and agility have reached a whole new level of importance as we see global regulatory guidance, support and consequent approvals of biologics that are relevant to the covid-19 pandemic. From the usual time frame of 12–15 years for a molecule to reach the market, we see not only the approval but also the ramped-up manufacture and commercialisation of these products in a fraction of the time. Speed and agility are tantamount to successfully ensuring that the right product is provided to the patient at the right time. Here, we also refer to time in the context of a product staying relevant as a function of the current but ever-changing healthcare needs.[4,5,6]

THE CONTINUING RISE OF BIOLOGICAL PRODUCTS

While it was expected that biologics approvals would waver in the last year due to pandemic disruptions, the US regulatory landscape saw an otherwise positive turn of events. In fact, 2020 was one of the US FDA's top three years (since 1996) when it comes to the total number of biologics approvals. Looking further at

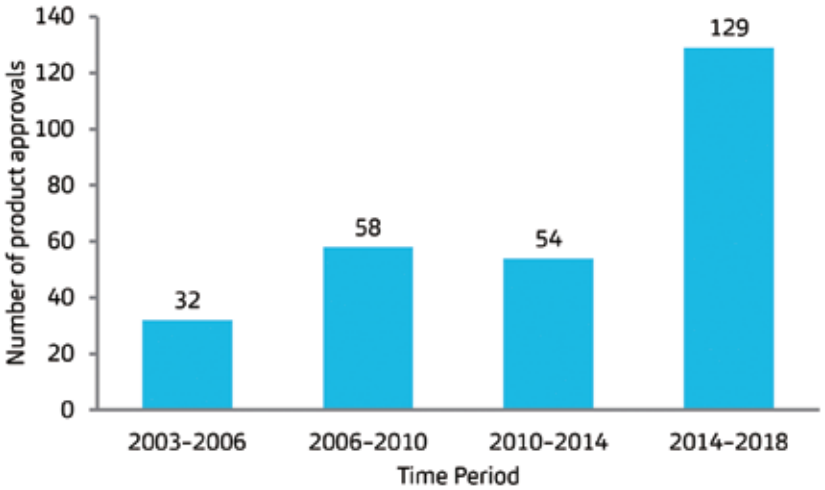

Figure 1. US and EU approvals of biopharmaceuticals over the years.

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data sets from the years 2003–2018 (Figure 1), the US and EU approvals of biopharmaceuticals remained strong, and many of these are available in self-injection formats targeting various diseases.

Over the years, autoinjector products have been treating rheumatoid arthritis, migraine, multiple sclerosis, type 2 diabetes, ulcerative colitis and Crohn's disease – and recently even addressing hypercholesterolaemia, as well as atopic disorders and weight management. It is worth enumerating such disease areas addressed by autoinjector products, most especially when news pieces – like those published in *Nature Biotechnology* – strongly associate prefilled pens with patient convenience and patient centricity.[7–10]

With decades of experience in the drug delivery space, SHL Medical has been at the forefront of co-developing these products with pharmaceutical companies, including some of the world's bestselling, essential medicines available in self-injection forms. SHL's experience in combination product development has matured into a track record of designing, developing and producing the device technologies for innovator biologics – the legacy products – and their biosimilars that are developed and approved across various regions of the world.[11]

LEGACY PRODUCTS AT A GLANCE

A legacy product, as has been known in various industries, usually refers to an item that is no longer sold, has lost substantial market share or is a version of a product that is not current. This, however, positively implies that a legacy product may have been a blockbuster unit in the past. In some cases, a legacy product may be one that is still in current demand. While being a legacy product certainly connotes polar, contrasting qualities, it is fallacious to say that a legacy product in the autoinjector space is rendered obsolete when flexible and adaptive device technology is built around the primary container.[12]

In meeting the constantly changing challenges in the self-injection space, SHL's philosophy and practice have always centred around being adaptive. For SHL, to create timeless device technologies is to create self-injection systems that are not only defined by their tangible form (core mechanism and specifications, device colour, geometry and industrial design) but also by their intangible and associated features. These attributes refer to the product offering's ability to adopt the requirements of the drug, the customer and its patient, and adapt to the ever-changing external market drivers – effectively creating an augmented product.

> "Leveraging device market, industry and regulatory insights, as well as looking upstream of combination product development to identify emerging trends and unmet needs, SHL sees the need to take PLM to the next level."

For example, SHL's second generation of Molly® that is built with a modular platform technology – and current DAI® (disposable autoinjector) products experiencing an unprecedented production ramp up – are the result of constant improvements in existing device technologies and their ecosystems. In a sense, this concept of augmentation can be closely related to product lifecycle management (PLM) in the autoinjector space.

SHL'S PLM STRATEGY

PLM, as generally defined in various industries, is the process of managing a product's lifecycle from inception, through design and manufacturing, to sales, service and eventually retirement. As a modern emerging discipline in the field of product development, the first recorded application of PLM dates back to the 1980s, when American Motors Corporation used a data-driven approach to track and improve the market performance of its products from inception to end of life. In essence, PLM brought into focus the necessity to effectively manage the lifecycle of a product and render it competitive, and this is why we have seen the rise of improved manufacturing concepts such as computer-aided design and automation, as well as database management, in the drug delivery systems industry.[13,14,15]

Leveraging device market, industry and regulatory insights, as well as looking upstream of combination product development to identify emerging trends and unmet needs, SHL sees the need to take PLM to the next level. In 2021, SHL further fortified efforts on its PLM strategy by expanding its dedicated team of experts that lead the global product management organisation. In brief, global product management (Figure 2) is a function that was created to define and continuously develop SHL's existing and future product and service portfolio, and facilitate product standardisation and modularisation, as well as create a tight-knit collaboration between SHL and pharma as a combination product matures over time.

In detail, SHL's product management strategy aims to further strengthen, support and ensure the success of products

Figure 2. An overview of SHL's product management activities, segmented according to product lifecycle phases.

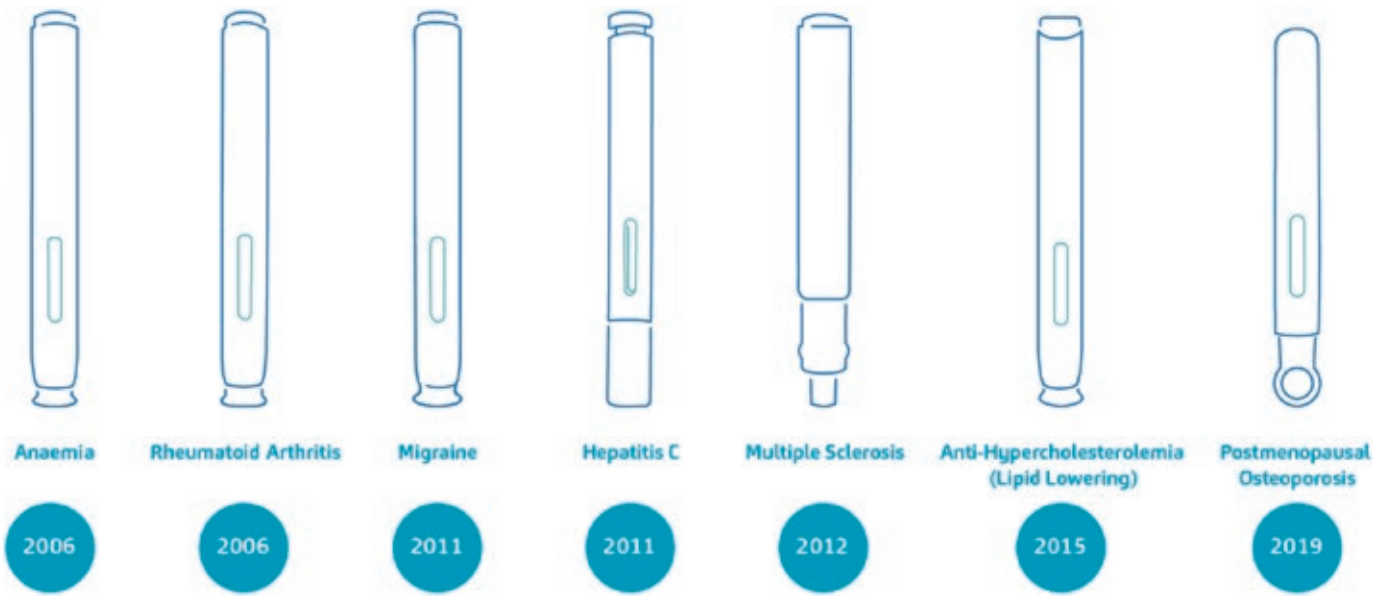

Figure 3. A non-exhaustive overview of combination products based on the DAI technology and their treatment areas. From the first DAI device, iterative developments over the years gave rise to devices inspired by the original version, and these were in the form of two- and three-step autoinjectors featuring manual or automatic needle insertion controls.

co-developed with pharma partners, made possible with the following checks and balances:

- Continuously building internal knowledge of pharma's needs by:
  - Forming two-way communication channels with customers
  - Identifying opportunities for new product solutions
- Monitoring product performance through:
  - Operational performance
  - Quality performance
  - Post-market surveillance
- Identifying improvement opportunities throughout a product's lifecycle by:
  - Engaging with internal and external stakeholders
  - Planning implementation of changes.

As products mature, the market itself becomes highly competitive. To this end, driving growth and marketability of SHL's device technologies and the pharma partner's combination products become an active pursuit rather than a passive endeavour.

LIFECYCLE MANAGEMENT IN ACTION

SHL's DAI autoinjector technology is a good example of how PLM has been proactively upheld within the organisation. Likewise, SHL's composite experience and learnings with DAI are a great precedent for modern, up-and-coming medtech device companies wishing to ensure a robust product offering in such a highly competitive industry. First launched commercially in 2006, the DAI is one of the world's first modern prefilled pens. The device is a button-activated, three-step autoinjector that houses 1 mL prefilled syringes, and its technical specifications certainly paved the way for how SHL's device portfolio matured and expanded. At present, SHL has developed an array of drug delivery systems that range from being two-step to three-step devices, as well as technologies that address pharma's biologics pipeline characterised by varying fill volume and viscosities.

As a case in point, there are two sides of the coin that we may evaluate here – DAI currently as a business-to-business device offering to pharma companies but also DAI as a legacy device technology that caters for some of pharma's longstanding blockbuster combination products. On the first point, it could be said that DAI has certainly helped shape the industry developments on two- and three-step devices, as well as manual versus automatic needle insertion controls. The latter point merits a crucial discussion and exhibits the importance of SHL's commitment to an active pursuit of product management with its pharma partners.[16]

Over approximately 15 years, the DAI technology has supported the regulatory approval and commercialisation of nearly 20 combination products. These self-injection devices, available in varying dosage presentations, are indicated for diseases such as rheumatoid arthritis, anaemia, migraine, hyperlipidaemia and osteoporosis, to name a few. Figure 3 exemplifies the depth and breadth of disease areas that the technology has addressed over time. From the original device design, iterative developments over the years gave rise to devices inspired by the original version, and these were in the form of two- and three-step autoinjectors featuring manual or automatic needle insertion controls. It could be said that these early developments have influenced the progression of SHL's device portfolio itself, and the trends within the drug delivery device industry.

A classic device that found success in its first project, SHL's DAI is the autoinjector technology behind a blockbuster product for rheumatoid arthritis. It also supports leading combination products indicated against anaemia and migraine – diseases with a high global prevalence and which present sufferers with disease burden and disability.[17]

The first DAI project was developed for a multinational biopharmaceutical company headquartered in the US. The accomplishments of this partnership gave rise to succeeding device projects under the DAI technology, effectively creating a product family for SHL's pharma partner. Given that the first project dates back to 2006, the present-day market landscape enabled SHL to evaluate upstream and downstream of the device development and production streams across the whole programme that it co-managed with the pharma partner. Applying a lifecycle evaluation approach across the board saw the need for a product portfolio consolidation; there was a need to scale up the programme.

"With more platform products emerging in the autoinjector space, SHL sought to redefine how platform device technologies can bring differentiation within the market."

This complex yet holistic activity was addressed through a streamlined approach to scaling up. The whole process touched upon all device designs, production and in-process controls, through to batch release testing across the programme, ensuring that complexities are minimised and process variations are reduced throughout. In brief, a design for manufacturability and assembly assessment was conducted to optimise the designs from an automated and scalable process perspective. This assessment allowed for maintaining brand recognition but also colour differentiation across the industrial designs of each device within the programme. With SHL moving towards automating many of its processes, this exercise also enabled centralisation of programme production flow. Now, the assembly process is automated across the programme, all the while incorporating historical learnings and controls.

A LIFECYCLE APPROACH TO PRODUCT STANDARDISATION AND MODULARISATION

The establishment of the Molly platform exemplifies SHL's product management and design philosophy, which is to incorporate standardisation as well as modularisation across its device technology offerings. Introduced in 2010, Molly is SHL's first preconfigured autoinjector designed to help pharmaceutical companies reduce initial investments and expedite development timelines. With a vertically integrated development model, Molly's platform-based infrastructures allow SHL to undertake various overlapping device projects. In 2016 alone, this preconfigured offering enabled the commercial launch of at least three combination products indicated for migraine, inflammatory and autoimmune diseases.

This is not to say that there may be no room for improvements for such a device technology. With more platform products emerging in the autoinjector space, SHL sought to redefine how platform device technologies can bring differentiation within the market. Further refined to offer the advantages of platform products while offering flexibility in the device's design, development and production, the Molly modular platform was born.

Building on the successes of its predecessor, this second generation of Molly has so far resulted in customised device families for one of SHL's leading pharma partners. Tasked to develop a device for two different biologics, the resultant combination products feature distinct industrial designs that are conformant to the primary container. Of important

Year approved	Device	Indication
2016		Autoimmune Diseases/Inflammatory
2016		Migraine
2016		Inflammatory Diseases
2017		Systemic Lupus Erythematosus
2018		Autoimmune Diseases/Inflammatory
2019		Autoimmune Diseases/Inflammatory
2019		Hypoglycaemia
2019		Autoimmune Diseases/Inflammatory

Year approved	Device	Indication
2019		Hyperlipidaemia
2019		Hyperlipidaemia
2020		Atopic Disorders
2020		Atopic Disorders
2020		Autoimmune Diseases/Inflammatory
2020		Type 2 Diabetes
2021		Severe Hypoglycaemia
2021		Autoimmune Diseases/Inflammatory
2021		Weight Management

Table 1: Combination products launched over the years that were built with the Molly autoinjector technology (brand names have been redacted and the list of disease indications is non-exhaustive).

note, the Molly 2.25 variant supported the development and commercialisation of one of the world's first autoinjectors in the higher volume range (≥2.0 mL). Incorporating a lifecycle approach has proven to be successful for the maturity of the Molly modular platform, and a list of its commercial successes can be seen in Table 1.

> "The fate of device technologies will always depend on a sound lifecycle management strategy."

CONCLUSION

The fate of device technologies will always depend on a sound lifecycle management strategy. Consequently, the importance, value and impact of combination products to end users will largely depend on the resonating beneficial experience when these products are used over time. To this end, SHL is committed to developing device technologies that are timeless. By timeless, we mean constantly adding value within the device chain as well as future-proofing the ecosystem surrounding device technologies. This includes taking proactive measures in sustainability by constantly evaluating the carbon footprint, as well as investing in the research and development of digital medicines. Transcending beyond dated device technologies and the medtech industry notion of offering "just devices" is a constant objective of SHL.[18]

The present SHL Medical portfolio and the suite of infrastructures surrounding each device technology offering came to be, not instantaneously, but by a series of holistic learnings and improvements applied over the years. The company's ultimate goal is enabling patients' independence and, to this end, it is dedicated to advancing its offerings, ensuring that they positively disrupt the healthcare landscape and influence the positive progression of the drug delivery space.

ABOUT THE COMPANY

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

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ABOUT THE AUTHORS

Andrew Moore is the Global Head of Product Management at SHL Medical, leading an international team of experts focused on taking product lifecycle management to the next level. With more than a decade of experience in the pharmaceutical and medical device industry, Mr Moore has held various positions in the fields of research, product development and product management. He holds a bachelor's degree in mechanical engineering and is currently pursuing a master's degree in bioinformatics. Mr Moore joined SHL as a Design Engineer in August 2013, over the years taking on more responsibility and was SHL's Director of Development prior to his current position.

Gene Rhode Fuensalida Pantig, RPh, is a Resident Molecular Biologist and Pharmacist at SHL Medical and is part of the organisation's marketing communications team. Prior to joining SHL, he worked for three years as a researcher in the Institute of Molecular Biology at Academia Sinica – Taiwan's national academy. He is trained in classic molecular biology techniques, having worked with Dr Sue Lin-Chao – whose mentor is Dr Stanley Norman Cohen, developer of genetic engineering methods still used today in the field of biologics.

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INTERVIEW

In this exclusive interview with *ONdrugDelivery*, Mathias Romacker discusses a broad range of topics, from his professional expertise and history seeing the parenteral sector evolve first-hand, to his personal experience as a Crohn's disease patient making use of the very devices he's seen grow and develop, ahead of his presentation, "My Lifelong Patient Journey as an IBD Patient: Insights from an Industry Insider", at the Parenteral Drug Association (PDA) Universe of Prefilled Syringes & Injection Devices 2021 virtual conference (October 5-6, 2021).

MATHIAS ROMACKER, EX-PFIZER, INJECTION DEVICES STRATEGY CONSULTANT

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Mathias Romacker is an independant Injection Devices Strategy Consultant. He was most recently employed as Senior Director, Device Strategy at Pfizer, having joined Pfizer in March 2015. In this commercial role, he focused on the front end of device technology. He worked with multiple functions and sites across the organisation with the goal of developing device strategies for Pfizer's pipeline and inline products.

Previously, he worked in the device area for nine years at Amgen. Before joining Amgen, he held multiple sales and marketing positions with Becton Dickinson and Gerresheimer, in Germany, South Africa, and the US. Mr Romacker holds a Master's equivalent degree in economics from the University of Freiburg in Germany, and is a member of the Board of Directors of PDA.

Q Many of our readers will know you already, but for those who do not, would you begin by giving as overview of your career path and how it led you to become a world leading technical and market expert in drug delivery systems, in particular parenteral drug delivery systems?

A That's a very kind way to frame the question, I appreciate it. In terms of my career path, I was lucky enough to be in exactly the right place at the right time – from the very beginning, even in my entry level job, I was stepping into an exciting story that was just about to evolve. As my career progressed alongside the rise of the parenteral delivery sector, I've spent about half my time on the supplier side and the other half actually on the pharma and biotech side, so at this stage I've got a broad range of perspectives!

Fresh out of college, my first job was with BD. I was in the pharmaceutical systems division and, at the time, the division's lead product was a prefillable glass syringe. For context, this was in the early 1990s – there was only a handful of customers in Europe interested in such a thing, mainly focused on anticoagulation drugs and vaccines. Today, in contrast, prefilled syringes are manufactured in the billions and are used across a huge range of therapeutic areas. That's the ride I've been on, accompanying prefilled syringes from a niche product to being broadly accepted and used by pharma companies to present their products in a user-friendly format, not to mention becoming the container of choice for disposable and reusable autoinjectors.

I was then approached by Amgen, and later by Pfizer, to bring the expertise and skill set I'd built on the supplier side and apply it to the pharma side. They saw that bringing on someone with my set of skills and experience would help them understand how device suppliers think and operate. I didn't miss the opportunity and moved to California to start at Amgen in 2006.

It was incredibly interesting. After being on the supplier side for all those years, you think you've got a good understanding of pharma, but when I crossed over I found I had much to learn about what the pharma side is actually like in reality. It was a great experience to be able to switch perspectives and look out from within pharma and see the supplier side from the outside.

And again, during the last 15 years, we've really seen the market evolve. In 2006 there were two prefilled syringe-based disposable autoinjectors commercialised; now in 2021 there are over 50. I count myself as very lucky to have been a part of this evolution. And then alongside that, during the same time span, other technologies, like wearable injectors and pen injectors, have also continued evolving.

All of this is, of course, in the context of an industry-wide push to move more injectable therapies from a clinical to a home setting. That's the main driver for all the innovation we see in parenteral devices and the rapid growth in the sector. It's been a privilege to have my career progress alongside it.

Q What fewer people will know is that, throughout much of your career, you have lived with Crohn's disease – a chronic condition treated using therapies delivered by the very parenteral delivery systems that you have specialised in over the course of your professional life. Can you give us a brief overview of Crohn's, with a particular focus on the treatments offered and their delivery systems?

A I've not been public historically about the fact that I'm also a patient, but I think it's given me a really interesting perspective that is worthwhile sharing. Think about it – when you're having conversations within pharma about ongoing projects, you're always talking about the patients and their perspective, so, if you are patient yourself, doesn't that put you in a really interesting position? For one thing, what's said in those conversations really hits home.

In brief, I was first diagnosed with a form of colitis in my late teens. Back then, it was believed to have psychosomatic

> "The experience was – I'm not sure if funny or ironic is the right word – but, all of a sudden, the very class of delivery systems that I'd been a part of talking about, testing and advocating for was something I had to use myself. I became a self-injector."

causes; we didn't really understand what an autoimmune disease was at the time. I was prescribed an oral medication, which probably wasn't very effective. I had a few relapses – it wasn't nice – but, over the years, it got better. I went into remission. I can't explain why, but it really did get better. After that, I had quite a few decades where I wasn't being medicated. Compared with other patients that I've talked to over the years, I was very lucky.

Then I had a bad relapse. I've no idea what happened, but it was a major inflammation. This time, however, compared with when I was a teenager, more was known about what Crohn's is, that your own immune system is in overdrive and causing a painful inflammation. The idea with autoimmune disease medication is to "level down" your immune response, ideally to the point that you no longer have any inflammation, or at least only a little.

It's at this point that I had my first encounter with biologics as patient. I went on a TNF inhibitor, which was delivered as a bi-weekly injection with a disposable autoinjector. For me, the experience was – I'm not sure if funny or ironic is the right word – but, all of a sudden, the very class of delivery systems that I'd been a part of talking about, testing and advocating for was something I had to use myself. I became a self-injector.

The loading dose was actually four injections at once, which I found a little bit unpleasant, as you can imagine. After that it was two injections after two weeks, and then one injection every other week. What I found out as a patient self-injecting with an autoinjector is that, while, from a professional perspective, they're all different products from different manufacturers, when I was looking at them as a group from a patient's point of view, they're actually really nice products in a way I hadn't appreciated before. Obviously, given my part in the industry, I thought it would be a bit embarrassing if I messed up an injection. I wouldn't call it anxiety, but I was very skittish and cautious about getting it right when I first started. But, in practice, I didn't mess up once.

As for actually self-injecting, I chose Saturday morning as the time to do it. So, every other Saturday, I had to take my drug out of the fridge and let it warm up to room temperature. I've found you can go after 30 minutes, but sometimes I waited a bit longer, which might be an expression of some kind of discomfort. Similarly, when you inject, you're supposed to hold the device against the injection site for 10 seconds, but I typically left it there for longer to just make sure I'd got the whole dose delivered. It was a very interesting, not to mention instructive, experience to do it myself.

Two and a half years ago, I was switched to an infusion therapy. For that, I have to go into a clinic once every eight weeks and the procedure is performed by healthcare professionals. I believe that the drug is actually available in Europe as an autoinjector and, if you were to ask me to choose, I would easily pick the autoinjector at home.

Q So, from a patient's point of view, is it your opinion that it's better to be able to self-inject with an autoinjector at home yourself rather than go into a clinic for an infusion?

A Let's start with the baseline that, obviously, the clinical result is the most important thing. No matter how nice a self-injection device is, I'd rather go into a clinic once a month for an infusion if it's going to give me clinically superior results. It really is the most important parameter for me. On the other hand, having convenience and the freedom to travel and go about life as normal, that's clearly a major upside to self-injection.

In my case, going in for infusion treatments hasn't been easy for a number of reasons. I have to be able to schedule clinic visits once every eight weeks, which presents extra difficulties if you're not settled down in one place for the long term. Then there's been the covid-19 pandemic, which has added a whole other set of problems. If I'd been given autoinjectors to self-inject my treatment, that would have been a lot easier.

As it happens, I understand that some pharma companies reported in their quarterly reviews that some of their drugs took a hit because patients, especially before vaccinations became available, were very concerned about going to a hospital or clinic to be injected during the pandemic. So, clearly, if more self-injected drugs had been available during the pandemic, it probably would have been better for patients and for pharma alike.

Q Could you tell us a little more about how, as a patient, the coronavirus pandemic impacted your experience of receiving your treatment?

A As I mentioned, it became much more difficult. I was fortunate in that I found a home nurse service, where a nurse would come to my house and administer my infusion. To be honest, with no vaccine available in 2020, I felt uncomfortable with the idea of going to a clinic, but I think that was a pretty universal experience. I managed, but it wasn't easy. There were a lot of hoops to jump through, and I think it's pretty obvious that if I could have had a delivery of autoinjectors, like I did when I was self-injecting, it would've been a lot easier and more convenient. Plus, when you want to isolate, self-injection is safer, because you're still seeing a nurse no matter what when you get your infusion and you don't need to see anyone when you self-inject.

Q Let's broaden the discussion a bit. Combining your perspectives from both the industry and patient points of view, can you talk a little bit more on how the parenteral sector is currently evolving and where it's going looking forward?

> "I know there's a buzz around connectivity, and that's something I'd like to see as a patient – I already spend hours a day on my smartphone, after all."

"I would expect that, moving forward, my peers in the industry will only become more interested in all things self-administration, especially as connectivity becomes normalised and more advanced electronic devices are able to provide proof that drugs have been administered correctly."

A Reusable devices are one thing that I'm keeping an eye on. My self-injection experience was with a disposable autoinjector, which, in practice, meant that I built up a collection of used autoinjectors that I needed to dispose of fairly fast. Even now, I know that some companies aren't offering a reusable electromechanical autoinjector as an alternative for their autoimmune disease products, which are weekly injections. The reusable devices – where the drug is basically in a prefilled syringe, which is held in a cassette that gets loaded into the main device, used for the injection, and then ejected and discarded afterwards – are one way that delivery systems are evolving at the moment. Personally, I think that the trade-off of the device having some additional use steps but creating much less waste is a good one.

As someone involved in the industry, I know there's a buzz around connectivity, and that's something I'd like to see as a patient – I already spend hours a day on my smartphone, after all. With the newer class of reusable electromechanical autoinjectors, some connectivity would be quite handy. They're in use for one of the multiple sclerosis drugs, but I think it would be good if this were to expand across other therapeutic areas over the years. I like the idea that you could log your injections, maybe keeping a diary with symptoms, letting you keep track of everything in one place. I personally think that could really enhance the patient experience moving forward.

Most people now are quite comfortable with smartphones and that area of technology, and that is increasingly true even of older demographics, who are the most likely to be using these treatments. The number of patients that could really get some use out of connectivity is getting bigger by the day, so why not leverage this for convenience, comfort and, of course, improved outcomes?

I should also talk about the fact that a new class of large volume injectors has evolved – that being on-body or wearable injectors. These devices could be a great opportunity for the loading dose to be administered more comfortably; remember how I said the loading dose when I started self-injecting was four injections at once? A wearable injector could have made that a lot less unpleasant. Thinking about them that way, while it might seem like a waste to train a patient on a device for one injection, wearables have the potential to be used by healthcare professionals in clinics as an alternative to infusion, which could improve safety and patient turnover.

A running theme with where innovations in the parenteral space are taking us is adherence. It's one of the major things pushing what are traditionally IV therapies towards subcutaneous delivery. I would expect that, moving forward, my peers in the industry will only become more interested in all things self-administration, especially as connectivity becomes normalised and more advanced electronic devices are able to provide proof that drugs have been administered correctly. Obviously, if a patient is not adherent you don't get the desired treatment outcomes, which leads to increased healthcare costs all around. This is an area to continue to pay close attention to.

"There are definitely a few more things we need to figure out when it comes to connectivity. Patients are concerned about privacy, data protection and security, and we need to allow them to be comfortable sharing data with a variety of stakeholders."

There are definitely a few more things we need to figure out when it comes to connectivity. Patients are concerned about privacy, data protection and security, and we need to allow them to be comfortable sharing data with a variety of stakeholders. It's no wonder that the better approach at this stage for connectivity is an "opt-in" one.

A lot of new companies are entering the connectivity space, offering ideas, as well as services and ecosystems. However, having been an industry watcher for many years, I think we're still waiting for something to catalyse mass adoption. I'm excited for the future here – we're going to see some interesting developments this decade.

Q Where industry talks about "unmet needs", a patient simply sees room for improvement in their treatment. As a patient, what do you wish was possible in terms of treatment, and how close is the industry to making those things happen?

A Obviously, an injection will always be an invasive process, so making it as quick and comfortable as possible comes near the top of the list. This is something I think about where it comes to wearable injectors – what trade-offs would I be willing to make for these slower, larger-volume injections? The number one priority is to make it a single administration event. That means only one needle prick regardless of the dose, whether it's a small or large dose, and balancing delivering it as fast as possible with minimising perceived pain, or any kind of discomfort.

Also, I place a lot of value on the "out of the box" experience. What is the size and shape of the device? What's the onboarding experience like? What sort of training is there? These are factors that really have an impact on how easy it is for patients to get to grips and become comfortable with their therapies, which is so important if you're going to self-inject.

It's something that comes up regularly in market research. On the whole, patients are currently quite happy, but there's still a feeling that some things can still be done better. One way of thinking about it is to imagine an example from a totally different area; as an example, let's say you asked somebody 20 years ago if they were happy with their cellphone. Most people probably

would've said yes, but then think about phones nowadays – everyone has a smartphone, right? I don't think there are many people who would like to go back to the kinds of phones we had 20 years ago. It's the same principle with autoinjectors, just because patients say they're mostly happy doesn't mean there isn't still plenty of opportunity for the industry to innovate and make an even better user experience.

Q On the subject of onboarding, from your experience as a patient, have you found that the reality lines up with the way we within the industry imagine onboarding is done?

A When I was onboarded, I got a needle-free demo device and had a travelling nurse available to train with me if I had felt that I needed it. I assume the nurse could have also been present during my first self-injection. However, given my background and the fact that I'm far more knowledgeable about these devices than the average person, I felt bad asking that nurse to come to my home, so gave that opportunity a pass. Overall I was quite impressed with how it was done.

Don't forget that this whole idea of onboarding patients by providing needle-free reusable training devices is only around eight years old. The first patients who self-injected didn't have anything like the tools we're discussing today. A training device to mimic the actual injection is a huge plus for making onboarding smoother and more comfortable for patients. Also, some of the newer therapies, anti-migraine for example, are monthly injections. I can't say for sure if a month is long enough to forget how to self-inject, but I can say that if you have one of those reusable onboarding devices available, you can always do a mock injection before you give yourself your real one if you're not entirely comfortable with the procedure.

Q To what extent do you feel that the industry is "in tune" with patient needs, or is there room for a better flow of information from patients back to the industry?

A There's probably always room for more communication, right? I mean, with all the conversations we have with patients, delivery devices are very important, but the drug is still the star – you still want to have the best possible drug in terms of efficacy and safety. You could have the most incredible, patient-centric device ever designed, but if the drug inside it doesn't help patients they're not going to be interested.

I do feel that, while we've gotten a lot better at devices during my time in the industry, the pharma industry does have a tendency to be very risk averse – companies are very prone to defaulting to the highly de-risked technologies they've relied on for years, or even decades! Even existing platform technology is higher risk than pharma is sometimes comfortable with, which may potentially inhibit looking at further advancements to make things more patient-centric and patient friendly. There's definitely an inherent idea that the drug is the absolute

> "I find this really interesting, that the same platform is leveraged across all of these therapeutic areas, even though the patient populations for each are very different."

priority, which unfortunately means that the device, while important, may not necessarily be a key focus for many pharma companies.

If you dig a bit deeper, you can see that the pharma companies that have multiple disposable autoinjectors on the market tend to use the same device platform across all of their products. A product portfolio could include, for instance, a rheumatoid arthritis drug, an anti-migraine drug and, say, something like a GLP-1, but they'll all be commercialised using devices based on the same autoinjector platform. I find this really interesting, that the same platform is leveraged across all of these therapeutic areas, even though the patient populations for each are very different. Think about it, the demographic for anti-migraine patients includes a large population of middle-aged women, while with rheumatoid arthritis patients you're looking at a lot more geriatrics and patients with limited dexterity. These are very different patient populations, but you still find pharma companies taking a one-size-fits-all approach with their platform choice.

Q Moving on to our last topic, tying all your experiences together into a broad perspective, what do you see as the major primary trends in the injectable drug delivery sector at present, and what are the top significant advances we'll see emerge over the coming years?

A The one that springs to mind most readily is drugs moving from IV to subcutaneous delivery. There are a few examples that have already been commercialised, such as for lupus and rheumatoid arthritis, but what is really interesting is that oncology, a huge therapeutic area, is really embracing this shift. It is pretty clear, if you just search online, that there are a lot of clinical trials for new IV-to-subcutaneous reformulations going on right now, and that I find very, very interesting. It doesn't guarantee that those therapies will be made available for at-home self-injection, but it absolutely opens the door to the possibility. I would tend to assume that they will try to mimic the same injection frequency as the IV version, so maybe once every four or six weeks. You can imagine the increase in comfort, especially if it could be administered in the patient's home.

"It is pretty clear, if you just search online, that there are a lot of clinical trials for new IV-to-subcutaneous reformulations going on right now, and that I find very, very interesting. It doesn't guarantee that those therapies will be made available for at-home self-injection, but it absolutely opens the door to the possibility."

Then, of course, there's the question of the delivery devices supporting this shift. I would speculate that a handheld autoinjector would be the preference from the patient's perspective. But if you need a larger dose and you still want to mimic the injection frequency of the IV, then this newer class of wearable injectors that can deliver doses of 10 to 20 mL, or in some cases even more, become a very interesting option for pharma companies.

Another topic that I hear a lot about is sustainability. Consider chronic diseases that require lifelong management, if you can move those patients onto reusable devices where the disposable piece you throw away is a lot smaller than a full-blown disposable autoinjector, you're significantly reducing the environmental impact of their self-injection regimens. If you could potentially recycle these disposable components, all the better.

We're discussing sustainability in so many aspects of our lives these days, why would it be excluded in pharma and drug delivery? Remember how I mentioned before that I was throwing away a lot while I was self-injecting? I think that's indicative of a shift in our general awareness. 20 or 30 years ago we wouldn't have thought twice, we'd just throw everything away in the same bin and it just went away and that was that. Whereas now, I find that having lots of waste piling up makes me feel uncomfortable, and I think it's the same for a very large – and growing – number of people. My feeling is that this discomfort will make itself felt in the industry, both from consumer preferences for greener products and from pressures to reduce carbon emissions coming down from governments and multinational organisations, all fuelling this trend towards more sustainable products and industry practices.

Finally, one other topic we as an industry talk about a lot, and have touched on already here, is optimising the patient experience. For example, it seems to me that needles keep getting thinner, certainly for pen injectors – they're now going down to 34 gauge! Also, what we learned over time is that if you're injecting into the subcutaneous tissue, you don't have to go very deep. It may not be a major topic, but I can absolutely imagine us really enhancing injection quality with shorter and even thinner needles. I can say from experience that, as a patient, every step forward in comfort and ease-of-use helps.

Mathias Romacker will give his presentation, "My Lifelong Patient Journey as an IBD Patient: Insights from an Industry Insider", at the PDA Universe of Prefilled Syringes & Injection Devices virtual conference, October 5-6, 2021.

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AIDAPTUS®: OWEN MUMFORD INTRODUCES ITS NEXT-GENERATION PLATFORM AUTOINJECTOR

In this article, Michael Earl, Director, Pharmaceutical Services at Owen Mumford, introduces the next-generation Aidaptus autoinjector, explaining how this latest platform device from Owen Mumford can contribute to a faster speed-to-market, increased flexibility during drug development and improved patient outcomes.

Autoinjectors have been used as a convenient and effective means of delivering subcutaneous injections since the 1980s, and recent healthcare trends have led to an increase in their use. Autoinjectors allow patients to administer their own medication outside of acute care facilities, without the need of a healthcare professional. This helps to address a number of healthcare concerns, including an ageing population, the increase in chronic conditions among patients and pressure on healthcare systems and budgets.

A further driver of autoinjector use is the emergence, and subsequent increase, of biologics and biosimilars over the past years. More low volume formulations are being developed for these drugs to allow administration via the subcutaneous route, facilitating patient self-administration. The ensuing increase in demand for autoinjectors has created greater competition in this area, with simplicity and ease of use for the patient being a major differentiator between devices.

THE PLATFORM APPROACH

Speed-to-market is a key consideration in the drug development process, meaning that commissioning custom devices for specific drugs may not always be the most cost-effective or efficient solution. In more recent years, pharmaceutical companies have tended to opt for platform devices, which are a quicker and more flexible solution. The base platform device is designed with a wide envelope of possible delivery capabilities so that it can be used for a variety of formulations, reducing the level of testing required at the device selection stage.

However, the challenge with platform devices is that they are not designed with a specific user group in mind; the devices must therefore accommodate the needs of multiple potential patient groups. This broad accommodation is critical to

Figure 1: Aidaptus – Owen Mumford's next-generation autoinjector.

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reassure pharmaceutical businesses that any use-related risk factors have been identified and addressed regardless of the patient demographics. Device developers must therefore devise inclusive testing strategies that cover patients with different levels of physical and cognitive abilities.[1]

BRINGING AIDAPTUS TO MARKET

A pioneer in the development and manufacture of autoinjectors, Owen Mumford Pharmaceutical Services has launched a new platform autoinjector offering next-generation benefits of flexibility and versatility (Figure 1). As with all other platform devices in the Owen Mumford Pharmaceutical Services range, the Aidaptus® disposable autoinjector was designed with a focus on ease of use and patient comfort.

However, the covid-19 pandemic began during the latter stages of the Aidaptus' development, meaning that final human factors testing could not proceed as usual. It is only through first-hand user feedback on a range of device prototypes that usability and human factors issues can be properly understood, so, to be able to move forward, the human factors team decided to prepare a new study design that would comply with the restrictions in place. For example, the prototypes were all packed at least three days in advance of the study by engineers wearing PPE, and were kept sealed until needed. Rather than handing out each prototype as usual, the moderator instructed participants on which prototypes were needed at each stage and which actions they needed to take.[2] This carefully adapted study provided the key data to allow the team to meet human factors requirements and to launch the product this autumn.

DESIGN BENEFITS FOR PATIENTS

Understanding the stages of needle insertion and medication delivery is key to helping patients to manage their injection process successfully and to be confident that they have administered their drug correctly. For this reason, the Aidaptus autoinjector provides patients with audible and visual notifications during the injection procedure (Figure 2). There are audible clicks at the start and end of dose delivery, as well as a bright yellow plunger rod clearly visible through the viewing window to confirm end of dose. The window is large enough for patients to easily see the drug before administration, and to check the drug's clarity and colour. There are no other internal mechanisms visible through the window, thereby providing an unobstructed view, as well as confidence, to the user. The needle itself is hidden before, during and after use to prevent needle exposure – a feature that may be particularly beneficial for patients with needle-phobia. On completion of the injection, the safety shroud locks in place to ensure that the needle cannot be exposed and present a risk to the user before disposal.

"Needle insertion and dose delivery take place as two separate phases, with each action controlled independently. This means that the delivery of the medication does not take place until the needle is fully inserted into the patient's skin, helping to prevent drug spillage prior to injection."

HELPING TO PREVENT WET INJECTIONS

An issue occasionally experienced while using autoinjectors is the occurrence of "wet injections" – patients may remove the autoinjector from the injection site too early in the drug delivery process, resulting in drug spillage and wastage. Aidaptus's design mitigates this through automatic pressure-activated needle insertion that creates a consistent user experience for all injections. Needle insertion and dose delivery take place as two separate phases, with each action controlled independently. This means that the delivery of the medication does not take place until the needle is fully inserted into the patient's skin, helping to prevent drug spillage prior to injection.

Figure 2: Aidaptus provides both audible and visual feedback to give patients confidence in their self-injection.

This dual-phase action also helps to prevent syringe breakage, which can be caused by the strong springs typically used to deploy the needle for skin insertion and the plunger for dose delivery. Furthermore, before the product even reaches the patient, the self-adjusting plunger helps to prevent breaches of container closure integrity by

"For maximum flexibility, the Aidaptus autoinjector is compatible with either a 1 or 2.25 mL prefilled syringe, with a minimal number of changed parts, whilst maintaining its small, discreet size (162 by 18 mm)."

Figure 3: Aidaptus makes use of a novel self-adjusting plunger to prevent breaches of container closure integrity and allow for flexible syringe fill volumes.

limiting the backwards movement of the stopper in the syringe barrel (Figure 3). This is critical in helping to prevent microbial ingress during transit from factory to patient.

VERSATILITY AND FLEXIBILITY

Apart from use considerations, pharmaceutical companies also need to take account of potential formulation and/or dose changes, a typical occurrence during the development and lifecycle of injectable drugs, and how these could affect their device choice. For maximum flexibility, the Aidaptus autoinjector is compatible with either a 1 or 2.25 mL prefilled syringe, with a minimal number of changed parts, whilst maintaining its small, discreet size (162 by 18 mm).

Additionally, the novel self-adjusting plunger allows the use of a range of syringe fill volume options without any changes to the device and with no change in parts. The ability to adjust the drug volume whilst maintaining the same device may have significant advantages during the clinical trial phases of development, when modifications to dosages are often required to determine optimum dosing volume and frequency for the intended patient population. From a drug filling perspective, the option to use either vented or vacuum filling provides additional flexibility and may also allow for a choice of contract filling partners.

Aidaptus is available in two presentations, one with a traditional opaque body and another with a transparent body and over-wrap, which can be printed and customised as required. This presentation allows for branding options, as well as flexibility of window size. There is scope for further optimising the patient benefits of the product by adding, for example, innovative new label technology solutions, such as new surface finishes and textures that aid grip and handling, integrated near field communication enabling connectivity options or temperature sensor technology.

> "Aidaptus is available in two presentations, one with a traditional opaque body and another with a transparent body and over-wrap, which can be printed and customised as required."

PROMOTING TREATMENT OUTCOMES

Self-administration is beneficial for overall treatment outcomes, allowing patients to take more responsibility for their treatment, which improves adherence in turn. Using autoinjectors for drug administration provides greater ease-of-use and convenience for patients compared with prefilled syringes, further helping to promote adherence. Drug formulators and device developers are developing innovative solutions to further enhance the patient experience – from creating longer-acting formulations to reduce injection frequency, to reducing needle size. Owen Mumford's Aidaptus autoinjector is designed to provide new solutions, facilitating both device selection for pharmaceutical companies and drug administration for patients.

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

Michael Earl joined Owen Mumford as Director of Pharmaceutical Services in November 2020. He was previously the Commercial Vice-President at Bespak (now part of Recipharm), leading the commercial team there to drive growth in their substantial medical devices business. Prior to that, he worked for a number of pharma, biotech and device companies. In a career spanning 35 years, he has been responsible for all aspects and stages of drug and device development and commercialisation. Mr Earl has also completed a substantial number of commercial, licensing and mergers and acquisitions transactions.

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A NEW MINDSET FOR COMBINATION PRODUCT DEVELOPMENT

In this article, Asmita Khanolkar, Senior Director, Cambridge Pharma, at SMC, outlines the latest trends in combination product development to overcome some of the current challenges of high dose/viscosity/volume delivery.

Based on the learnings from the covid-19 pandemic, it is time to emphasise the changing mindset towards a forward-looking design and development process for combination products. The new outlook for the pharmaceutical industry is very different from the one we knew prior to the pandemic. The new normal encompasses rapid development of treatments and new regulatory pathways to support the urgency towards faster times to clinic.

Treatments are now administered outside traditional hospital care settings, including clinical studies conducted at home. We have seen a dramatic shift from a one-size-fits-all approach towards rising personalised medicine. Novel therapies considered too complex and complicated previously are now available in the hands of patients, and there is an unmet need for enabling device technology that can handle the challenging formulations. Finally, global digital transformation is modernising the overall healthcare experience.

Moving forward, as we balance the time to market and risk for novel therapies, we can anticipate several trends, including: a changing mindset in areas of combination device development focused on enabling device design for challenging applications for optimising delivery; patient-centric interfaces for self-administration to eliminate user errors; and integrated drug-device development iteration cycles to minimise any risks for clinical outcomes. The latter highlights a technological paradigm shift and focus on developing combination products at pandemic speed.

COVID-19 IMPACT ON THE DRUG DEVELOPMENT PROCESS

The drug development process can be broadly divided into three segments – drug discovery through preclinical, clinical evaluation through approvals and finally commercial launch. Each of these segments were significantly impacted by the pandemic but in different ways (Figure 1).

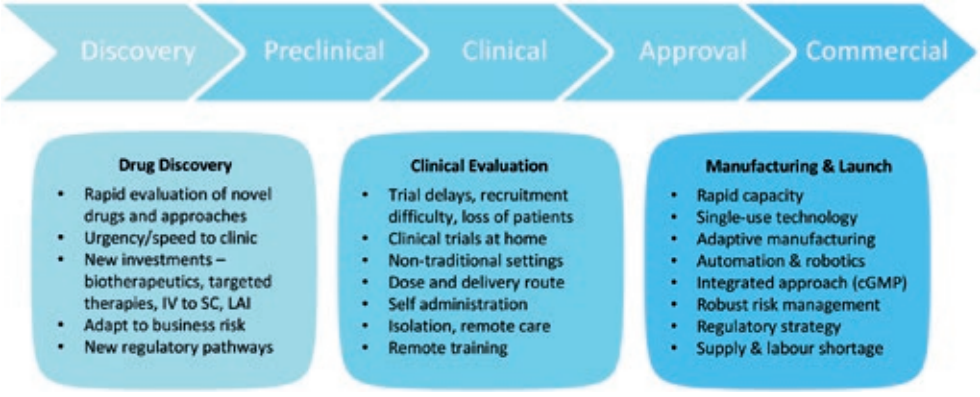

Figure 1: The impact of covid-19 on the drug development process.

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"With the pandemic and the difficulty of getting patients to a hospital, the trend has moved towards subcutaneous delivery and increasing the timing between treatments."

The drug discovery segment saw the urgency of getting therapies to clinic faster than ever with patients in need from both the pandemic infectious disease itself and the amplification of struggles with chronic and crisis diseases created by the pandemic. Previously for parenterals, an intravenous (IV) version would be considered for first release and the fastest path to patients. With the pandemic and the difficulty of getting patients to a hospital, the trend has moved towards subcutaneous (SC) delivery and increasing the timing between treatments – resulting in more challenging formulations for higher concentration, larger volumes and long-acting injectables (LAIs). New faster regulatory pathways for approvals for unmet needs further justified rapid evaluation of novel therapies and faster parallel approaches, posing multiple paths towards faster time, to clinic but, at the same time, accepting more business and investment risks.

The clinical evaluation segment saw tremendous delays, difficulties in recruitment and loss of patients. We saw clinical trials move to non-traditional home settings from hospitals. Patients were not willing to go to hospitals during the pandemic and hospitals were overwhelmed with the pandemic response. It became apparent that clinical trials had to be decentralised from the hospital to home. This brought tremendous patient logistics and clinical trial supply management challenges.

The commercial launch segment saw the need for rapid capacity increases while supply shortages and labour resource management made it difficult to deliver the product. Single-use technology, adaptive manufacturing and automation trends were implemented to overcome some of these challenges, along with implementation of robust risk management procedures.

"The impact of covid-19 on the drug development process poses and necessitates a significant paradigm shift for combination products."

SIGNIFICANT PARADIGM SHIFT FOR COMBINATION PRODUCT DEVELOPMENT

The impact of covid-19 on the drug development process poses and necessitates a significant paradigm shift for combination products. Rapid development of therapies that took years has now been reduced to months. This necessitates simultaneous development of drug and device. In addition, the complexity of formulations and challenging needs brought to light challenges of the legacy platform device technology that may not be suited for these novel applications. The risk increases especially for novel drug products that are complex molecules – and due to unknowns and uncertainties with the new delivery methods and large dosage. Other risk factors include patient tolerability and acceptability. The pharma industry is also looking for avenues for market differentiation. The success of the clinical outcome is dependent on the delivery optimisation in these situations and thus the realisation of an unmet need for an enabling design for early-stage characterisation and development of drug-device combinations for challenging therapies and unmet patient needs.

The shift of clinical trials to home has brought the focus on to self-administration for clinical trial supplies early on. The importance of optimal drug-device combinations in terms of user needs becomes critical for successful clinical outcomes. We are now looking at targeting designs for eliminating user errors completely. The healthcare professionals' visits to patients at home have emphasised the need for streamlined devices. In addition, some of the novel targeted therapies – such as cancer treatment and biologic drugs – are costly. Administering them in hospitals over long periods of time can become unaffordable for patients. As a result, many targeted therapies and precision medicines are now being designed to be self-administered.

Finally, the complex formulations are not an exact fit to deliver with existing standard device technologies, and the device needs to be designed to deliver the specific formulation appropriately. In addition, formulations have to be optimised for delivery and for the therapy outcome. This results in iterative development cycles and the need for customisable processes, flexible lines and adaptive manufacturing technologies that can support the many facets of joint development of customised drug-device therapy for successful clinical outcomes (Figure 2).

CHALLENGING FORMULATIONS

Novel formulations involving LAIs and complex biotherapeutics pose challenges to the traditional drug delivery device platforms. In the case of biotherapeutics, we

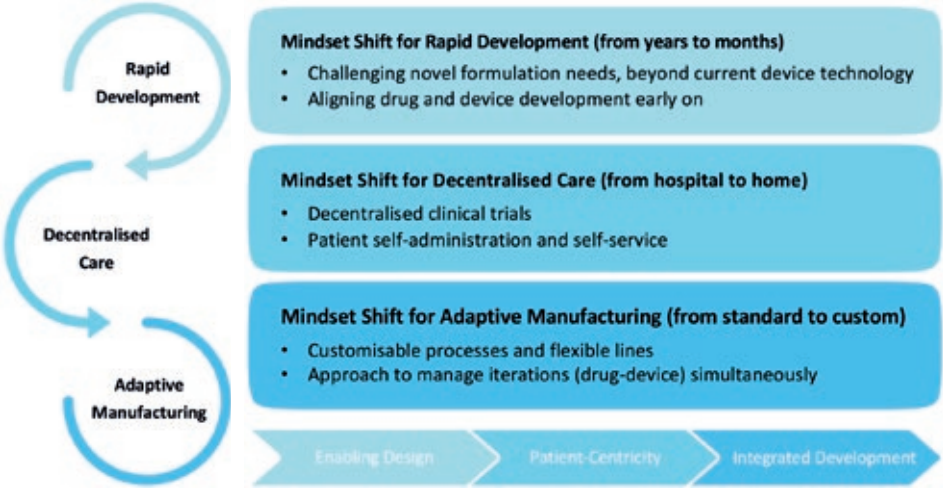

Figure 2: New mindset for combination product development.

are dealing with complex high-molecular-weight molecules, such as monoclonal antibodies (mAbs) (Figure 3). Additionally, these biologic molecules are fragile – and stability in the primary drug container is also important throughout the shelf life of the product. This requires clean systems free from any potential interactions, thus the need for silicone lubricant-free and tungsten-free systems. Trends of IV to SC delivery require high dose concentrations and large delivery volumes for administration subcutaneously. This requires a high-pressure system with reasonable and consistent delivery time. Previously, in glass syringes, patients have experienced variability of injection times – resulting in wet injections. In the case of biologic drugs, this can potentially cause an immunological response. Therefore, for such applications, traditional legacy primary packaging materials may not be suitable.

LAIs are formulated for extended times, supported over monthly, bi-monthly or even a three-month period. This is achieved through controlled release of the drug, typically through adjusting or reducing the solubility of the LAI. The approaches to developing slow-release formulations typically involve high-molecular-weight

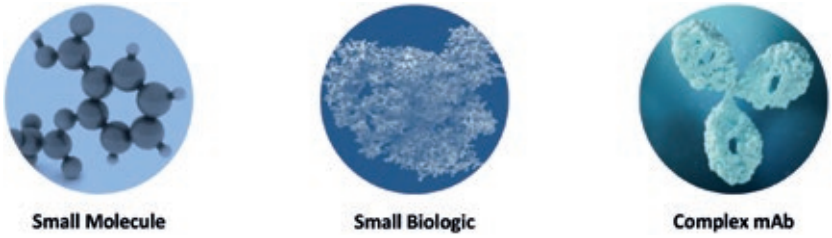

Figure 3: Complex molecules of biotherapeutics and biologics.

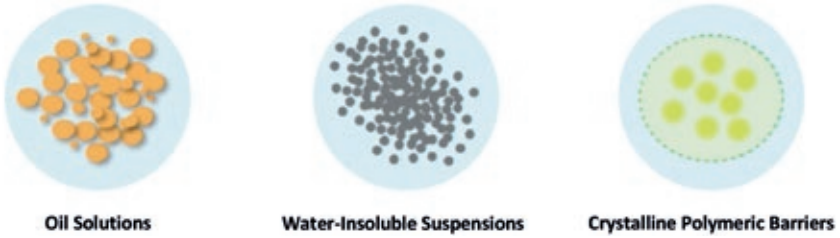

Figure 4: Formulation vehicles for LAIs.

vehicles such as oil solutions, water-insoluble suspensions or crystalline polymeric barriers (Figure 4), which, in turn, increase the viscosity of the entire formulation and can also lead to non-Newtonian behaviour and increased sensitivity to environmental conditions. Delivering these via autoinjector can be further complicated by other characteristics of suspensions, such as settlement in storage, particle agglomeration or clogging. This puts great onus on the delivery mechanism for high-pressure systems to overcome and manage delivery requirements.

The API is released from the carrier vehicle by either diffusion or degradation, both of which can occur most rapidly at the surface of the drug bolus. A bolus with a larger surface area will often release its API at a faster rate than one with a smaller surface area, reducing the effective duration of the dose. The shape of the bolus formed can therefore have a significant impact on the pharmacokinetic profile of the formulation. A spherical bolus is usually ideal as it reduces the release rate of the drug, potentially allowing a longer dosing interval. Delivery parameters such as injection speed can have an impact on the shape of the bolus and therefore the pharmacokinetic profile. The delivery parameters need to be optimised in conjunction with the formulation.

> "It is evident that one size does not fit all, whether it be the personalised and targeted dosage regimen, control of needle depth due to physiological differences, emotional status of patients, population diversity or cost of the therapy."

ONE SIZE DOES NOT FIT ALL

These discussions lead towards what the device architecture should look like going forward – it has to fulfil a lot of criteria, from the previously mentioned technical challenging needs of the formulations to the patient interface side of things when considering self-administration and self-service (Figure 5). It is evident that one size does not fit all, whether it be the personalised and targeted dosage regimen, control of needle depth due to physiological differences, emotional status of patients, population diversity or cost of the therapy. This brings us to the unmet need of an enabling design that can be customised internally to the challenging technical needs of the application and external customisation to patient touchpoints towards eliminating user errors and successful self-administration.

ENABLING DESIGN SOLUTION – ARQ-BIOS AUTOINJECTOR

Oval has developed a high-power, single-use autoinjector called the ArQ-Bios, which offers the ability to deliver high-viscosity or high-volume dose options for SC delivery in the same device. This allows flexibility for formulation development, early engagement with the device and reduced risk and time to market. Low-to-medium-viscosity formulations under 100 cP can be delivered

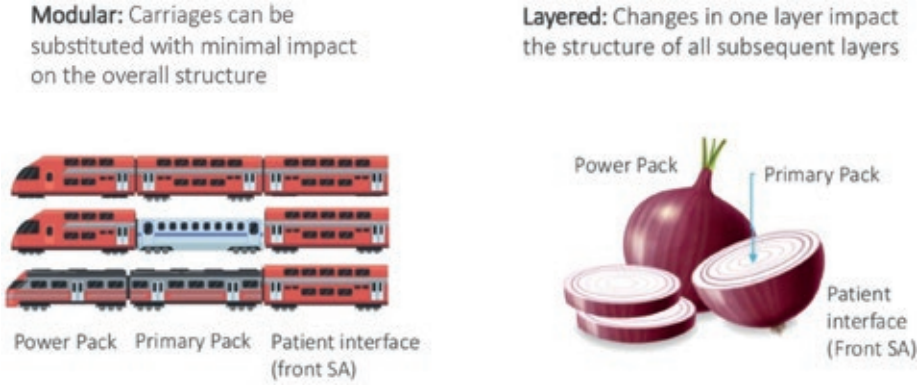

Figure 5: Device architecture for a flexible platform.

up to 10 mL and high/ultra-high viscosities up to 10,000 cP can be delivered between 0.5 and 3 mL. Owning and manufacturing the primary drug container allows integrated devices to be designed for the needs.

Oval's proprietary patented "cup seal and foil" technology is built around a high-pressure cyclic-olefin copolymer primary drug container (PDC). The PDC can safely tolerate significantly higher pressure than glass, allows stronger springs and enables devices to generate higher pressures than other market offerings. The high-pressure cup seal design overcomes the friction challenges of traditional rubber plunger seals. By decoupling the microbial and liquid seal barrier functions, conflicting requirements can be managed separately. The polyethylene piston component provides liquid seal with the stability to manage high pressures and sufficient lubricity to prevent excess glide forces. The induction-welded foil provides a microbial barrier and is a robust solution for high-viscosity delivery. The design aims for a superior patient experience and fewer wet injections due to highly consistent drug delivery times, independent of product age or manufacturing tolerances.

The ArQ-Bios also incorporates a proprietary hydraulic valve release mechanism. The valve enables quiet and gentle activation of the device, even when the drug is pressurised at 300 bar. These unique features make ArQ-Bios an enabling technology for high-viscosity or high-volume applications for the demanding needs of LAIs or biotherapeutic SC delivery (Figure 6).

Digital and mathematical transformation techniques – such as predictive modelling and simulation – can be used to predict the delivery time of challenging formulations and predict the shear-dependent behaviour of LAIs and biologics. Using these models, a simulation can be created to predict autoinjector performance. The simulations can look at likely variations of injection times across millions of simulated devices constructed by random selection of different input variables. This can help with optimisation of the design (Figure 7).

Figure 6: Enabling design – ArQ-Bios autoinjector technology.

Figure 7: Patient interface focus – gentle self-administration.

INTEGRATED ADAPTIVE MANUFACTURING

The final consideration when discussing challenging formulations is the integrated drug-device-patient approach combining concurrent development, manufacturing and test cycles. This removes the fragmented approach and can substantially reduce time to clinic.

Especially in the case of LAI formulations, integrated studies are required throughout the development to optimise formulation parameters, API release and pharmacokinetics performance. Biotherapeutics have their own challenges of bioavailability optimisation from preclinical to clinical models, complex molecular structures and are typically administered in larger volumes and require optimisation of formulation and delivery for the route of administration. Oval's ArQ-Bios platform offers a flexible platform for early-stage development for large-volume and high-viscosity biologic and LAI formulations. Engaging early with the device provides a unique solution to the challenge of delivering better solutions to patients (Figure 8).

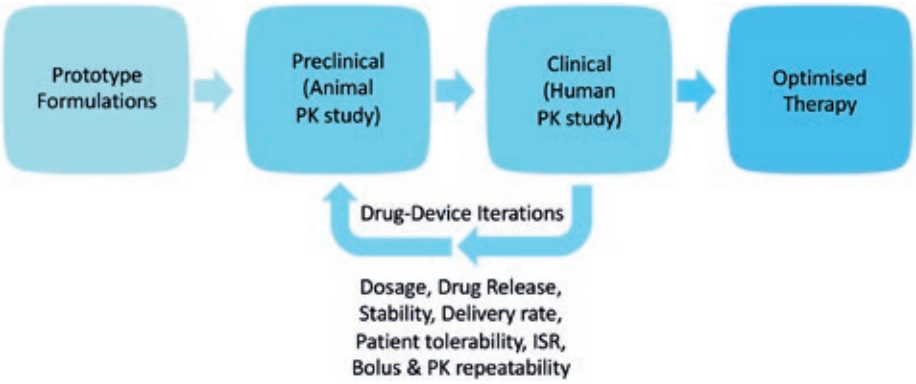

Figure 8: Iterative drug-device development.

In addition to the enabling design, adaptive manufacturing and flexible processes are needed for the optimisation iterative cycles. Starting from moulding and assembly, PDC moulding flexibility and design for manufacturing inputs are key manufacturing considerations. PDC moulding allows customised designs to be tailored to the needs of each drug. Tolerance control on the device assembly stack ensures repeatability and enhances device performance reliability. Fixturing and automation development early on help accelerate special processes industrialisation, including fill-finish and secondary packaging processes. Adaptive manufacturing, including customisable processes and flexible lines capable of GMP manufacturing, is key to the successful development through to commercial launch of novel therapies (Figure 9).

In summary, this article has outlined the new mindset for combination product development to overcome some of the current challenges of high-dose/viscosity/volume delivery with enabling device design, self-administered home treatment, customised patient interfaces eliminating user errors and methods of adaptive manufacturing to provide pathways for

Figure 9: Integrated manufacturing from early research to launch.

simultaneous drug-device development. As the pandemic continues, the focus on virtual care, longer times between hospital visits and the need for at-home care for chronic diseases will continue. This further translates into a growing need for self-administering biotherapeutics and LAI formulations subcutaneously. ArQ-Bios technology overcomes the limitations of existing legacy technology, providing enabling delivery technology for challenging formulations and better solutions for patients.

ABOUT THE COMPANIES

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

SMC is a global device manufacturer for the healthcare industry specialising in drug delivery, medical devices, diagnostics and pharmaceutical services. With over 33 years of experience, SMC provides an end-to-end integrated solution for clinical and commercial product manufacturing. SMC provides product services from initial concept through to the final packaged device; including programme management, design and development, product manufacturing, clinical manufacturing, electronics integration and global supply chain management. SMC has global GMP manufacturing sites in the US, UK, Costa Rica and India for moulding, assembly and automated package integration.

ABOUT THE AUTHOR

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

ON drugDELIVERY

2021/22 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
Oct/Nov 2021	Drug Delivery & Environmental Sustainability	Oct 14, 2021
November	Pulmonary & Nasal Drug Delivery	Oct 21, 2021
December	Connecting Drug Delivery	Nov 4, 2021
January 2022	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Dec 9, 2021
February	Prefilled Syringes & Injection Devices	Jan 6, 2022
March	Ophthalmic Drug Delivery	Feb 3, 2022
April	Pulmonary & Nasal Drug Delivery	Mar 3, 2022
April/May	Drug Delivery & Environmental Sustainability	Mar 17, 2022
May	Delivering Injectables: Devices & Formulations	Apr 7, 2022
June	Connecting Drug Delivery	May 5, 2022
July	Novel Oral Delivery Systems	Jun 2, 2022
August	Industrialising Drug Delivery	Jul 7, 2022
September	Wearable Injectors	Aug 4, 2022
October	Prefilled Syringes & Injection Devices	Sep 1, 2022

THREE PHASES TO SUCCESS IN STERILE INJECTABLES TECHNOLOGY TRANSFER

In this article, Jennifer Quint, Senior Manager at Pfizer CentreOne Technical Services, offers insights into how to plan and execute technology transfer effectively, explaining Pfizer CentreOne's three-phased approach that can successfully support this pivotal event in a drug product programme's journey to commercialisation.

Central to every commercial relationship with a contract development and manufacturing organisation (CDMO) is the technology transfer. A number of subject matter experts from both the sponsor and the CDMO may be involved in developing and manufacturing a product, making the technology transfer process both complex and critical to success.

Many organisations have their own definition of what constitutes a technology transfer, but the US FDA points to ICH Q10, "Guidance for Industry Q10 Pharmaceutical Quality System" published in 2009, to define its guidance. "The goal of technology transfer activities", the guidance states, "is to transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realisation. This knowledge forms the basis for the manufacturing process, control strategy, process validation approach and ongoing continual improvement."

As explained in ICH Q10, this internationally harmonised guidance is intended to help pharmaceutical manufacturers by describing a model for an effective quality management system. It is a systematic, logical procedure that transfers the documented knowledge and experience gained during chemistry and formulation development to an appropriate, responsible and authorised commercial manufacturing entity.

> "With sterile injectables, both the SU and the RU need to gather additional information – and do so as early in the process as possible."

A priority for many sponsors, therefore, is finding partners with the specific scientific and technical capabilities to transfer their formulation chemistries from a source unit (SU) to the commercial-scale receiving unit (RU) in compliance with regulatory guidance. All successful technology transfers require discipline and collaboration. However, when it comes to the aseptic finishing and filling of sterile injectable therapeutics, obtaining this base knowledge can present specific challenges (Figure 1).

START A WELL-DEFINED SCOPING PROCESS

With sterile injectables, both the SU and the RU need to gather additional information – and do so as early in the process as possible. The earlier a well-defined discovery begins, the better it will be at communicating and transferring the main agenda of the drug

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Figure 1: Technology transfer is never a simple process, but there are additional challenges when dealing with sterile products such as injectable therapies.

programme. Four key considerations should feature prominently when scoping sterile injectable technology transfer:

Geography

The location of the RU may impact the completion of a compliant, efficient technology transfer, as changes that are permissible in one jurisdiction may not be allowed in another due to the regulatory environments in which they operate.

Compliance

Although compliance is a broad term, a "compliant" technology transfer begins with a careful evaluation of the applicable regulatory guidance that pertains to a product's finished commercial state. For example, more mature commercial product transfers may see more compliance challenges in the dossier and equipment/facility contemporisation.

Technical

Sterile injectables are typically considered to be a high-risk product, in large part due to the duration of a drug development project. Sterile injectables can take 2–10 years to move from Phase I clinical trials to full commercialisation. Such a project is prone to outside factors, such as regulatory changes (e.g. nitrosamines, elemental impurities) or supplier changes, impacting the overall project scope and timeline. Defining the technical bases and outlining process elements should be a part of early discovery and a critical dialogue that sets the stage for a more formal technology transfer process.

Project and Site Talent

It is also critical to engage with the CDMO's core team and subject matter experts early and to continue to ask questions throughout the process. As with any aspect of drug development, a technology transfer can only be successful if all teams actively work together from the start.

PICK THE PROFESSIONALS AND ALIGN ROLES

When a sterile injectable technology transfer project involves multiple partners, additional protective measures are called for. Before actual due diligence is conducted, there should be a confidentiality agreement signed and in place. Programme managers and sponsors should both know that, throughout the drug development programme, all project information and data must remain confidential and secure.

> "Conducting a deep dive and thorough assessment of gaps between the SU and the RU can help the project team understand, document and manage the risks associated."

Role alignment is another tactic that supports a successful technology transfer. All outcomes should be documented on an ongoing basis, such as having a comprehensive product transfer plan (PTP), so that a mutual understanding is shared across all team members and stakeholders from the beginning of the project to the very end.

THE THREE PHASES OF A SUCCESSFUL STERILE INJECTABLE TECHNOLOGY TRANSFER

In most "lessons learned" shared among sponsors and commercial partners, the common reasons for technology transfer failure include:

- Not anticipating the impact of changing facility or equipment (batch failures)
- Not anticipating the new regulatory environment or requirements (scope creep)
- Tacit knowledge of the product not captured or transferred to the partner or RU.

Taking a systematic approach during the scoping phase of technology transfer is important. Conducting a deep dive and thorough assessment of gaps between the SU and the RU can help the project team understand, document and manage the risks associated. Pfizer CentreOne, defines three key phases of a technology transfer (Table 1):

- "Define and Scope"
- "Plan"
- "Execute".

	Phase One – Define and Scope	Phase Two – Plan	Phase Three – Execute
Key success factors	• Knowledge gathering • Gap analysis • Risk assessment	• Establish project schedule • Check and optimise • Have a risk management plan	• Collect project data • Analyse variance • Mitigation plans • Communicate project progress

Table 1: Pfizer CentreOne defines three phases that are a key part of any successful technology transfer.

"The benefit of having a documented charter and a PTP is that it ensures that there is a shared understanding of the project and its objectives."

PHASE ONE – DEFINE AND SCOPE

Phase One defines the scope of the project and helps to establish organisation and a project charter. This is accompanied by a knowledge-gathering process that encompasses the programme's current status and future outcomes. Phase One also sets the stage for a gap analysis and failure modes and effects analysis risk assessment. Lastly, long lead-time items are covered, and the transfer protocol is defined. At a high level, at the beginning of the project, it is important to define what is in and out of scope:

- What type of transfer is it – is it from development to commercialisation or is it transferring from an existing commercial site to a new one?
- What is the status of each receiving site – is it a green field site or is it GMP certified? How many receiving sites are involved in the project?
- Is this an intra-company transfer or is it an inter-company transfer?
- If an external partner is involved, what is in the contract regarding the technology transfer scope, roles and responsibilities?
- How many stock-keeping units are involved?
- What are the targeted markets in which the sponsor intends to file?
- What is the current supply chain (APIs, raw materials, excipients, etc) versus the future supply chain?

Even though the teams may not have concrete answers to these questions up front, they must be asked, documented and tracked so that information stays visible and can be actioned by the team.

It is never too early to define the project charter or to work on the PTP. The benefit of having a documented charter and a PTP is that it ensures that there is a shared understanding of the project and its objectives. The project charter and PTP are also tools to facilitate project planning.

PHASE TWO – PLAN

In Phase Two, the planning stage, the CDMO's technology transfer team will develop a work breakdown structure and outline critical milestones. This phase includes the development of the preliminary schedule and the generation of resource estimates. During this phase, the involved parties each develop their own risk management plans, refine transfer protocols, establish a clear schedule and lay the groundwork for the transition to the execution phase.

Why is Planning Important?

Not having a project schedule can lead to confusion pertaining to which stakeholder is responsible for each activity at each stage and whether the end goal of the project is still on track. Too little detail can paint an unclear picture, whereas too much detail can obscure important information. With the right amount of information, the project may be tracked and managed effectively. Ideally, every project plan should have some lag built into the schedule to accommodate any unforeseen circumstances.

Optimise Project Review Frequency

Determining the right frequency to review and, if need be, optimise project timelines and charters can be just as important as the amount of detail that is put into each document upon its creation. If managers check too infrequently, they might miss something. On the other hand, if managers review too frequently, then it may appear that the project is not moving along as it should be. Additionally, reviewing the project charter against the timeline ensures that the project goals that have been communicated to key stakeholders are in alignment with the project's current progress.

Define a Risk Management Plan

A risk management plan can track items that were not scoped and assign a level of risk to activities that could impact the overall project timeline. Such plans also function to define the project's overall agreed risks and provide a good communication tool when checking in with sponsors and key stakeholders. A risk management plan can help to reduce the risk of failing to file in accordance with the agreed timeline.

The risks associated with a technology transfer project include technical risk, regulatory risk and supply chain risk. Technical risk assessment, also known as a robustness assessment, employs various tools to identify the highest risks associated with the technical aspects of the technology transfer. The technical risk assessment relies on the development and manufacturing history of the product and is a documented, data-driven process.

A regulatory gap assessment handles strategies associated with various change scenarios, as well as contemporisation requirements. The outcome of the regulatory gap assessment is typically a regulatory strategy document, also known as a risk registry, which is used throughout the transfer project to communicate and manage the regulatory risks.

A supply chain risk assessment will yield a supply chain transition plan. This includes supply chain changes that might impact the robustness and regulatory assessments. The outcome of the technical and regulatory assessment will be used as the basis for the supply chain transition plan.

PHASE THREE – EXECUTE

Phase Three is an exciting milestone where the programme team tracks and manages the project and collects status data. As operational data arrives, the programme team analyses variances and looks for adaptive actions to ensure that quality and process optimisation goals are met. Project status reporting is vital during this phase to ensure transparency and clear communication.

Depending on the complexities of the programme, weekly team meetings

"It is crucial to pay close attention to the transfer process, carrying out proper definition and planning prior to any execution. Failure to do so could lead to unnecessary delays and downtime, with implications for project timelines."

and sometimes sub-meetings may be necessary to track actual progress against the established PTP and timeline. Check-ins can become even more critical when unforeseen issues arise. Working together to troubleshoot and correct issues can have a significant impact on a timeline in the long run, but might also make a process more robust.

Communication within the CDMO's team is often just as critical as communication with programme stakeholders. All stakeholders want to know is:

- Are there any issues or emerging risks that could significantly impact the project?
- How is the programme tracking against the agreed budget and timeline?

FOLLOWING THE PROCESS IS CRITICAL TO PROGRAMME SUCCESS

Technology transfer is complex, particularly for sterile products. With this in mind, it is crucial to pay close attention to the transfer process, carrying out proper definition and planning prior to any execution. Failure to do so could lead to unnecessary delays and downtime, with implications for project timelines.

Working closely with the CDMO and other stakeholders from the very beginning of the definition and planning phases is an essential part of any effective transfer. Such collaboration can ensure that any potential pitfalls and risks are accounted for and mitigated against before they become a problem. It can also help all parties ensure that they have the capacity, capability and infrastructure in place ready for the project handover, helping to ensure development continues smoothly and efficiently.

ABOUT THE COMPANY

Pfizer CentreOne is a large global CDMO within Pfizer and a leading supplier of specialty APIs. Its service offering is broad, spanning development and manufacturing services for sterile injectable and oral solid dosage forms. Pfizer CentreOne's manufacturing network includes more than 35 sites across six continents.

Pfizer CentreOne was founded in 2015 when Pfizer CentreSource, a global leader in specialty APIs, and Hospira One 2 One merged. Backed by Pfizer resources, the company delivers technical expertise, global regulatory support and long-term supply.

ABOUT THE AUTHOR

Jennifer Quint is the Senior Manager for the Pfizer CentreOne Technical Services team. Ms Quint leads a team of chemists and microbiologists who execute compendial and method development in support of internal and external Phase II/III technology transfer projects. Her focus is on GMP compliance while driving alignment of cross-functional development teams. Ms Quint joined Abbott in 2003 and has been a part of the Pfizer CentreOne organisation for over 17 years with experience in leadership, science and customer manufacturing business activities.

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CHALLENGES IN HIGH-VISCOSITY, HIGH-VOLUME DRUG DELIVERY

In this article, Michael Roe, Senior Director of Development and Industrialisation at Kaléo, discusses the development of the Aerio™ Platform of gas-powered injection systems.

In 2020, biologics accounted for more than half of the world's 20 top selling drugs.[1] The molecules that comprise most biologics, including monoclonal antibodies (mAbs), have molecular weights in the hundreds of thousands of Daltons (Da). As the concentration of drug formulations increases, so does the drug's viscosity or "thickness". The higher the viscosity, the greater the force required to push the drug through the narrow cannulas typically used for parenteral delivery, especially at lower temperatures.

The force needed to push a fluid through a cylinder is governed by the Hagen-Poiseuille equation:[2]

$$F = \frac{(128Q\mu LA)}{(\pi D^4)}$$

Where:

- F is the plunger force
- L is the length of the needle
- μ is the viscosity
- Q is the flow rate
- A is the area of the plunger
- D is the internal diameter of the needle.

Figure 1 shows the pressure drop needed to deliver the indicated volume in 15 seconds. Increased viscosity requires a corresponding increase in pressure to ensure delivery of the volume in the same length of time. For viscous fluids (50 cP), the required pressure can be as high as 600 psi for a 2.25 mL volume.

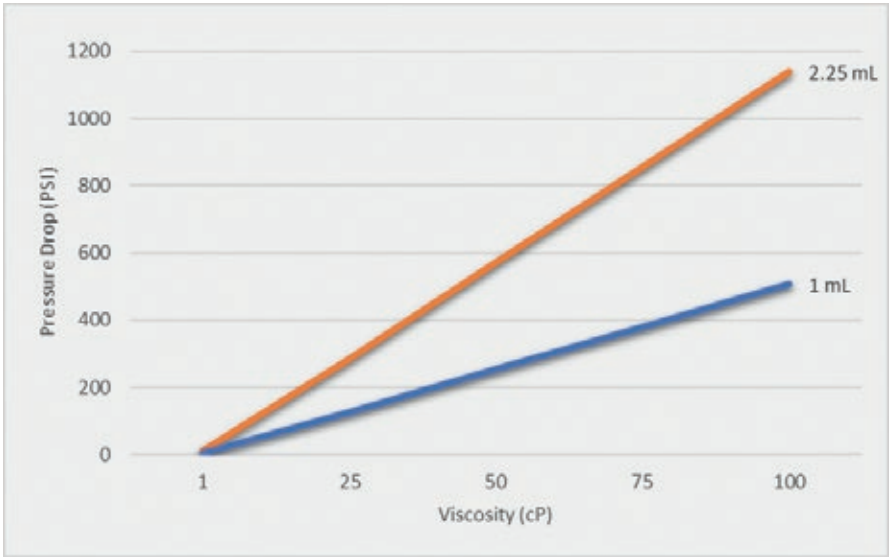

Figure 1: Pressure drop needed to deliver 1 mL or 2.25 mL of fluid of indicated viscosities in 15 seconds.

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Many higher molecular weight formulations can also be susceptible to molecular shear at higher flow rates.[3] Shear force can break apart weaker hydrogen bonds present in the structure, which can denature or "tear" proteins. This can result in aggregation and a loss of solubility, to the point that the protein can no longer perform its intended function. This problem may be exacerbated by the move to smaller cannulas and quicker injection times, which require an increased flow rate of fluid through the needle.

Concurrent with the rise of higher concentrations of mAbs has been a shift in delivery trends. Currently, large doses of high-concentration drugs are most commonly administered intravenously (IV) by a healthcare professional at hospitals, clinics and infusion centres. Most IV infusions are given over several hours, during which time the patient must stay at the infusion location and remain relatively sedentary. Even before the covid-19 pandemic upended daily life, such infusions could be inconvenient and time-consuming for both patients and healthcare professionals.[4,5] Pharmaceutical companies have responded by introducing formulation technology that allows high-volume IV formulations to be administered instead via subcutaneous injection over the course of minutes rather than hours.[4] In addition, market trends indicate a move towards less frequent dosing schedules to increase convenience and, potentially, prescription adherence.[4] Pharmaceutical companies are responding to these pressures by increasing the duration of activity of their products through encapsulation and other timed-release technologies. The result is the potential for longer periods between injections, during which time it is plausible that the patient or caregiver might become less familiar with the correct operation of the injector.

Biopharmaceutical and drug delivery stakeholders have therefore sought injection systems that improve high-volume and high-viscosity performance while simplifying the self-injection process to facilitate home use.

"Kaléo successfully developed and marketed a line of gas-powered autoinjectors. This same proven technology is used in Kaléo's Aerio Platform of pressurised gas-powered injection devices."

To address these needs, many injection systems have emerged with novel drives (e.g. compressed gas, electromechanical, chemical) that enable the delivery of viscous formulations at a constant rate while maintaining a small form factor and improving ease of use.

Devices for the subcutaneous administration of medicinal products have typically consisted of two types: needle-based and needle-free, with needle-based products comprising the bulk of the offerings. Within the needle-based class, there are manual injection pens and autoinjectors. The manual injection pens are used primarily by patients with diabetes who require multiple injections of small, precise doses during the day. Autoinjectors typically administer a dose that does not need to be adjusted and are commonly used by individuals with chronic or emergent (life-threatening) conditions. A pressurised gas-powered autoinjector was envisioned by twin brothers with severe food and other allergen sensitivities. They sought a compact adrenaline autoinjector to facilitate transport while also incorporating features that would enhance ease of use. The resulting company, Kaléo, successfully developed and marketed a line of gas-powered autoinjectors. This same proven technology is used in Kaléo's Aerio Platform of pressurised gas-powered injection devices.

As the container diameter increases – as often happens with larger containers – the force at the plunger must also increase to counter the increase in the plunger's surface area and provide consistent pressure. A conventional device would require the use of larger, higher-force springs. A gas-powered device would be largely unaffected by the container diameter because the same gas pressure applied to a larger area results in a higher force; thus, gas-powered devices are largely immune to the impact of container diameter. This attribute allows the use of a larger diameter container in the design, which reduces overall length.

The patented non-coaxial layout of the Kaléo system can reduce the overall length of the device by placing the drive system adjacent to, rather than in line with, the primary container. The Aerio Platform does not require a separate piston to drive the plunger, resulting in a device that, in many instances, is only slightly longer than the container/needle assembly. These features provide greater flexibility to the designer to tailor the device to the unique aspects of the use/carry environment of the therapy under consideration.

In addition, while spring force typically drops with plunger travel distance, gas pressure remains relatively constant throughout the injectable length. These factors make pressurised gas well suited for the delivery of higher volumes of high-viscosity formulations from a variety of primary container closures.

Using the same proven gas-powered technology used in the company's US FDA-approved products, along with additional enhancements, Kaléo has developed the Aerio line of injection systems to enable injection of larger volumes of high-viscosity formulations. The Aerio Platform consists of four different types of autoinjector: AerioUno (single container), AerioDuo (dual container), AerioMix (dual chamber) and AerioOn-body (Figure 2).

The Aerio Platform is designed to have the following capabilities:

- Constant delivery rate through gas-powered technology
- Reliability
- Accurate and precise administration of dose volumes ranging from 0.1–40 mL
- The ability to deliver high-viscosity formulations through a range of needle gauges

"Using the same proven gas-powered technology used in the company's US FDA-approved products, along with additional enhancements, Kaléo has developed the Aerio line of injection systems to enable injection of larger volumes of high-viscosity formulations."

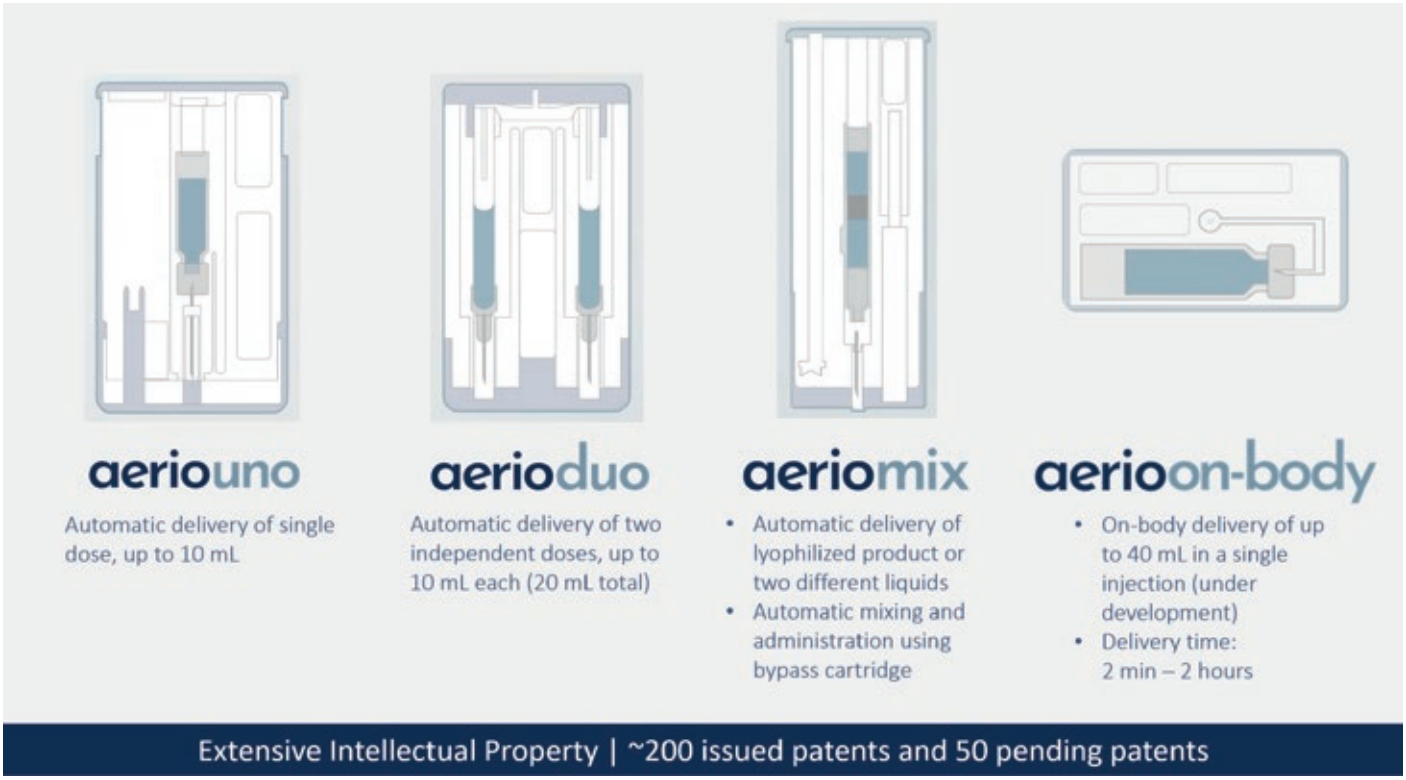

Figure 2: The Aerio Platform from kaléo.

- Potential flow velocity ranging from 1 mL/min up to 90 mL/min
- The ability to use standard or custom syringes or cartridges
- Rapid automatic needle insertion and retraction (the patient never sees the needle)
- Injection steps tailored to the use environment
- Form factor flexibility to suit a variety of patient needs.

All Aerio devices use Kaléo's proprietary non-coaxial configuration, which enables a shorter overall length than conventional spring-powered autoinjectors. This, combined with the company's proprietary plunger-drive technology, means that in many instances, the Aerio device is only slightly longer than the combined length of the drug constituent container and the needle. In addition, the pressure in the gas cylinder can be modified to accommodate larger volumes and higher viscosities without an increase in cylinder size, whereas the spring in a conventional autoinjector must typically increase in length or diameter. This results in a compact unit that is designed to be easy to handle and configure according to specific patient/caregiver needs.

With gas power, the Aerio Platform has the ability to deliver high-volume formulations at a constant rate, regardless of injection stroke or delivery time. This helps make the injection more predictable and comfortable, as there is no immediate "rush" of flow at the start, as can be experienced with the high initial spring force that comes with conventional autoinjectors.

> "Through Kaléo's proprietary gas flow modulation technology, Aerio devices can control the drug injection flow to protect formulations that may be damaged by high-velocity molecular shear."

As part of a post-marketing commitment to the FDA, Kaléo evaluated the reliability of two approved autoinjectors and verified 99.999% reliability (otherwise known as "five nines") for successful injection. This was documented using a quantitative fault tree analysis of the manufacturing process to assess the system-level reliability. Additionally, the two products were subjected to "worst-case" sequential testing to mimic the results of product condition throughout the shelf life. The result of this work was verification that the products met the FDA's draft requirement for reliability for emergency-use injectors. The FDA recently published its draft guidance containing this recommendation for emergency-use autoinjectors.[6]

Kaléo was also chosen to develop a 10 mg naloxone autoinjector using the Aerio Platform for the US Department of Defense. During this development, Kaléo has demonstrated that its 10 mg naloxone autoinjector meets the rigorous requirements of MIL-STD-810H testing.[7] This same approach to reliability and ruggedness would be applied to the Aerio Platform to assure consistent device performance.

The Aerio Platform can use either cartridges or syringes as its primary container, with drug volumes of 1–40 mL. The primary container can be either standard or custom and can be made of conventional glass or polymer technology. Furthermore, any standard or custom elastomer can be used to seal the container. The power of the pressurised gas technology can also enhance the ability to inject high-viscosity formulations through small bore needles.

Through Kaléo's proprietary gas flow modulation technology, Aerio devices can control the drug injection flow to protect formulations that may be damaged by high-velocity molecular shear.

In addition, Kaléo has developed proprietary connected health technology capable of the following:

- Automatic pairing with a mobile device to facilitate setup
- Motion detection to confirm proper carrying and adherence
- Automatic detection of proper activation
- Automatic temperature trend notification to warn of unsuitable temperatures
- Last known location feature to help locate the device and/or user
- Power management features to facilitate extended battery life.

Any of these features can be added to any of the Aerio Platforms (Uno, Duo, Mix, On-body).

Kaléo is also the first company to include electronic voice prompts to guide the user through the injection process. This has proven to be very useful for first-time users and in the high-stress environment emergency-use autoinjectors are typically used in.[8] This prompt system is intended to guide users through the administration process, which may be helpful in situations where there are long durations between injections. Kaléo has also developed an electronic trainer to aid instruction on correct use to keep the patient/caregiver current on training between injections.

Kaléo's proprietary pressurised gas technology, combined with its patented non-coaxial configuration, automatic needle insertion and retraction, and proven reliability, makes the Aerio Platform well-positioned to address the emerging need for home administration of high-volume, high-viscosity formulations.

ABOUT THE COMPANY

Kaléo is a pharmaceutical company dedicated to building innovative solutions that can help empower patients with certain life-threatening medical conditions. Kaléo believes patients and caregivers are the experts on how medical conditions impact their lives, and so the company includes them as integral part of its development process, and puts their needs at the forefront. Kaléo products combine established drugs with innovative delivery platforms. Kaléo is a privately held company headquartered in Richmond, VA, US.

ABOUT THE AUTHOR

Michael J Roe, is Senior Director of Development & Industrialisation at Kaléo. He leads a team that develops autoinjectors and on-body delivery systems, as well as connected health and digital solutions. Mr Roe has published articles and presented in the areas of innovation, device development and drug delivery, and holds several patents. Prior to joining Kaléo he spent over 20 years at Eli Lilly and Company in device development. Mr Roe has degrees in Engineering and Business from Duke University (Durham, NC, US) and is a registered Professional Engineer. He serves as convener of the ISO Technical Committee 84, which is responsible for injection device standards.

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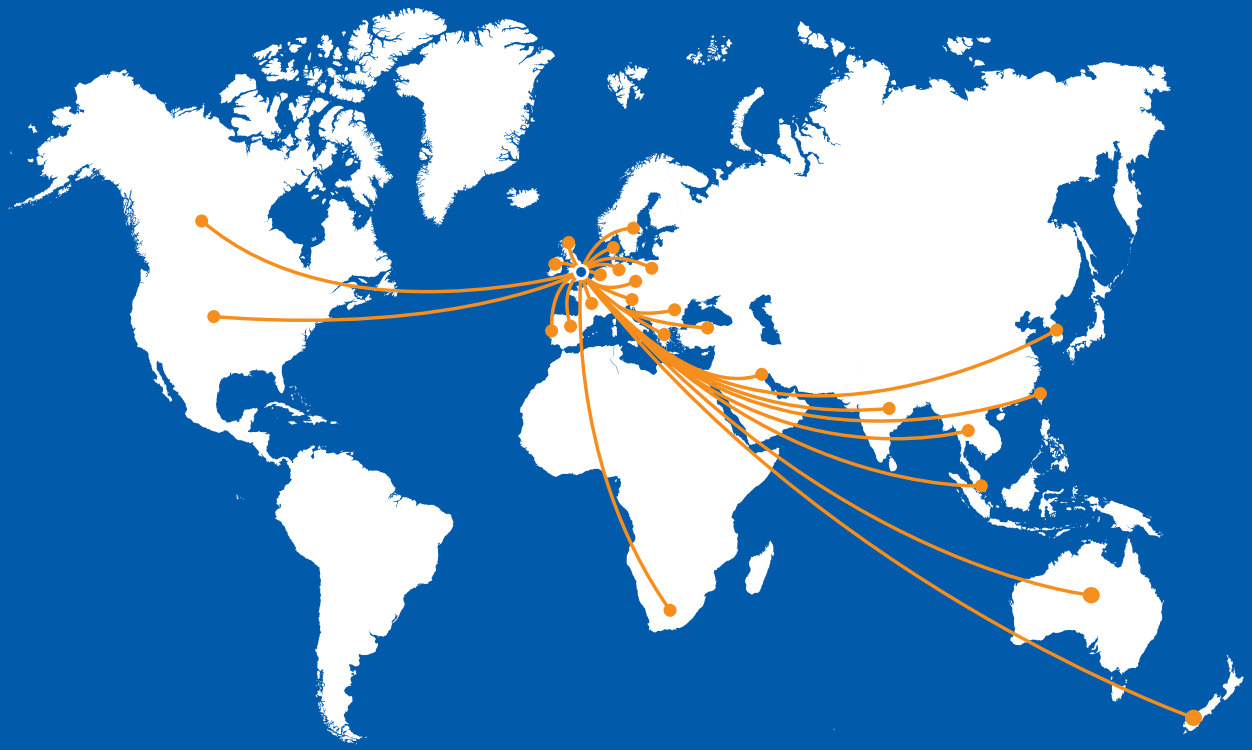

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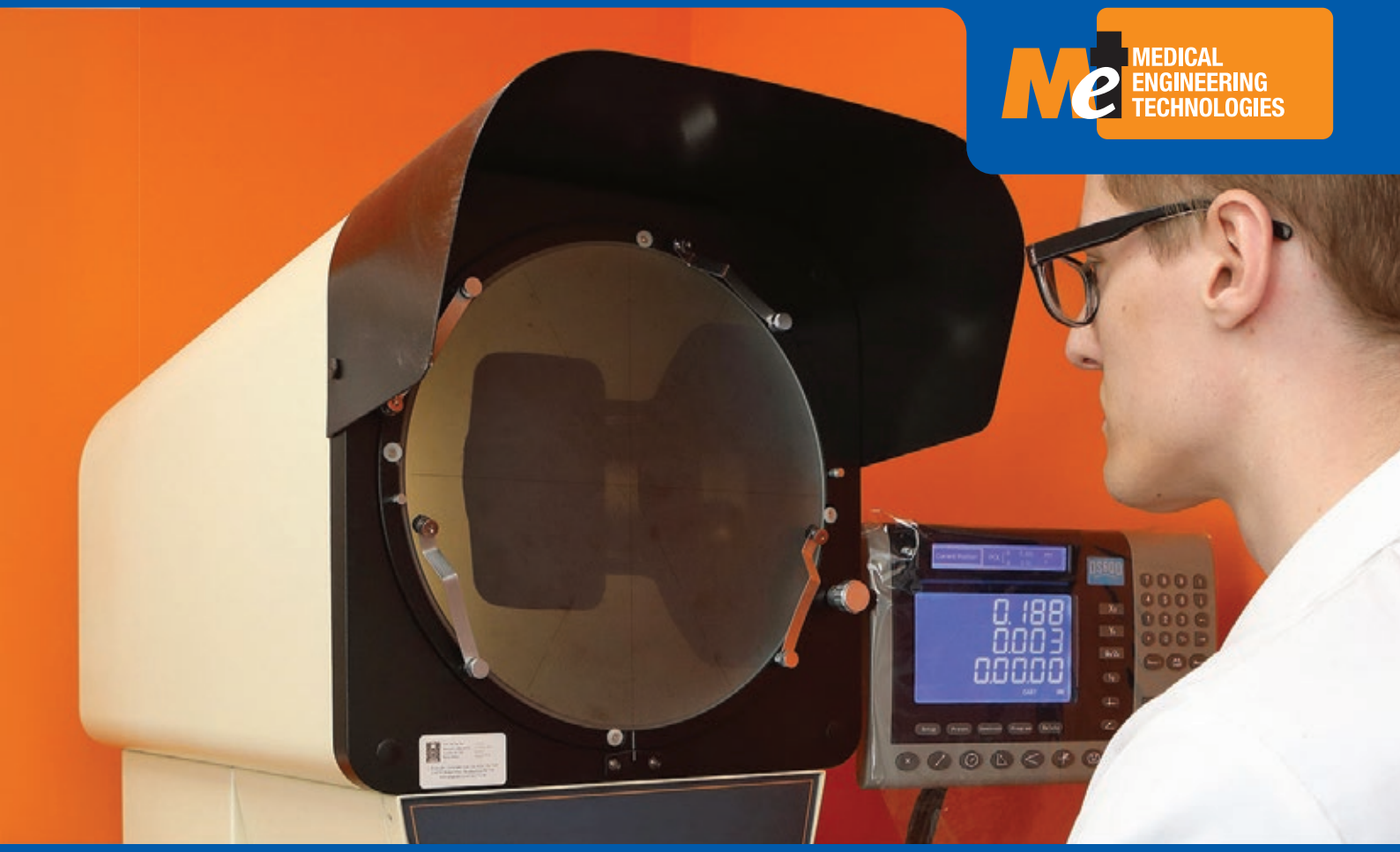

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KEY CONSIDERATIONS FOR AN OPTIMAL EMERGENCY-USE AUTOINJECTOR

In this article, Adam Stops, PhD, Drug Delivery System Product Manager at Stevanato Group, and William Fortina, Business Development Director at Duoject, introduce Maverick, an emergency-use autoinjector, and discuss key considerations during the device design and development, for primary packaging and manufacturing and assembly.

Some life-threatening medical emergencies – such as anaphylaxis shock, uncontrolled hypoglycaemia or opioid overdose – require swift injection with life-saving drugs. Emergency-use autoinjectors (EAIs) have become the device of choice in these situations, due to their quick administration and systemic action.

Regulators understand the importance of the EAI's reliability for such circumstances and have established higher device reliability requirements as a result. The US FDA's latest guidelines, for instance, require manufacturers to achieve a 99.999% functional reliability with a 95% confidence level.[1]

> "Creating an EAI starts from the device design, with multiple aspects requiring consideration before even building prototypes, and throughout various design iterations as well."

Multiple aspects require careful consideration to achieve these standards and create an optimal emergency autoinjector. This article introduces Maverick, an innovative autoinjector for emergency use, by reviewing key factors of consideration during the device design and development, for primary packaging and during manufacturing and assembly.

DESIGN CONSIDERATIONS

Creating an EAI starts from the device design, with multiple aspects requiring consideration before even building prototypes, and throughout various design iterations as well (Figure 1).

Understanding the Use Scenario

First and foremost, designers must thoroughly understand the use scenario(s): the user, the drug, its characteristics, the medical emergency's circumstances, the patient's reaction, possible bystanders (family, friends, co-workers, strangers), to name a few key aspects. Before

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Figure 1: Patient interviews and user studies are important tools to design an optimal device.

"Emergency parenteral administration is often challenging, yet even inexperienced users must be able to effectively deliver the injection. Making the user experience seamless, while not compromising on reliability and safety, will support the goal of mitigating misuse."

conceptualising its Maverick EAI, Duoject conducted a thorough use scenario analysis and several patient interviews. This exercise highlighted three major concerns:

- First, the level of user experience with emergency treatments varies greatly from one user to the next.
- Second, as an article published in The Psychologist[2] explains, cognitive failures in emergency situations mean that actions taken can be ineffective at best and, in some cases, can even reduce chances of survival. In other words, during life-threatening events, humans tend to demonstrate difficulties in making rational decisions that could transform even the simplest action into a complex one. A critical factor to consider for creating an optimal EAI design.
- Finally, since medical emergencies happen unexpectedly and require immediate care, patients must have access to their EAI at all times, and administer it within an acceptable time span.

EAI Optimisation by Design

This use scenarios analysis tells us that minimising or eliminating potential misuse becomes a matter of patient survival. Consequently, the ideal EAI design must incorporate the following qualities – first, the device must be as straightforward to use as possible. During a medical emergency, the user should not have to deal with packaging removal, assembly steps or dose setting, and the use sequence must accommodate both naïve and experienced users. Second, the system should be foolproof to prevent any use other than the intended one – and avoid losing a life-saving dose. Third, the design must be convenient to carry around at all times. Finally, to avoid any additional health risk, the EAI must prevent reuse and needlestick injuries.

Duoject designed its Maverick EAI to integrate these attributes; for instance, its patented double-trigger system minimises the chance of activation in the wrong orientation or before the intended use. Once activated, the device's injection mechanism is fully automated, including its needle retraction sequence. Its compact size also fits in regular trouser pockets while maintaining acceptable ergonomics. Finally, cartridges helped achieve both this pocket-sized format and better sterility assurance than syringe-based systems.

Optimising User Experience

As previously mentioned, emergency parenteral administration is often challenging, yet even inexperienced users must be able to effectively deliver the injection. Making the user experience seamless, while not compromising on reliability and safety, will support the goal of mitigating misuse. The ideal EAI design must therefore strike a fine balance between integrating fail-safe features and remaining quick to use and intuitive for all.

The Maverick EAI was designed to enhance ergonomics: the colours, shape and on-device instructions for use were created and refined through various human factor studies to be as intuitive as possible. For instance, the red colour of the finger trigger is universally recognised as a call to action. Meanwhile, the triple feedback – visual, tactile, auditory – of the mechanism signals to the user the injection is completed.

In summary, a close examination of use scenarios reveals that an optimal emergency autoinjector must be easy to carry around, extremely intuitive for even the most inexperienced users to administer a dose correctly, and with a foolproof design to prevent misuse in the most stressful situations.

DEVICE DEVELOPMENT CONSIDERATIONS

Once a design fulfils the needs of life-saving parenteral administration, the development of the EAI becomes the focal point. Done well, it ensures the reliability of the mechanism, validates its drug compatibility and confirms it is used correctly by patients. Two essential considerations arise during this process.

Planning for Superior Reliability

The first is to build a robust test plan to prove the design's reliability with the highest confidence level practically possible – remember that the patient's life depends on the EAI's reliability to perform the injection. This implies adhering to more standards, performing more tests, and using a significantly larger number of samples and more stringent pass criteria.

"Stevanato Group combined its glass expertise with proven testing protocols focused on mechanical characterisation methods and statistical analysis to engineer a stronger cartridge solution compared with the standard ones."

Sterility Options and Validations

The second is to develop and guarantee the sterility of the drug's fluid path. The validation of the sterilisation process must be impeccable and the device must remain sterile until activation. This must be true even under the most challenging conditions. For instance, users could remove the cap without the intention to activate the device; there can be exposure to extreme temperatures, humidity, dust or sand; or the EAI may be dropped or knocked around during its shelf life.

Duoject responded to these challenges by devising an appropriate test plan for its Maverick EAI to reach a high reliability confidence level. The development team also used a cartridge as the primary container, to allow the fluid path to remain sterile even when uncapped – as opposed to prefilled syringe autoinjectors exposing the needle when the cap is removed – and to increase is tolerance to high stress during injection.

SG NEXA®

The experience gained from developing primary containers, analysing the interaction with drug delivery devices and performing contract manufacturing services has enabled Stevanato Group to gain an intimate perspective of the critical path for any medical device project. This know-how is used to streamline processes and harmonise products and services.

To meet the market requirements, Stevanato Group developed highly resistant glass cartridges suitable for EAIs that can be easily integrated with such injectors. Stevanato Group combined its glass expertise with proven testing protocols focused on mechanical characterisation methods and statistical analysis to engineer a stronger cartridge solution compared with the standard ones. Enhanced performance was achieved by improving the production line to reduce the number and the depth of potential inner glass flaws, and by applying silicone to the outer surface of bulk packaging to prevent friction defects. In fact, Nexa® 3x glass cartridges are characterised by superior cosmetic quality and mechanical resistance, due to a 100% camera inspection and Stevanato Group's proprietary highly automated process know-how around critical no-metal-to-glass and no-glass-to-glass operations.

Nexa® 3x glass cartridges benefit from Stevanato Group's in-house proprietary inspection controls to check the most critical dimensions (such as total length, internal diameter and mouth and shoulder) and cosmetic defects (such as scratches).

Nexa® 3x cartridges are also available in EZ-fill® format, which, in addition, provides reduced variability in forced breakages – which is of particular interest, given the importance of reliability for emergency autoinjectors.

All these improvements are made with the entire pharmaceutical development process in mind, which is one of the advantages of Stevanato Group being a full-solution provider. A concrete example is interpreted by Nexa® 3X cartridges, with its optimised and high-value features suited to the specific needs of the Maverick autoinjector.

HIGH-PRECISION TOOLING

Once there is a stable design for the device, the first step when manufacturing injection-moulded components is to design an appropriate mould that can produce the parts in a uniform and stable process. While the moulding process has a large influence on the consistency and capabilities of the moulded components, the foundation is the injection-moulding tool. It needs to provide the necessary architecture for a controlled and consistent flow of the polymer through the hot runners, which is done by rigorous design qualification procedures and built-in sensors which then monitor the process during the operation. These tools also require appropriate temperature control through well-designed cooling channels, also with the appropriate sensors in place.

Following the approach of using advanced sensors and software enables constant high-quality outcomes throughout the production cycle. Certain parameters to optimise the moulding process – such as temperature, pressure, flow and cooling – are provided, all under the close watch of Stevanato Group's in-house moulding experts. The data recorded by those sensors can then be used to assess the quality of the moulded parts – ensuring only high-quality moulded components are used during assembly of the device (Figure 2).

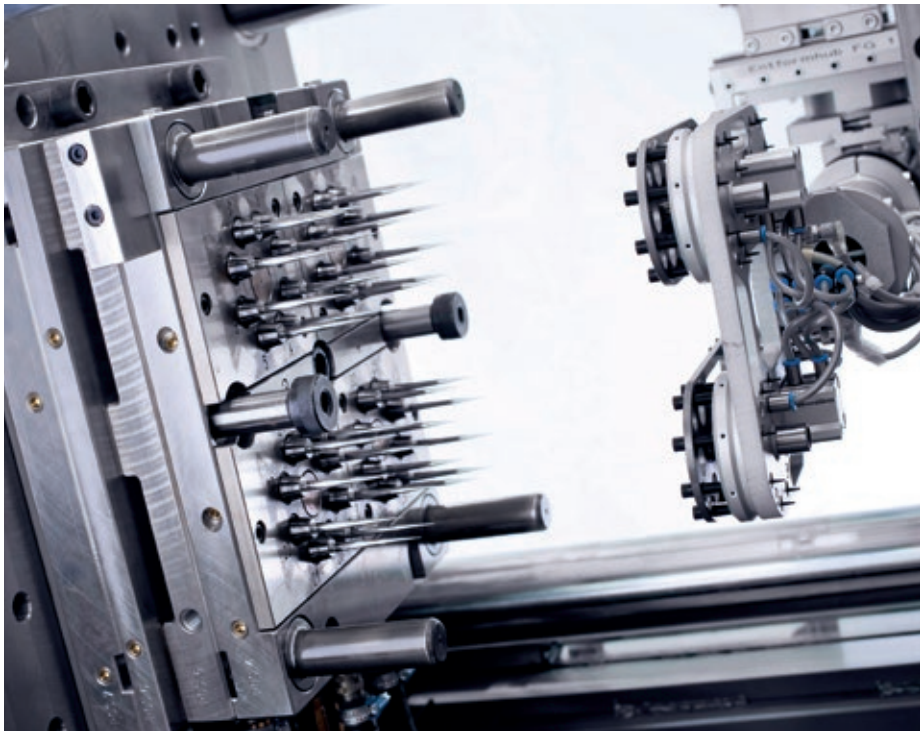

Figure 2: Achieving maximum-quality outcomes with high-precision tooling.

To ensure the quality of the tools, Stevanato Group has a carefully selected group of trusted suppliers that work closely with the company's own highly qualified mould process engineers and device design engineers to guarantee good adaptation of the moulds to the injection-moulding process. The company also has a small group of in-house tool makers and tool maintenance engineers who work closely with suppliers.

All these experts are involved in the specification and design of the mould tools, together with the tool makers. This multidimensional approach is crucial to achieve high-dimensional capabilities with state-of-the-art technology, all enabling Stevanato Group to manufacture with reliable processes. With more than 160 high-precision injection-moulding machines – some of them having up to 128 cavities and clamping forces of up to 500 tones – the company produces on average 1.5 billion plastic components a year.

ROBUST ASSEMBLY PROCESSES

The assembly equipment offered by Stevanato Group for the Maverick assembly processes performs 100% inline inspection. While Stevanato Group typically ships sub-assemblies directly to pharma companies for final device assembly, with Maverick, it is possible to perform the assembly process through Novocol Pharma, Duoject's parent company, using equipment supplied by Stevanato Group. With extensive experience in providing automated assembly equipment to leading pharmaceutical companies for drug delivery devices, Stevanato Group has built automated assembly equipment for its customers that is currently being used to manufacture millions of devices every year.

Similar to the approach in moulding, inspection and measurement are key to maintaining control over manufacturing processes. If it is possible to control as much as possible early in the process, then downstream critical functions will be better controlled. To achieve this, Stevanato Group has fully validated camera inspection systems that can be used at every step of the assembly process, including snap-fit clips and mechanical features. Force and torque monitoring algorithms can then be programmed, along with the precise position of the axis, to control and verify the assembly – providing valuable measurement data.

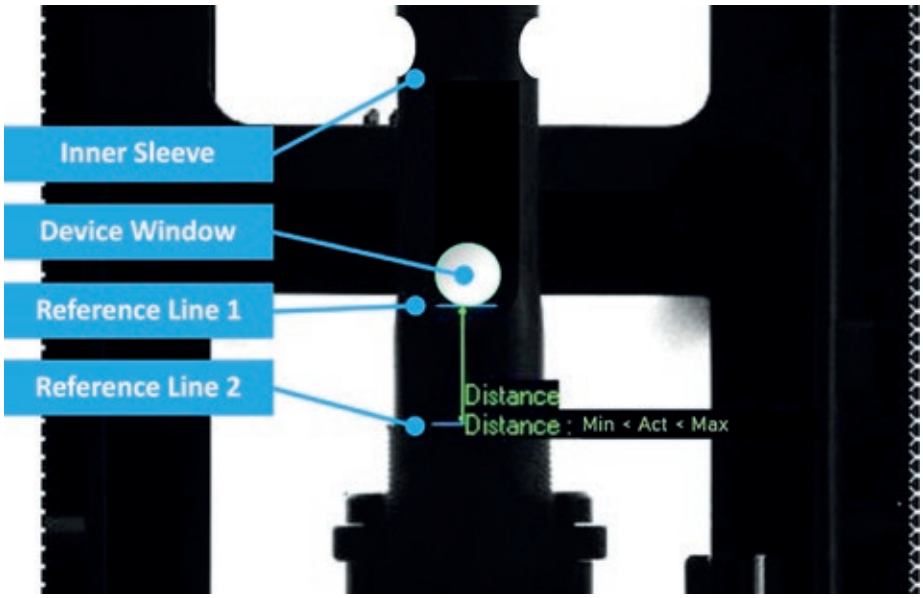

Figure 3: With 100% in-line controls, sensors can check, amongst other things, if device components are in the correct position, and if not, automatically reject the device.

> "In every autoinjector design, the goal is always simplicity in the assembly process, but there are still multiple steps that must be completed, each using technology to measure and verify the correct assembly – which is essential to achieve high reliability."

For Maverick – as with most autoinjectors – there are two main sub-assemblies for roughly 10 injection-moulded parts and some metal components. In every autoinjector design, the goal is always simplicity in the assembly process, but there are still multiple steps that must be completed, each using technology to measure and verify the correct assembly – which is essential to achieve high reliability.

Furthermore, there are sensors for assessing functional aspects in the assembly – to verify functionality in every device; all inline and with 100% inspection. As an example, if a component within the device is not in the correct position after assembly, the device is automatically rejected. However, if the component is in the correct position, it continues through the remaining assembly processes – ensuring the device meets the requirements for reliability and functionality. Besides positional features, these sensors can also be used for distances, shapes, colours, barcodes and even small visual defects, with every inspected item being pretested in bench conditions. These technologies provide valuable measurement data, which are important when considering reliability requirements for emergency autoinjectors (Figure 3).

Stevanato Group designs its equipment in a modular fashion, so whether the need is for low-volume clinical batches or high-volume full-scale production, they all share the same modules – enabling scalability. An example is a top-mounted visual inspection system to monitor the integrity of the glass cartridge when placed into position during final assembly. This system inspects for glass defects and foreign objects. Once the system identifies a defect, it automatically rejects the single component. Stevanato Group can also equip its lines with many other modules, including dimensional measurement systems and functional testing modules.

While Stevanato Group handles the sub-assembly process in its FDA-audited production site in Germany, Novocol can perform final assembly, using Stevanato Group's assembly equipment. In addition, Novocol can also support clients with formulation and fill & finish, if required. In case customers need additional in-process controls for the filled cartridge, it can

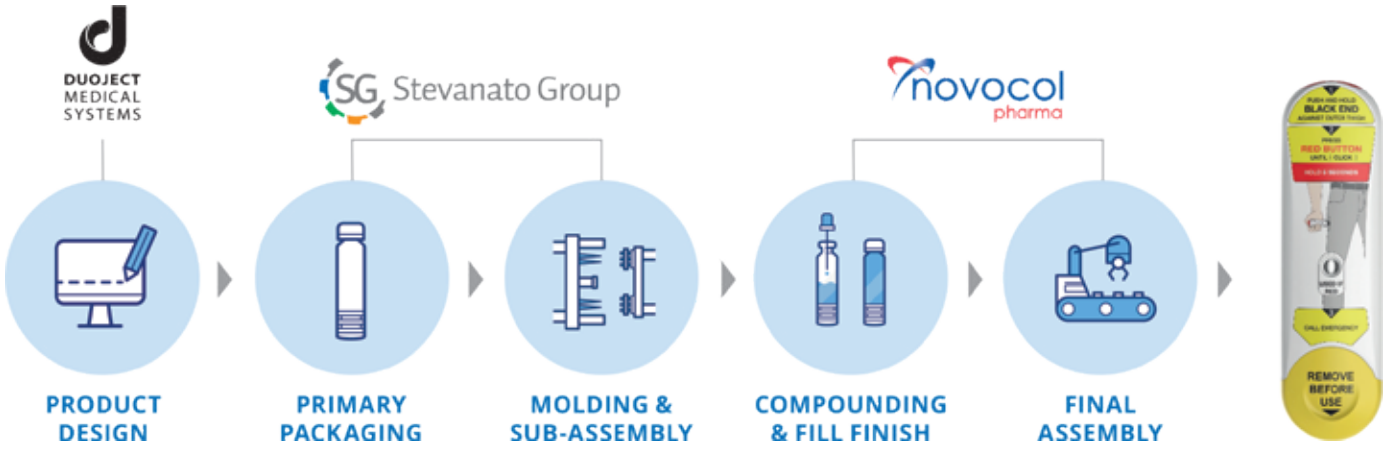

Figure 4: The one-stop-shop solution offered for Maverick is a way to better keep under control the key development steps linked to device reliability.

be part of the one-stop-solution service offered. Stevanato and Novocol performing production and assembly during the device development phase also means there would be no need for revalidation or technology transfer once a customer switches from clinical to commercial. These are just two of the many advantages this one-stop-shop solution offers to pharma companies.

CONCLUSION

When a medical emergency requires parenteral administration of a life-saving medication, the injection device used must demonstrate superior reliability and ergonomics to comply with strict regulations and preserve patients' lives. To develop and to produce such a device requires special expertise and careful consideration at every step of the development and production. The Maverick emergency autoinjector combines Duoject's expertise in device design, Stevanato Group's outstanding drug containment, moulding, tooling and assembly capabilities and, optionally, Novocol's experience in formulation and fill-finish. Together, these companies offer a one-stop shop for the highest standard emergency autoinjector that is ready today to perform the final device customisation to suit the client's unique drug needs (Figure 4).

ABOUT THE COMPANIES

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. The 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.

Duoject Medical Systems designs and develops advanced medical devices for the pharmaceutical industry. The company collaborates with its clients to create custom solutions aligned with their unique needs and goals. Duoject's technologies improve upon industry standards in safety, precision and ease of use to optimise patients' adherence to treatments. In addition to being a design and engineering partner for medical devices, Duoject provides a 360-degree service to support its partners' missions at every step of the development process, including through regulatory affairs, manufacturing and project management support. Every project the company works on creates a strong IP background to ensure its clients' commercial success for many years to come.

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ABOUT THE AUTHORS

Adam Stops, PhD, is Drug Delivery Systems Product Manager at Stevanato Group, managing autoinjectors, prefilled variable and fixed-dose pen injectors, large-volume wearable injectors and inhalers. With a PhD in mechanical engineering and an MBA in business management, Dr Stops has broad experience in the design, development and product management of devices and parenteral products. Throughout his career, he has worked with innovative multinational companies, leading teams of experts in device research, design and industrialisation.

William Fortina is Business Development Director at Duoject Medical Systems, where he leads sales and marketing activities as well as strategic initiatives. He graduated from the University of New South Wales, Sydney, Australia, with a Master of Commerce before taking on sales roles in China, France, the US and Canada. Prior to joining Duoject in 2019, Mr Fortina worked for a leading drug delivery device manufacturer on projects involving ophthalmic, nasal, dermal and injectable delivery devices.

Introducing Maverick: When device reliability meets patient safety

SG Nexa® cartridge inside

Maverick is an innovative emergency-use auto-injector designed for IM injection with integrated mechanical feature guaranteeing full dose delivery and automatic needle retraction mechanism. It is born by the collaboration between Stevanato Group and Duoject.

SG Nexa® bulk and **SG EZ-fill®** option available for 1.2 mL cartridge, container-closure system terminally sterilized

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Integrated mechanical feature **guaranteeing full dose delivery**

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UNDERSTANDING YOUR PROCESS RELIABILITY: COMPLIANCE CONSIDERATIONS FOR EMERGENCY-USE DELIVERY SYSTEMS

Here, Richard Motruk, Chief Operating Officer, and Nathan Blazei, Head of Quality, both at Kymanox, discuss the issues to be considered in light of the US FDA's tightened reliability standards for emergency-use autoinjectors.

There are many different varieties of drug delivery systems, including oral, pulmonary, transdermal and parenteral. The use of nasal sprays for emergency-use drug delivery is increasing but, historically, autoinjectors have been the predominant method of delivery for therapeutics involved in emergency-use scenarios (e.g. adrenaline, naloxone and similar). Autoinjectors are designed for self-administration, whereby patients have the convenience of receiving the injections in a non-clinical setting (e.g. home or office).

> "Since autoinjectors automatically carry out an injection cycle once actuated, patient compliance is improved compared with manual delivery devices, such as syringes."

Since autoinjectors automatically carry out an injection cycle once actuated, patient compliance is improved compared with manual delivery devices, such as syringes. This capability is particularly important for emergency treatments, as an autoinjector can reliably administer the necessary dose in high-pressure situations, whereas more manual delivery devices could be prone to user error and result in drastic outcomes for the patient. Because autoinjectors are typically the delivery device of choice for emergency medications, they come with increased scrutiny from regulatory bodies regarding their safety and effectiveness.

In the US, an autoinjector is regulated as a combination product, which is a device and a drug (or biological product) assembled as a single entity or packaged together for assembly by the user. The increased regulatory scrutiny is necessary to ensure that patients receive their life-saving treatments without error or delay. Publicised recalls,[1] in which the reliability of an autoinjector has come under examination due to failures in the field of use, have resulted in the FDA altering its expectations for manufacturers. The FDA has requested some manufacturers of emergency-use autoinjectors demonstrate overall system reliability of 99.999% at a 95% confidence level – or a 1:100,000 failure frequency. This requirement has been applied not only to new product applications but also to previously marketed products and is consistent with the FDA guidance document[2] issued in April 2020.

This reliability requirement becomes a large cause of concern for developers and manufacturers when system reliability at or above 99.999% was not considered during

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the design stage of commercially approved products prior to the tightened standards. In some cases, reverse engineering of an autoinjector was required to improve its reliability, which led to shortages of critical therapies while improvements to the autoinjector were carried out. In other cases, manufacturing and inspection techniques required modification to obtain higher-precision components with improved quality levels. Although these modifications have improved reliability, they have also increased costs, which are met with resistance from payers and users alike. Thus, meeting the compliance requirements poses a significant challenge for developers and manufacturers.

Essential performance requirements (EPRs) are used to assess autoinjector reliability and to drive design efforts. Autoinjectors are assessed relative to the following four EPRs:

1. **Activation Force** – the force required to trigger the device, extend the needle, and dispense the therapeutic dose through the needle cannula into the targeted tissue
2. **Extended Needle Length** – the distance the needle travels beyond the protective sheath of the device following dose delivery
3. **Delivered Volume** – the volume of drug dispensed during activation
4. **Dispense Time** – the time to deliver the therapeutic dose.

Statistical tolerance intervals, or k-factor analyses, are widely accepted for estimating the reliability of data, as described in ISO 16269-6, Statistical Interpretation of Data: Determination of Statistical Tolerance Intervals. These calculations can be performed manually but industry-accepted statistical software packages, such as Minitab or JMP, make the calculations easier.

When considering tolerance intervals, there are two critical characteristics. First, the desired reliability or coverage is selected for each EPR. For the case of emergency-use devices, the FDA is mandating a minimum reliability/coverage of 99.999% at what it describes as the system level. If you consider a fault tree analysis (FTA) diagram, the system level would be the very top failure identified in that fault tree. However, one layer down from the system level within the fault tree is where the EPRs are listed, each with their own branches of contributing failure modes (faults).

> "Manufacturers must adjust the sampling plans to the appropriate sizes, and their evaluation of the data sets must switch from a pass/fail evaluation to the use of variable data."

At this level, the FDA, for most applications, accepts 99.99% reliability.

The second characteristic of the tolerance interval estimation is the statistical confidence level. A 95% confidence level is the industry standard and is what the FDA will expect. For each EPR, a 99.99% tolerance interval with 95% confidence is calculated. The lower and upper limits of the tolerance interval calculation can then be compared with the applicable specification limits.

Consider an autoinjector with a specification for extended (deployed) needle length of 17.0–20.0 mm. A sub-sample of devices is triggered, and the resulting extended needle length is measured and recorded. From that sub-sample, the results are analysed using tolerance interval calculations at the 99.99% tolerance/95% confidence level and determined to be 17.6–19.4 mm. These tolerance interval limits fall inside the specification limits, and therefore the process is at least 99.99% reliable.

A commonly observed issue when retrospectively establishing reliability performance (e.g. for already marketed products) is that the tolerance interval range exceeds the specifications. Possible reasons for this excursion could be that the data were not evaluated at the appropriate intervals or that more data than necessary were compiled into the tolerance interval calculation. For example, a manufacturing process may use multiple tools to produce the moulded components of the device. The inter-tool variability is often larger than the intra-tool variability. This variability often leads to subtle (within tolerance) but statistically significant shifts in the data. If moulded components from unique, qualified tools are never mixed but the data are grouped without isolating the tool, an artificially inflated standard deviation used in the tolerance interval calculation may result. Thus, an overestimation of the tolerance interval width for the EPR is observed, leading to a false conclusion that the desired reliability is not being achieved.

> "All manufacturing processes are unique and need to be addressed as such."

Another common pitfall faced by manufacturers of emergency-use autoinjectors is that the device was not designed with these tightened reliability standards in mind. Historically, most design verification efforts targeted 99.9% as the reliability endpoint; 99.9% (1/1000) makes it logistically feasible to evaluate the performance of a batch of devices with pass/fail (or attribute) scoring and maintain reasonable certainty that the performance is meeting the reliability thresholds for each of the EPRs. Unfortunately, whether considering 99.99% or 99.999% as the new reliability target, pass/fail scoring requires a total number of samples that is entirely impractical to demonstrate the achievement of the required reliability. Consequently, manufacturers must adjust the sampling plans to the appropriate sizes, and their evaluation of the data sets must switch from a pass/fail evaluation to the use of variable data. This approach allows for the tolerance interval calculations to be carried out as previously discussed.

All manufacturing processes are unique and need to be addressed as such. A good rule of thumb to account for these issues would be to segment the data intelligently. For example, evaluating the reliability for each lot may not produce successful results, especially if the sample size for a product not originally designed with a 99.999% system reliability target is underpowered at that reliability threshold. Likewise, trying to evaluate multiple quarters or years of production into a single calculation may result in an artificially inflated tolerance interval that is not representative of the product. A frequency for evaluating the tolerance intervals needs to be established, and then the performance of the autoinjector relative to each EPR over time can be trended. Once this exercise is completed for each EPR, goals can be determined. Sub-teams can be created to investigate and remediate any areas that are not performing as expected.

One recommended approach to addressing identified reliability concerns with EPRs is to start with a reliability analysis tool such as FTA, which allows the visualisation of the reliability "equation" using component-level reliabilities to calculate the system-level reliability. The FTA can identify the primary cause(s) of reduced reliability to further target opportunities for improvement at the component level. Autoinjector manufacturing processes are often highly automated, with in-line or off-line automated inspections, creating "AND" gates in the FTA. For a defective component or defective sub-assembly to negatively impact the reliability calculation, two things need to happen:

- A defective component or sub-assembly must be presented to the inspection system
- The inspection system must fail to correctly reject (or falsely accept) the part.

Therefore, it may be necessary to execute intelligently designed studies to precisely characterise the false acceptance rates of the relevant inspection systems.

The proper analysis tools and techniques will enable manufacturing teams to ensure that the analyses are meaningful, valid and appropriate for the application. Designers and manufacturers should plan accordingly during the design stage to select components and technologies that can meet these evolving reliability expectations, otherwise crippling regulatory field actions may result, which will ultimately limit patient access to life-saving treatment options. Understanding the manufacturing and inspection processes down to the component level is necessary to help organisations achieve the product reliability requirements that the FDA expects for emergency-use autoinjectors.

"The proper analysis tools and techniques will enable manufacturing teams to ensure that the analyses are meaningful, valid and appropriate for the application."

ABOUT THE COMPANY

Kymanox is a life science professional services organisation that offers engineering, scientific and compliance support to companies exclusively in the biotechnology, pharmaceutical, medical device and combination product industries. With its diverse team of experts, Kymanox helps clients navigate commercialisation challenges that arise throughout a product's lifecycle – from early development to post-market – with optimised safety, quality, efficacy and accessibility. Kymanox was founded in 2004 and is headquartered in Morrisville, NC, US.

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ABOUT THE AUTHORS

Richard Motruk, Chief Operating Officer, Kymanox, has extensive experience in medical device and pharmaceutical manufacturing management, including quality assurance, engineering, maintenance and reliability, technology transfer, clinical research and continuous process improvement. Mr Motruk has been at the forefront of new FDA requirements regarding emergency-use, life-saving devices related to modelled and demonstrated device reliability. Prior to joining Kymanox, he held operating and leadership roles at Teva Pharmaceuticals (Petah Tikva, Israel), OraSure Technologies (PA, US) and bioMérieux (Marcy-l'Étoile, France). Mr Motruk holds a BSc degree in Biochemistry and Molecular Biology from Pennsylvania State University (PA, US).

Nathan Blazei, Head of Quality, Kymanox, has nearly two decades of life science industry experience in various quality management system tools, regulatory strategy and filings, product and process development, process validation, continuous process improvement methods, auditing and gap assessments, risk management, and regulatory inspection preparation, facilitation and remediation. Outside of Kymanox, Mr Blazei has worked for Liquidia (NC, US), Novartis Vaccines and Diagnostics (Basel, Switzerland), Grifols (Barcelona, Spain) and its predecessor Talecris Biotherapeutics, ev3 (now Covidien) (MN, US) and Boston Scientific (MA, US). Mr Blazei holds a BSc degree in Chemical Engineering from the University of Notre Dame (IN, US) and an MEng degree in Bioengineering from the University of California, San Diego (CA, US).

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RELENTLESS PRECISION DELIVERS VALUE IN NEEDLE-HANDLING AUTOMATION FOR COMBINATION PRODUCTS

In this article, William Jaworski, Sales Director, and Dr Michael Gunner, PhD, General Manager, both of Mikron Corporation Denver, discuss the precision and complex manipulation of needles required for the latest combination medical products.

The ageing global population, combined with the burden of chronic disease and new investment in novel pharmaceutical therapeutics, has led to dramatic growth in parenteral drugs over the last decade. Syringes are still commonplace in drug delivery. However, the global demand for complex injection devices is growing rapidly.

Today's drug delivery devices are elaborate. It does not matter if the device is a peripheral venous catheter, a syringe, a pen injector, an autoinjector or a wearable injector (pump), the most common element in each device – and arguably the most important – is the needle. In fact, although it begins as a blank stainless-steel rod, by the time a patient uses the injection device, the needle has undergone a dramatic transformation.

The wide variety of needle customisations presents a unique challenge. Blank needles are not very precise products. They are a raw commodity with imprecise lengths, uneven wall thicknesses, varying bevel angles and other imperfections. Many needles are bowed or have a preset bias due to how they are formed during the metal drawing process. Typically, they are mass produced and have been historically used at the end of a simple syringe. For most syringe applications, slight variations have not traditionally been of much concern.

"The latest medical devices require significantly greater precision and complex manipulation of needles."

The latest medical devices, however, require significantly greater precision and complex manipulation of needles. Due to the high demand, mechanical complexity and ever-decreasing size of these advanced medical devices, manufacturers have turned to automation to aid in their assembly. A variety of needle handling capabilities that may be required for complex medical devices is summarised in Box 1.

As an industry leader in pharma/medtech scalable and customisable assembly systems, Mikron Automation has a unique perspective on the complex challenges and innovative solutions regarding precise yet forgiving needle handling.

Based on the customer's design, the length, gauge and tip of the needle will vary widely from device to device. Some require systems that handle needles as fine as 31 gauge (0.261 mm in diameter) or about twice the thickness of a human hair, while others are built around significantly larger needles, such as 16 gauge (1.651 mm). The bevel angle on the tip of the cannula is also customised based on a customer's specific design. This becomes critical, as the bevel of a needle in most complex devices becomes a key reference for the assembly. Mikron systems account for the smallest of bevel inconsistencies among thousands of blank needles.

In a typical automation solution for the assembly of drug-delivery devices, thousands of needles must be processed in order for the system to attain the required production rate. Needles are typically fed

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BOX 1: NEEDLE HANDLING

Mikron Automation has experience with the following needle assembly requirements:

Needle feeding:
- Format: bulk, "sushi rolls", cassettes
- Speeds: 1–1000 ppm
- Gauges: 16–31
- Lengths: 0.625–3.0" (1.588–7.62 cm)

Final geometry:
- Straight/standard
- Single bend
- Multiple bend
- Multiple planes

In-process inspections:
- Push-pull test
- Flow test
- Leak test
- Occlusion test

Joining processes:
- Microdispensing adhesives
- LED UV spot curing
- UV tunnels

Vision inspection:
- Platform:
  - Cognex
  - Keyence
  - Shaman
- Typical inspected attributes:
  - Needle length
  - Bend length
  - Needle orientation
  - Seam location
  - Gauge verification
  - Bevel dimension
  - Tip quality

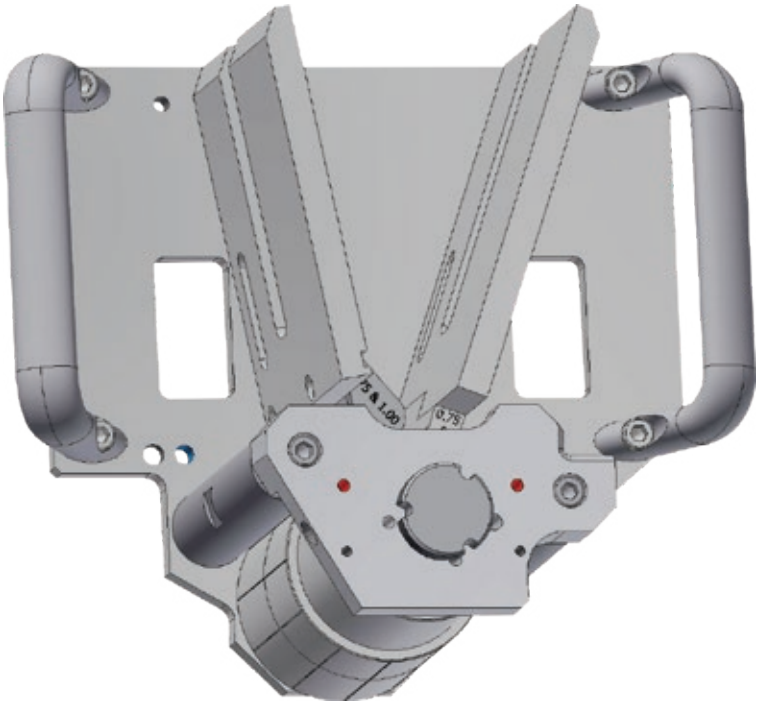


Figure 1: An example of a cannulator with V-shaped hopper for singulation of bulk needles.

into the system via a hopper or a specifically designed cartridge and then readied for individual selection. One method of creating this "singulation" is by means of a rotating drum which provides the means to select one needle into well-defined grooves with a vacuum assist. This allows Mikron to present individual needles to the system at speeds of up to 2,000 needles per minute. Through years of experience, Mikron has developed technology to optimise the hopper and drum design to compensate when needles are warped or stick together from surface lubrication or from simple static electricity.

At Mikron, even the "simple" process of feeding the prepackaged needles into the machines is scrutinised for precision to ensure meticulous automated assembly – a standard in keeping with the celebrated tradition of exceptional Swiss watchmaking. The feeding system (Figure 1) features operator handles for transportation and manual loading, as well as a V-shaped hopper that feeds blank needles through the cannulator.

After singulation, the individual needle is presented and tested by a vision system that inspects needle attributes including – but not limited to – length, needle position, bevel angle and seam location. Mikron, as an industry leader in machine vision, deploys accurate and repeatable vision solutions with its in-house experts, using the latest technology, such as 21 MP cameras, providing micron-level precision (Figure 2).

> "At Mikron, even the "simple" process of feeding the prepackaged needles into the machines is scrutinised for precision to ensure meticulous automated assembly."

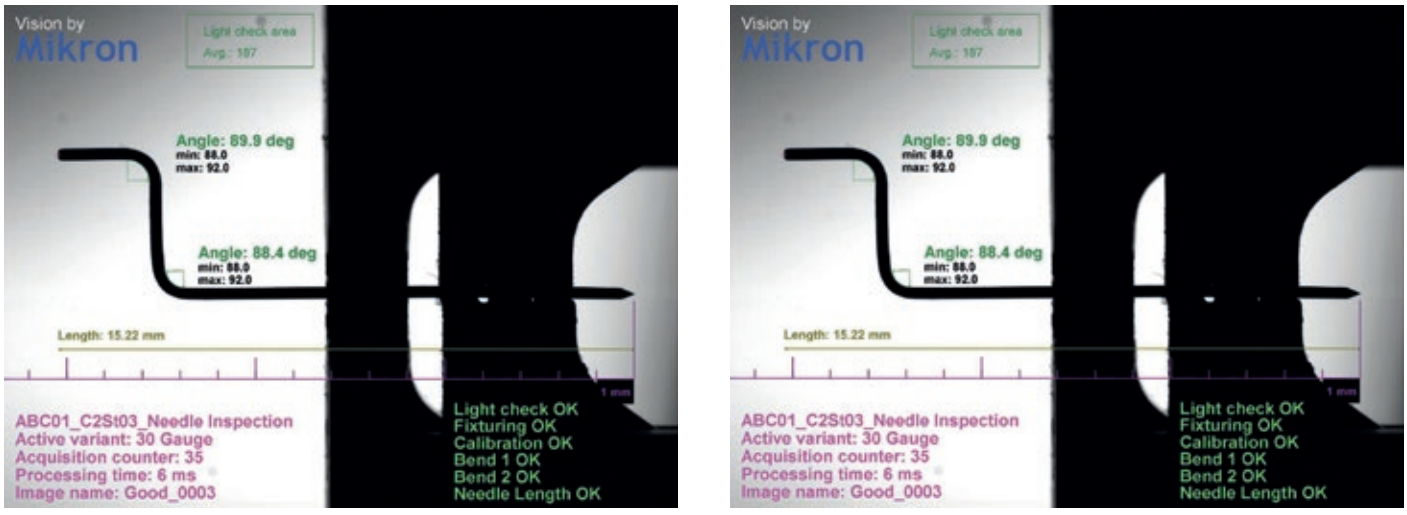


Figure 2: Mikron has become a leader in machine vision and the deployment of high-speed inspection systems to verify needle processing.

The results of the vision inspection are important assembly requirements as the needle is transformed into a precise medical device.

The next operation of a single cannula for a complex device is often to change its shape dramatically. However, the bending of a needle presents its own set of complexities. Due to their initial forming through the drawing process, stainless-steel needles undergo intense strain hardening and become extremely hard. Specialised tooling must be designed for parts of the system that handle and come into contact with the cannula to minimise premature wear, thus ensuring long-term performance.

As this specialised tooling firmly grips the needle, the system will carefully bend the cannula around the tooling or mandrel to form the required bend angle (Figure 3). Through its experience and understanding of the steel's elastic properties, Mikron knows precisely how much to overbend the cannula so that it can then relax to exactly the desired angle. Some designs require multiple bends of the needle, and others may require bending in several dimensional planes, resulting in a very complex shape with compounding tolerances (Figure 4). The complexity and precision are even further challenged by the speed of the system, which can achieve up to 40 cycles per minute.

Verifying the quality – that the process step completed was successful and within specifications – can be just as challenging as the operation itself. At this point in the process, Mikron verifies that no damage has occurred during needle transformation, verifying through vision, for example, that the needle tip has not been damaged.

"Transforming an imprecise cannula into one with complex geometries with fine dimensional tolerances of up to ±200 microns has become a differentiating strength of Mikron."

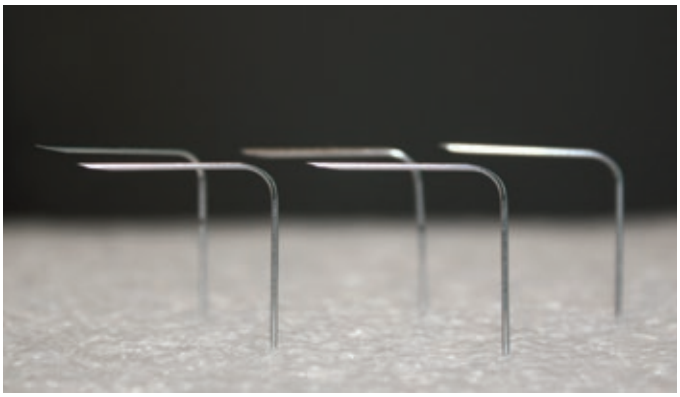


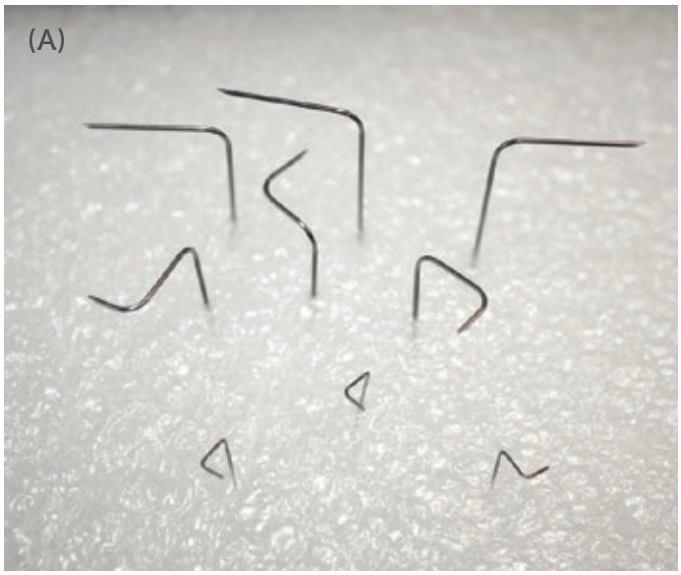
Figure 3: To ensure 100% safe use and functionality of the medical device, precise and repeatable needle bending needs to accommodate the input of imprecise bulk needles.

Other types of in-process checks, such as occlusion and flow tests, also be deployed to ensure quality. These checks verify the integrity of the newly transformed needle and the fluid path prior to assembling the formed needle into the main device. This process helps confirm that the pharmaceutical formulation will travel uninhibited through the needle to its intended destination.

As part of a drug-delivery device design, needles in many instances require the application of a coating that, for example, may minimise patient discomfort. Mikron has leveraged its experience in microdispensing of fluids to apply a fine and homogenous coating of these required substances to needles. In many ways, this precise process is one of the more intimate, as it is where the system can impact the patient's experience with the device the most.

Not only are these processes intricately challenging but the need for ever-sophisticated device designs is also growing rapidly. Transforming an imprecise cannula into one with complex geometries with fine dimensional tolerances of up to ±200 microns has become a differentiating strength of Mikron. Its specialised knowledge and process understanding helps ensure its systems repeatably produce quality needle products for complex drug-delivery devices.

Mikron has more than 100 years of experience in designing and creating dependable automated solutions. Today, Mikron has



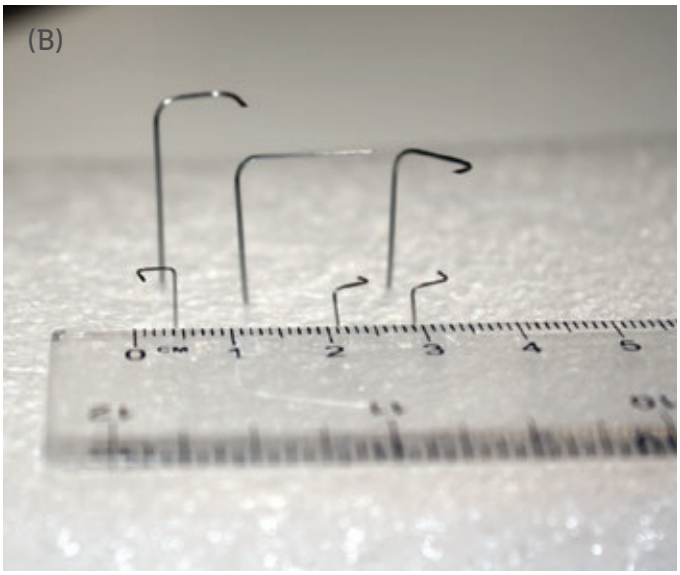


Figure 4: Complex geometries (A) and thinner and smaller cannulas (B) mean that needle handling is challenging and demands expertise for the design of the process station.

> "Mikron supplies precision-focused automation solutions with the highest productivity."

not only become a global leader in terms of scale and volume – it has also become a preferred option for the most difficult, complex and unique projects. Mikron supplies precision-focused automation solutions with the highest productivity, meeting the needs of some of the largest medical device and pharmaceutical customers worldwide.

Rooted in the Swiss culture of precision and innovation, Mikron Automation enables its customers' success through expertise in optimising product development, deploying scalable manufacturing solutions and providing post-installation care.

ABOUT THE COMPANY

Mikron Automation is a leading partner for scalable and customised assembly systems – from the first idea to the highest performance solutions. Distinguished by a commitment to innovation, flexibility, unparalleled customer service and an evolving platform portfolio, Mikron delivers state-of-the-industry solutions to the most complex assembly and testing demands. Mikron Automation has produced and installed more than 3,800 assembly and testing systems worldwide to customers in the pharmaceutical, medtech, automotive, electrical/industrial and consumer goods markets. With 700 employees, Mikron Automation is headquartered in Switzerland and also has sites in the US, Singapore, China and Lithuania. It is a member of the Mikron Group, a publicly traded company with more than 100 years' experience in precision machinery.

ABOUT THE AUTHORS

William Jaworski is Sales Director at Mikron Corporation Denver, helping enable the success and positive experience of Mikron's partners in North and Central America. Previously, he has held a variety of strategic roles at the intersection of healthcare and technology in automation companies as well as directly for medical device manufacturers. During his career in product management, marketing and sales, he has worked in the space between customers' needs and delivering to those needs – helping cultivate a deep understanding and delighting the customer.

Michael Gunner has a BSc and a PhD in electronics engineering from the University of Hull, UK. He has lived in the US for 29 years, working first as a visiting assistant professor at North Carolina State University before transiting to various automation companies in the US. Dr Gunner joined Mikron Corporation Denver in 2010 as the Applications Engineering Manager and became the General Manager in 2012.

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HERE TODAY AND DEFINITELY NOT GONE TOMORROW: WHY SIMPLICITY AND EASE OF USE ARE THE KEY FOR A NEW GENERATION OF REUSABLE INJECTORS

Here, Kate Hudson-Farmer, PhD, discusses how a new electronic reusable autoinjector – the Aria Smart Autoinjector from Phillips-Medisize – has been designed and user-tested to challenge the preconceived ease-of-use notions about electronic autoinjectors, in addition to addressing how macro trends and personal consumer subtleties could become increasingly important in creating a competitive position as devices seek to improve patient engagement.

THE BARE NECESSITIES AND A BIT MORE

Autoinjectors can generally be placed into one of two categories: disposable single-use and reusable. As the autoinjector market has grown rapidly over the past 15 years, it has come to be dominated by disposable single-use platform products. Such devices provide good needle safety features, as well as user feedback and cues before, during and after injection. In most situations, this design choice has appeared to offer a good trade-off between functionality, usability and cost. Additionally, whilst electronic devices have entered the market, they have tended to be more niche and bespoke, typically designed around one product for one drug by one pharma company, and not as a platform product.

> "In previous ONdrugDelivery articles, Phillips-Medisize has argued that emerging market trends around usability and the need for connectivity are changing the market in favour of reusable electronic devices."

In previous ONdrugDelivery articles, Phillips-Medisize has argued that emerging market trends around usability and the need for connectivity are changing the market in favour of reusable electronic devices. However, for the market to shift in this direction, it is important to show that these devices can offer safety and ease of use at least comparable to that of the leading disposable devices, as well as being cost competitive and offering improved functionality.

Reduction of use error is one of the most important goals to address when developing a new autoinjector. Accordingly, new devices require favourable results from human factors studies in order to be approved for use by the US FDA or similar bodies. Limiting the number of steps, providing clear visual and audio guidance and feedback, and limiting in-use errors and needlestick injuries are all seen as critical factors.

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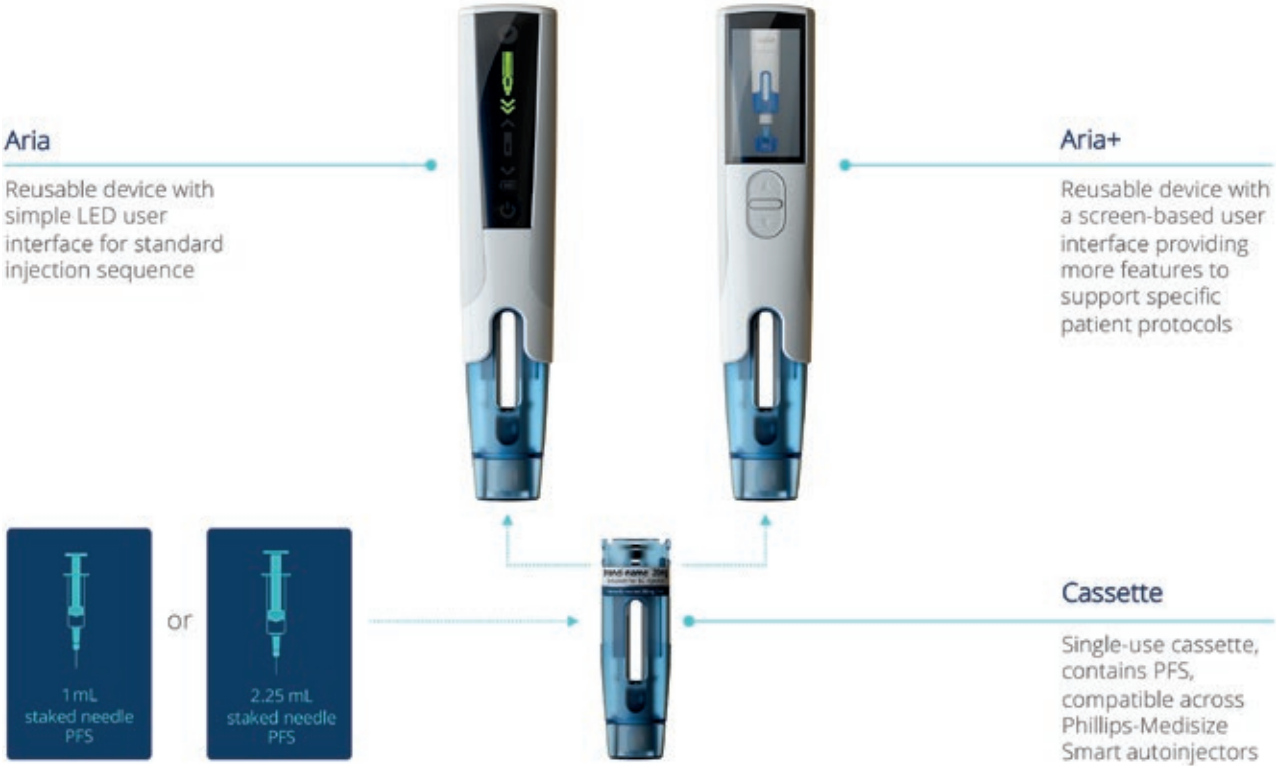

Figure 1: The Aria and Aria+ autoinjectors.

"Electronic devices offer opportunities for improving injection guidance and limiting use error via a broader array of visual and audible signalling than is possible with a single-use disposable device."

Use errors in particular have been extensively considered in the literature – a literature review by Weinhold *et al* identified 232 instances of use errors and close calls.[1] Common issues cited included the inability to remove the cap, holding the device the wrong way round, removing the device from the skin too early and confusion regarding the audible and visual feedback. Newer disposable autoinjector designs have addressed many of these issues, although there is evidence that visual and audible feedback from disposable devices can be inconsistent and early lifts, resulting in wet injection, are still all too common.[2] As such, although the usability of current disposable autoinjectors is good, there is still room for improvement.

Electronic devices offer opportunities for improving injection guidance and limiting use error via a broader array of visual and audible signalling than is possible with a single-use disposable device. Although these benefits have been reported in the literature, there are also trade-offs that need to be considered, such as size, the need to load the primary drug container into the device before each injection and the presence of a user interface that may intimidate some patients even if it reassures others.

A good example of the differences in usability between current electronic and reusable devices is the work by Colier *et al* evaluating patient preference for the electronic autoinjector AutoTouch® compared with the disposable SureClick® device (both by Immunex, now Amgen).[3] They concluded that AutoTouch® was preferred in the categories of ease of self-injection, ability to follow injection progress and providing clear confirmation of when the injection was completed, whereas SureClick® was preferred for having fewer steps and experiencing less injection site discomfort or pain. An ideal device would combine these benefits in a single design.

ARIA

Achieving such an ideal device was the objective Phillips-Medisize set itself when developing Aria, a reusable platform autoinjector. This goal required a reduction in size when compared with other electronic reusable autoinjectors, along with the drive to improve ease of use and convenience, and reduce use errors. Additionally, meeting emerging macro needs around connected health and reduced environmental impact would provide benefits, as would building in design flexibility in order to meet the needs of varying drug properties and delivery volumes.

As shown in Figure 1, Aria consists of a reusable electronic power unit, coupled with a disposable cassette that contains the prefilled syringe (PFS) and provides needle safety using a moveable shield. The cassette can accommodate both 1 mL and 2.25 mL PFSs. There are two main models, Aria, which has a simple user interface, and Aria+, which offers several advanced features, including a graphical user interface. Both models include Bluetooth connectivity.

"The original vision for Aria – to come close to the size, form factor and user steps achieved by disposable single-use devices – was explored in Phillips-Medisize's studies."

Aspect	Aria versus disposable	Comments
Audible and visual signaling during injection	Enhanced	Aria has sound and visual light indication for injection progress and clear green light and check mark for dose completion with an associated audible sound – dwell time is included in the signalling so no manual counting is required for dwell time
Other audible and visual signals	Enhanced	Aria includes audible and visual signals for early lifting of device, inserting the wrong/used cassette, battery depleted
Cap lock	Enhanced	Aria has a safety feature which locks the cap onto the cassette to prevent removal of cap until the cassette is inserted in the device
Needle safety	Same	The needle sleeve extends when removing the device, locking in the extended position to prevent needlestick injury and contamination
Viewing window	Same	Aria has a large front-to-back window to view the drug in the syringe
Number of steps	Similar	Aria requires insertion and removal of the cassette (user steps are similar once the cassette is inserted). However, Aria benefits from inclusion of dwell time in injection completion notification
Size	Larger	Aria is more compact than other electronic devices and similar in length to disposables, particularly 2.25 mL devices

Table 1: Comparing some use aspects of Aria to disposable single-use autoinjectors.

In order to gather user input during the design process, Phillips-Medisize has conducted four studies over the last two years, involving over 50 participants, including both experienced and injection-naïve users. These studies assessed how Aria addresses usability, user interface, device design, packaging and instructions for use, and how Aria compares with disposable autoinjectors in these areas (Table 1). Phillips-Medisize has also investigated the benefits of connectivity and apps, and perceptions around sustainability.

The original vision for Aria – to come close to the size, form factor and user steps achieved by disposable single-use devices – was explored in Phillips-Medisize's studies. The fact that Aria operates in a very similar way to two-step disposable devices, once the single-use cassette is inserted, was liked by users (Box 1). The extra step of inserting the cassette was not perceived to be a challenge by most users.

Aria includes a large front-to-back viewing window to observe the drug (Figure 2). The device automatically turns on when the cassette is inserted, a feature incorporated into the design based on feedback from earlier user studies. This aligns the user experience more closely to that of a two-step disposable autoinjector. However, the device still retains a button to turn it on and off as many users expect this on an electronic device. Also, in line with two-step autoinjectors, there is no button to initiate the injection – activation is achieved by a moveable needle sleeve that also provides needle safety after the injection.

A key safety feature Phillips-Medisize added to the design to reduce unintended use and misuse was locking the cap onto the cassette until it is inserted into the device. This feature has been well received by pharmaceutical customers, who perceive advantages relating to drug wastage, needle contamination and reduction in drug degradation if a device is uncapped for a long period before use.

As discussed prior, the ability for electronic reusable autoinjectors to provide enhanced audio and visual feedback is a key opportunity. Based on user feedback, Phillips-Medisize iterated the design to develop a clear audible and visual signalling sequence during delivery and a green check mark and end-of-dose sound to indicate dose completion (Figure 3), which was very positively received (Box 1).

Many injectable drugs require an additional dwell time after the plunger has stopped moving to ensure complete delivery and avoid a wet injection. As such, users are often instructed to hold their device against the skin after the dose completion sound for a prescribed period of time. With Aria, a continuation tone is provided during the whole injection time and then the end-of-dose signal and green check mark is provided after any dwell time. This simplifies and essentially removes a dwell time step from the user sequence compared with most spring-based devices (Box 1).

RESPONSE FROM USER STUDIES

In Phillips-Medisize's user studies, these clear features have enabled very good injection success rates, low early lifting rates and very positive feedback from users, particularly regarding the dwell time

BOX 1: QUOTES FROM ARIA USER STUDIES

"Very easy, it's spot on." – On loading and using Aria.

"Yeah absolutely got the dose, the green light and check mark is a nice indicator, job done." – On Aria green check mark light.

"You don't have to count, it does it all for you." – On the lack of a dwell time step.

"It was much better than expected, it was gentle to use and felt really good." – On using Aria.

"Should be attractive even if it is a medical device, maybe even more so, want to be happy to use it." – On Aria from a consumer perspective.

Figure 2: The drug-containing cassette has a large viewing window to enable users to see the progress of their injection.

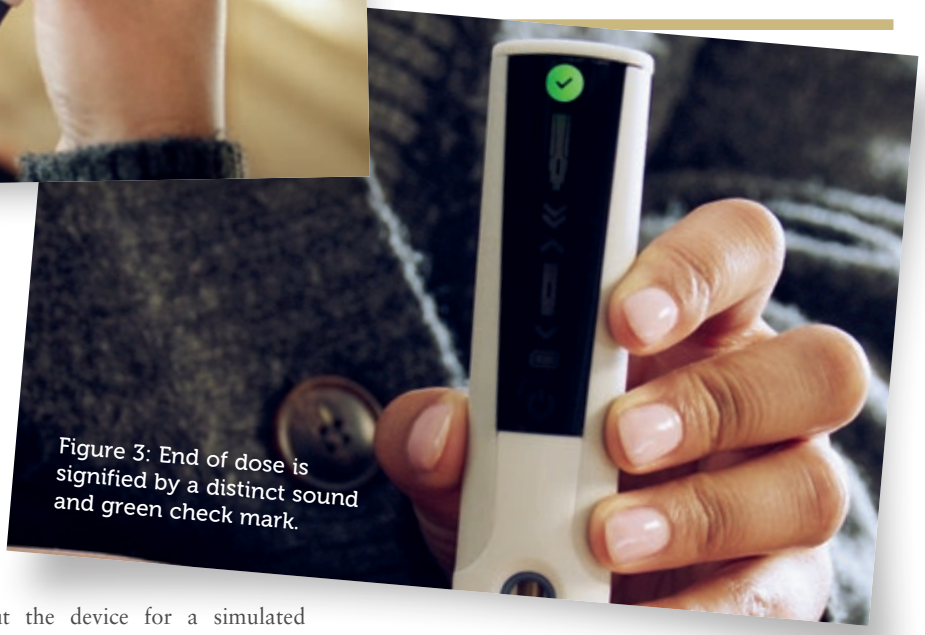

Figure 3: End of dose is signified by a distinct sound and green check mark.

inclusion. Users have noted how easy Aria is to use, citing the green check mark and audio signalling as particularly easy to follow. Notably, in Phillips-Medisize's latest user study (with six experienced and seven injection-naïve participants), there were no early lifts from 26 uses. This is a very encouraging result, as early lifts are among the most, if not the most, common user errors.[4]

In this particular study, Phillips-Medisize provided a quick reference guide (QRG) and presented the participants with a scenario in which they were given the device and cassettes and told they needed to use it for a long period of time to treat a chronic disease. Without any training, but with access to the QRG, they were invited to perform a simulated injection. Phillips-Medisize captured their initial thoughts and perceptions on being told they had to use a device to self-inject, and then asked them again after having used the device.

At the beginning of the session, naïve participants were typically apprehensive about using the device. However, after trying out the device for a simulated injection, most users were reassured, with many commenting on how simple the device was to use. Several commented that the motor sound and robustness of the device made them feel assured and gave them a sense of comfort, in addition to a few noting that they thought that the motor-driven injection was gentler than spring-based disposable autoinjectors (Box 1). These observations have demonstrated the importance of more subtle aspects of device design to the overall user experience, beyond the ability to use the device correctly. A few participants stated that these factors could influence their choice of a device.

"Phillips-Medisize's user studies showed that sustainability has a definite influence on device choice – users would choose a more sustainable device, such as Aria, provided it was comparable to other devices with respect to safety and precision."

Considering the use of visual and audible signals to improve safety, the ability of Aria to halt the injection progress if there is an early lift and prevent any drug spray or waste was seen as positive, as were the warning sounds and lights to indicate that an early lift had occurred, or that a used cassette has been inadvertently inserted.

EXTERNAL INFLUENCES AND CONSUMERISM

Although sustainability is a global issue and a strong driver for pharma companies in selecting medical device technology,[5] Phillips-Medisize had not anticipated it to factor into user opinion quite as strongly as it did in its studies. The Aria Smart Autoinjector has been designed with sustainability very much in mind, with a 50% reduction in waste compared with fully disposable autoinjectors being Phillips-Medisize's target. It also anticipated to have a much lower environmental impact, with approximately 60% less CO_2 emitted per injection, when the full product lifecycle is considered. Phillips-Medisize's user studies showed that sustainability has a definite influence on device choice – users would choose a more sustainable device, such as Aria, provided it was comparable to other devices with respect to safety and precision.

Connectivity is an area of growing interest for pharma companies, as it can bring commercial benefits and contribute to patient engagement and patient centricity. As noted in a recent Deloitte article,[6] in part accelerated by the covid-19 crisis limiting direct access to healthcare professionals, patients are taking more interest in managing their health and are seeking to communicate in new and different ways with their doctors. There are indicators that patients are changing

"In Phillips-Medisize's latest user study, there were no early lifts from 26 uses. This is a very encouraging result, as early lifts are among the most, if not the most, common user errors."

their attitude to data privacy, showing more willingness to share data remotely with healthcare professionals.

In Phillips-Medisize's studies, the company had positive feedback from users on this new paradigm, with the vast majority opting for a companion app with a device like Aria, if it could assist them with aspects such as reminders, dosing history and injection site rotation assistance. In the company's most recent study, 10 out of 13 participants would opt for the companion app if they were using an Aria device. Evidence is emerging that connectivity can play a role in improving healthcare,[7] and it is reassuring to see that patients are eager to support this.

The Deloitte article also points towards more consumer-based influences in healthcare, an aspect on which Phillips-Medisize gained insightful feedback during its user studies. As safety and ease of use of devices are addressed, there appears to be a shift from ensuring patients "are able" to use a device to them "wanting to use" a device. As with consumer products, personal choice becomes more important as patients make decisions aligned with their lifestyle.

As such, in crowded drug markets where differentiation around drug efficacy becomes harder, other factors, such as how a therapy fits into a user's lifestyle, come into play. In Phillips-Medisize's user studies, participants emphasised the importance of the appearance of the Aria device, liking its "modern" look and feel. Equally, many saw the device's colour and design having a role to play not as a matter of choice, but how it may make them feel – many felt strongly that devices could be in attractive colours rather than the more standard medical colours such as white and blue (Box 1). Also, because these devices are intended for use outside of a hospital setting, they are more a "part of life" and need to be attractive and make a user feel "happy to use" them.

CONCLUSION

Ease of use for a self-injection device remains a leading driver in its uptake. Although this can be achieved by both disposable and reusable electronic devices, such as Aria, it is clear from Phillips-Medisize's research, and in results published elsewhere, that improvements can be made by the latter. Key benefits include:

- Clearer and more persistent audio and visual feedback of both dose progress and completion
- Elimination of the need to manually count out the dwell time prior to lifting the device
- The ability to pause or stop injection if the device is lifted early from the injection site, meaning there is no drug spray or waste, or drug on skin
- The ability to lock the cap in place before injection to reduce the risk of premature cap removal and enabling a timeout or warning if the injection is not completed soon after the cap is removed and the sterile barrier broken
- Detection of early lifting, allowing user feedback to enable course correction.

Considering broader issues, including sustainability and consumer preferences such as feel, look and style, there is a strong argument in favour of reusable electronic autoinjectors over their conventional mechanical counterparts. Although evaluating the merits of these points requires further research and analysis, with over 75% of participants from Phillips-Medisize's user studies preferring Aria over a single-use disposable, there is already a strong case in their favour from a user point of view.

Factoring in better sustainability, which is valued by users and pharma companies alike, as well as the flexibility to adapt the design to meet the needs of broad drug portfolios and the economies of scale through development and industrialisation of the product as a platform, Phillips-Medisize is confident that there is an exciting future for reusable electronic products such as Aria. Over the coming few years, Phillips-Medisize will continue to develop and test the design, firstly in further user studies, then in clinical trials with customers, which are planned for 2022. Phillips-Medisize anticipates that the first finished combination products utilising the Aria Smart Autoinjector platform will be introduced into market by its customers towards the end of 2023, pending approval by the FDA and similar regulators in other jurisdictions.

"Considering broader issues, including sustainability and consumer preferences such as feel, look and style, there is a strong argument in favour of reusable electronic autoinjectors over their conventional mechanical counterparts."

ABOUT THE COMPANY

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

Bring Your Vision to Life

Design, development and manufacturing on a global scale with lower risk.

Bringing Possibilities to Life

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

Get started today at
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ABOUT THE AUTHOR

Kate Hudson-Farmer is a Director of Front-End Innovation at Phillips-Medisize. She has been with the company for over five years, focusing on bringing drug delivery devices from initial design through to market, meeting the needs of the pharmaceutical industry, stakeholders and patients. In addition, Dr Hudson-Farmer has a significant role in developing new concepts and platform products in drug delivery and connected health areas. She currently leads market and sales activities for the Aria autoinjector platform, including market analysis, competitive positioning and strategy, user studies, design direction, business development and customer relationship management.

Dr Hudson-Farmer started her career as a research scientist in the UK following a PhD in molecular biology and medical microbiology. She transitioned to a technology transfer and business development position at a leading university, managing numerous pharma and biotech licensing deals, public/private partnerships and spin-out company formations with one of the largest bioincubators in the UK, in addition to gaining an MBA. Following this, and before Phillips-Medisize, she worked for over 10 years as a senior consultant in strategic and product consulting, covering due diligence and mergers and acquisitions for pharma and medical devices, with a focus on drug delivery, diagnostics and surgical devices.

MITSUBISHI GAS CHEMICAL

PHOTOSTABILITY TESTS OF ANTIBODY DRUGS

In this article, Yoshiko Sakuma, Researcher, and Tomohiro Suzuki, Associate General Manager, of Mitsubishi Gas Chemical, provide an overview of the company's OXYCAPT multilayer vial and syringe, with a particular focus on the recent investigations into the interaction of OXYCAPT's UV barrier with the photostability of antibody drugs, compared with standard cyclo-olefin polymer and Type 1 glass.

OXYCAPT™ is a multilayer plastic vial and syringe developed by Mitsubishi Gas Chemical (MGC), offering a number of advantageous qualities as a primary drug container, including:

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

MGC has continuously conducted a series of studies to confirm these excellent properties. The second half of this article will focus on a recent set of photostability tests conducted on antibody drugs using OXYCAPT, Type 1 glass and cyclo-olefin polymer (COP). Before that, the first half of this article will provide an overview of OXYCAPT multilayer plastic vial and syringe (Figure 1). The material consists of three layers – the drug contact layer and the outer layer are made of COP, and the oxygen barrier layer is made of MGC's novel polyester (Figure 2).

OXYCAPT OVERVIEW

There are two types of OXYCAPT multilayer plastic vial and syringe – OXYCAPT-A and OXYCAPT-P. OXYCAPT-A offers a glass-like oxygen barrier. According to internal studies, thanks to its oxygen-absorbing function, OXYCAPT-A can maintain lower oxygen concentrations in the headspace than Type 1 glass. OXYCAPT-P also provides an excellent oxygen barrier, although there is no oxygen-absorbing function. For example, the oxygen barrier of an OXYCAPT-P vial is about 20 times better than that of a COP monolayer vial (Figure 3).

OXYCAPT also provides an excellent UV barrier. Although 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.

> "Although about 70% of 300 nm UV light transmits through glass and COP, only 1.7% transmits through OXYCAPT. MGC has confirmed that this feature contributes to the stability of biologics."

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Figure 1: The OXYCAPT multilayer plastic vial and syringe.

Figure 2: Multilayer structure of OXYCAPT.

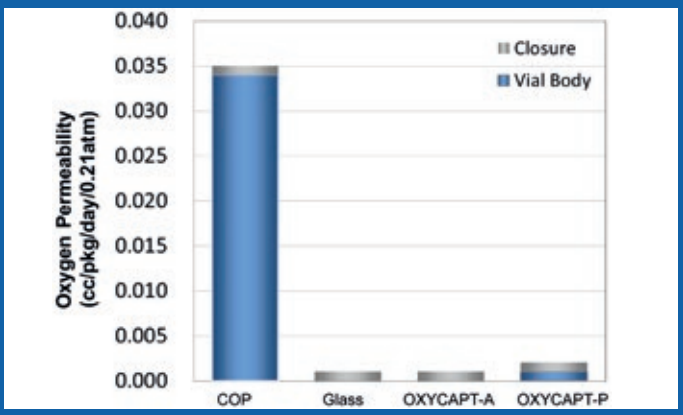


Figure 3: Oxygen permeability comparison of a typical COP, glass, OXYCAPT-A and OXYCAPT-P.

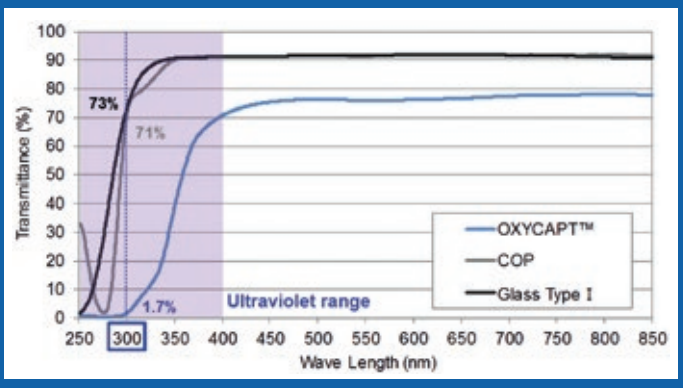


Figure 4: UV light transmittance comparison of a typical COP, Type 1 glass and OXYCAPT.

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 of Technical Requirements for Pharmaceuticals for Human Use (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, NaCl, NaOH and H3PO4) 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, 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, and with a better extractables profile than Type 1 glass. Lower levels of inorganic extractables are known to contribute to better pH stability in drug products.

OXYCAPT vial and syringe are produced by co-injection moulding technology. Although this technology has been used in the production of beverage bottles for many years, MGC is the first company to succeed in applying it to the production of multilayer plastic syringes. MGC has also developed inspection methods for testing the oxygen barrier layer. All of the containers are fully inspected by state-of-the-art inspection machinery.

MGC can offer bulk vials, ready-to-use (RTU) vials and RTU syringes. Regarding the RTU products, vials and syringes are provided in ISO-based nest and tub formats. The nest and tub are mainly sterilised using gamma rays. There are 2, 6, 10 and 20 mL variants for vials, and 1 mL long and 2.25 mL variants for syringes (Table 1). MGC is willing to provide samples for initial testing free of charge.

"MGC believes OXYCAPT multilayer plastic vial and syringe with its strong oxygen and UV barrier is the best candidate for antibody drugs."

Each polymer meets the requirements of United States Pharmacopeia (USP) regulations USP<661>, USP<87> and USP<88>, as well as those of the European Pharmacopeia, and has been filed in the US FDA's drug master file (DMF). The vials and syringes are also compliant with each pharmacopoeia and have been filed in the DMF. The syringes are produced and controlled in accordance with ISO 13485.

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 would be well-suited to emergency adrenaline, which is well-known as an oxygen-sensitive drug, because OXYCAPT combines both an oxygen barrier equivalent to Type 1 glass and the breakage resistance of a polymer. Furthermore, some drug developers have recently started evaluating the OXYCAPT vials for their gene and cell therapy; the RTU vial is sterilised by gamma radiation, making it ideal for protein-based drugs.

Type	Volume	ISO	Parts	Option
Vial	2 mL	ISO 8362-1	Vial	Bulk or RTU
	6 mL	ISO 8362-1	Vial	Bulk or RTU
	10 mL	ISO 8362-1	Vial	Bulk or RTU
	20 mL	ISO 8362-1	Vial	Bulk or RTU
Syringe	1 mL long	ISO 11040-6	Barrel, Tip Cap, Stopper, Plunger Rod	RTU
	2.25 mL	ISO 11040-6	Barrel, Tip Cap, Stopper, Plunger Rod	RTU

Table 1: MGC's OXYCAPT product portfolio.

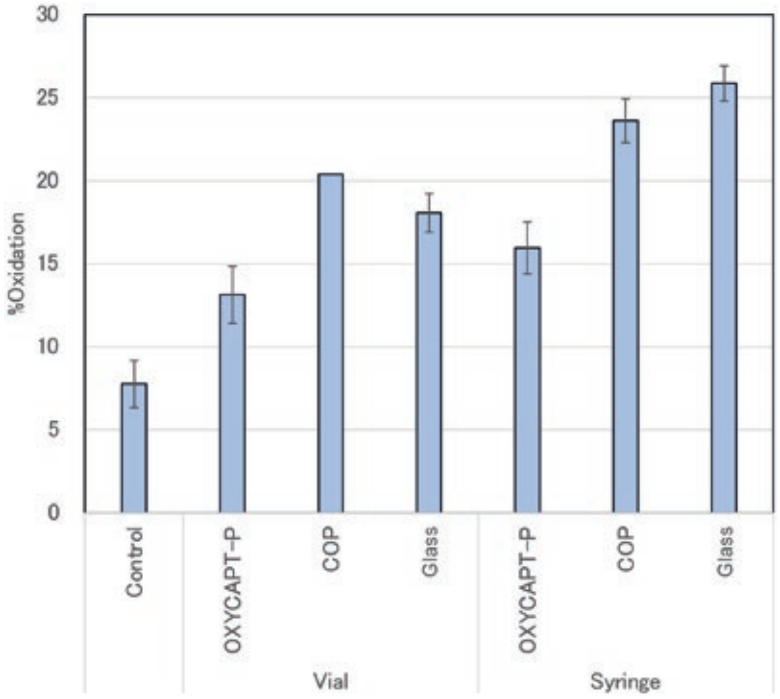


Figure 5: Oxidation rate of methionine.

PHOTOSTABILITY TESTS

Studies have shown that the oxidation of antibody drugs is caused by oxygen and UV light and that such factors have a negative impact on their potency and half-life in blood. Also, the methionine residue located on the CH_3 domain of the fragment crystallisable (Fc) region of an antibody is structurally exposed to the environment and is likely to be oxidised. Moreover, some researchers have reported that the oxidation of said methionine tends to bring about deterioration of structural stability and aggregation upon heat treatment. Therefore, MGC believes OXYCAPT multilayer plastic vial and syringe with its strong oxygen and UV barrier is the best candidate for antibody drugs. To test this belief, MGC recently conducted photostability tests of commercially available antibody drugs in OXYCAPT, Type 1 glass and COP containers.

To obtain results in a shorter time span, MGC first removed any polysorbate-80

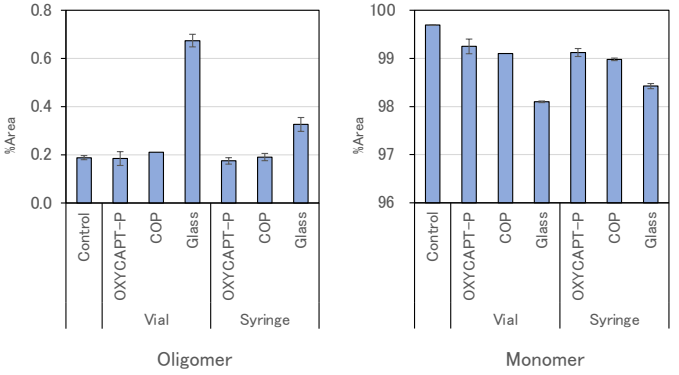


Figure 6: Results of SEC-HPLC (percentage of each ingredient).

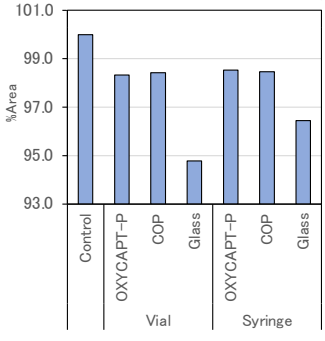


Figure 7: Average monomer rate of each container.

(PS-80), a non-ionic surfactant as a stabiliser, from commercially available antibody drugs based on immunoglobin G (IgG) subtype IgG1. Secondly, OXYCAPT-P, COP and Type 1 glass vials and syringes were filled with the antibody drugs without PS-80 in a nitrogen chamber. All the samples were exposed to light (totalling 1.2 million lux-hours) at 25°C. Finally, oxidation rates and quantities of aggregates in the antibody drugs were measured.

Oxidants of methionine were quantified by liquid chromatography with tandem mass spectrometry (LC-MS-MS). For the protein aggregates, soluble proteins were analysed by size chromatography (SEC), with micro-particle counts and size distributions obtained by flow injection analysis (FIA). Throughout the study, commercially available antibody drugs that had not been exposed to light were used as a control.

With regard to the quantitative analysis of oxidants by LC-MS-MS, each average oxidation rate (+/- the standard distribution) of the samples' DTLMISR peptide sequence, including methionine located on the CH_3 domain of the Fc region, was calculated (Figure 5). The study results showed that the oxidation rate of the antibody drug contained in the OXYCAPT-P vial and syringe was lower than that of those in Type 1 glass and COP containers. Considering that the oxidation rate in Type 1 glass, which has a strong oxygen barrier, was the same as that in COP, with a poor oxygen barrier, MGC believes that the exposure to UV light accelerated the oxidation rate of the tested antibody drugs.

MGC also used SEC analysis to calculate what percentage of the total area of each peak concerned oligomers, monomers and fragments of the antibody drugs (Figure 6). Compared with Type 1 glass, the rate of oligomers and fragments in OXYCAPT-P and COP was lower, the polymer containers maintaining a higher rate of monomers. Also, a T-test showed that the OXYCAPT-P syringe maintained a significantly higher rate of monomers than the COP equivalent.

Figure 7 shows the average proportion of monomer in each container with the control regarded as 100%. Since a loss of monomer was observed in all the containers, it can be assumed that decompositions and aggregations of antibody drugs were caused by the exposure to UV light.

Figure 8 shows the particle concentrations in each container obtained by FIA. The particle concentrations in OXYCAPT-P and COP were much lower than those in Type 1 glass, while no significant difference was observed between COP and OXYCAPT-P. Although the vials' particle concentrations were generally higher than the syringes', it can be assumed that the bigger head space in the vials led to more vibration stress on the antibody drugs during transport, and, as such, reducing said head space will prove a useful measure for preventing the increase of particles.

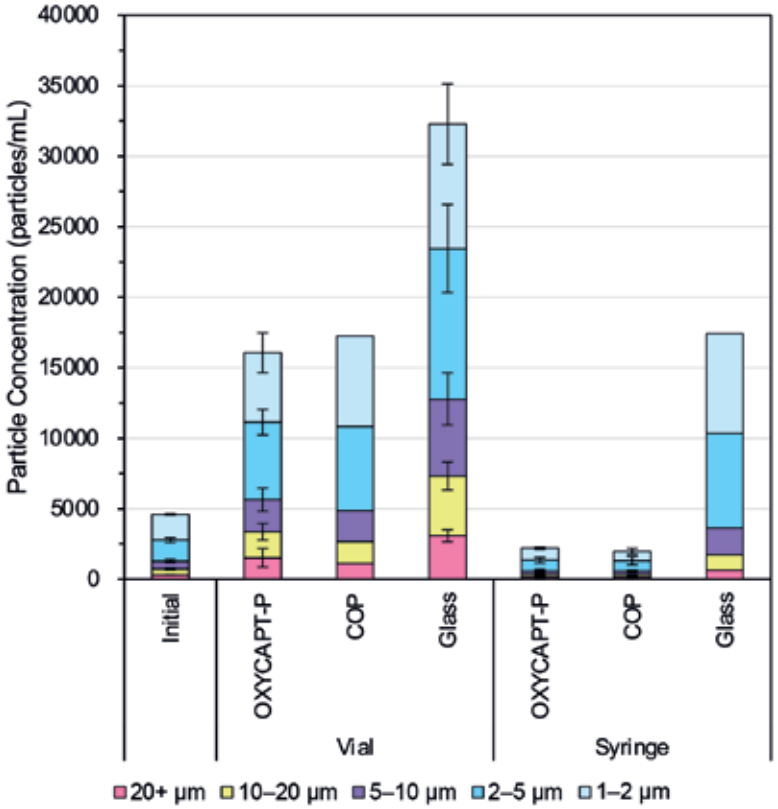


Figure 8: Particle concentrations in each container.

CONCLUSION

In conclusion, the latest results have verified OXYCAPT's superior properties. In addition to the special features of COP, such as its strong water vapour barrier, high breakage resistance, very low extractables and low protein adsorption, OXYCAPT can provide excellent an oxygen and UV barrier. MGC believes OXYCAPT brings significant and varied benefits to the rapidly growing biologics and gene/cell therapy sector.

ABOUT THE COMPANY

Mitsubishi Gas Chemical is a major chemical products manufacturer operating across a wide range of industries. In the field of drug delivery, the company has developed OXYCAPT vial and syringe from a novel polymer, as an alternative to glass primary packaging.

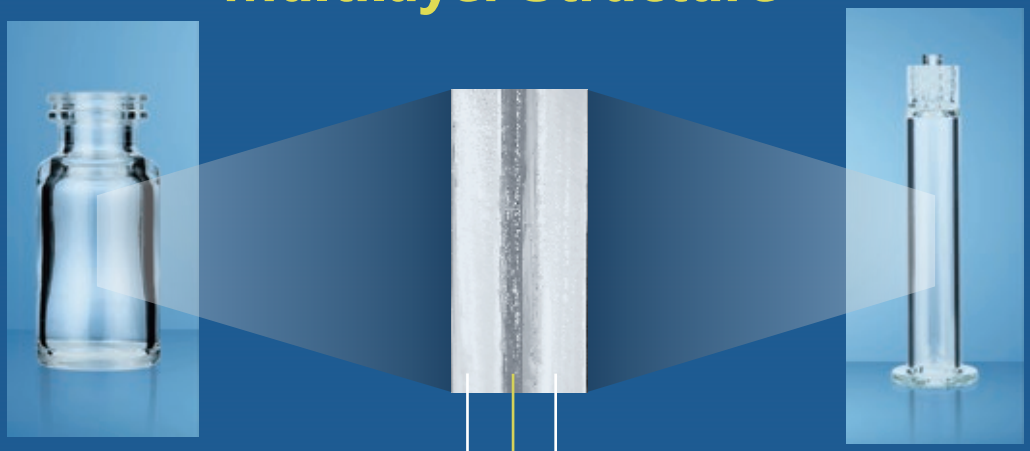
ABOUT THE AUTHORS

Yoshiko Sakuma joined Mitsubishi Gas Chemical in 2008. She belonged to a biological research team, including research on pharmaceutical antibodies, as a quality control engineer, focusing on optimisation and manufacturing, until 2015, and then was part of a safety test team until 2019. Her current responsibilities include evaluating OXYCAPT using commercially available drugs at an MGC laboratory in Kanagawa prefecture in Japan.

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 OXYCAPT vial and syringe. His current position is Associate General Manager.

OXYCAPT™ Plastic Vial & Syringe

Multilayer Structure



Water Vapor Barrier Layer (COP)

Oxygen Barrier Layer (New Polymer)

Drug Contact Layer (COP)

- Excellent Oxygen Barrier
- High Water Vapor Barrier
- Very Small Extractables
- Low Protein Adsorption
- Excellent Ultraviolet Barrier
- High Break Resistance
- High pH Stability
- Silicone Oil Free Barrel
- Gamma-sterilized Vial & Syringe
- Customizable
- For Biologics & Gene/Cell Therapy

2, 6, 10, 20mL Vial

Nest & Tub for Vial

1, 2.25mL Syringe

Nest & Tub for Syringe

MITSUBISHI GAS CHEMICAL

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gerresheimer

GX INNOSAFE – GREATER PROTECTION AGAINST NEEDLESTICK INJURIES

In this article, Wenzel Novak, PhD, Senior Global Director Business Development, Medical Systems, and Stefan Verheyden, Global Vice-President, Gx Biological Solutions, both of Gerresheimer, introduce Gx InnoSafe, a novel integrated passive needle safety system for preventing needlestick injuries and accidental reuse of syringes that minimises additional burden on healthcare workers during injection and can be integrated into existing pharmaceutical filling operations without the need for adaptation or conversion of processing lines.

Used syringes with exposed cannulas present a source of risk in surgeries, laboratories and hospitals the world over. Although existing needle protection systems reduce the risk of injury for the end user, they make prefilled syringes more complex for pharma companies to fill during manufacture and must be handled by medical specialists in the clinic. These challenges have left a gap in the market for an innovative needle safety system.

To tackle this unmet need, Gerresheimer has developed the Gx InnoSafe (Figure 1) – a syringe with an integrated passive safety system that:

- Avoids inadvertent needlestick injuries
- Prevents repeated use
- Is designed with pharmaceutical companies' production processes in mind
- Is optimised for simple and intuitive use by medical specialists.

In addition to these unique safety features, a special feature of the Gx InnoSafe syringe is that it can be processed on all existing filling lines without additional preparation or conversion steps. In addition, it is compliant with all appropriate regulations without additional investment, making it as painless as possible for pharmaceutical companies to integrate Gx InnoSafe into their production process.

GX INNOSAFE IN THE CLINIC

For healthcare workers, handling used hypodermic needles is a part of their day-to-day job. However, in some cases, accidental needlestick injuries occur. It is estimated that around one

> "Unlike many existing solutions, the needle shield mechanism is activated automatically and does not require any additional manipulation by the end user."

Figure 1: The Gx InnoSafe syringe by Gerresheimer.

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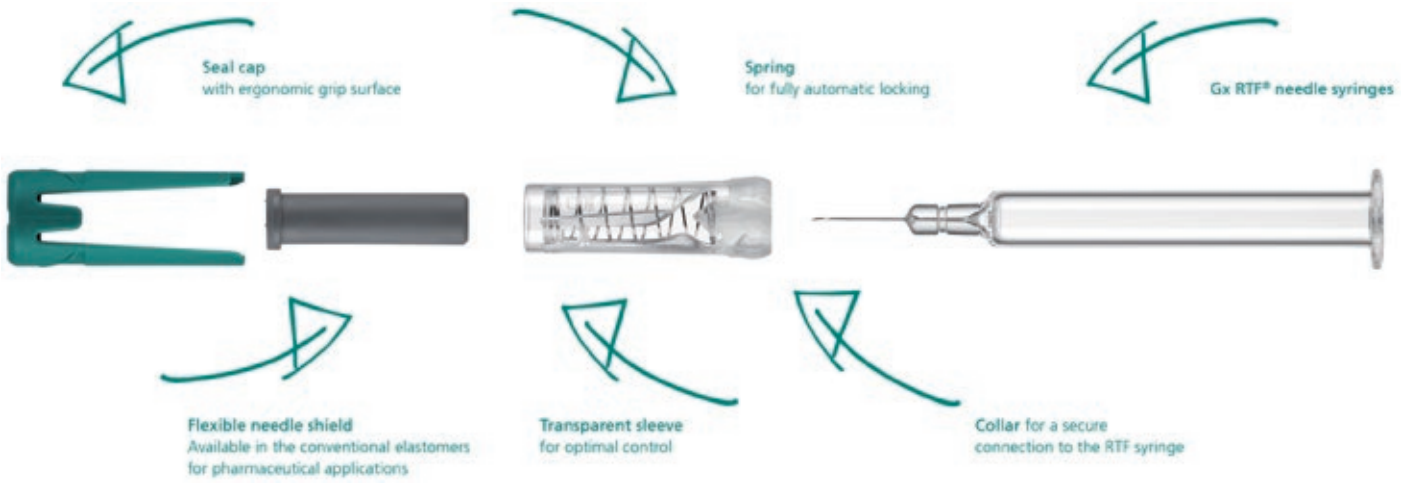

Figure 2: The design of Gx Innosafe and Gx RTF glass syringe allows for injectable administration as usual with no extra steps.

million needlestick injuries occur in Europe every year, which, in the worst cases, can lead to the transmission of serious diseases or cause dangerous infections. There is also the risk of used syringes being used for a second time by accident.

Gx InnoSafe reliably protects against inadvertent needlestick injuries and prevents repeated use. Unlike many existing solutions, the needle shield mechanism is activated automatically and does not require any additional manipulation by the end user. As such, Gx InnoSafe is therefore what is known as a "passive needle protection system". Furthermore, the fact that Gx InnoSafe syringes can be processed on filling lines in a nested state, without any major changes to manufacturing systems, is just as beneficial to pharmacists as it is to filling companies. Gx InnoSafe arrives in pharmacies fully assembled and ready-to-use, eliminating the need for an additional step to assemble the safety system, as is standard for needle safety systems currently on the market.

Gx InnoSafe was designed with clinicians and medical specialists in mind and, in addition to its benefits for pharma companies, the syringe is intuitive and easy to use. Clinical end-users want a safety system that:

- Does not change the familiar injection procedure
- Has intuitive and ergonomic handling
- Requires no additional manual activation to secure the cannula before it is disposed of.

As part of the manufacturing process, the Gx InnoSafe safety system is installed on Gx ready-to-fill (RTF) glass syringes in a cleanroom environment, just like a standard needle shield. The syringe body is completely visible so that the presence of the API, its purity and its administration can be observed and monitored.

> "After the removal of Gx InnoSafe's ergonomic sealing cap with an integrated, flexible needle shield, the syringe is placed on the injection site, the cannula is inserted into the patient's tissue and the active ingredient is injected – just as with a standard syringe."

Gx InnoSafe's design places no demands on the injection process, meaning that the drug can be administered as usual without additional burden (Figure 2). After the removal of Gx InnoSafe's ergonomic sealing cap with an integrated, flexible needle shield, the syringe is placed on the injection site, the cannula is inserted into the patient's tissue and the active ingredient is injected – just as with a standard syringe.

The safety system cannot be activated inadvertently because the mechanism is not preloaded before the injection – the system is only activated when the cannula is inserted, and it automatically ensures that the safety mechanism is permanently locked when the syringe is removed from the injection site. This guarantees that the cannula is reliably covered, meaning that the syringe cannot be reused, thus preventing needlestick injury.

GX INNOSAFE IN PHARMACEUTICAL MANUFACTURING

Gx InnoSafe provides advantages for pharmaceutical companies in the filling process of RTF syringes. The safety system is

Figure 3: Gx InnoSafe is fully compatible with standard nest-and-tub formats.

installed during the RTF process entirely automatically, and it is fully checked for any punctures and positioning with a visual inspection. The syringes are then packaged into trays of 100 in nest-and-tub format, including the safety system, and are then sealed and sterilised with ethylene oxide gas (Figure 3). They can be processed on existing filling lines without any additional preparation or assembly steps.

The design of the safety mechanism avoids inadvertent activation during filling, packaging and transport. The flexible needle shield part is available in all standard market elastomers for pharmaceutical applications.

Every filler can fill the InnoSafe safety syringe easily, without the need for additional investments on existing filling lines for syringes. It is precisely this feature of the Gx InnoSafe syringe that differs from conventional safety syringes and is a world first.

CONCLUSION

The Gx InnoSafe syringe represents a step forward in syringe safety systems, both from a clinical and pharmaceutical filling perspective. For healthcare workers, Gx InnoSafe passively prevents needlestick injuries and accidental reuse of syringes without requiring any additional steps or expertise on top of well-established administration practices. For pharma companies, Gx InnoSafe can be reliably and easily integrated into existing production lines and filling processes without the need for expensive and complex preparation and conversion work. Gx InnoSafe is ready to integrate for pharma and ready to use for clinicians.

ABOUT THE COMPANY

Gerresheimer is a leading international partner to the pharmaceutical and healthcare industries. The company contributes to health and well-being with its range of glass and plastic products. Gerresheimer has a worldwide presence, with around 10,000 employees; locations in Europe, Asia, and North and South America; and an annual turnover of around €1.4 billion (£1.3 billion). The company's product offering includes insulin pens, inhalers, micro pumps, prefillable syringes, injection vials, ampules, bottles and containers for liquid and solid medications with sealing and safety systems, as well as packaging for the cosmetics industry.

ABOUT THE AUTHORS

Wenzel Novak, PhD, began his career working on keratinocytes for wound healing as head of laboratory in a Swiss biotech-company. He then joined Gerresheimer in charge of project management and, as head of production for presterilised syringes, he designed the manufacturing area, built up the process and quality systems and operated the start-up phase of production. He then took role as Chief Innovation Officer at a pharmaceutical equipment supplier, developing new methods of sterilisation and filling processes. During two years spent working in the US, he developed the market for cell and gene therapy equipment. In 2018, Dr Novak returned to Gerresheimer in a new global senior role for business development. He studied biology and gained his PhD in physics at the Max Planck Institute for Neurochemistry (Munich, Germany).

Stefan Verheyden has been active in the pharma and biopharma industry for more than 25 years. He started his career in product management in the lab chemicals industry, before moving into leading sales and business development roles in production chemistry, raw materials and APIs at two major companies. After 20 years Mr Verheyden moved into the pharma packaging industry, taking over a global role as Senior Vice-President at one of the players within the industry. He moved to Gerresheimer in 2017, heading both the syringe business as well as a new business unit supporting the fast-growing biological market segment. Mr Verheyden studied chemistry at the University of Brussels (Belgium).

Protection against needlestick injuries

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and CPhI worldwide | November 9 – 11, 2021 | Milano, Italy | booth 6J50

Gx InnoSafe®

- Protection mechanism is activated automatically
- No accidental reuse possible
- Delivered pre-assembled in nest and tub

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INTERVIEW

Stephen Perry and Nicholas Ciccarelli discuss the August 2021 acquisition of Neuma by Kymanox, highlighting how the acquisition has positioned Kymanox to lead the development of particularly complex drug delivery systems and cutting-edge medical device technologies, providing additional services to progress combination products to market.

STEPHEN M PERRY

Kymanox
Your Life Science Solutions Partner

Stephen M Perry, Chief Executive Officer and Founder of Kymanox, has more than two decades of experience in biopharmaceutical manufacturing with an emphasis on design engineering, scale-up, start-up and regulatory approval. Mr Perry has participated in the US FDA commercial approval of over two dozen unique drugs, devices, biologics and combination products. In 2004, he created Kymanox, a professional services firm specialising in the commercialisation of modern medicines. Prior to this, he held leadership roles at M+W Group (Stuttgart, Germany), Abbott Laboratories (IL, US), FujiFilm Diosynth Biotechnologies (TX, US) and Human Genome Sciences (MD, US). He holds a Bachelor's degree in chemical engineering from the University of Notre Dame (IN, US) and studied at graduate level at Purdue University (IN, US).

NICHOLAS CICCARELLI

NEUMA by Kymanox

Nicholas Ciccarelli, PE, President and Co-Founder of Neuma, an engineering services company, is a principal product development engineer with 12 years of experience in the fields of medical devices and drug delivery. He focuses on analytical design and the development of devices for high-volume manufacture while prioritising design for manufacturing and design for assembly. He has worked extensively on cross-functional teams that span the US, Europe and China. His experience includes individual component design (including plastic injection moulding, stamping, machining, glass, rubber), sub-assembly layout and top-level system integration. He has been heavily involved in design verification activities, *in vivo* study design and execution, and the preparation of premarket notification submissions.

Q How did Kymanox and Neuma team up to work on product development prior to the merger?

NC We have been working together since early 2019, and our teams have established a good rapport. Early on, Neuma was supporting Kymanox on the quality engineering side and, when Neuma engineers were exposed to Kymanox projects, we saw opportunities for educating the Kymanox team on what we do while also learning more ourselves.

Kymanox was uncovering issues with products, documentation, testing and product design and we saw the possibility to bring in more of what we work on – prototyping, building and testing. It's a complimentary set of activities, so this partnership was just building on the strong projects and work that Kymanox was already doing.

> "The collaboration between Kymanox and Neuma provides tremendous value to the marketplace. Kymanox is tuned to support commercialisation initiatives while Neuma excels in early stage prototyping and development of that base design."

SP Michael Denzer, our Vice-President of Technical Solutions and a member of the Kymanox Executive Leadership Team, made the Neuma introduction shortly after he joined Kymanox. Right away, the two companies were heavily engaged on a post-market programme – the products were already approved, on the market and being used at relatively high volumes. A high-volume product can easily show why it is successful, but problems also come to light. The Neuma engineers got to see something they normally do not get to see: commercial products where the design was being used in the real world every day and generating problems.

That feedback from real-world use then informs Neuma's design approach for next-generation products. Also, the Neuma team

"A device needs to work every time, so if you are going to let people self-administer, you need the utmost confidence in the device's reliability to get the job done."

can provide feasible product updates to improve the design without fundamentally changing a product.

The collaboration between Kymanox and Neuma provides tremendous value to the marketplace. Kymanox is tuned to support commercialisation initiatives while Neuma excels in early stage prototyping and development of that base design. Bringing these two worlds together – having a design and early development team exposed to products that are being prepped for and used on the market every day – makes for better designs and better outcomes for both our clients and their patients. It is a closed loop, and one of the main premises for putting the two organisations together.

Q At what point did this acquisition become a clear path and why?

NC As we gained more familiarity with each other while working together, it became clearer and clearer that the teams were complementary, and that our capabilities could be used on the commercial and post-market side as well as in the earliest stage of development. That both teams could leverage one another in all those areas became more and more apparent.

SP We also validated that the company cultures, including core values, were similar. We both take care of the project and customer, and how we deliver the work is similar in almost every aspect. We felt bringing our teams together would be synergistic.

Plus, while we knew that we did not need each other – we could continue to both be successful on our own – we also knew that we could be more successful together! A lot of our discussion centred on the idea that, together, we can get more done in a shorter amount of time and with better results. We like to characterise the merger of the companies as "one plus one equals three".

External validation came from private equity firm WestView Capital Partners (MA, US) and lender Abacus Finance (NY, US). They looked at the potential merger from both a business and financial lens. They also brought in industry advisers to examine it. Their investment validated the equation, and we have been together for over a month now. We are already seeing the synergies play out and both teams are very energised. We can do "more, better, faster" – one plus one really does equal three.

Q What trends do you see in the prefilled syringe and injection devices space?

NC One is the desire to move some medicine administration to self-administration and at-home care getting people out of doctors' offices and giving them a little bit of their lives back. Many see a specialist or physician multiple times a week, particularly when dealing with chronic illness. Most would rather be at home on their own schedules. Our goal is to help commercialise those injection technologies that allow people to administer medication on their own or with the help of a family member.

There are also connectivity and data analytics aspects, which can be a double-edged sword. People want simplicity – one press of a button – along with detailed insight into how healthy or unhealthy they are. It is a delicate balance for engineers to design the fewest number of steps possible to use a device, but with an extensive ecosystem, underlying data, data analysis and feedback.

With self-administration, reliability becomes even more important. A device needs to work every time, so if you are going to let people self-administer, you need the utmost confidence in the device's reliability to get the job done.

Another growing trend is sustainability. With millions of products made from glass, plastic or other materials going into landfills, we do not have all the answers we need for a greener industry just yet. But we are cautiously optimistic that those problems can be solved in the near future, whether through materials that are more biodegradable or through recycling and reuse. Companies want their products to be more sustainable and more environmentally friendly.

SP The ramifications of medicine administration matter. Getting family members to the doctor is a strain, and home-based medication eliminates a lot of the logistical problems and potential health hazards.

It can also be part of the solution for making existing therapies better. For example, I have data on one product showing that if you switch a monthly intramuscular injection done at the doctor's office to a weekly one done at home, you get better efficacy, reduced side effects and improved efficiency. In this one case, you reduce the delivered dose by a factor of six and introduce it subcutaneously; the patient needs more injections, but the needle is significantly smaller and the injection is less painful. We are able to improve the performance of existing drugs just by altering the prescribed regimen with the support of optimised delivery systems (e.g. mini prefilled syringes, multidose autoinjectors). This is a game changer.

Both Kymanox and Neuma can more fully support their customers with the wealth of resources and expertise the other brings

"Both Kymanox and Neuma can more fully support their customers with the wealth of resources and expertise the other brings to the table."

to the table. With fully integrated teams, we have multiple people working together, providing significant horsepower to push projects and products along no matter where they are in the product lifecycle.

NC We are not waiting for an outside external expert to help us. All the expertise, the know-how and the doer mentality is right here. We can execute on it. We can do it. We can rely on our internal expertise and proven past performance. It is all here and can be deployed for our customers when it comes to new or existing products.

The cross-functional collaborative work between the teams is where true blending occurs, which is a solid win for clients and for the industry to get more done.

ABOUT THE COMPANIES

Kymanox is a life science professional services organisation that offers engineering, scientific and compliance support to companies exclusively in the biotechnology, pharmaceutical, medical device and combination product industries. With its diverse team of experts, Kymanox helps clients navigate commercialisation challenges that arise throughout a product's lifecycle – from early development to post-market – with optimised safety, quality, efficacy and accessibility. Kymanox was founded in 2004 and is headquartered in Morrisville, NC, US.

Neuma is an engineering services company focused on the development of robust, verifiable, reliable and manufacturable drug delivery devices. The company's experience includes work on novel, custom and platform device adaptations across prefillable syringes, autoinjectors, reconstitution devices and wearable injectors.

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PRODUCT SHOWCASE: ZwickRoell – Comprehensive Automated Testing Solutions

AUTOMATION TRENDS IN TESTING OF SYRINGES, AUTOINJECTORS AND PENS

The testing of components and finished medical devices is becoming increasingly automated, as even the smallest variances can change the measured values. Time-consuming or monotonous work is also more commonly being left to robots. Global market leader ZwickRoell offers comprehensive solutions to partially or fully automate tests on medical devices, such as prefilled syringes, autoinjectors or pens. The automation stages range from multiple tests within a machine to complete automation with robotic sample feeding.

MULTIPLE TESTS ON AUTOINJECTORS

The correct injection depth and dosage are crucial for a drug to achieve optimal therapeutic success. Therefore, pharmaceutical manufacturers strive for a high degree of automation in the handling of their autoinjector products. The patient simply removes the safety cap, places the autoinjector in the correct dosing location and pushes a button to start the injection. While the full automation of the injection process offers many advantages, it also means that all relevant functions of the injector must be tested prior to the market release of the production batches. These tests must follow the ISO 11608-5 standard.

Figure 1: Fully automated testing systems for autoinjectors.

> "Global market leader ZwickRoell offers comprehensive solutions to partially or fully automate tests on medical devices such as prefilled syringes, autoinjectors or pens."

ZwickRoell has developed a testing system capable of conducting up to 15 consecutive test steps (Figure 1). These include safety cap removal force, activation force, injection time, injected volume, injection depth and needle shield blocking force.

ZwickRoell test solutions offer the advantage of performing all these test steps on a single autoinjector, which reduces the required effort and cost, speeds up testing and, above all, guarantees reliable test results. The testing system can be extended at any time to accommodate additional tests and thus meet different market requirements or product developments.

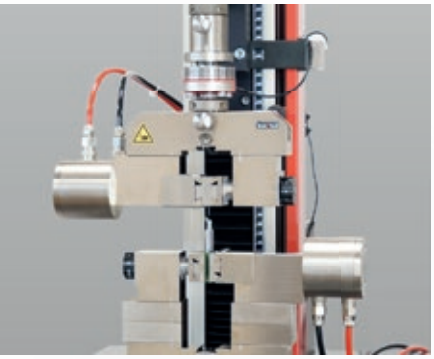
PARALLEL AND SEQUENTIAL GLIDE FORCE TESTS ON SYRINGES AND CARTRIDGES

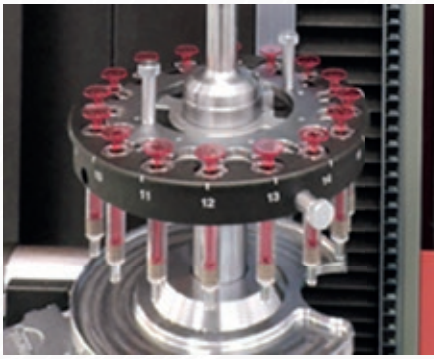
One application involves syringes used in syringe pumps, where the syringes are expressed over a longer time period. To reduce the test time, the testing machine can be extended to eight test axes with an equal number of load cells. This makes it possible to individually capture the force of each syringe. For laboratory use, as well as for in-process control, the various friction forces between the syringe plunger and cylinder, or the syringe's sealing rings, can be tested.

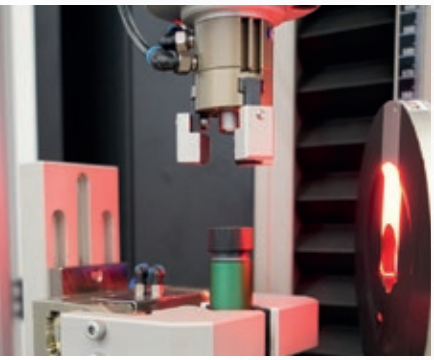
When it is necessary to test a high volume of syringes or cartridges with a short test duration, a materials testing machine with a rotary table or an XY table can be used. In this case, a larger number of samples can be placed into the testing machine via a magazine. The syringes or cartridges are then automatically tested one after the other. This reduces operator influence and leads to higher stability in Gage repeatability and reproducibility (R&R) studies.

Testing systems

for the medical and pharmaceutical industry







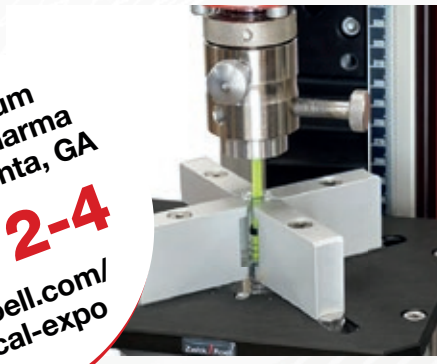


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Figure 2: When conducting a high volume of tests, it is sensible to make use of a robotic handling system to increase throughput and reliability.

"With a high volume of tests, it makes sense to expand the testing machine with a robotic handling system. This ensures safe and economical testing of pharmaceutical packaging and medical products."

FULLY AUTOMATED TEST SOLUTIONS WITH ROBOT INTEGRATION

With a high volume of tests, it makes sense to expand the testing machine with a robotic handling system (Figure 2). This ensures safe and economical testing of pharmaceutical packaging and medical products. Typical applications include autoinjectors, insulin pens and syringes. Depending on the requirements, collaborative robots (smart robots) or industrial robots can be used. Graphical visualisation can transfer the system status in real time to mobile devices, such as smart phones and tablet PCs. This ensures full process control over all common browser programs. This visualisation increases the efficiency of the automatic testing system through reduced downtimes. Due to the modular design of the automated testing system, manual tests can be carried out on the machine at any time.

"Due to the modular design of the automated testing system, manual tests can be carried out on the machine at any time."

ZwickRoell offers different forms of test automation for all test applications in the medical technology and pharmaceutical industries, with a number of significant features and advantages:

- The elimination of operator influences (hand temperature, humidity, off-centre or oblique insertion, etc) results in high reproducibility of the test results
- Qualified laboratory personnel are relieved from performing menial, routine tasks and are available for more complex activities
- The machine can be used during idle times (lunch break, night shift), the possible load is increased and "faster" results are possible
- The testing system reduces the cost per sample and pays for itself very quickly
- The system enables secure documentation and long-term statistical monitoring
- The automation levels range from multiple tests within a machine to complete automation with robotic sample feeding.

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team technik
PRODUCTION TECHNOLOGY

FULLY AUTOMATED ASSEMBLY AND FUNCTIONAL TESTING FOR PEN INJECTORS AND AUTOINJECTORS

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Here, Carsten Köhler, Vice-President Sales & Project Management, Umit Ismail Tsavous, Senior Control Engineer, and Gerd Vosshage, Applications Engineer, all of the Medtech Division at teamtechnik, explain the company's processes for the automated assembly and testing of pen and autoinjectors.

For more than a decade, teamtechnik has specialised in assembling and testing medtech injection systems. The company has gained know how and experience from numerous customer projects that have enabled it to create, for example, measuring systems for pen and autoinjectors of unparalleled precision.

> "teamtechnik analyses customer requirements accurately and develops customised system concepts, including qualification, following GMP requirements."

CUSTOMER REQUIREMENTS

Patient safety, product quality and the integrity of the production data are the highest priorities for pharmaceutical companies. During the manufacturing phase, it is important to employ trusted processes and production methods that comply with GMP principles.

The long service life of production systems demands regular optimisation and extensions. Accordingly, pharmaceutical companies place high value on modular machine designs and processes that allow for maximum flexibility. Standardised mechanical, electrical, software and subsystem interfaces enable a diverse combination of system components and also allow changes and qualifications to be performed independently of the overall system.

Selecting the right vendor is another important factor for success. A good production system supplier engages closely with the requirements of its customers. Thus, teamtechnik analyses customer requirements accurately and develops customised system concepts, including qualification, following GMP requirements. Whether using standard components or high-end solutions, teamtecknik's solutions are always tailored to the individual application.

INJECTORS

Pen injectors and autoinjectors are playing an increasingly important role in the pharmaceutical products market. Patients place great trust in the dosing accuracy and safety of these drug delivery devices. In particular, their ease of use is appreciated, even by patients with reduced physical strength or deteriorating manual dexterity.

Figure 1: Integrated assembly and test line for a pen injector.

Autoinjectors consist of a power pack and a holder for the prefilled syringe. The injection procedure is started manually by triggering the autoinjector on the body; a pre-tensioned spring force in the autoinjector ensures that the medicament is injected automatically.

Pen injectors normally consist of two assemblies: the dosing mechanism and a cartridge holder containing a carpule. The dosage quantity is adjusted by means of a rotary button at the end of the pen injector. The rotary button impels a dosage adjustment sleeve (graduated tube) inside the injector. A display window on this shows the set dosage quantity. When unscrewed, the rotary button moves around the dosage path and out from the pen. By manually turning the rotary button back, the medicament is injected and the dosage sleeve is reset to zero. Pen injectors can be used for multiple dosages until the carpule is empty.

To ensure that pen injectors can be used reliably in practical situations, they must undergo function checks during the production stage in which the torques, compressive forces and frictional resistance during triggering are accurately measured. For this purpose, teamtechnik develops and implements precision production systems with integrated measuring systems designed specifically for the customer's products and measurement requirements – from solutions with configurable measurement technology through to high-end test systems for the most demanding requirements.

FUNCTION TESTS

The TEAMED platform from teamtechnik consists of standardised function modules that can be used to create custom assembly lines. teamtechnik developed the production system platform and has been using it successfully for many years. The platform is compatible with ISO 7 cleanroom requirements. The company has developed the know-how for automating demanding medtech processes in recent decades from its experiences project planning many assembly and test lines for medical products and for other markets. For example, teamtechnik is developing production systems for injection systems, contact lenses, inhalers and point-of-care products, as well as for individual assemblies for medical products.

Thanks to the tried-and-tested standard components used, the TEAMED platform enables short delivery times and highly reliable production processes to be achieved. Test benches for the testing of complete pen injectors, autoinjectors and dosing mechanisms are available both inline and offline. If the component being tested can be reset, the test bench can be installed inline for 100% testing. If the testing is destructive, finished systems are tested for fault-free functioning on the basis of random samples at the goods inward or outward stage.

The fully automated test process of the TEAMED injector test covers parameters including the quantity of medicament delivered, force and travel measurement of the piston movement, and the triggering moment of the adjusted dosing stroke. Additionally, the needle length, the condition of the injection needle, the force for removing the pen cap and the readout from a dial can be monitored and/or measured. Depending on the inspection scope, a testing cycle can last between 5 and 30 seconds.

One unique selling point of teamtechnik is the measurement technology, which is not offered by any competitor in this form. The measuring element is an analogue sensor whose output is read by special software. The software filters out the noise elements and then performs a high-precision oscillation analysis. This arrangement offers a resolution accuracy that no other large-scale measuring system on the market has yet achieved. In practice, this results in false reject rates of less than 0.1%. Even the combined false reject rate for both assembly and testing is less than 0.5%, which is far below the standard requirement of not more than 2.5%.

While competitors' systems can also achieve these levels, thus far they have only done so under specific environmental conditions and with small unit volumes. teamtechnik achieves this precision even with fully automated large-scale production with high unit volumes. A further customer benefit is that the measurement technology is individually developed for the specifications and requirements of the project. Thus, teamtechnik supplies its customers with sensors and software that achieve exactly the required precision from simple, configurable measurement systems to high-end test systems for the highest demands.

All production data, along with the functional testing data, are stored in teamsoft, the comprehensive production control system from teamtechnik. From here they can be accessed at any time for more accurate analysis. The innovative test software teamsoft-TEST allows test cycles to be created in a web-based graphical environment and enables a test task to be divided into individual test modules that can then be reused and recombined for further new test tasks.

INLINE TEST STATION

One customer order for teamtechnik included an assembly line for dosing mechanisms followed by complete testing of the dosing mechanisms, inline within the assembly fully integrated (Figure 1). The solution created by teamtechnik offered an output of 25 dosing mechanisms per minute, producing three basic versions of the

mechanism with sub-versions for different dosage quantities. The work steps are spread across 38 stations. All individual parts are fed in carefully as bulk material via teamtechnik feeder systems. Complex parts are monitored using camera systems and rotated to the correct rotation angle before being inserted into the assembly position, such as the graduated tubes for the rotational mechanisms of the dosing drive. Figure 2 shows the high-speed assembly solution from teamtechnik for pen injectors.

The subsequent inline test is performed on a number of identical measuring stations in parallel. Each measuring station consists of a measuring module and a handling unit for loading and unloading the measuring module. The measuring modules are assembled on a separate base frame that is decoupled from the assembly line. The modules are mounted on vibration dampers as a further measure for preventing outside interference from affecting the sensitive measurement technology.

teamtechnik installs the measuring modules on a separate precommissioning bench. Only after test approval is received, based on certified calibration standards, are the individual test modules approved for installation in the test bench. This approach enables rapid commissioning of the production system. For example, the first test module can act as a development module that the customer can use to test pre-series pens or dosing mechanisms before the series assembly line is ready for operation. The development module can then later be integrated into the inline measuring station. Figure 3 shows a process bench for six test modules.

The test spectrum for dosing mechanisms includes:

1. Testing multiple pen types with different dosage settings
2. Torque measurement function test when setting the dosage
3. Pen injector disassembly function test
4. Injection force measurement
5. Presetting of dosing mechanism at final assembly.

All function tests are performed in one process position (Figure 4). This means that the test objects are clamped into the test bench just once and are then successively tested in this position. On the one hand, this does away with time-consuming additional handling procedures while, on the other hand, resulting in more accurate measurements, since the same reference zero point is used throughout.

During the dosage setup, the torque and the angle of rotation are measured, recorded and evaluated. The torque is measured using a torque sensor in the measuring module, while the angle of rotation is measured using a shaft encoder on the gripper unit. A unique feature is the dynamic torque and force test combined in a single process, which has proven more realistic and precise than static tests. This method enables a resolution of up to 0.001 nm in the torque test and a resolution of up to 0.01 N for the ejection force.

In the “pen disassembly” function test, the rotary button is pulled from the pen in a tensile test and the path and the necessary

“teamtechnik has developed a stand-alone offline test bench designed to meet the measurement specifications of the customer, based on the TEAMED platform.”

Figure 2: teamtechnik’s high-speed assembly solution for pen injectors.

Figure 3: Process bench for six test modules.

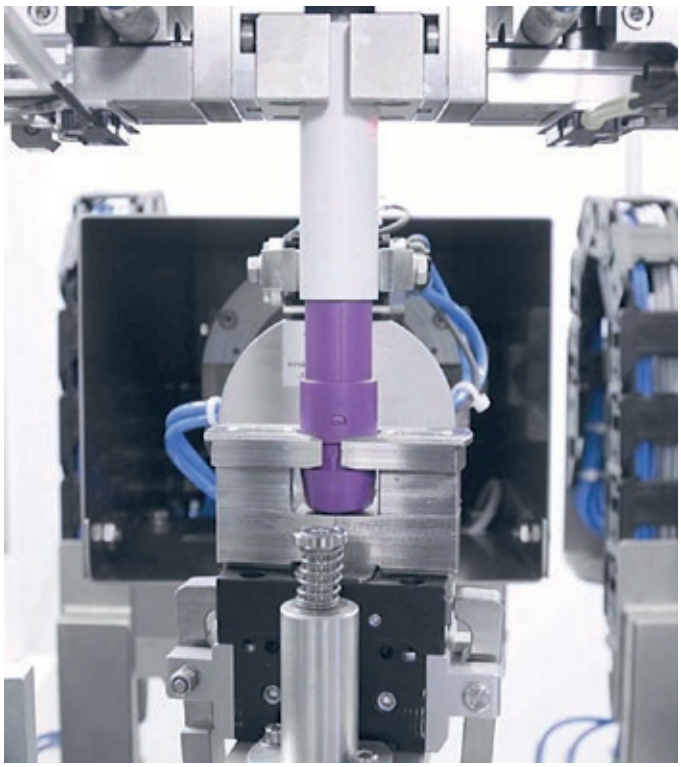

Figure 4: All function tests on the dosing mechanism are performed in one process position.

tractive force are measured. After this, the injection force is determined when the pen is pressed out. Here, the pen is pressed vertically from below at constant speed, while a constant counterforce from above simulates the pressure in the cartridge container. The teamtechnik measurement method enables the dosing stroke to be defined precisely to up to 0.04 mm and the ejection force precisely up to 0.3 N. Finally, the dosing spindle is pre-adjusted to a defined distance from the housing before the dosing mechanism is uniquely labelled and removed from the measurement device.

OFFLINE TEST SYSTEM

If the test object is a non-resettable product (such as a ready-for-sale autoinjector), offline testing is used. Here, small fractions of the production batch are randomly tested. This also calls for an extremely reliable measurement with minimum tolerances because any measurement errors will prevent approval of the batch and could cause significant economic damage.

Figure 6: teamtechnik achieves dynamic torque and force testing in a single process.

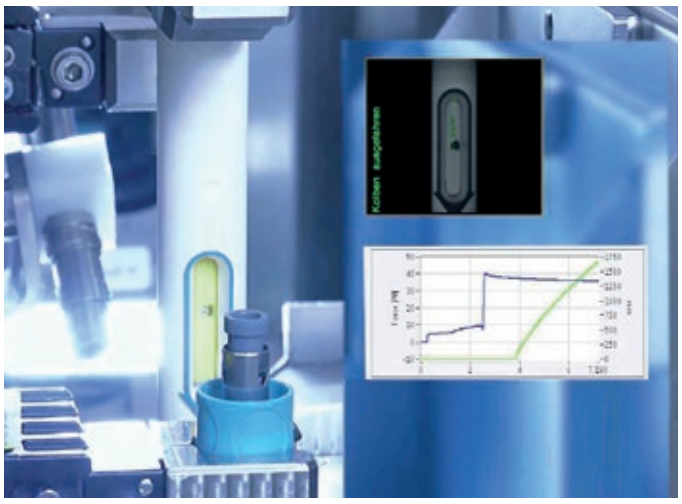

Figure 7: Triggering the set dosing stroke and piston monitoring.

Figure 5: The offline TEAMED test bench is a testing system for batch approval and quality assurance.

For this application, teamtechnik has developed a stand-alone offline test bench designed to meet the measurement specifications of the customer, based on the TEAMED platform (Figure 5). As with the inline solution, all function tests are performed in a single process position and, in some cases, the same tests are run. These might include torque measurement when setting the dose, with dynamic torque and force testing in the same process (Figure 6), measurement of the injection quantity and the needle length, or camera-aided reading of the dosing scale.

To obtain the most accurate simulation of handling by the user, multiple separate tests are performed on the offline test bench. The protective cap is removed fully automatically from the pen and the process is recorded in a force-displacement diagram. The dosing process is also evaluated using a force-displacement diagram. Additionally, a camera takes multiple images per second during the injection process. The evaluation software can, for example, superimpose multiple force-displacement curves on each other to visualise the scatter of the measured values and to better analyse them (Figure 7).

QUALIFICATION PROCEDURE

By using a multi-stage qualification process, teamtechnik ensures product quality, patient safety and data integrity. GMP summarises all the requirements and regulations that a machine and production system manufacturer must satisfy, such as VDI directives, machinery directives, ISO standards and the specific quality requirements of the product. In computer systems within the scope of GMP, the standards and guidelines of national and international organisations must be complied with. For the automated production of medical products in particular, the EU GAMP-5 guideline defines the foundations of all qualification tests.

The qualification process begins with the conception phase of the system and applies to the development, assembly, software, test systems and feeder technology equally. A GMP-compliant production system is given operational approval once the experts from teamtechnik have completed the qualification process without errors. The customer can then be confident that the teamtechnik assembly line satisfies all requirements for manufacturing pharmaceutical products.

SUMMARY

Quality, safety and cost efficiency are the driving forces in the growing market for medical products. System solutions from teamtechnik are a benchmark for the assembly and testing of medtech products. In particular, the high-precision measurement technology for fully automated injector function tests remains unmatched in the high-volume segment. These measuring systems are fully aligned with customer requirements and deliver practically 100% dependable results. This does more than just secure product quality and customer satisfaction for complex medical injectors. teamtechnik TEAMED injector tests also protect manufacturers of medical products from the costly barring of product batches as a result of critical measurement values being taken inaccurately and thereby failing the batch.

ABOUT THE COMPANY

teamtechnik has been involved with automation since 1976. Today, the company is part of the Dürr Group (Bietigheim-Bissingen, Germany) and one of the largest assembly and functional test systems specialists in Europe. Teamtechnik focuses on high-volume assembly and test solutions for injection systems, diagnostics, inhalers, medical disposables, dialysis filters and eye-care products.

ABOUT THE AUTHORS

Carsten Köhler is Vice-President Sales & Project Management in the Medtech division of teamtechnik. For more than 10 years, he has specialised in automation solutions for medtech devices. Before joining teamtechnik, Mr Köhler led specialised teams for medtech automation as a Director of Engineering. His overall competence is comprehensive: project planning, mechanical/electrical design, software, qualification and documentation.

Umit Ismail Tsavous is Senior Control Engineer in the Medtech division of teamtechnik. For more than eight years he has specialised in automation solutions for medtech devices, focusing on measurement programmes for pen injectors and autoinjectors. Mr Tsavous is also studying computer science with a focus on artificial intelligence.

Gerd Vosshage is Applications Engineer in the Medtech division at teamtechnik. Project planning, design and commissioning of assembly lines have been his speciality for 38 years. In recent years, his focus has been on medtech assembly lines for injection systems.

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BUILDING A BETTER PREFILLED SYRINGE FOR COVID-19 VACCINE PACKAGING

In this article, Carina Van Eester, Global Platform Leader, Prefilled Syringes and Cartridges, at Datwyler, shares key learnings since the launch of the company's NeoFlex plungers at the start of the covid-19 pandemic.

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At the onset of the covid-19 pandemic, Datwyler launched its NeoFlex plungers onto the market. A year later, more is known about the virus, the vaccines being developed to fight it and how NeoFlex plungers can be an effective tool in distributing the vaccines to the global population.

> "With more filling lines being developed to process ready-to-fill vials, cartridges and PFSs, the demand for ready-to-use stoppers and plungers is growing every year."

As is standard for most new drugs entering the market, vials are the preferred option for packaging the drug product. For covid-19 vaccines, this is especially true since vials hold more doses of the vaccine, allowing for more vaccinations, and vial components and filling lines are more widely available to drug developers. Even though vials are the preferred initial packaging for covid-19 vaccines, syringes are the ideal packaging application due to ease of administration, reduced risk of contamination, minimised risk of injuries during use and improved accuracy. With these clear benefits to packaging the covid-19 vaccine in a syringe application, Datwyler's NeoFlex plungers are well-equipped for packaging this life-saving drug product.

NEOFLEX PLUNGERS FOR SENSITIVE DRUG PRODUCTS

NeoFlex plungers for prefilled syringe (PFS) and cartridge applications are part of Datwyler's platform of coated products, which also includes OmniFlex stoppers for vial applications. Both OmniFlex stoppers and NeoFlex plungers are made with the same high-quality compound formulation, FM457, and proprietary fluoropolymer spray-coating technology. By using the same compound and technology for the various components, customers can easily transition from an OmniFlex stopper for a vial to a NeoFlex plunger for a syringe or cartridge, with minimal risk to compatibility.

COMPATIBILITY WITH VARIOUS STERILISATION METHODS

One of the biggest differences between OmniFlex stoppers and NeoFlex plungers is the preferred method of sterilisation. In general, stoppers are typically steam sterilised by the manufacturer, whereas plungers are supplied to the customer ready to use (in combination with ready-to-fill syringes packaged in tubs). With more filling lines being developed to process ready-to-fill vials, cartridges and PFSs, the demand for ready-to-use stoppers and plungers is growing every year, and with more demand comes more variety in how these components are processed and sterilised by pharmaceutical companies. To meet the various requirements from customers all over the world, NeoFlex

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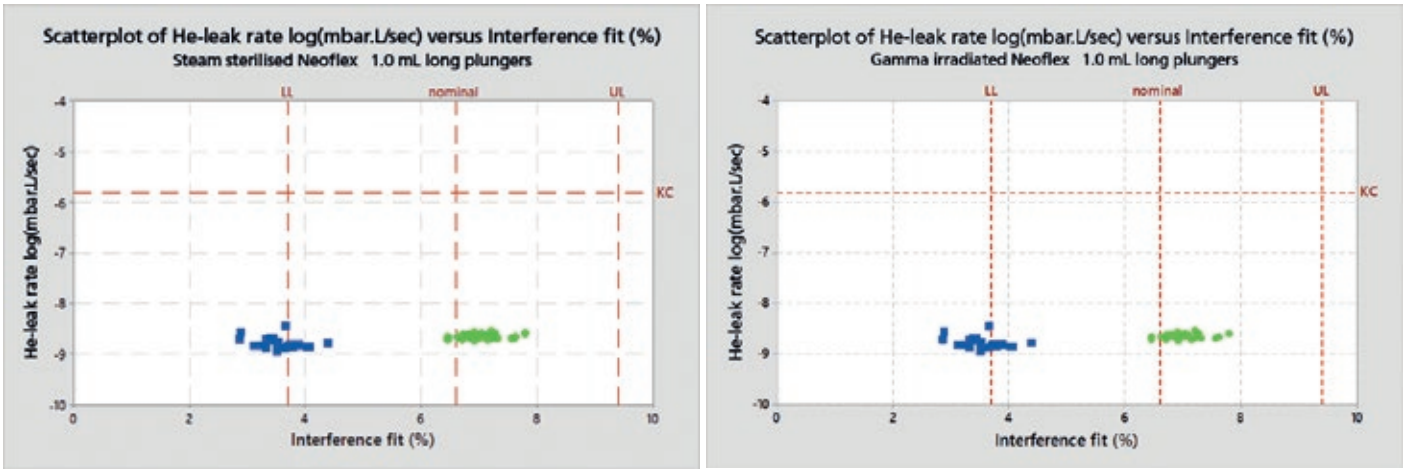

Figure 1: He-leak rates of gamma irradiated 1 mL long NeoFlex plungers with different interference fits. All cases easily meet the Kirsch Criterion (1.6x10−6 mbar.L/sec). Even with the worst-case scenario of a low interference fit, the seal integrity is still maintained.

plungers were designed to be compatible with a variety of sterilisation methods. Studies have been conducted to assess the influence of different sterilisation methods on the chemical and functional properties of Datwyler's fully coated components and the results were positive.

Chemical Properties

To determine the chemical properties of FM457 and NeoFlex, the components were tested according to ISO 8871-1, which encompasses the most stringent requirements of the applicable compendial chapters on rubber closures – namely US Pharmacopeia (USP) General Chapter <381>, and European Pharmacopoeia (EP) Chapter 3.2.9. After irradiation up to 40 kGy and storage times of two years, FM457 and NeoFlex continue to adhere to ISO 8871-1 and thus, also adhere to USP <381> and EP 3.2.9. No significant difference is observed between steam sterilisation and gamma irradiation in the standard chemical testing of NeoFlex, and the same is true for extractables.

Functional Properties

The functional properties of NeoFlex plungers, specifically container closure integrity, gliding properties and plunger movement, have been investigated in worst-case conditions.

Container Closure Integrity

Helium (He) leak testing of the plungers treated with steam sterilisation, as well as plungers irradiated with 25 kGy gamma irradiation, show safe He-leak rates for all NeoFlex designs. This test is conducted with nominal plungers and with plungers that are 0.2 mm smaller than the nominal in order to simulate the worst-case conditions for container closure integrity (simulating the plunger at minimum specification and the barrel at maximum specification). Also, as a result of this study, it can be concluded that even the plunger/barrel with the lowest interference shows excellent He-leak rates regardless of whether they were gamma irradiated or steam sterilised (Figure 1).

Gliding Properties

The break-loose force of NeoFlex plungers slightly increases over time and is higher at room temperature and 40°C, but the impact of gamma irradiation versus steam sterilisation is minimal and still within an acceptable range with regard to usability and end-user acceptance criteria. The data that were created with plungers 0.2 mm larger than the nominal (which should represent the worst-case conditions when the barrel is small and plunger is big), show that no significant difference is detected between steam sterilisation and gamma irradiation for break-loose and gliding forces. The same is true for the gliding force. As a result, no difference is detected between steam sterilisation and gamma irradiation (Figure 2).

Plunger Movement

This test simulates the conditions of an aeroplane using a pressurised cabin corresponding to an altitude of 8,000 ft, non-pressurised. The test is also performed in worst-case conditions where the plunger is 0.2 mm smaller than nominal to simulate the scenario in which the smallest plunger is positioned in the largest barrel. The plunger impact is the same for both steam-sterilised and gamma-irradiated plungers. In both cases, it can be concluded that syringes filled with a head space below 7 mm will show plunger movement that is lower than the distance between the third and the second rib, and likely can count on two ribs to secure the container closure integrity (Figure 3).

A ROBUST DESIGN FOR COLD STORAGE CONDITIONS

During the functionality testing of NeoFlex plungers, testing was done at 5°C, room temperature and 40°C. In the context of covid-19 vaccines, extremely low temperature storage is required, e.g. -20°C and -80°C. From a theoretical perspective, it can be concluded that storage at -80°C may pose a challenge but storage at -20°C is possible.

When temperatures drop, elastomers harden and become less flexible, and when the temperature reaches the glass transition temperature, elastomers lose their rubber-like properties entirely. At extremely low temperatures, i.e. the brittle point, elastomers may crack. Changes in elastomer properties due to low temperatures are typically physical and fully reversible. For halobutyl rubber –

> "One of the main advantages of NeoFlex plungers is that the compression in the barrel is rather high compared with other coated plungers on the market."

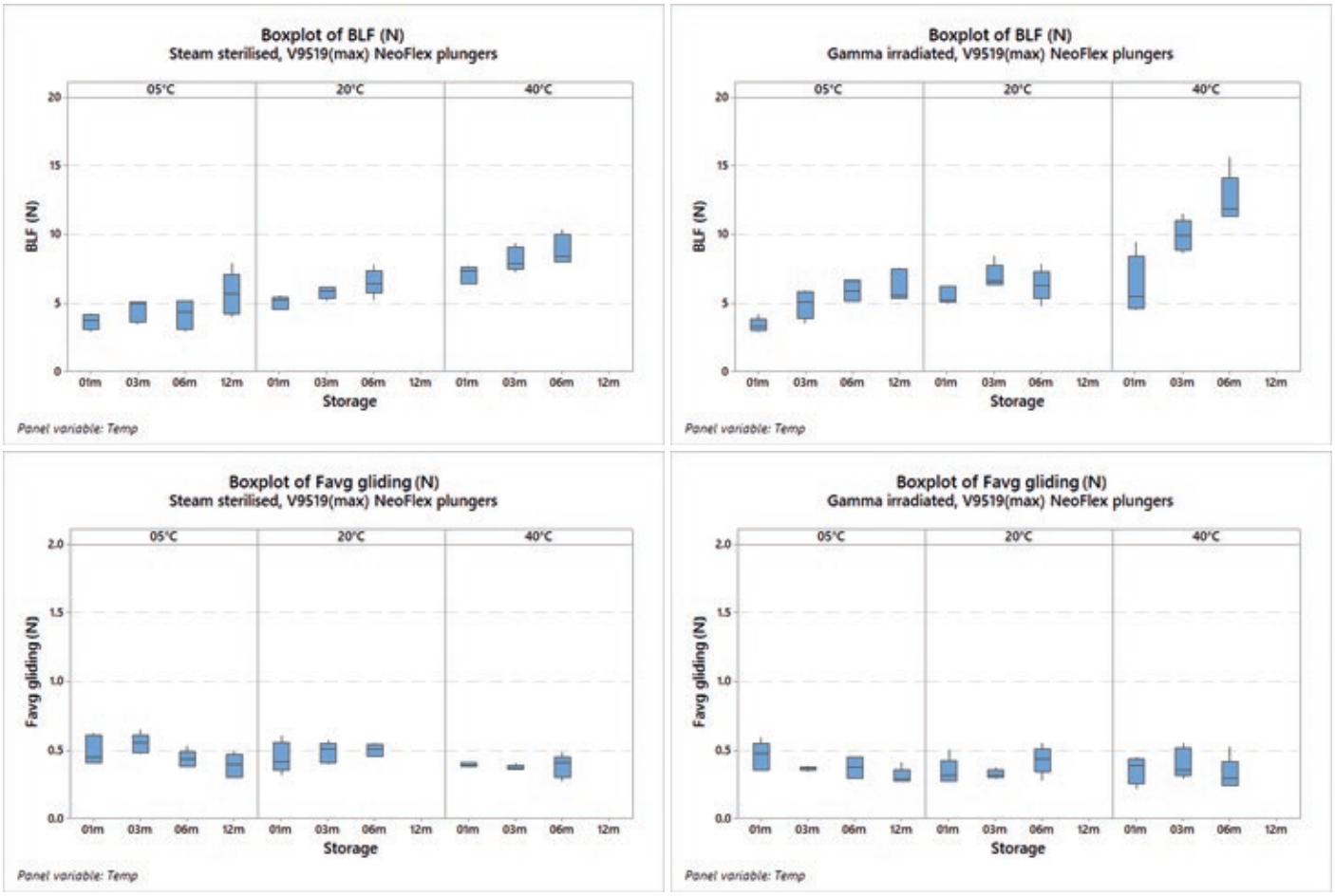

Figure 2: The above graphs show the consistency in break-loose force and gliding forces for both steam and gamma irradiated NeoFlex 1 mL long plungers.

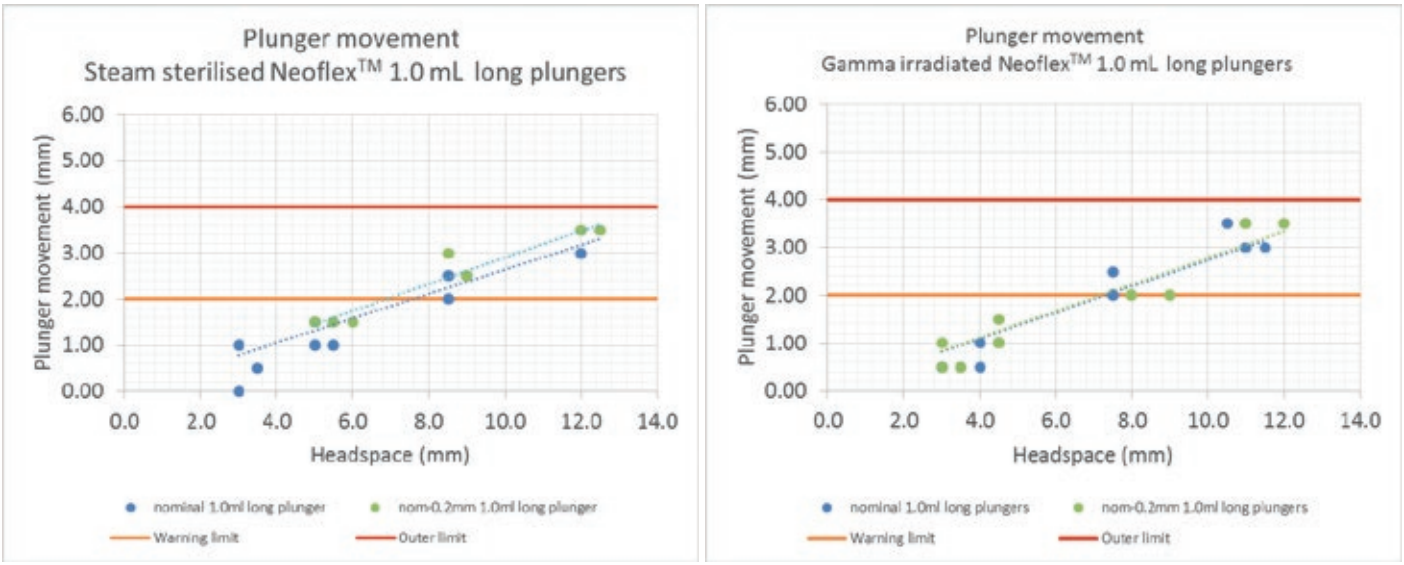

Figure 3: The above graphs show that, for plungers in a highly pressurised setting, plunger movement is minimal and well below the outer limit, regardless of whether the plungers were steam sterilised or gamma irradiated.

the most common type of rubber used for plungers – the glass transition temperature is around -60°C. For styrene-butadiene rubber – the rubber used for needle shields and tip caps, such as Datwyler's FM30 – the glass transition temperature is only around -40°C. Thus, the best-case scenario for sealing at low temperatures can only be guaranteed at a minimum temperature of -40°C for syringe applications.

One of the main advantages of NeoFlex plungers is that the compression in the barrel is rather high compared with other coated plungers on the market. NeoFlex has a nominal compression between 6% and 6.6% while other coated plungers have a nominal compression between 2.8% and 3.8%. In addition, the fluoropolymer coating is thin and flexible, which prevents it affecting the sealing properties (Table 1).

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	1 mL			1–3 mL		
Compression %	min	nominal	max	min	nominal	max
NeoFlex™	3.73	6.62	9.42	3.85	5.98	8.06
Partially coated plunger 1	0.77	3.79	6.72	0.57	2.81	5.00
Partially coated plunger 2	2.27	5.22	8.09	2.23	4.42	6.56

Table 1: Comparison of compression percentages between different coated plungers on the market. NeoFlex has a higher compression than other coated plungers on the market, which should have a positive effect on container closure integrity during storage in extreme cold conditions.

In addition to container closure integrity of the plunger and barrel, other functional aspects of the syringe need to be investigated in these extreme cold conditions before a system can be provided and deemed successful at these low temperatures.

"The processability of a coated plunger helps to determine the success of a packaged drug."

NEOFLEX PLUNGERS COMPATIBLE WITH MULTIPLE PLUNGER POSITIONING TECHNOLOGIES

The processability of a coated plunger helps to determine the success of a packaged drug. In general, it is known that most existing syringe fill-finish lines are equipped with vent tube stoppering for stopper positioning. It is also known that this technology poses challenges for coated plungers. During vent tube placement, the plunger is compressed to a high extent in the vent tube, then a plunger rod pushes it through the vent tube and finally into the syringe where the plunger is deflated and seals the syringe. When the plunger passes through the vent tube, high forces are required and temperature increases. The high forces can be improved by applying a bit of silicone (10–25 µg silicone/cm²) on top of the coating. Figure 4 shows that, during plunger positioning, the temperature increase goes down from 57°C to 38°C and the force required for stoppering goes down from 40 N to 25 N. Of course, this is only a viable solution if the drug is not sensitive to silicone.

Another option for plunger positioning is to use a short insertion tube with vacuum assistance. In this scenario, the vent tube can have a larger diameter, which means less compression of the plunger and less friction. Ultimately, the ideal positioning option for coated plungers is using vacuum placement. With the understanding that each technology has specific requirements that impact the final syringe product, NeoFlex plungers were designed to work with each positioning technology and the successful placement of the plungers has been proven with testing at different machine manufacturers.

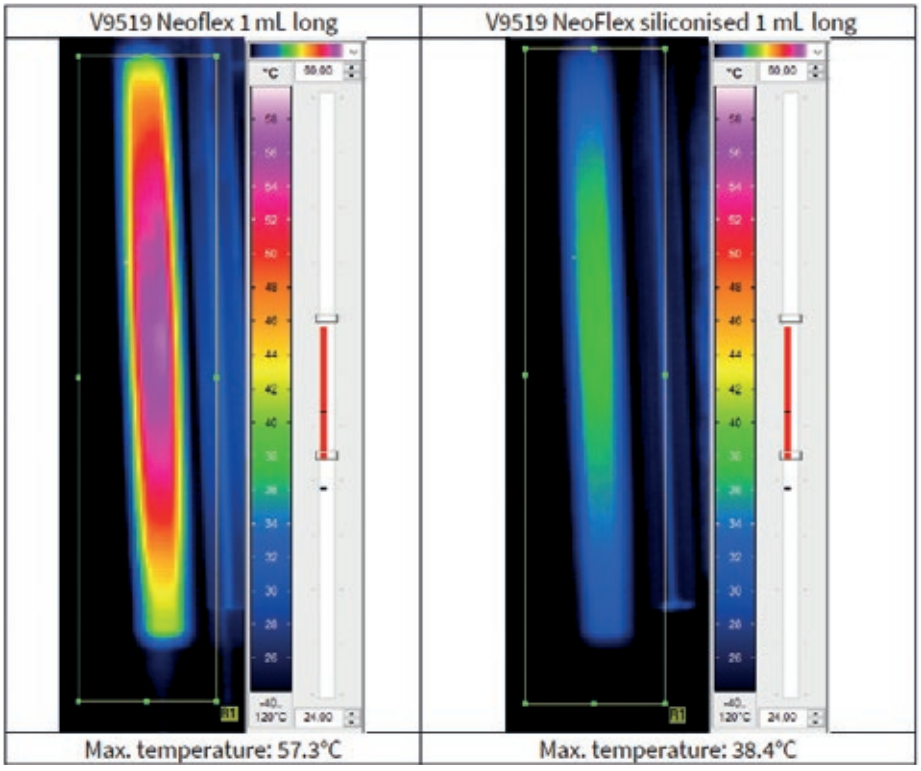

Figure 4: Temperature of vent tube in combination with NeoFlex 1 mL long and NeoFlex siliconised 1 mL long. Data provided by Bausch & Stroebel pharma services.

COMPATIBILITY WITH A VARIETY OF SILICONISED BARREL MATERIALS

While glass is still the most widely used material for syringes, plastic barrels in cyclic olefin copolymer (COC) and cyclo olefin polymer (COP) are also emerging as viable options for syringe manufacturing. With regard to the covid-19 vaccines, glass, COC and COP barrels are all being considered to package certain vaccine products due to worldwide shortages of raw materials.

Guaranteeing proper gliding in a syringe with a traditional halobutyl rubber

"With an accelerated timeline for manufacturing and distributing the various covid-19 vaccines, it is important that pharmaceutical companies have the necessary packaging available to them as the vaccine transitions from vial applications to PFSs."

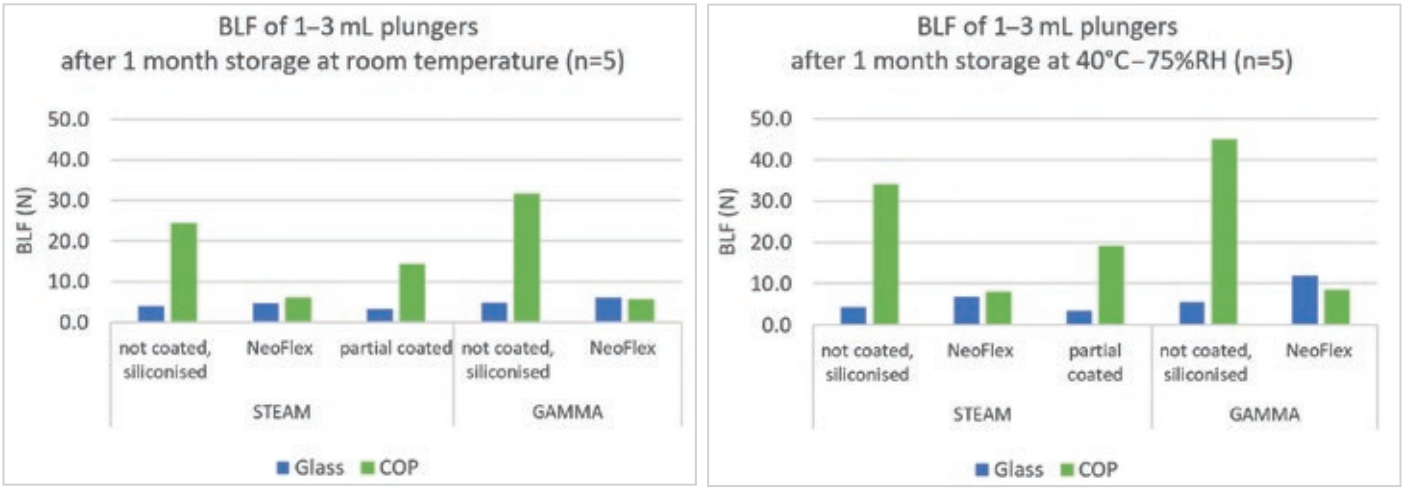

Figure 5: The above graphs show that uncoated and partially coated plungers give much higher break-loose forces then NeoFlex in COP barrels.

plunger requires that the barrel, regardless of composition, is uniformly siliconised. Depending on the sensitivity of the drug product to silicone, standard siliconised barrels, low siliconised barrels and baked-on or plasma-treated siliconised barrels can be used.

For each of these iterations, NeoFlex plungers perform without concern. Due to the 100% coating of the NeoFlex plunger, the halobutyl rubber never comes into contact with COC or COP barrels, causing the break-loose and gliding forces to be identical to the results obtained in glass barrels. This is not the case with partially coated plungers (Figure 5). NeoFlex plungers were also tested in combination with barrels from different suppliers and only small differences were detected.

CONCLUSION

With an accelerated timeline for manufacturing and distributing the various covid-19 vaccines, it is important that pharmaceutical companies have the necessary packaging available to them as the vaccine transitions from vial applications to PFSs. Datwyler's NeoFlex plungers are not only ready to be used for these vaccine products but represent an important piece of the puzzle in building a better vaccine packaging solution for drug manufacturers combatting a global pandemic.

ABOUT THE COMPANY

Datwyler focuses on high-quality, system-critical elastomer components and has leading positions in attractive global markets such as healthcare, mobility, and food and beverage. With its recognised core competencies and technological leadership, the company delivers added value to customers in the markets served. With more than 20 operating companies, sales in over 100 countries and more than 7,000 employees, Datwyler generates annual sales of more than CHF 1,000 million (£809 million). Within the healthcare solutions business area, Datwyler develops, designs and manufactures solutions for injectable packaging and drug delivery systems to help customers create a safer medical environment for the future.

ABOUT THE AUTHOR

Carina Van Eester graduated as an industrial engineer in chemistry and started her career in pharma, where she gained 15 years of experience as a packaging development engineer and project manager. She has been with Datwyler for 12 years, spending seven years as a Technical Key Account Manager, providing technical support to customers, and four years as a Global Qualification and Validation Manager. She moved into the role of Global Platform Leader for Prefilled Syringes and Cartridges in 2018, making sure that the standard portfolio of rubber components used for these applications secures Datwyler's position as a market leader.

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