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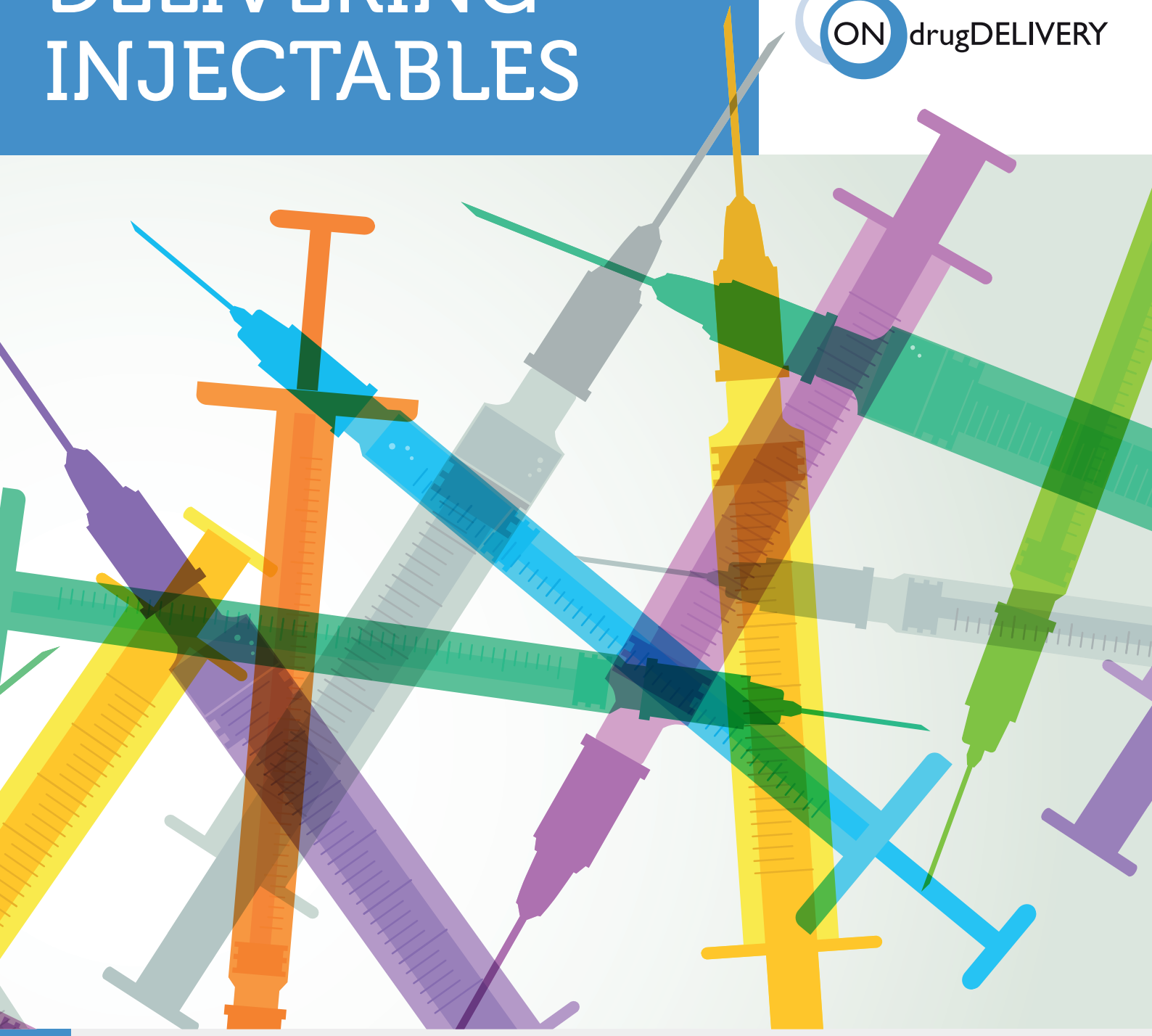

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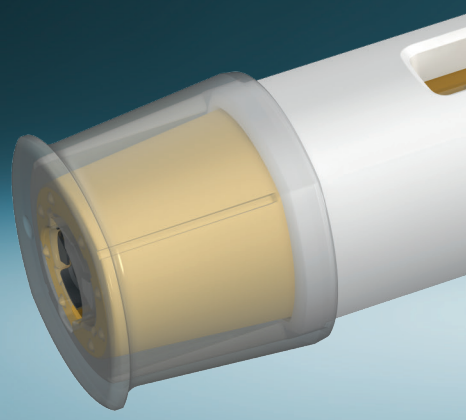

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ONdrugDelivery Issue N° 107, May 28th, 2020

DELIVERING INJECTABLES

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Aug	Industrialising Drug Delivery
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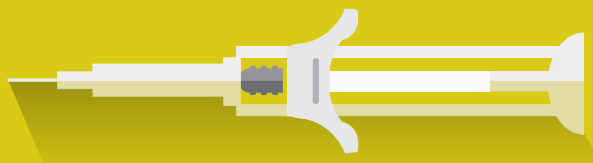

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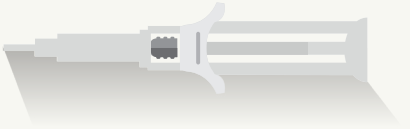

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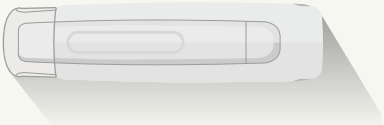

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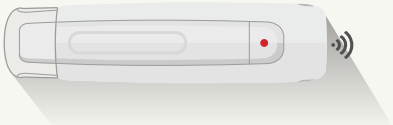

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SHL GROUP

ESTABLISHING DATA-DRIVEN DESIGN AND MANUFACTURING FOR MEDICAL DEVICES

In this article, Frederick Gertz, Manager of Data and Process Innovation at SHL, explores the benefits for medical device design and manufacturing organisations of adapting to the use of big data and analytics.

Drastic changes in the development and manufacturing landscape mean the typical tools established for decades in the manufacturing space – lean processes, total quality management, just in time and enterprise resource planning (ERP) systems – no longer provide the edge or the guarantee of competitive profits that they once did.[1,2] Industry stalwarts will point to a variety of reasons: lower costs, globalisation and increased regulations being the common scapegoats as the medical device industry tries to pinpoint the exact genesis that leads us to where we are now. But everyone agrees the last few decades have seen a drastic change within the community as it shifts to becoming increasingly competitive, cost sensitive and high paced.

"Everyone agrees the last few decades have seen a drastic change within the community as it shifts to becoming increasingly competitive, cost sensitive and high paced."

The introduction of multiple consumer tech players such as Google, Amazon, Samsung and Apple has only served to increase the pressure, pushing established and new players alike to innovate both in product and process. Modern enterprises are now turning to big data and analytics to guide them in producing enterprises that are more agile, efficient and robust. These data-driven enterprises are increasingly becoming the norm in the industry, although adapting your organisation to such a paradigm is full of challenges and opportunities.[3] SHL is currently undergoing its own digital transformation and beginning to use a variety of tools, including machine learning and predictive modelling, to leverage new advantages within our organisation.

Certainly, the advantages of following an organisation-wide, data-driven methodology are well established. Studies show that organisations following these practices can gain 4-6% increases in productivity[4] over their competitors, so it is small wonder that only 30% of the industry would consider themselves data mature.[5] Despite the success of these philosophies at places like Google, relatively few medical device contract development organisations (CDOs) and contract manufacturing organisations (CMOs) have taken the step to commit to a corporate-wide data-driven enterprise.

With much of the medical device industry built on legacy models – and with a much stronger need to include risk mitigation and regulatory oversight into the process – the sector has been slow to adapt to overcome the challenges of becoming an industry of fully data-driven design methodology (DDDM) organisations.

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Figure 1: The challenges of moving to a data-driven design methodology organisation.

UNDERSTANDING THE CHALLENGES

With so much pressure placed on the industry and with such well-established upsides, why has data-driven design and manufacture not become the norm within the space? Even with the wide acceptance that data-driven methodologies will offer many benefits, it should be noted that the transition to a true DDDM organisation is not without its own challenges (Figure 1).

First, the necessary infrastructure and organisational change requirements appear daunting.[6] Pharmaceuticals is a great example, with many companies making investments in the hundreds of millions of dollars, establishing large portfolios in analytics and transforming their IT core to be capable of handling the required data. Smaller organisations that have not yet established mature infrastructure for data analytics frequently question what sources they can use to generate high-quality data,[7] with data availability being one of their largest concerns. Frequently, they overlook opportunities both internally and externally to collect data. Many technical organisations will overlook the wealth of data being generated by their marketing and business units.

As infrastructure such as NoSQL databases becomes more common, the ability to collect and harness the ephemeral data throughout the company becomes more and more achievable. Tools such as natural language processing (NLP)[8] and unsupervised machine learning techniques offer a wealth of opportunity to begin finding value within the data already on hand in virtually any organisation.

> "Tools such as natural language processing and unsupervised machine learning techniques offer a wealth of opportunity to begin finding value within the data already on-hand in virtually any organisation."

One of the largest shortcomings of many manufacturing and design operations is the focus on data internally. External data such as customer feedback data, patient data and external marketing data all provide vital input for all phases of the product lifecycle. Competition analysis, including through the US FDA's adverse events database, can serve as a critical function for benchmarking current product offerings to competitors.

Analysis of possible features available in the space can further support the identification of future needs. For complicated combination products such as autoinjectors, performance may be based on components provided by a variety of contractors, with no clear exchange of manufacturing and performance criteria between them. All this information can, in theory, serve a vital purpose for the technical design and manufacturing team.

Engineers should be made aware of the competitive space and patient/customer feedback on their designs so as to ensure it is incorporated into later updates or subsequent products; manufacturing should be made aware of challenges faced by the design team, as well as from product recalls related to manufacturing issues. This shows how data from later stages in product development – which is not always made available to the technical teams – can be some of the most important data for those teams to gain access to. Empowered with the knowledge of how design and manufacturing decisions impact customers and patients, organisations develop DDDM with direct impact on the market.

Beyond that, many larger organisations, thanks to low-cost Internet of Things (IoT) sensors,[9] industry-wide digital transformations and the very nature of modern work, have produced massive amounts of data during the product lifecycle. Estimates of the growth of worldwide corporate data are currently in the zettabyte range,[10] with companies increasingly turning to large cloud platforms to handle their mass data production.

> "By making data more transparent, designers gain better insight into manufacturing capability and manufacturers gain increasing insight into product function and areas of criticality."

Even with all this corporate information, surveys have found that 44% of employees do not know where to find information they need to perform day-to-day work.[11] This only goes to show that the quality of the data collected, and the tools used to gain insights into that data, are far more important than the sheer amount of data. Other surveys point to a host of issues with data being considered siloed, incomplete or resulting in insights that are not actionable.

Finally, mindset becomes the largest barrier for many organisations, no matter what size. The implementation of data-driven methodologies requires a clear change away from intuition-based decisions and a commitment throughout the organisation to drive decisions based on a company's data, even if that requires going through the necessary processes and experimentation to gather more. Organisations with the desire to become truly data-driven will need to drive the culture through the organisation from the top, using centres of excellence and internal champions of DDDM to ensure that the methodology is instilled throughout the enterprise. With these challenges, many organisations will struggle to see the numerous benefits that await fully DDDM organisations.

INTEGRATING DESIGN AND MANUFACTURING

By making data more transparent, designers gain better insight into manufacturing capability and manufacturers gain increasing

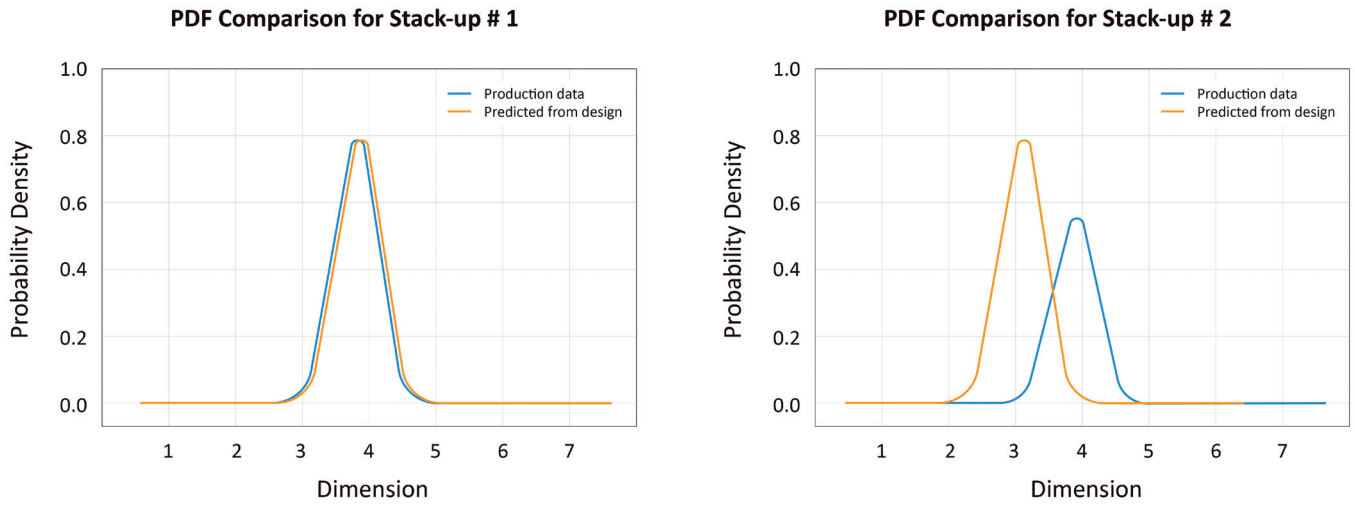

Figure 2: The overlapping probability distribution functions between manufacturing and design data for two different stack-ups.

insight into product function and areas of criticality. Data transparency indicates easier access to historical data for designers, reliable simulations and models for the testing of design decisions, accurate design output and customer feedback.

Thus, organisations with DDDM gain considerable insight and advantage. Product lifecycle management tools[12] have evolved over the last two decades to enterprise-wide solutions that combine the technical data produced in design and simulation with data from manufacturing execution systems (MES), supply chain, ERP and business informatics to allow access across a product's entire lifecycle. These systems alone will not solve the problems but the wide availability of these mature infrastructures, when combined with big data and analytics, form the basis of any modern organisation's DDDM. By creating a single source of truth, stakeholders across the organisation can more easily interact and ultimately collaborate to make products with the highest level of value to everyone.

SHL has a unique opportunity within the medical device manufacturing landscape. As a vertically integrated company that combines design and manufacturing, we are uniquely situated to see the impacts of data-driven decision making across these functions. With a variety of functions – including design, tooling, automation, moulding and assembly as well as management functions such as project management and business development – it is vital that, moving forward, SHL has a clear understanding of how these entities affect the overall structure of a product's lifecycle.

Initiatives are underway to communicate the process capability transparently to our engineers so that, when undergoing design for manufacture (DFM), activities are already aligned between those teams. More importantly, we are supporting the design process by making historical design decisions more transparent at the beginning of projects, effectively helping designers by giving them content and knowledge to work with on day one. This supports designers for future products and manufacturing when conducting investigations or carrying out their standard continuous improvement duties.

Figure 2 shows the historical process improvement when compared with the predicted process used in our engineering tolerance analysis. Furthermore, this data has potential for a variety of uses. The left image shows a stack-up of parts being produced just as the design engineers intended, while the right image shows that there is a shift from the designers' nominal value in production. Using this information, designers can decide whether certain components need adjustment to account for the manufacturing processes, while manufacturers can compare their processes to the designers' ideal. By comparing these production shifts to the original failure mode and effects analysis (FMEA), designers and manufacturers can almost immediately calculate the risk associated with a process shift.

> "Data-driven organisations can better plan logistics, adaptably shift workloads and quickly solve problems."

Models developed from historical data can form the basis of predictive analytics that analyse batches and forecast performance and quality issues. Internal MES systems can be leveraged, along with a robust maintenance programme that uses predetermined key performance indicators to ensure tools are still producing quality parts throughout the lifetime of the programme and react proactively to possible issues, allowing for preventative actions to be taken. All of this can be linked with our logistics data directly to determine impact on both supply teams and business units.

TURNING CHALLENGES INTO OPPORTUNITIES

This level of interactivity shows how the transparency of a single piece of data can yield results across multiple stakeholders. Now, with the impact understood, the organisation is empowered to make decisions that can mitigate and manage the areas where uncertainty still exists. As organisations become more empowered by data, they become more capable of reacting much faster and gaining competitive advantages across several fronts. These capabilities are also in reach for a variety of manufacturers across the industry who all stand to gain from the use of DDDM.

Data-driven design, contrary to popular belief, does not intend to replace the designer or, more frequently, team of designers in this process but to improve the starting point and design process. Does the design meet the requirements? Is the design compliant from a regulatory perspective? Can the design be manufactured with the available manufacturing process capabilities? These questions and more are very much at the

core of the data-driven design methodology and very much the questions that DDDM intends to make more transparent. Using a variety of tools, designers can link their designs directly to the requirements they are fulfilling – clearly demonstrating how their designs match the requirements.

Modern factories are required to be more flexible and agile than ever before. Especially in medical devices, where regulatory burden is high, applying appropriate risk mitigation techniques is paramount. In fact, unexpected losses due to quality concerns within the medical devices industry account for >US$4 billion (£3.2 billion) in lost revenue for the industry.[13] By using big data and modern analytics, manufacturers can gain true understandings of their processes as well as simulating and assessing the risk in making changes. Data-driven organisations can plan logistics better, adaptably shift workloads and quickly solve problems.[14–16] Fully understanding variation within the manufacturing system is now achievable and can lead to much quicker resolution of errors.

Simulations and rapid prototyping of these now linked features allows for quick feedback into the design process to validate whether specifics of the design are accomplishing their goal, at quicker rates and smaller costs than have been used in the past. Hybrid approaches that leverage model-based approaches with data-driven approaches have begun to be used, allowing for leverage of historical big data and simulated data.[17] Digital twin methods[18] fall on the far end of the simulation spectrum and encourage designers to create near-exact virtual replicas of the product, allowing for changes and parametric design space exploitation using a variety of heuristic, statistical and machine learning techniques.[19–22] This sort of transparent data sharing has been used in other industries such as semiconductor manufacturing, with foundries providing process capability information directly to designers to facilitate the simulation and yields of the design.[23]

These insights allow for more adaptable organisations, ready to respond when errors arise in their complex operations. Using increasing amounts of advanced analytics, including advanced AI methods,[24,25] manufacturers are able to model complex processes rapidly and explore change decisions to reach optimal outcomes, frequently by leveraging data that has already been collected. The other added benefits are that this level of insight into process also allows for automated optimisation algorithms to find unexpected cost savings in materials, energy and other logistic areas, sometimes drastically improving operations management.

CONCLUSION

It should be apparent that modern organisations will have to continue to adapt to the use of big data and analytics while continuing to drive change towards an objective DDDM. As SHL undergoes its own digital transformation, the advantages of leveraging different types of data are already beginning to confer advantages to our own process. Organisations that undergo these changes will reap benefits and gain significant strategic advantage while gaining an insight into their processes that can be enjoyed across the entire organisation.

ABOUT THE COMPANY

SHL Group is a world-leading solutions provider in the design, development and manufacturing of advanced drug delivery devices such as autoinjectors, pen injectors and advanced inhaler systems. It offers a full range of in-house core competencies and services in the fields of medtech and patient care. With >4,000 employees worldwide, SHL Group consists of several distinct group companies: SHL Medical designs, develops and manufactures advanced drug delivery devices for leading pharma and biotech companies across the globe; SHL Healthcare develops and manufactures equipment solutions for home, hospital and long-term care use; and SHL Technologies provides contract manufacturing and engineering services for the production of complex medtech products.

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ABOUT THE AUTHOR

Frederick Gertz is the Manager of Data and Process Innovation at SHL. His focus in the company is on facilitating data-driven methods across the organisation and providing unique insights from data using a variety of techniques, including artificial intelligence and deep learning. Prior to SHL, Dr Gertz worked in the medical device start-up space where he focused on bringing novel processes and techniques, including machine learning, into the biotech industry. He holds a PhD in Electrical Engineering from the University of California, Riverside (US) where his research focused on biophysics and spintronics.

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EU MDR DEADLINE DELAY: WHAT DOES IT MEAN FOR THE MEDICAL DEVICE INDUSTRY?

With the compliance deadline for the EU Medical Device Regulation recently delayed by a year due to the novel coronavirus pandemic, Beth Crandall, Managing Director, Global Solutions Delivery Leader at Maetrics, looks at what it means for the medical device industry.

The medical device industry has been working hard for some time to meet the EU's Medical Device Regulation (MDR) compliance deadline – and it has been a challenging journey for many. The recent delay of a full year to the date of application is therefore a welcome development, especially now that businesses are facing new and extraordinary challenges due to the global health crisis. However, it is important to be aware of the changes that have actually been made and also what is not changing, to fully understand the scope of this recent development.

"The delay only applies to the MDR – and the regulatory requirements remain the same for medical device manufacturers, notified bodies, authorised representatives, importers and distributors."

THE DETAIL

The MDR's new date of application – May 26, 2021 – was approved by the European Parliament in an amendment to the original regulation. The vote to delay was approved by an overwhelming margin on April 17, 2020 and the amendment was published in the Official Journal of the European Union on April 23, 2020. The delay only applies to the MDR – and the regulatory requirements remain the same for medical device manufacturers, notified bodies, authorised representatives, importers and distributors. There is no change to the In Vitro Diagnostic Regulation (2017/746).

"The amendment introduces staggered implementation dates for reusable devices which bear the Unique Device Identification carrier on the device itself. This is a clarification welcomed by the industry."

KEY TAKEAWAYS

Firstly, there is no change to the transition dates for CE Mark certificates under the previous EU Medical Device Directive (MDD). CE Mark certificates under the MDD will still expire no later than May 26, 2024 and devices in service or already on the market as of May 26, 2021 may continue to be made available until May 26, 2025. However, Article 120 now clarifies that the transition dates also apply to Class I devices for which an assessment to the EU MDR requirements would require a notified body.

Secondly, the amendment introduces staggered implementation dates for reusable devices which bear the Unique Device Identification (UDI) carrier on the device itself. This is a clarification welcomed by the industry, as the implementation of the UDI requirements impacts regulatory documents and product labelling. The earliest UDI date is now May 26, 2023 for implantable devices and Class III devices. Class IIa and IIb devices are May 26, 2025, and Class I devices are May 26, 2027.

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There are also updates to Article 59 – Derogations from the conformity assessment procedures. This pertains to exceptions to the rules for conformity assessments that allow non-CE marked products deemed of "humanitarian use" to be used for the good of public health. The amendment also now specifically references the corresponding articles in the MDD (Article 11.13) and Active Implantable Medical Device (Article 9.9). By including these references to the directives, the derogations adopted under the directives may apply or be extended using Implementing Acts once the May 26, 2021 date of application is reached. This is important in the context of the efforts to get products quickly and yet safely on the market related to the global pandemic.

IMPLICATIONS FOR DRUG-DEVICE COMBINATION PRODUCTS

Pharmaceutical, biopharm and biologic companies must increasingly stay informed about the implications of EU MDR and EU In Vitro Diagnostic Regulation. EU MDR particularly impacts combination products currently regulated as medicinal products. These are ancillary drugs or biologically active components that function as the principal therapy outcome mechanism of the device. An insulin pump is an example of one such product, where the medical device's intended purpose is the delivery mechanism for the integral drug or biologic component. EU MDR inclusion results from combination devices' increasing design and production complexity, thus ensuring equivalent risk management and safety scrutiny as a standalone device must demonstrate.

Under EU MDR, combination products are categorised as Class III devices by the presence of a medicinal substance. The product Class III classification implications are significant regarding the clinical investigation structure, clinical evaluation report data collection and analysis methods. Standard drug company practice of three production lots for product validation is insufficient to demonstrate device compliance under EU MDR. This extension greatly benefits biopharm companies for whom clinical investigations and data gathering protocols are more aligned with traditional pharmaceutical development practices versus the enhanced clinical requirements of EU MDR, affording them more time to prepare.

> "With this delay comes a significant opportunity for manufacturers to use this time wisely."

Another important consideration for biopharm combination devices as a result of the EU MDR extension is the degree of substantial changes to product design, and addition and replacement of components or medicinal substances that manufacturers should consider during the extension period. Biopharm combination products currently authorised for sale in the EU should assess EU MDR requirements for any proposed or future device changes until the conclusion of the extension to ensure those changes do not impact the device's current market access status. Significant or substantial changes during the extension period could result in regulatory review and approval being required prior to the extension conclusion.

So there are significant hurdles that biopharma, biologic and pharmaceutical companies may not be set up for, as opposed to their medtech company counterparts. Partnering with a regulatory consultancy that can bring relevant industry insight and hands-on experience can be a critical strategic move to hit the new May 2021 deadline.

OPPORTUNITIES FOR MANUFACTURERS

With this delay comes a significant opportunity for manufacturers to use this time wisely. Being ready for quality and regulatory compliance will give companies an edge over their competitors and reduce the risk of products being taken off the market. Many businesses were struggling to meet the deadline fully and will be able to use the additional time to make sure they are completely prepared by, for example, reviewing their clinical evaluations and technical file documentation, assessing post-market surveillance documentation and properly evaluating economic operator relationships and agreements. The clarification in UDI timelines also allows for more robust planning and implementation.

ABOUT THE COMPANY

Founded in 1984, Maetrics is a global life sciences consulting firm focused exclusively on regulatory, quality and compliance solutions for medical device, diagnostic, pharmaceutical and biotechnology companies. With offices throughout Europe and North America, Maetrics can assist with local, regional and global compliance needs.

ABOUT THE AUTHOR

Beth Crandall is a respected leader who brings over 15 years of experience in the life sciences industry, specialising in the regulated medical device market. She also possesses a strong background of leading large quality system programmes and implementing changes to related policies, procedures and systems. Ms Crandall uses organisational change techniques to maximise productivity while achieving business and compliance objectives. She gained a BA from the College of St Thomas (MN, USA) in Business Administration, Human Resource Management.

STEVEN KAUFMAN, STEVANATO GROUP & URI BARUCH, CAMBRIDGE DESIGN PARTNERSHIP

Steven Kaufman is Vice-President, Drug Delivery Systems at Stevanato Group, responsible for managing business development, proposal management and project management as well as strategic initiatives in the group's drug delivery systems business. He has been active in the drug delivery device field for more than 15 years, working with leading multinational biopharmaceutical companies to provide pen injectors, autoinjectors and wearable injection systems, as well as test equipment, assembly equipment and final device assembly services.

Uri Baruch is Head of Drug Delivery at Cambridge Design Partnership (CDP), where he has led a large variety of design projects including an award-winning needle safety device, an emergency autoinjector, a pen injector packaging design for delivery devices, and inhalation products. He is presently heading the collaboration with Stevanato Group on pen injector projects.

In this interview, Mr Kaufman and Mr Baruch discuss the recently announced collaboration between their two companies to accelerate the development of a new variable-dose, cartridge-based pen injector platform for diabetes care based on the Axis-D technology licensed from Haselmeier.

Q Congratulations on the recent announcement on the collaboration for the development of a new diabetes pen injector. Please could you give us a brief rundown of what this agreement is about, its objectives?

SK We are excited about this collaboration. It has a powerful objective to bring together different capabilities and services from Stevanato Group, within our existing collaboration with Haselmeier, and now in particular with CDP, to bring this SG pen – a new pen injector platform based on Haselmeier's variable-dose pen injection technology, Axis-D (Figure 1) – into the diabetes space for the delivery of, for example, insulin/insulin analogue products and GLP-1s.

Haselmeier has over 100 years of tradition and a history in bringing complex pen injectors to market. We talked extensively with them about Axis-D and, in October 2019, we were able to secure a licencing agreement for the technology, covering the diabetes therapeutic area. Haselmeier has done a terrific job. It's a proven technology in that a version is currently on the market today having been launched by a major pharmaceutical company and approved by both the FDA and EMA.

In the crowded diabetes space, we are seeing some pharmaceutical companies struggling to find a device solution that's a good fit. Factors such as intellectual property and freedom to operate are given a lot of attention of course, but pharmaceutical companies are also looking at which companies can provide a more complete solution based on expertise and track-record. So, Axis-D, as the basis of our SG pen, has significant potential.

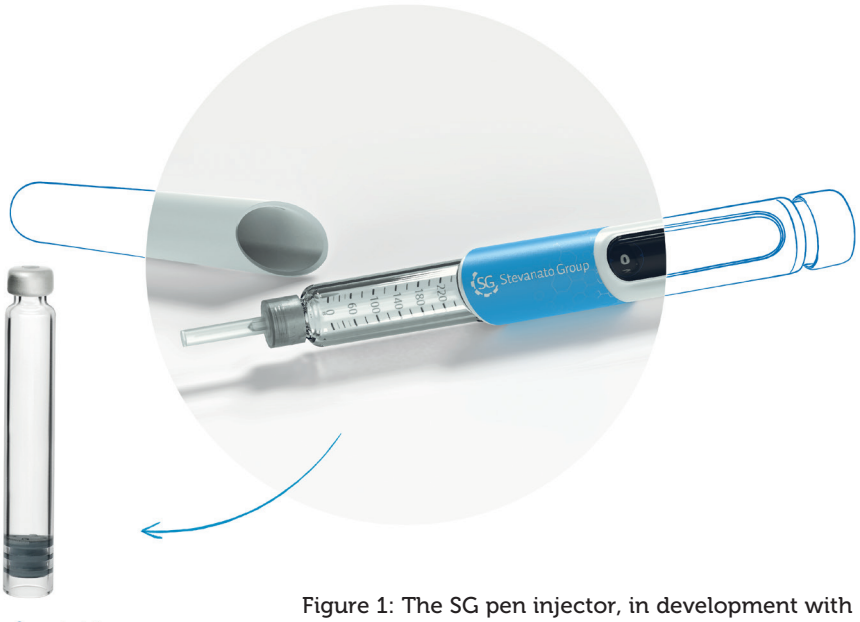

Figure 1: The SG pen injector, in development with CDP, is based on Haselmeier's Axis-D technology and IP and features a high-resistance 3 mL glass cartridge.

"With this unmet need in mind, we realised that we should look to a partner to support in the development of the SG pen based on Axis-D, and that's where CDP came in."

There are terrific companies that make pen injectors in the market today. We hold them with very high regard, both pharmaceutical companies and device companies. But it would appear that in the diabetes area, demand for insulin and GLP-1 products is continuing to grow. It's simple supply and demand – there are too many companies seeking pen injector solutions from a limited number of players in the market.

With this unmet need in mind, we realised that we should look to a partner to support in the development of the SG pen based on Axis-D, and that's where CDP came in. Stevanato Group had already been working with CDP for some time, and we'd had the opportunity to see the quality of service that CDP can provide. On an individual level, Uri and I have known each other for more than a decade. By collaborating with CDP on this SG pen injector project, we will be able to customise and bring our offering to market at a greater speed as well as be more in tune with customer and patient needs.

When I think of Haselmeier and CDP, I see two great companies with the industry pedigree, that legacy, pharma is looking for in its device partners. Combined with Stevanato Group's own 70-year heritage in glass containers, and our complementary skills in manufacturing, laboratory services, and equipment – it's the total package.

UB CDP has extensive experience in the variable-dose injection pen space, we've worked with market leaders, and there is intellectual property relating to injection pens with our name on it. We're aware of how dense this space is.

Likewise, CDP and Stevanato Group have known each other for a long time and have had several previous successful working relationships, which were similar to this current SG pen injector project in many respects. CDP has worked with Haselmeier in the past too. Clearly these two companies have the ability to bring this pen injector to the diabetes market. Where we can help them is with accelerating time to market.

When you're working with a large number of clients as Stevanato Group does, on multiple projects, you spend large amounts of time and resources, recruiting, training, equipping manpower to meet those demands. But inevitably demand fluctuates – sometimes it tails off, sometimes it peaks. Where we see the fit between CDP and Stevanato Group is that we can help in those surges. We can come in and get moving quickly, to meet the demand and help augment the existing staff, the existing design team. It's very much a supporting role.

In terms of the objective of this collaboration, it is to take the existing Axis-D offering, which is actually a very successful launched product in another therapeutic area, and adapt it to the needs of the diabetes market. We want to create a world-class offering in a short timeframe for existing and newly developed therapeutics that are coming onto the market.

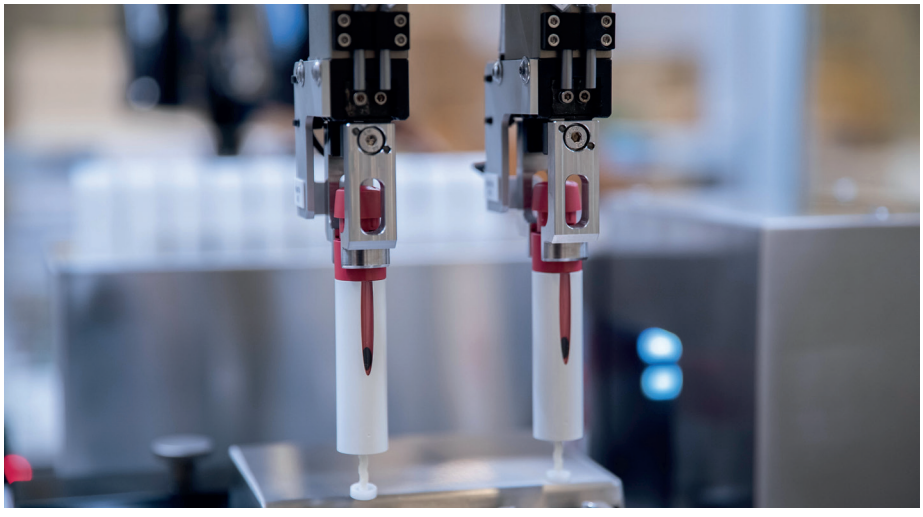

Figure 2: Stevanato Group provides advanced equipment for the final assembly of a pen injector, based on Haselmeier's Axis-D technology.

Q How does this collaboration fit with your companies' wider offerings and strategies in the drug delivery devices space?

SK Over the past few years, Stevanato Group has strategically expanded its drug delivery systems team and broadened its offering to include capabilities and services as an integrated solutions provider. In the past our Ompi brand, specialised in glass primary packaging, was the most familiar to people. Now, under the Stevanato Group brand, we're offering a broader range of solutions to our pharmaceutical partners such as contract manufacturing of devices, which is key, to produce their autoinjectors, pen injectors, wearables and inhalers. It also enables us to collaborate in a more meaningful way on a greater number and variety of programmes.

Primary containers, cartridges and prefilled syringes are at the heart of our offering. We're the largest supplier of cartridges to the pen injector market for insulin in the world today.

We brought SVM on board, a Danish company, which has been producing high-speed and intermediate-speed equipment for sub-assembly and final assembly of pen injectors for decades. And in 2016 we acquired Balda, a contract development and manufacturing organisation (CDMO) with facilities in Germany and the USA, specialising in plastics, with strong expertise in tooling and manufacturing of diagnostic components as well and pharmaceutical and medical devices. Balda too have been involved in the diabetes space with experience supporting the manufacturing of lancing devices and blood glucose meters. Pulling it all together, with our laboratory services, we have a very strong truly integrated offering – providing a multi-dimensional approach.

Thanks to Stevanato Group's integrated approach and capabilities, pharma companies, instead of having to speak to many different suppliers to bring a product to market, need only speak to one or two. The total one-stop-shop approach is not viable for every project, companies can look for a provider only for the primary container, or for the device and primary container.

And if you can provide both of those, with laboratory services, characterisation of drug product, and equipment, then you have a package. Stevanato Group's offering covers a range of competences and capabilities that can be applied according to different project needs and that's the value proposition we are taking to the market for a range of drug delivery systems. The SG pen based on Axis-D, for which Stevanato Group provides advanced assembly equipment (Figure 2) is a key part of that strategy.

One important point I want to make though is that our strategy of offering integrated solutions does not limit us from collaborating with others as well. We don't want people to assume that. While the company is currently investing in integration, Stevanato Group has always built relationships with other players, and we will continue to collaborate and develop key partnerships in the future. As these agreements with CDP and Haselmeier demonstrate.

UB CDP has been involved in many projects where there's a need to align with external suppliers, for example an external assembly equipment manufacturer or an external container closure manufacturer, which is possible of course, it is common, and it is what we do. As Steven said, there is rarely a complete one-stop-shop, but when as much as possible is under one roof as is the case with Stevanato Group's broad integrated offering, with other aspects being brought in by partners talking to each other very, very closely, then you can really present a united business case, the project as a whole is stronger, everything is much easier. With separate companies, you can achieve alignment of course but there is no single business case – they all have their own business cases. This project with Stevanato Group achieves that united business case. It is a collaboration between the two teams and we all bring our insights. Like every type of relationship that we enter into, every contract we sign, we view this as a long-term relationship. We learn from our partners as well, so we can strengthen each other. This is our role with many of our partners. Gone are the days where we would just take a project on, work on it in isolation, and then at some point hand it over complete. We've done this in the past but such projects were always few and far between. And today the model is increasingly collaborative.

At the same time we recognise that our partners, device companies and also pharma companies, naturally want to retain the knowledge, and want to retain control internally. They do not want to feel like we've stepped in to the point where they're losing control of the project. That's an important factor. It must be a supportive collaboration.

Q **Finalising and signing this agreement under the restrictions arising from the novel coronavirus outbreak must have been difficult. Can you talk about that a little, and also perhaps comment on how the pandemic is affecting your companies?**

UB Our overarching concern regarding the pandemic, as a company that does a lot of hands-on work, has been to maintain our staff's safety while still delivering projects. We moved everyone who didn't need to be in the office, home, leaving key people in the office who had to be there. These people could spread out to a much larger extent, taking over all the meeting rooms and offices. A lot of the meeting rooms have been converted to labs. A member of the senior management team goes into the office every day to make sure people are supported, looked after and they're all safe.

In terms of the impact of the pandemic on the current collaboration with Stevanato Group, we were all working on this for a while beforehand and I think some of those initial meetings would have been difficult if we couldn't have travelled and met face-to-face. But actually, perhaps counterintuitively, contract negotiations themselves and negotiating the agreements became easier in a lot of ways in my view as the pandemic unfolded, rather than harder. For example, I found that people were more available for phone calls, they had more time, were more focused, not in as many meetings, and there were fewer distractions working from home. So of course the pandemic did have an impact but it was not all negative by any means.

We've seen a lot more activity, definitely, since coronavirus hit. Again, probably counterintuitive to what many would think, but remember we work in healthcare, and so activity has increased across pharma, diagnostics, and medical technology. There are more resources and more capital being made available to fight the outbreak. And we need to make sure this doesn't happen again too, so there's investment in preparedness for possible future pandemics. CDP is currently working on a number of projects related to the pandemic including a major project to expand COVID-19 testing, as well as supporting the NHS Visors project to manufacture emergency personal protective equipment (PPE). Healthcare in general is much more of a focus for governments, for society, for everyone, and we are seeing an increase everywhere, not just with projects that are directly related to the virus.

SK Truly we are living in unusual times. Everyone has been impacted by COVID-19 on some level but in our collaboration with CDP, and working with Haselmeier, we found that there was minimal impact from having to finalise the negotiation and sign the agreement under these circumstances. I think probably the simple reason for this is, both as companies and individuals, we already knew each other well and had a history of successful collaboration.

Our CTO, Paolo Patri, who led the programme with his R&D team, has highlighted in recent presentations how Stevanato Group continues to grow its R&D organisation internally with ongoing recruitment and several key hires this year to better meet the needs of our clients that want to work with us for their devices, or for one of ours. Working with a range of consultants, such as CDP, allows us to conduct more projects, offer a range of expertise and expand the bandwidth of our R&D resources.

There was of course due diligence, working with our facility in Germany as well as our facilities in Italy and Denmark. If anything, as Uri has said, not having the extensive travel allowed everyone to be

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laser-focused in reviewing agreements and getting them signed. The fact of the matter is that we had potential clients already in active talks with us for quite a while starting from when we were doing our market evaluations and market sounding to understand client needs related to pen injectors. We knew that timing was a key element to these discussions, as was having the right resources.

Now, just as important is how are we working with CDP and going forward with the lockdown restrictions still in place. We've had a strong kick-off meeting, we've had great alignment, and a number of the key engineers and other staff have been put in place on our side and theirs and are already working well with our executive leadership. We have a steering committee tasked with making sure that not only the development programme goes well but also that we're addressing immediately some of the needs of the customers we think are going to sign up or have signed up for the SG pen injector.

Turning to the pandemic and its impact on our organisation, Stevanato Group has 14 facilities throughout the world and we're one of the largest suppliers of primary containers to the global pharmaceutical market, meaning that we have a strong connection to any vaccines or any drug product that are going to be used to potentially fight the virus.

I've only been in the company for about a year and a half, and I'm prouder than ever to work with this team in this organisation. In the early days when we first saw there was something happening, Stevanato Group had the foresight to set up two teams, one led by HSE, responsible to ensure the health and safety of our staff, while guaranteeing the business continuity. The second, an *ad hoc* task-force composed of the commercial, supply chain, technical and quality support teams responsible for proactively responding to the needs of our pharma clients, and continuously committed to quickly and effectively secure products, technologies and services for use in potential vaccine development and treatment. The company has made that one of our highest priorities, with daily meetings.

Within the device team, drug delivery systems, we have quite a few partner and client companies who have accelerated some of their requests, some of their programmes or devices. There has been no pullback since the outbreak, quite the opposite.

Society in general is prioritising healthcare more, and people are now seeing the real value of being able to take medication at home. Drug delivery systems are what make self-administration at home possible. How do you achieve it? What technology are you using? Are the instructions for use clear? Can the patient see the viewing window well? Can someone with limited dexterity use this? These considerations are always front and centre within the world of drug delivery device development. And whereas these things were previously not priorities for a lot of people, now they've become more important questions because so many patients are isolated in their homes less able to go and visit their doctor. More stakeholders are paying closer attention to these aspects.

Q Returning to the details of the agreement, why was Haselmeier's Axis-D chosen as the most suitable technology for this collaboration? And also, can you provide some detail on the terms of the licence agreement for Axis-D?

SK Stevanato Group has explored the combination product space extensively; in particular, drug delivery systems in four categories: pen injectors, autoinjectors, wearables and inhalers. On inhalers we're working with Iconovo with their capsule-based inhaler system. For wearables we have a cartridge-based wearable pod device, through the ownership of a company called Medirio. In autoinjectors we've announced collaborations with companies like Duoject Medical Systems for an emergency use autoinjector, and we will make further announcements on autoinjectors in the future.

For pen injectors there were several strategies we could have adopted. One example was to acquire the technology through a design house who would develop intellectual property workarounds and so on. There is a number of other possible approaches. But the most straightforward approach was to find a company with a proven track-record that has several pen injectors on the market and that was willing to collaborate. That was Haselmeier with its Axis-D technology, which has already been launched on the market with a very large pharma company for a major therapeutic area.

One of the key reasons Axis-D was a good fit relates to intellectual property and the designers of the technology. We wanted to utilise a pen injector technology where the core IP was well established, covered by a number of patents, and already on the market. We had the opportunity to speak to the original designers of the technology and that meant a lot. The passion they had for the device and the confidence they had on how it could help more patients. More broadly, Haselmeier as a company ticked all the boxes with its 100 years of history, strong family-owned business, great board leadership, excellent sales and marketing, and a portfolio of other device platforms. Our collaboration with Haselmeier allows both companies to benefit and, crucially, it allows Stevanato Group to provide an integrated solution in the pen injector space, a key part of its overall ability to provide integrated solutions for combination products.

Q Thinking forward to the point where the device is developed and ready, what is your estimate on the timeline for that, and what is your strategy regards the resulting device's incorporation into pharma products?

SK We have been working behind the scenes for well over a year, engaging with some very well-known biopharmaceutical companies who've approached us. We're in active talks with those companies about providing solutions in the diabetes space. The teams are already set up, people are working daily on this, speaking to those pharma companies and finding out exactly what their requirements are to meet their needs.

In some cases we are working towards aggressive timelines, in others we see companies looking to have a pen injector that can be used as a platform for drugs beyond diabetes. If you know the market, you know the timelines regarding generic GLP-1 agonists and insulins/analogues, then you have a pretty good indication of what we're working towards – there is absolutely time pressure but, with CDP working with our internal R&D team and with the support of our partner Haselmeier, we believe we can meet client needs.

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UB The Axis-D platform has been launched with a product already, which is a huge advantage, but every new application, and every new client, requires some customisation and modification. It is not ever as easy as just plug and play, never. I think all the players in the market know that, they understand that there is more work to be done. The timelines Stevanato Group is going for are challenging and that's exciting! We're really looking forward to delivering this. Both companies welcome the opportunity to show the capability to move very, very quickly after committing to a goal. We're glad for the opportunity to do this together and to show that it's possible.

Q Finally, as always, this is ultimately about patients. Can you explain how this collaboration and the resulting delivery device will benefit patients?

SK Our responsibility to our clients is always a priority, but even more important than that is the responsibility we have to patients – the people carrying these products with them in their briefcases, their purses and their backpacks. These are people living with different challenges and they need reliable products that help them get through their lives, especially now during the COVID-19 pandemic.

However, the fact is, a lot of people still don't know enough about these devices. We know because it's our industry and we've been lucky enough to be part of it for many years, but patient populations need better education, more videos, clearer IFUs, training devices, greater support from marketing, not about selling the device but about educating people. We need more white papers that talk about how patients can benefit from these devices and what learnings different companies have had with the range of pen injectors on the market today.

Having worked with some of the biggest biopharma companies in the world and having had the chance to work in three great companies now during my career, I am really pleased by the direction we are taking at Stevanato Group and what it means for patients. I see pharma now engaging device companies or pharma solution providers as true partners, as collaborators, because they see the benefit that drug delivery devices can bring to patients.

On an industry level, the key to successfully delivering products to patients when they need them is being open to collaborations and partnerships. This is exactly what we're doing here.

UB CDP is honoured to have this opportunity to work on a platform that can touch so many patients' lives. With some of the potential therapies in the future that this will address, beyond insulin and GLP-1 agonists, it has huge potential. So there is need in the market both in the nearer term with insulins/insulin analogues and GLP-1 agonists, and beyond in the longer term, working with biopharma companies' generics. There is need in the market for new devices, for new offerings like this SG pen that will allow access for a larger patient population to improved therapies, helping them manage their disease.

ABOUT THE COMPANIES

Established in 1949, **Stevanato Group** is the world's largest, privately owned designer and producer of glass primary packaging for the pharmaceutical industry. From its outset, Stevanato has developed its own glass converting technology to ensure the highest standards of quality. The group comprises a wide set of capabilities dedicated to serving the biopharmaceutical and diagnostic industries: from glass containers with its historical brand Ompi, to high-precision plastic diagnostic and medical components, to contract manufacturing for drug delivery devices, to vision inspection systems, assembly, and packaging equipment. Stevanato also provides analytical and testing services to study container closure integrity and integration into drug delivery devices, streamlining the drug development process. Thanks to its unique approach as a one-stop-shop, Stevanato Group can offer an unprecedented set of solutions to biopharma companies for a faster time to market and a reduced total cost of ownership.

Cambridge Design Partnership is an employee-owned technology and product design partner, located in Cambridge (UK) and Raleigh, North Carolina (US). CDP provides an integrated and holistic product development capability through a highly qualified team, well equipped development labs and ISO 13485/9001 approved methods. This encompasses research and strategy, design, technology and digital innovation, product development and regulatory and manufacturing support. CDP experts are able to take combination products through a full design cycle and submission, enabling customers to launch products that are user-centric and commercially effective.

Stevanato Group

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SENSOR ADVANCEMENTS IN DRUG DELIVERY IMPROVE COMPLIANCE

In this article, Salvatore Forte, Innovation Engineer at Flex, discusses various advancements in sensors that are transforming drug delivery systems, making complex devices more automated, easier to use, and improving patient compliance as a result.

Technology advancements in sensors have helped drug delivery systems evolve from manual but simple to automatic and increasingly complex, while becoming even easier to use. This is because sensors shoulder the variables, instead of forcing the user to do so. Sensors can provide both quantitative and qualitative data (e.g. amount of contact pressure and orientation in space) as well as integrate input from multiple transducers (e.g. contact, temperature and humidity). In helping to automate injections, they facilitate compliance, proper usage and safety while requiring very little from the patient.

> "Sensors can truly become a major tool to solve the challenges presented by novel therapies and enable the development of a new class of drug delivery devices."

Original equipment manufacturers operating in this field have been challenged to create smaller, smarter, safer and more integrated drug delivery devices that can ease the therapeutic journey of patients – and therefore achieve a better acceptance rate in the marketplace. The evolution in sensors over the last few decades and, more specifically, in silicon manufacturing processes, has played a major role in such outcomes.

Today, sensors have achieved an outstanding level of features integration by embedding multiple micromachined transducers into miniature footprints along with signal conditioning, a local computational core, digital interfaces and

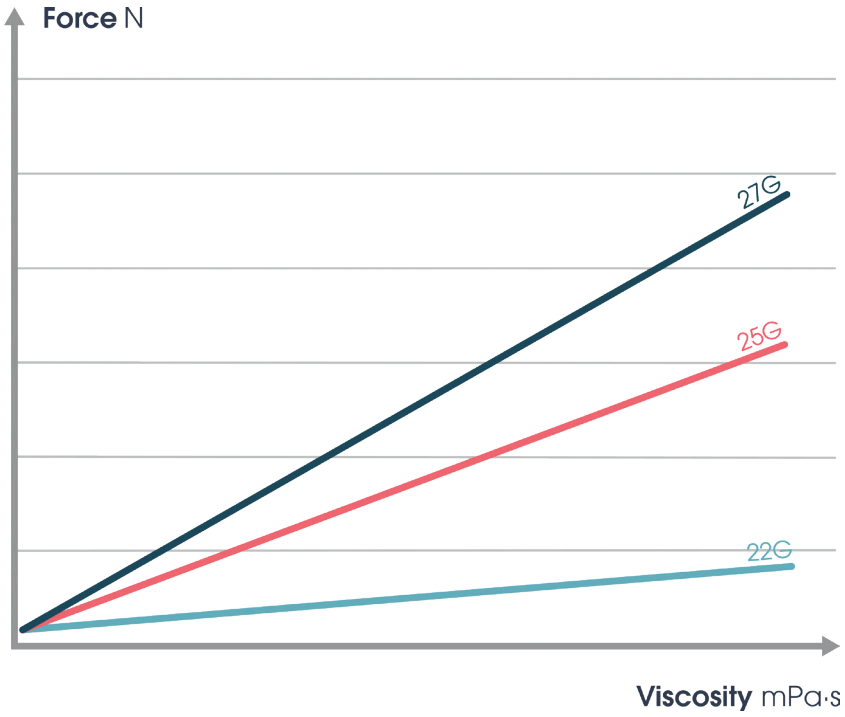

Figure 1: Variation of injection force as function of the drug viscosity, for different needle gauges (measure of needle thickness, and defined by its inner diameter: the higher the G, the thinner the needle). At the same drug viscosity, the force to dispense is proportional to the G value.

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memory for storing factory-calibration parameters. In addition, sensors came to the rescue with the push towards longer-lasting, battery-powered devices because they could reduce power consumption – the availability of enhanced sleep modes with wake-up capabilities can extend battery life by keeping the sensor in a very low consumption state for most of the time.

DEALING WITH HIGH VISCOSITY AND COLD STORAGE

So how can medical device makers fully leverage the continuous progress in sensor technology to design more patient-centric products – including drug delivery devices that foster compliance and adherence to the prescribed treatment, as well as being easy to use?

Sensors, and their underlying processing architecture, can truly become a major tool to solve the challenges presented by novel therapies and enable the development of a new class of drug delivery devices. In recent years, pharma companies have invested in the development of novel biologic and biosimilar drugs for the treatment of different health conditions, including chronic and autoimmune system diseases. Most biologics are administered through injection, so pharma companies are presenting the drug delivery devices industry with a growing demand for autonomous drug delivery systems that address the challenges of biologic formulations, with the ultimate objective to increase the therapeutic value of the drug.

Compared with more traditional drugs, the administration of new biologic formulas through injection comes with additional complexity due to their high viscosity. They demand higher pressure and force being applied to dispense the medication at a proper delivery rate (Figure 1), and they usually cause more patient discomfort. Moreover, biologics often require cold chain storage to maintain their therapeutic efficacy, and this magnifies the burden since the viscosity tends to increase exponentially as the temperature is reduced (Figure 2). It is therefore imperative that injector systems are designed with appropriate countermeasures to tackle their administration.

One can use sensors to monitor relevant parameters, such as injection force and drug temperature, and design novel drug delivery systems to accommodate the increased complexity and variability of new biologics with differentiated injection profiles. The injection system may implement smart features to dynamically optimise settings, depending on the fluid properties of the drug based upon actionable insight provided by those sensors. This could ultimately become the differentiating factor that provides a positive patient experience for effective at-home self-administration and supports the success of new biologics on the market.

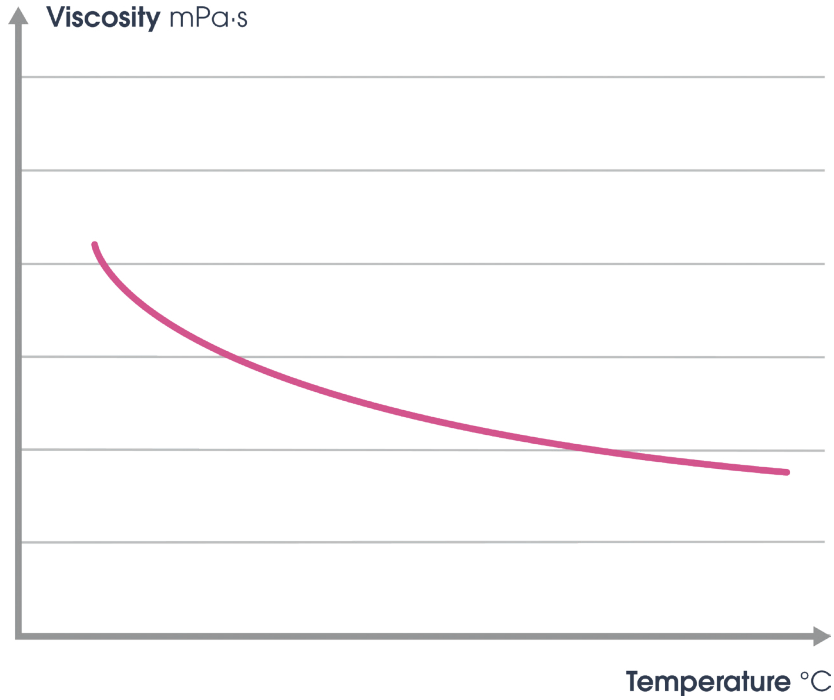

Figure 2: Variation of drug viscosity with temperature.

MULTIPLE SENSORS CONTROL INJECTION PROFILE

Let's consider the case of an autoinjector that, in this age of self-administered therapy, has become a well-adopted drug delivery device. The autoinjector is an electromechanical device that comes with a reusable drive unit and a disposable cassette, which represent the plastic housing for the cartridge that holds the drug. The reusable unit is equipped with a printed circuit board (PCB) that drives a DC motor to actuate and put in motion the plunger rod, which is the element that engages with the plunger within the container to push the medication out of the needle and ultimately under the subject's skin.

Conventionally, a closed-loop system allows precise control of the plunger position and injection speed. The system dynamically adjusts the power delivered to the motor, based upon active feedback continuously provided by sensors, such as an optical or hall-effect rotary encoder, to match with a target speed profile and ensure accurate and predictable delivery rate with a fixed injection time.

To accommodate for drug and force requirement variability, multiple sensor technologies could be employed at the same time. A first example might be the integration of an ultra-thin force sensor on the top surface of the plunger rod to measure the relative change in the force experienced while engaging the plunger in the attempt to dispense a higher-viscosity drug (Figure 3). The system controller can then be configured to receive output signals from the force sensor and compare these values with pre-set thresholds to trigger the appropriate action. One action might be to increase the voltage supplied to the motor; another to stop operation if the remaining battery capacity can't guarantee the optimum delivery injection.

> "As autoinjectors become increasingly automated, the ability for sensors to check the temperature of the drug is a compelling feature to make sure the device is operated as intended."

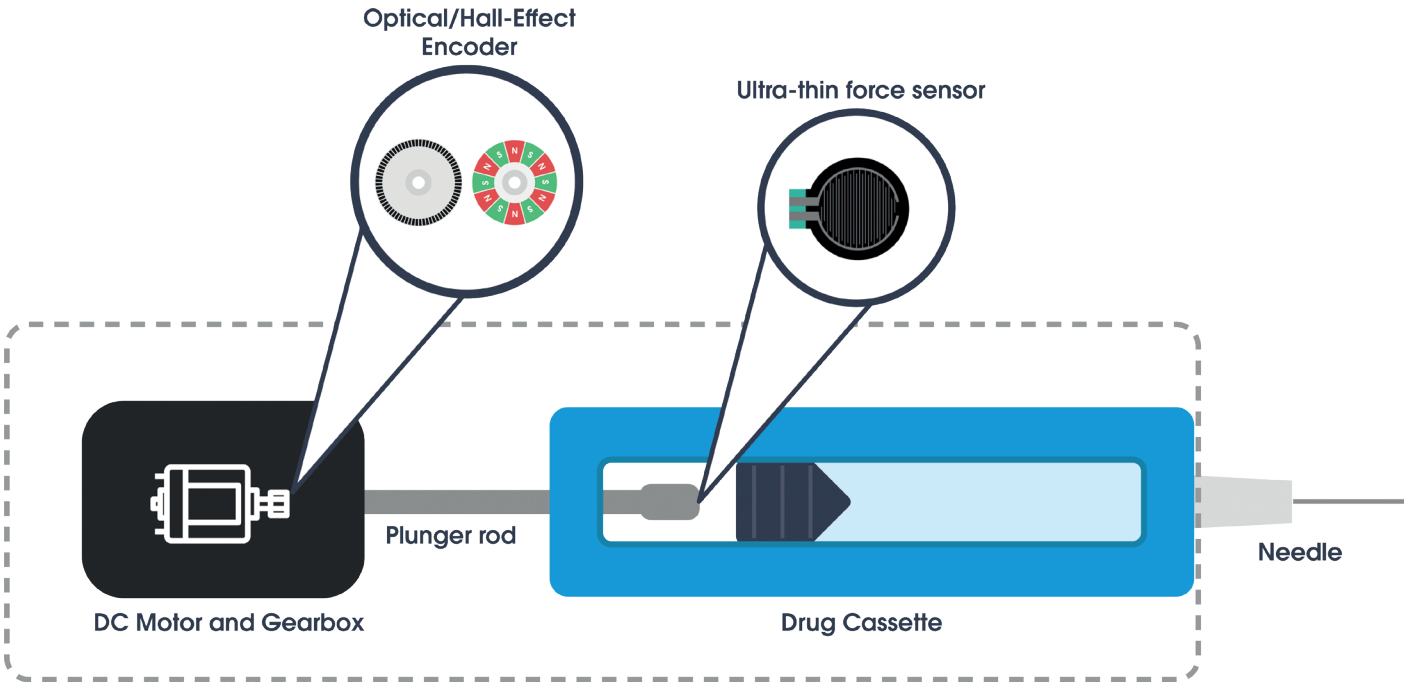

Figure 3: Autoinjector system design with rotary encoder and force sensor.

Embedding the ability to capture small changes to the actuation force on such tiny areas requires minimal electronics overhead to interface with the sensor – but greatly enhances the system's reliability, since the autoinjector can now leverage interoperable control loop systems, each individually driven by feedback provided by dedicated sensors (Figure 4).

TEMPERATURE SENSING IN AUTOINJECTORS

Temperature monitoring of the drug also becomes crucial when designing autoinjectors for biologic formulations. Traditionally, the patient had to remember to let the drug adjust to room temperature prior to injecting. While this may seem reasonable, it does not prevent the patient injecting when the drug is still cold, which may be painful.

As autoinjectors become increasingly automated, the ability for sensors to check the temperature of the drug is a compelling feature to make sure the device is operated as intended – removing that burden from the user. The system could leverage temperature measurements either to block the injection from starting if the temperature is not in the operating range or adjust the plunger speed to increase the dispense duration to compensate for cold drug temperature, which would result in higher viscosity.

Pre-warming the drug when the container is placed inside the injection system is another option by pairing the temperature sensor with a miniature heater. Based on the temperature sensed, the controller unit powers up a polymer-based flexible heater, which can sit conformally within the same cassette compartment of the unit. The heater can warm up the medication to make it reach the target temperature faster, possibly within minutes.

Polymer-based heaters can reliably operate with low voltages and no additional electronics are required to control the heating, other than supplying the heater with the appropriate voltage level. The caveats are that they may draw

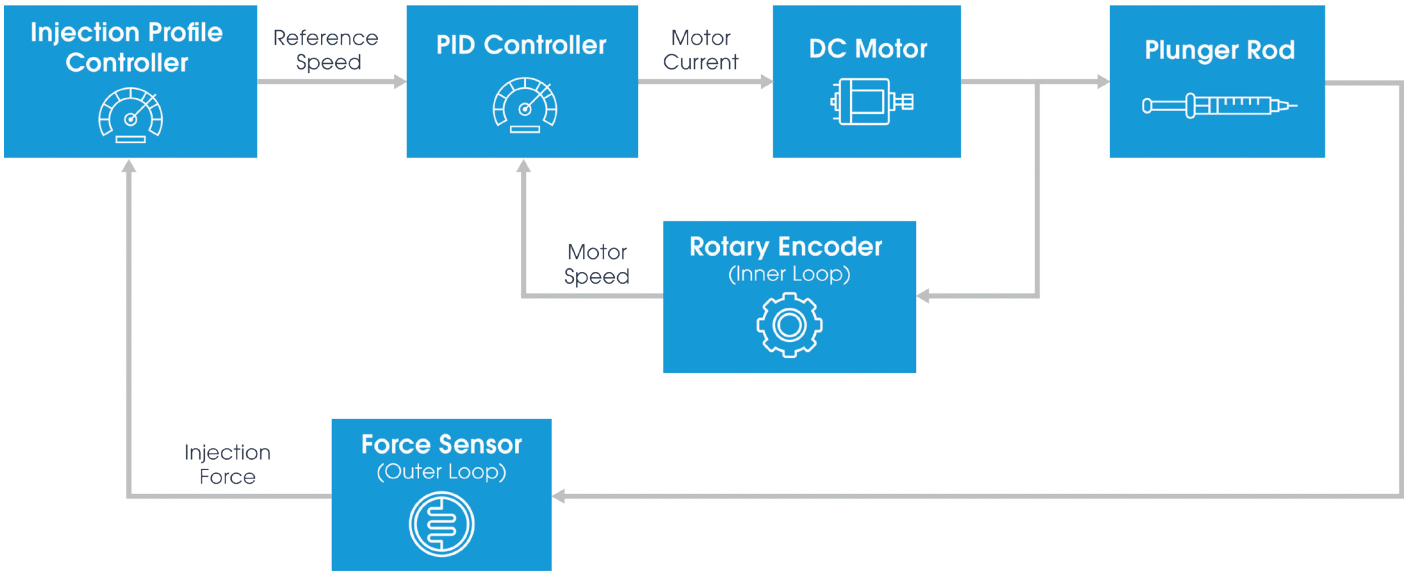

Figure 4: Block diagram of the closed double-loop feedback system used to control the speed of the DC motor that drives the plunger rod.

relatively high current and, most importantly, a pre-conditioning strategy would be required to ensure uniform temperature distribution and a controlled warm-up cycle to preserve drug stability and efficacy.

MEASURING TEMPERATURE WITH AN INFRARED SENSOR

Sensing drug temperature once the cassette is in place inside the device is challenging, given space and contact considerations. One solution could be to integrate an infrared (IR) temperature sensor that does not require physical contact with the drug container to perform measurement. High-precision IR thermal sensors are traditionally delivered in bulky metal TO-can (transistor outline can) packages, so they are not configured to support integration into tightly spaced injector devices. Also, a good understanding of the sensor field of view (FOV) is crucial when designing applications because a FOV that is too large will be affected by other elements and return an inaccurate reading.

Small IR thermal sensors with narrow FOV and excellent thermal stability, even in thermally challenging conditions, have been recently deployed to fulfill the demands of this forthcoming class of medical device (Figure 5). This is essential expertise in this application. The latest generation of IR sensor integrated circuit (IC) can draw as little as hundreds of microwatts (µW) of power, even while executing measurements continuously, with a sensor that remains active without entering any sleep-mode states. That represents a considerable achievement for enabling power-sensitive implementation in battery-powered autoinjectors.

NFC SMART TEMPERATURE SENSING

As an alternative to IR sensors, a passive near-field communication (NFC) sensor tag may also be employed for monitoring the drug's temperature. The smart tag provides a complete temperature sensor solution, along with an NFC interface that can be conveniently manufactured into ultra-thin labels. Thanks to its small size and backing adhesive, the tag can be easily installed onto the exterior of the disposable cartridge directly after fill finishing.

The electronics board attached to the reusable unit is equipped with an NFC reader IC, paired with a coil antenna for

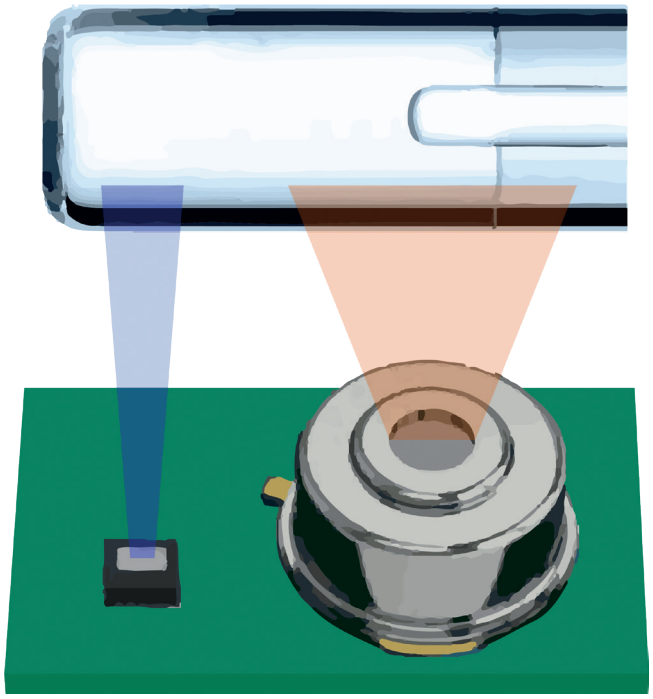

Figure 5: Infrared temperature sensor in both SMD and TO-can packages. Narrow FOV and optimum distance from the cartridge must be selected for accurate sensing.

communicating temperature data and other relevant information as factory programmed into the tag's IC internal memory (e.g. type of drug, volume, expiration date, etc.) through the contactless NFC interface. Glass drug containers add thermal mass, so any embedded firmware must be properly calibrated to deliver an accurate temperature.

The NFC sensor tag itself does not have batteries and is powered entirely by the energy harvested from the reader's RF field. Thus, smart sensor tags are specifically designed to accommodate for tight-spaced application needs, and NFC-enabled autoinjectors can ultimately assess the drug's temperature compliance conveniently and cost effectively.

ACCURATE BATTERY GAUGING IN NOVEL AUTOINJECTORS

Sensors are just one part of a much broader ecosystem within drug delivery devices, which also includes motors, PCB assemblies with processor and power management control, precision plastics with tight mechanical assembly constraints, and battery. For the latter, an extensive system-level characterisation based on knowledge of load profiles should be carried out to understand energy requirements and select the appropriate battery to use within the final device.

Depending on drug viscosity and temperature, the system may require more energy to exert a force on the plunger rod to dispense the medication with a defined delivery rate, which may end up draining the battery faster. Bigger batteries to accommodate for larger injection forces are undesirable since they will result in a bigger, heavier autoinjector design. Nonetheless, automated control of injection profiles to accommodate higher force requirements is still highly desirable to inject medication with higher and variable fluid viscosities.

In autoinjectors operated by lithium-ion batteries, it is important to have an advanced battery fuel gauge IC that can accurately and continuously determine the battery state-of-charge (SOC). Fuel gauge ICs can deliver best SOC accuracy across all device operating conditions by combining

"Integrating multiple sensors into novel autoinjectors that are specifically designed for administration of biologics can vastly improve user compliance."

the advantages of Coulomb counting with more traditional voltage-based gauging. They measure battery voltage, battery current (through a dedicated sense resistor) and battery temperature, typically with an on-chip temperature sensor.

Latest fuel gauge ICs operate off a very low quiescent current (few µA) while still delivering SOC updates regularly. Energy requirements can ramp up quickly in a novel autoinjector, while a poorly designed gauge can result in a premature and abrupt system crash – potentially harming the user. Thus, accurate knowledge of SOCs under different conditions is critical for reliable and safe operations. Based on the calculated battery SOC, and knowing the discharge characteristic for a known force profile that must be applied, fuel gauge ICs can determine if the remaining battery capacity is sufficient to dispense the full dose without risk of motor stall, and can warn the system accordingly to prevent the injection even starting.

AUDIO FEEDBACK WITH MEMS SPEAKERS

As previously mentioned, an increase in dispense duration to compensate for higher viscosity is also an option, which may result in more comfort for the patient while injecting. However, longer injections can cause adherence issues, as the user may erroneously assume that the full dose has been delivered and detach the needle from the skin prematurely. To tackle adherence issues, design engineers can enrich the system with additional features, such as audible feedback achieved via tiny micromachined (microelectromechanical) speakers, which can assist the user throughout the administration process, and ultimately notify the user when the injection has been completed.

SENSORS IMPROVE USER EXPERIENCE & DEVICE PERFORMANCE

Integrating multiple sensors into novel autoinjectors that are specifically designed for administration of biologics can vastly improve user compliance. Sensors are key to successful implementation of autonomous drug delivery systems that will accommodate drugs with a range of viscosities. Rotary encoder and force sensors can be used together to arm the motor driving unit with more accurate data to support different injection profiles and deliver a consistent patient experience.

Accurate temperature sensing is also of utmost importance since many biologics require cold chain storage. The automated injector can verify the temperature of the drug and either prevent the injection starting, warm up the drug via active heating or adjust the injection force. Careful design of power management with precise battery gauging is also crucial to optimise system run time as well as ensure the required level of safety and reliability.

ABOUT THE COMPANY

Flex is a global provider of design, engineering, manufacturing and real-time supply chain insight and logistics services to companies worldwide. Flex Health Solutions focuses on medical device and drug delivery design, development, injection moulding and manufacturing solutions for pharmaceutical and medtech companies. Its approach is supported by US FDA-registered and ISO 13485 compliant and ISO 11608-1 accredited facilities, with a world-class quality system.

"The automated injector can verify the temperature of the drug and either prevent the injection starting, warm up the drug via active heating or adjust the injection force."

ABOUT THE AUTHOR

Salvatore Forte is an Innovation Engineer at Flex's Design Center in Milan. In the past three years, he has been leading strategic internal research and development projects to expand awareness in the sensors and connectivity space within the medtech and other industries. He conducts research and technology assessment of emerging sensing technologies for ultra-low power devices, and delivers proof-of-concept units that can be turned into product solutions. His main area of technical investigation includes health monitoring devices, personal point of care, sensors for gas level and air quality control, and low-power connectivity solutions targeting Internet of Things embedded systems.

an Aptar pharma company

SUPPORTING IMPROVED PATIENT ONBOARDING AND ADHERENCE WITH TRAINING SOLUTIONS

In this article, Bill Guilliouma, Marketing Manager at Noble, an Aptar Pharma company, looks at the role of platform training solutions for patient onboarding and adherence to treatment regimens.

With more biologics and drug delivery device options entering the market in recent years, pharma companies can decide whether it would be easier for patients to self-inject with an autoinjector or prefilled syringe, depending on drug viscosity and other factors. Some biologics also offer patients and their healthcare providers (HCPs) the ability to choose between the two drug delivery devices, depending on patient preference and ability.

A recent study found that 77% of patients who self-inject biologics at home prefer to use an autoinjector when administering their therapy rather than a prefilled syringe. There are many reasons for this but chief among them is that 95% of the patients from the study consider autoinjector use "extremely easy or easy", whereas 74% of these patients said the same was true for prefilled syringes. What's more, 89% of these patients reported a "favourable or extremely favourable" overall impression of autoinjector use, compared with 73% of patients saying the same for prefilled syringes.[1]

> "The autoinjector platform is created after a specific device but pharma companies can use their own branding and other specifications for customisation, such as injection time, plunger location and labels."

These statistics support Noble's ongoing effort to create best-in-class patient training devices that replicate the exact form and function of true autoinjectors for patients to practise at home. To achieve our goal of creating top-tier training devices for patients, we continue to develop and launch platform training solutions, which offer benefits such as speed to market, lower cost of entry and the ability to customise the training devices to brand specifications.

Think of these platform training solutions like a car assembly line. The main, larger parts of one make of car are the same – like a car chassis – and can be quickly put together. Once the frame is in place, various other parts of the car are easily assembled and more customisable. For example, buyers can choose between various engines, whether they want two- or four-wheel drive, and what colour they want – but the main framework of the car is the same.

Noble's platform training solutions mimic this process: the autoinjector platform is created after a specific autoinjector drug delivery device but pharma companies can use their own branding and other specifications for customisation, such as injection time, plunger location and labels.

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Figure 1: Noble's YpsoMate training solutions with packaging, as displayed at the PDA show in Europe in 2019.

There are many advantages to these platform training solutions. As mentioned, speed to market is a key benefit. Secondly, pharma companies can customise their training devices to their brand guidelines and product specificity. Meanwhile, Noble ensures that accurate injection time simulation, auditory feedback and so on replicate that of the true drug delivery device. This ensures the most realistic training experience possible. Our platform training solutions use our patented technologies to provide repeatable and reliable training experiences. All platform products are developed and tested under Noble's ISO 9001-certified quality management system.

YPSOMATE AUTOINJECTOR PLATFORM

One of Noble's platform training solutions is based on Ypsomed's 1 mL and 2.25 mL automated, disposable two-step YpsoMate autoinjectors.

Proprietary Features

Noble's YpsoMate training platform (Figure 1) replicates the actual device and incorporates innovative features that are intended to give patients a realistic and repeatable simulated injection experience.

These proprietary features, which are not found in other training devices, further support patients during their self-injection journey by offering an even more realistic injection simulation.

OVERCOMING FEAR TO IMPROVE OUTCOMES

It is widely understood that approximately 20% of the world's population has some degree of needle fear, while 10% of people are so fearful of needles they're categorised as having trypanophobia – a phobia of needles. This fear of needles is higher the younger a patient is and tends to decrease as patients get older.[2]

Additionally, this fear causes 45% of patients who rely on self-injection therapies to either skip or cease their injections. To acclimate patients to the feeling of the needle prick, Noble's YpsoMate training devices have the option to incorporate a patented agitator tip option. This feature slightly pricks – but does not at all puncture – the skin at the start of the injection to create the sensation at the injection site. Noble's agitator tip can replicate varying needle forces and ranges, depending on what the pharma company needs to best replicate its drug delivery device experience.

This helps patients mentally prepare for the timing and sensation of needle insertion to help build confidence when self-injecting. In addition, patients are less likely to experience a wet injection, which occurs when patients remove the needle before the full dose has been delivered from the device – which can impact the efficacy of the drug.

So why does Noble invest time, money and energy in creating training solutions for pharma companies? Because, at the end of the day, these training solutions reach patients worldwide and help them achieve the confidence to properly self-inject and attain full efficacy from their therapies.

> "As pharma companies develop therapies that permit longer intervals between injections, and therefore improve the patient experience, patients risk forgetting critical proper injection steps and losing the confidence needed to self-inject."

There are several factors that play into patients' potential for self-injection therapy nonadherence. The first is a longer period between injections at home. For example, in psoriasis, AbbVie's Humira (adalimumab) is injected every two weeks, whereas AbbVie and Boehringer Ingelheim's Skyrizi (risankizumab), which was more recently approved, is injected every 12 weeks. As pharma companies develop therapies that permit longer intervals between injections, and therefore improve the patient experience, patients risk forgetting critical proper injection steps and losing the confidence needed to self-inject. This 12-week decay period in the example case of Skyrizi, during which patients are not injecting, introduces the training risks associated with the forgetting curve.

The forgetting curve theory posits that, without practice and repetition, retention and recall of information degrade over time – strikingly. The theory finds that half of newly learned information is already forgotten in one hour. That means, by the time the patient gets home after receiving injection training from their HCP, they have already lost half the information needed to inject properly. This patient memory decay has the potential to lead to increased injection errors as patients forget critical steps. To combat this, training devices can be used not only directly before injecting but also between injections.[4]

SURVEYS HIGHLIGHT IMPORTANCE OF TRAINING

A Noble survey sent to HCPs who work with patient groups most often prescribed self-injectable biologics – such as rheumatologists and gastroenterologists – found that these HCPs value training for their patients but are still not doing it. This occurs for many reasons, chief among them that HCPs themselves are not being trained. Specifically, the survey found that 43% of HCPs don't receive any device training.[5]

What's more, 71% of HCPs said they would be "very likely" to prescribe a self-injected medication that came with a robust training solution for their patients.

Noble's YpsoMate training platform includes more than just the training device that replicates Ypsomed's YpsoMate autoinjector. It also includes training instructions for use (IFU) that also teach users how to reset the training device for future use (Figure 2). There is also an option to include a how-to video demonstrating proper use of the training device. These elements work together to prepare patients properly for the true injection.

The survey also uncovered many other statistics that point to how useful training solutions can be for patients:

- 91% of HCPs believed patients would be more confident self-injecting if they had a training device to practise with between injections and immediately prior to injecting
- 88% of HCPs believed patients would experience less anxiety self-injecting if they had robust training solutions as support
- 89% of HCPs believed patients would be more adherent to their therapies with the support of training solutions. This increased adherence to therapies can lead to patients staying on one specific therapy longer – realising greater therapy efficacy and, for pharma, increasing patient retention.

Even while HCPs agreed that training solutions are imperative for patients who self-inject, the same survey found that 50% of patients who received training in an HCP office were only trained once for 10 minutes or less and rarely sent home with a training device for ongoing practice.

Another survey, from 2017, reiterates the above findings from the HCP survey but from a patient perspective, shedding light on the importance of training. The survey uncovered four common problems in the overall healthcare that patients received – most notably that patients were not empowered and often felt they lacked input in their therapies, information and control in treatment decisions. This goes hand in hand with the HCP survey findings that stated HCPs find value in training but simply don't have the time and tools available to do it.[6]

Even more striking was that patients surveyed believed HCPs were focused on disease treatment but not the overall patient experience, and that HCPs didn't fully explain how to perform injections, leaving patients to figure it out via trial and error. This corroborates HCPs' admissions that, if they train their patients at all, they only do so for a maximum of 10 minutes due to time constraints.

"Patients surveyed believed HCPs were focused on disease treatment but not the overall patient experience."

Figure 2: Noble's YpsoMate training solutions with packaging. These solutions include training devices and instructions for use in high-quality packaging.

PLATFORM SOLUTIONS POISED TO HELP

With both HCPs and patients confirming the value of training for patients who self-inject, but an extremely restrictive amount of time for training in-office, how can stakeholders ensure patients receive the support they deserve?

Noble's platform solutions are designed to help, by being quick to market and less expensive than bespoke solutions. Training devices allow patients to take ongoing training with them, relying less on one-off training in an HCP office.

Noble's platform solutions, like the Ypsomed YpsoMate autoinjector platform, are created to ensure patients and HCPs are provided with these training resources to help patients start on a therapy that works for them sooner and that they stay on longer, realising full therapy efficacy and helping them live a longer, happier, healthier life.

ABOUT THE COMPANY

Noble is focused on fostering healthy patient outcomes for those who self-administer drug therapies, through the development of robust training devices and onboarding solutions for some of the world's top pharma brands and biotech companies. Noble manufactures and commercialises training devices that mimic the feel, force and function of drug delivery devices such as autoinjectors, prefilled syringes and onbody, nasal and pulmonary devices in order to increase patient adherence and confidence, and decrease usage errors. Noble is an Aptar Pharma company.

ABOUT THE AUTHOR

Bill Guilliouma, Marketing Manager at Noble, an Aptar Pharma company, is responsible for identifying and developing Noble-branded platform product opportunities. In addition, he is responsible for development and implementation of strategic and product specific marketing initiatives. Mr Guilliouma holds both a BSc in marketing and an MBA with a focus on marketing.

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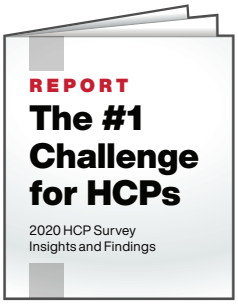

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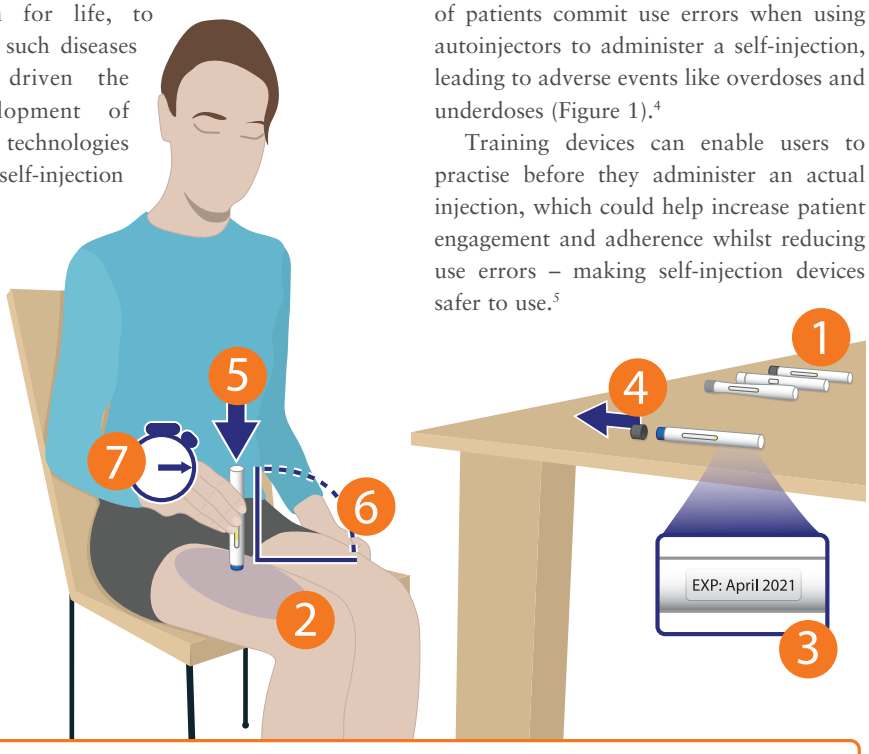
DESIGN CONSIDERATIONS FOR IMPROVING TRAINING DEVICE SAFETY AND EFFECTIVENESS

In this article, Yvonne Limpens, Managing Human Factors Specialist, and Brenda van Geel, Senior Human Factors Specialist, both of Emergo by UL, explore the design considerations that need to be taken into account when developing training devices that are safe and effective – and support patients in learning how to administer an injection correctly.

Globally, an increasing number of people are depending on injectable medications. The expectation is that the value of the injectable medication delivery market will surpass the oral medication delivery market by 2026. This is due to the high prevalence of chronic diseases such as diabetes and multiple sclerosis and the fact that the novel therapeutics to treat them are biologics, which are not readily suited for oral delivery and are therefore injected. The need for repeated dosing over prolonged periods, often for life, to treat such diseases has driven the development of new technologies and self-injection devices, leading to the emergence and rapid growth of products for self-injection.[1,2]

You might think self-injection devices are relatively simple and safe to use. However, they are typically used by patients who don't have any specific clinical knowledge and, therefore, the US FDA considers self-injection devices, like autoinjectors, to be among the medical devices on the market with the clearest potential for serious harm resulting from use error.[3] Furthermore, research has shown that 84% of patients commit use errors when using autoinjectors to administer a self-injection, leading to adverse events like overdoses and underdoses (Figure 1).[4]

Training devices can enable users to practise before they administer an actual injection, which could help increase patient engagement and adherence whilst reducing use errors – making self-injection devices safer to use.[5]



1. Selecting an incorrect injection device (i.e. differentiate between injection devices)
2. Selecting an incorrect injection site
3. Not performing the safety checks (i.e., expiration date, damage, drug colour)
4. Not removing the device's cap prior to an injection
5. Not activating the injection device
6. Administering the injection at an incorrect injection angle
7. Holding the injection device against the skin too short (not delivering the full dose)

Figure 1: Common use errors observed during Emergo by UL-led usability testing of self-injection devices.

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"Focusing on user needs and potential risks early in the design process helps lead to successful development of devices that are safer by design."

To understand the training device's design requirements, it's best practice to adopt a user-centred design approach. Focusing on user needs and potential risks early in the design process helps lead to successful development of devices that are safer by design. This can be done by involving users at an early stage within both the injection device and training device development processes to provide a comprehensive understanding of the intended use, users and use environment.

UNDERSTAND THE USE, USERS AND TRAINING ENVIRONMENT

While it might be obvious that training devices reduce use errors, there's not one training device that "fits all". Imagine you're diagnosed with diabetes and require daily injections of insulin. A healthcare provider (HCP) demonstrates how to use the injection device. The following morning you start using the device to self-inject insulin.

Now, imagine you're diagnosed with a severe allergy and are prescribed an injection device to use in an emergency. Your HCP demonstrates how to administer the injection but you might not need to use the device for the next few weeks, months or even years.

"How do you develop a training device that's sufficiently representative but remains differentiable from the actual device?"

These two scenarios clearly illustrate that training needs can significantly differ. Specifically, the insulin training device will likely only be used when the HCP trains the patient how to use the device while providing verbal guidance. The emergency training device might be used in a home setting and the allergy sufferer might use the training device periodically for an extended period without any additional guidance from an HCP. As such, it's important to understand the training device's intended use, users and environment (Table 1).

THE NEED FOR REALISM AND DIFFERENTIATION

Everyone will understand that a training device should be very similar to the actual device in its look and feel (i.e. same size, shape, material) and act the same as the actual device (e.g. user activation method, accurate force application) – but should not contain a needle or medication. However, a training device that is very similar to the actual device could also introduce new use errors. A key example would be the need for users to distinguish between the training device and the actual device, especially in an emergency-use scenario.

As such, the question is: How do you develop a training device that's sufficiently representative but remains differentiable from the actual device? The answer depends on the user interface and risk assessment for the device in question. Specifically, one must consider essential device features on which the user must be trained and features whereby the training device provides risk control, as well as features that help distinguish between the training device and the actual device.

Intended use	What the use of the device will be How frequently the device will be used What the training program and process will look like
Intended users	Who the training device's users are
Intended training environment	Where the training device will be used

Table 1: Questions to understand the training device's intended use, users and training environment.

Training devices aren't only a way to reduce use errors through practice – they can also be developed to support users in self-correcting use errors. For example, if users need to hold the injection device for five seconds to administer an injection, a training device could teach users to hold the injection device for exactly five seconds. However, the speed with which we count isn't always very accurate. Developing a training device that teaches users to hold the injection device for a little longer by means of audible feedback, for instance, might ensure that users hold the device for a sufficient amount of time to complete the injection. The training device doesn't simply need to mimic the actual device but could truly support users in learning how to administer an injection correctly.

TRAINING DEVICE DESIGN CONSIDERATIONS

Below, we discuss some general and device-specific design considerations that could support manufacturers in developing a training device that's safe, effective and representative of actual use but also sufficiently different from the actual device.

Colour & Labelling for Easy Differentiation

It's important to differentiate the training device from the actual device to ensure users don't accidentally use the training device when they need to administer a real injection. An easy way to differentiate training devices from actual devices is to use colour. A different colour could be used for the device's hardware elements (e.g. cap and/or body) or for the device's (on-product) labelling.

However, medication is frequently available in different strengths and/or variations (e.g. dosage form, administration route) which is also often reflected by use of different colours and/or graphical elements. Therefore, additional means might be warranted for users to be able to successfully differentiate between the training device and actual devices of various strengths – like a "TRAINER" label and/or a written explanation of its use.

Tip: Some visual impairments (e.g. colour blindness) impact users' ability to differentiate between devices based on labelling and colour. As such, take these into account when developing a training device with colour differentiation (Figure 2).

Figure 2: Colour and labelling variations impact users' ability to differentiate between training and actual devices, including visual deficiencies such as red-green colour blindness.

Internal Reactivation Mechanism for Repeat Use

Users may practise injecting repeatedly. That's why it's important to consider how the training device can be reactivated. Considering the users' manual capabilities and how frequently they will use the training device will help to determine which reactivation feature(s) would be optimal. For example, if the training device will mainly be used by HCPs to train multiple patients a day, a very durable, robust, ergonomic and efficient reactivation feature will help the HCP to use the training device effectively when used frequently. This might be of less importance when the training device will only be used sporadically by a patient at home.

Tip: Dexterity impairments might impact users' ability to interact with and reactivate the device (e.g. the reactivation feature requiring a certain force). Therefore, it's important to consider potential dexterity impairments when developing a training device.

Representative Sensory Feedback

Several self-injection devices provide sensory feedback (e.g. visual, audible and/or tactile feedback). Some devices produce an audible "click" to indicate that medication delivery has started, and another "click" when it has finished. It's essential to replicate sensory feedback in the training device and ensure that changes made to device features that facilitate training purposes – such as reactivation features – don't elicit additional or different feedback. Any different sensory feedback might confuse users when using the actual device to administer an injection.

Tip: Hearing impairments might impact users' ability to hear audio feedback provided by the training device. As such, consider various hearing impairments that might be prevalent in your intended user group(s) when developing a training device.

Guidance on Use Sequence & Injection Performance

Patients who interact with the training device under the supervision of an HCP should receive guidance and feedback on their performance from the HCP. Therefore, HCPs have the opportunity to correct any mistakes patients make. Alternatively, patients who use the training device independently might not have received such training from an HCP or might forget their instructions and continue training independently at home. For such expected use cases, it's important that the training device guides users in learning how to administer a correct injection in lieu of an instructor. This is particularly important when developing a training device for emergency use where there is rarely an instructor in real use and it concerns a life-and-death situation.

The most straightforward guidance on use sequence and injection performance would be through labelling – such as clear, written instructions supplemented by illustrations. These documents are useful but have limitations because users need to locate and comprehend the necessary information. More advanced yet promising guidance employs sensor-based error correction technologies that use visual and audio feedback to guide users through the injection process, while communicating their performance (e.g. committed use errors).

"More advanced yet promising guidance is sensor-based error correction technologies that use visual and audio feedback to successfully guide users through the injection process, while communicating users' performance."

Such technology could be implemented in the training device itself or developed as part of multisensory smart packaging or smart device applications.

Visual Inspection of Medication & Delivery Confirmation

In some cases, visually inspecting the medication for discolouration prior to injection is considered a critical use-step. Users might also need to visually inspect the plunger after administering the injection – to determine if the medication was delivered. In pen injectors and autoinjectors, visual inspection can be done through a so-called viewing window. There are currently training devices on the market that, unlike the actual device, don't contain a viewing window. In addition to colour and labelling differentiation, the absence of a viewing window might be a strong design feature that supports users in differentiating between the training device and actual device.

The decision as to whether to outfit the training device with a viewing window depends on whether visual inspection is considered a critical task that's mitigated by this design feature. If checking the viewing window to ensure the medication was delivered is a critical task, then developing a training device with a viewing window might be essential.

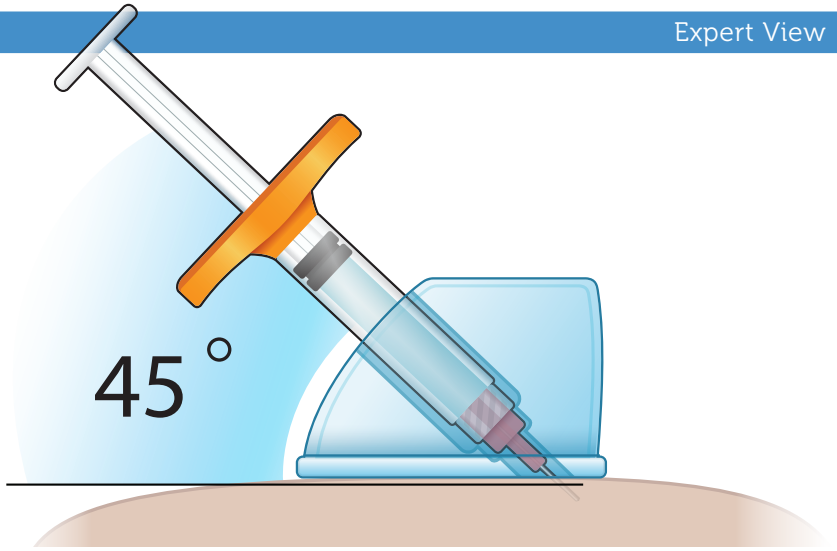

Figure 3: Component teaching users to inject at the prescribed injection angle.

Assistance with Injecting at Prescribed Angle

Depending on the injection device type and its intended use (e.g. formulation, injection site), injections are administered at different angles (i.e. 90°, 45°, 25° or 10-15°). One commonly observed use error is that users don't always achieve the prescribed injection angle. Supplying the training device with a component that guides users into positioning the training device at the prescribed injection angle will likely help users to understand the correct angle. Equipping the actual device with such a component might obstruct the user's view during injection and increases production costs (Figure 3).

[Continues...]

Instructional Information Highlighting the Differences

A training device will evidently differ from the actual device in one or multiple ways. Therefore, it's essential to communicate the extent to which the training device is similar to and differs from the actual device. Training devices that are expected to be used without any guidance from an HCP will require more comprehensive, yet still inclusive, written information highlighting these similarities and differences.

For training devices that are being used by or under the supervision of HCPs, condensed written information might be sufficient because HCPs can verbally communicate the differences to patients as needed. Furthermore, the information that will be provided should be tailored to its users. For example, use of clinical jargon is acceptable for HCPs, whereas it isn't for users without clinical knowledge or prior injection experience.

CONCLUSION

Developing a training device that's safe and effective – and supports users in learning how to administer an injection correctly – requires a comprehensive human factors engineering (HFE) approach. Involving users throughout the training device's development process – and thinking through the use and environment – is fundamental in developing an optimal training device that can truly support users in learning how to administer an injection correctly and that doesn't elicit additional use errors.

ABOUT THE COMPANY

Emergo by UL is a regulatory consultancy specialising in medical device, combination product and IVD compliance. Its human factors research & design global team specialises in early-stage user research, product design, usability testing and user interface design.

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HOW SHORTER NEEDLES WITH THINNER WALLS ARE SET TO IMPROVE THE INJECTION EXPERIENCE IN CHRONIC CARE

Aurélie Pager, Clinical and Human Factors Program Leader; Brigitte Duinat, Senior Engineer; and Barbara Alves, Regulatory Affairs Specialist, all of BD Medical – Pharmaceutical Systems, reporting on several patient studies, look at how new BD Neopak™ XtraFlow™ prefillable glass-based syringes with shorter, 8 mm needles and thinner wall cannula technology are set to improve the injection experience for subcutaneous drug delivery in chronic care.

For decades, the most commonly used needle length for subcutaneous chronic drug delivery has been half an inch (12.7 mm).[1] As a result, most secondary injection devices have been developed around 12.7 mm staked needle prefillable syringes (PFSs) and the exposed needle length for manual injection has remained mainly focused around 12.7 mm.

However, there is a proportion of self-injecting patients who do not apply[2] the recommended subcutaneous injection technique (45° with or without skin pinch, 90° with skin pinch),[3] thereby increasing the risk profile of accidental intramuscular injection when using needles of this length. Therefore, the 12.7 mm needle length may not be optimal for subcutaneous drug delivery.

State-of-the-art innovation processes[4] have evolved and are now more centred on end users' needs (patients, healthcare workers and lay caregivers) rather than on developing new products around existing constraints. Additionally, needle length and, most importantly, needle inner diameter are key parameters influencing injection force for a given injection time and solution viscosity.[1] Reducing the injection force required to deliver solutions by manual injection is a parameter influencing patient preference, especially when high viscosities are injected.[2]

Leveraging findings in the diabetes care space, where there have been a series of innovations including reducing exposed needle lengths,[5] BD Medical – Pharmaceutical Systems is launching BD Neopak™ XtraFlow™* – a prefillable glass-based syringe solution featuring an 8 mm needle with thinner wall cannula technology. Enabling the transition from the 12.7 mm needle length towards shorter 8 mm needles, in combination with thinner wall needle technology to reduce pressure drop and enhance flow,[6] can provide improved PFS solutions for subcutaneous drug delivery both for end users in chronic care settings and for pharmaceutical companies.

The BD Neopak™ XtraFlow™ syringe is set to improve subcutaneous drug delivery and the injection experience through three main benefits: by allowing the possibility of delivering higher drug viscosities and/or volumes without compromising the end user experience through substantial reduction of injection effort or time;[2,6,7] by increasing the chances of targeting the right tissue even if the recommended injection technique is not applied,[8] thereby supporting the efficacy of manually administered chronic therapies; and by potentially reducing patients' needle-related anxiety.[2]

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In the remainder of this article, we will present several frequently asked questions from BD pharma partners, split into three groups according to each of our areas of expertise.

The questions cover research and design mindset applied to the development of the BD Neopak™ XtraFlow™ solution, and how the anticipated clinical benefits of 8 mm needles[9] will support their broad adoption over time for subcutaneous drug delivery, particularly for use in chronic care settings.

The Importance of Human Factors Evidence – Aurélie Pager (AP)

Q What did BD identify as priority areas of improvement for chronic subcutaneous drug delivery and how is BD Neopak™ XtraFlow™ set to address these?

AP A recent market research study[10] allowed us to identify three main areas of priority:

1. Enabling subcutaneous bolus delivery of high viscosity and higher volume drugs (up to 2 mL) without compromising the end-user experience
2. Reducing the risk of accidental intramuscular (IM) injections
3. Reducing needle-related anxiety and pain perception.

> "We aim to enable the injection of high drug viscosities without increasing injection force."

By addressing these areas, we believe we can contribute to improving the patient experience[2,7] and that of all end users.

The development of the BD Neopak™ XtraFlow™ prefillable syringe with 8 mm, thinner-wall needle technology is an important next step for the treatment of chronic diseases in addition to diabetes, where there has been a decades-long trend in reducing needle lengths for drug delivery.[5] We saw this trend in diabetes care where, due to clinical relevance,[9] shorter needles largely and successfully replaced 12.7 mm needles which had previously been the *de facto* needle length, based on industry convention rather than on clinical directive.

This shift to shorter needles occurred due to concerns about patient safety, as insulin absorption into muscles could lead to hypoglycaemic episodes.[11] While increased safety for a similar efficacy was the most important outcome of the move to shorter needles in the diabetes treatment space,[9,11] another key finding was that shorter needles also significantly reduced needle-related anxiety and perceived pain,[12] which led to a substantial increase in patient comfort.[13]

With the introduction of the 8 mm BD Neopak™ XtraFlow™ needle, we aim to enable the injection of high drug viscosities without increasing injection force[6] for other chronic disease treatments, given the range of injection volumes and viscosities that exist.[1] The BD Neopak™ XtraFlow™ syringe is designed to enable an acceptable injection force[6] or an acceptable holding time (e.g. up to 10 seconds for 1 mL injections)[14,15,16] when delivering higher drug viscosities and volumes. Needle length and, most importantly, needle inner diameter are dominant factors influencing injection force for the same injection time and a determined viscosity, based on our calculations derived from the Bernouilli – Poiseuille equations simulating fluid and pressure drop (Figure 1).[6]

Q The BD Neopak™ XtraFlow™ prefillable syringe enables a tangible reduction in injection force. How was this determined and perceived by end users?

AP When combined with thinner-wall technology, such as with ultra-thin wall (UTW) needles, BD Neopak™ XtraFlow™ enables a reduced injection force or injection time required to push on the plunger rod to deliver the

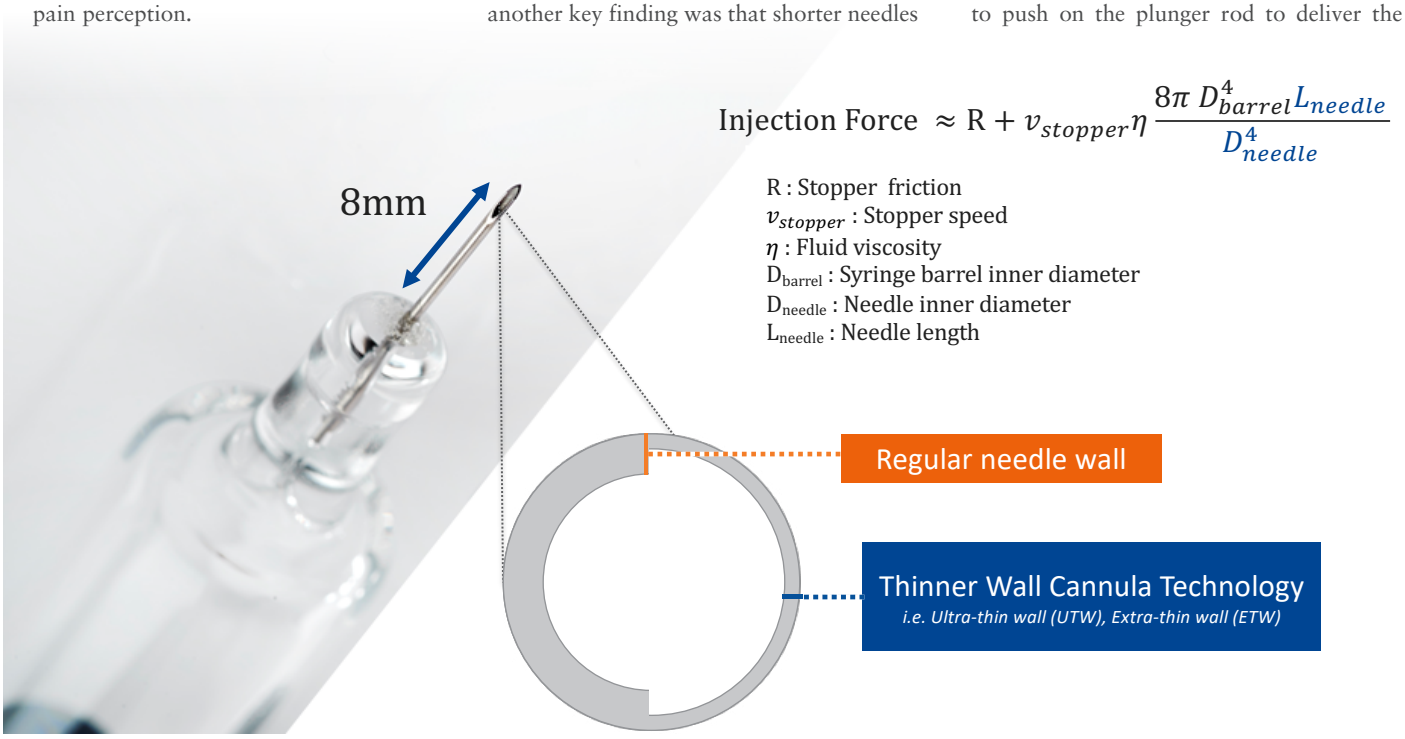

Figure 1: The BD Neopak™ XtraFlow™ glass prefillable syringe platform with staked 8 mm needle and thinner wall cannula technology options. Injection force equation (top right), derived from the Bernouilli – Poiseuille equations, can be used for fluid and pressure drop simulations, respectively.[6] This equation illustrates how the needle inner diameter and, to a lesser extent, needle length, influence the injection force for a given injection time and solution viscosity. (Negligible terms simplified in the equation.)

"There can be significant deviation from recommended subcutaneous injection techniques, even for experienced users."

injectable.[6] With patients increasingly taking on the responsibility of self-injecting, they may want less frequent dosing schedules.[17] This means that drug delivery systems must be capable of delivering higher volumes and/or higher viscosities.[1,17]

Improving the patient injection experience was one of the key objectives in the development of the BD Neopak™ XtraFlow™. BD's expertise and experience in needle manufacturing and needle wall technology allowed us to adjust needle length and wall thickness to increase fluid flow, while introducing minimal change from an industrial, PFS fill and finish process perspective.

For example, when compared with 27G special-thin wall (STW) 12.7 mm needles, BD Neopak™ XtraFlow™, with the combination of 27G UTW and 8 mm needle length, reduces injection force by ~46% at a viscosity of 30 cP and by ~34% at a viscosity of 10 cP for a similar injection time, according to a mathematical modelling simulation.[6] These differences in force were shown to be perceptible to end users in recent human factors studies.[2,7]

Indeed, a 2019 BD human factors study showed that over 50% of chronic disease patients, including both naïve and experienced self-injecting patients, have a preference for the BD Neopak™ XtraFlow™ syringe over commonly used syringes. They attributed the main reason for their preference to the reduction of injection force, with the second most-cited reason being the shorter needle length.[2] BD intends to share these results in a future peer-reviewed publication.

Q What evidence supports the notion that BD Neopak™ XtraFlow™ helps target the correct tissue, assisting in the proper delivery of subcutaneous injections?

AP Similarly to the enhancements achieved in the diabetes space, we expect that the 8 mm BD Neopak™ XtraFlow™ will increase the chances of targeting the subcutaneous tissue, even if the recommended injection technique is not performed correctly,[8] and it may reduce patient needle-related anxiety – thus potentially improving the overall patient self-injection experience.[2,7]

Self-injecting is never an easy task for patients, even for those with years of experience. In the same human factors study, we saw that there can be significant deviation from recommended subcutaneous injection techniques, even for experienced users.[2] In our study, patients used the non-recommended injection technique of 90° injection angle with no skin pinch 35% of the time. With commonly used 12.7 mm needles, and when the recommended injection technique is not followed or is done incorrectly (no skin pinch or an incorrectly done one), we estimate this will increase the risk of injecting into the intramuscular (IM) tissue.

By adopting a shorter, 8 mm needle, our simulations[8] show that the risk of accidental IM injections could be reduced at both the abdominal and thigh injection sites between two and eight times, without increasing the risk of accidental intradermal (ID) injections, considering both 90° and 45° injection angles, without skin pinch. This reduction was derived from a mathematical model based on a study assessing human skin layer thickness at various injection sites, conducted among 388 adults (of various ages, genders, ethnicities and body mass index scores).[5] This potential reduced risk of IM injection applies to all types of patients, including at-risk populations such as children and lean adults who have less subcutaneous fat.[18]

The BD human factors study cited earlier allowed us to assess the injection techniques used and thus three different user groups were represented: "naïve" participants, "experienced" participants, and participants "experienced but with hand impairment" (e.g. patients diagnosed with rheumatoid arthritis or multiple sclerosis). For those with hand impairment, following recommended injection techniques can be consistently challenging.

"The risk of accidental IM injections could be reduced at both the abdominal and thigh injection sites."

This subpopulation showed a rate of non-recommended injection technique at 90°, without skin pinch, three times more often than when compared with non-hand-impaired, experienced patients. The highest rate of injection error was observed in the naïve patient population.[2] The 8 mm needle length of BD Neopak™ XtraFlow™ could reduce accidental IM injection for all patients performing non-recommended injection techniques, as discussed previously.[8] BD Neopak™ XtraFlow™ also provides the possibility of reducing the pressure required to deliver drug therapies and facilitate self-injection, especially for users with hand dexterity issues.[2,7]

Q How did you substantiate the positive impact that BD Neopak™ XtraFlow™ has on patients' needle-related anxiety?

AP Over the last 20 years, a number of scientific studies in the diabetes care space have established that needle-related anxiety and perceived pain can be reduced with shorter and thinner needles. For example, in 1999, Ross *et al*[19] evaluated both visible 8 mm (30G) needles and 12.7 mm needles in diabetes treatment on a number of parameters, including pain perception. The subjects using 8 mm needles reported less perceived pain than those using 12.7 mm needles.

Bergenstal *et al* (2015)[11] subsequently reported diabetic patient evaluations favouring short needles in terms of pain, ease of use and overall patient preference.** In addition to peer-reviewed articles, BD's innovations in diabetes care contributed to our understanding of the relationship between needle length, needle diameter and the patient experience in the context of chronic diabetes care.

For the development of the BD Neopak™ XtraFlow™, the abovementioned human factors study evaluated patient use of syringes, needle-related anxiety, ease of use, acceptance and preference, compared with commonly used 12.7mm 27G STW needles.

In this study,[2] we looked at needle-related anxiety in patients suffering from chronic diseases. The study population included both naïve and experienced self-injecting participants. Prior to any simulation, two uncapped syringes with visible needles were presented to the naïve participants to assess their anxiety level. The results show that the BD Neopak™ XtraFlow™ syringe (8 mm 27G UTW)

was rated as less anxiety-inducing than a similar-looking syringe which had a longer needle (12.7 mm 27G STW).

After the simulated injections, the experienced participants were asked if they usually felt anxiety when self-injecting with either PFS or syringe and vial treatments. It is noteworthy that over 40% of these participants still feel anxious, even after many years of self-injecting. Additionally, nearly all experienced participants saw advantages to the shorter needle length of the BD Neopak™ XtraFlow™. Indeed, they found it less intimidating, eliciting the impression that it would be less painful and more comfortable to use than the 12.7 mm needle.

Q **Secondary delivery systems are increasingly being adopted to help end-users in chronic care to deliver higher viscosity or high-volume therapies. How does BD Neopak™ XtraFlow™ impact the injection experience with such delivery systems?**

AP We recently tested the benefits of the BD UltraSafe PLUS™* 2.25 mL safety system in combination with the BD Neopak™ XtraFlow™ in a human factors validation study.[7] The user groups included in this study were healthcare professionals, and both naïve and experienced self-injection patients, with and without hand impairment. The study shows that, with a commonly used 12.7 mm 27G needle, the system is usable and test subjects express confidence that the system will indeed protect them from needlestick injuries.

However, when tested with a viscous 30 cP solution, a perceptible reduction in injection force is provided when combined with BD Neopak™ XtraFlow™. More than 120 injection simulations were performed in this study, with the rate of operational difficulties observed during the simulated injections being lower with BD Neopak™ XtraFlow™ than with other, commonly used syringes. Users also perceived a reduction in the force needed to push the plunger during injection.

Indeed, the percentage of users who rated the plunger as "easy or very easy to push" increased by up to five times across all user groups. BD UltraSafe PLUS™ 2.25 mL, when combined with BD Neopak™ XtraFlow™, may provide a better experience for end users, including self-injecting patients, with and without hand impairment.

Needle Robustness and Systems Expertise – Brigitte Duinat (BD)

Q **How would BD Neopak™ XtraFlow™ and its thinner needle wall configuration perform with regards to needle mechanical resistance?**

BD A key driver in the development of BD Neopak™ XtraFlow™ was to keep needle mechanical properties comparable to currently marketed needles (i.e. 12.7 mm 29G thin wall and 27G special-thin wall needles) to support acceptable resistance to bending and buckling. Calculations performed through well-established mechanical laws included estimations of resistance to bending and buckling.[20]*** These figures indicate needle mechanical resistance when challenged with a perpendicular or axial force until it reaches plastic deformation.

Resistance to bending and buckling for different BD Neopak™ XtraFlow™ configurations, including the 8 mm 27G UTW and the 8 mm 29G extra-thin wall (ETW) configurations, demonstrated equivalent, and sometimes even superior, mechanical resistance when compared with those of 12.7 mm 29G thin wall, commonly used needles. Our study shows that combining shorter needle length with thinner needle wall technology maintains, and may even improve, needle mechanical resistance to bending and buckling.[20]

Q **What is BD's integrated system solutions approach and what is its role in the design of new needle technologies?**

BD Our partnership with biopharmaceutical companies for the past 30 years has taught us that developing and launching drug-device combination products is a long and expensive journey for pharmaceutical companies and their partners. BD is well positioned to support the development efforts and success of our pharmaceutical partners through more robust, better-designed system solutions, using our history with and experience in combination products.[21,22]

For combination products, not only is it necessary to have excellent compatibility between the drug and the PFS primary container, but there is also a growing need to secure system integration with a safety device or an autoinjector. Such complex systems increase the number of functional interfaces and thus introduce several challenges,[23,24] particularly when these systems are sourced from multiple vendors. BD is able to manage all the requirements, from the delivery of system requirement definitions to sub-system, component and manufacturing process requirements.

Moreover, our capabilities cover all design control aspects, including usability (human factors) engineering, and preclinical and clinical evaluation. BD Neopak™ XtraFlow™ syringes, which will soon expand our solution portfolio for chronic drug delivery, will benefit from robust integration with BD injection devices, including the BD Intevia* 2.25 mL large-volume autoinjector and BD UltraSafe PLUS™ safety devices.

Regulatory Considerations When Adopting New Needle Technologies – Barbara Alves (BA)

Q **Are there any specific challenges regarding the registration of a drug device combination including a syringe with a shorter, 8mm needle and an enlarged inner diameter, such as with the BD Neopak™ XtraFlow™?**

BA There is no change in the type of regulatory submission needed with the BD Neopak™ XtraFlow™ compared with a BD glass prefillable syringe with a commonly used 12.7 mm needle. BD Neopak™ XtraFlow™ is part of a combination product in the US and is also part of an integral drug device combination (DDC) in Europe, including a drug and syringe only or additional devices such as a needlestick injury prevention accessory or an autoinjector.****

According to Article 117 of the European Medical Device Regulation, the integral DDC has to be assessed first by an MDR-accredited notified body, who should focus on the safety and performance of the device part of the DDC. (The latest official date for implementation of European Medical Device Regulations, article 117, was May

"There is no change in the type of regulatory submission needed with the BD Neopak™ XtraFlow™ compared with a BD glass prefillable syringe with a commonly used 12.7 mm needle."

26th, 2020, though this is expected to be extended by one year following the vote on an amendment by the European Parliament on April 17th, 2020.)

The applicable General Safety and Performance Requirements (GSPR), Annex I of the EU MDR are part of the design input specifications of BD Neopak™ XtraFlow™, which means that BD will provide supportive evidence of safety and performance to its biopharmaceutical partners to help them build their own GSPR packages for the DDC. BD Neopak™ XtraFlow™ will be included in our existing glass syringe drug master file type III in the US, meaning no change for drug combination product registration in that country.

It is interesting to note that there is no requirement, specific standard or guidance that recommends needle length for subcutaneous injections and that health authorities have already approved 8 mm needle devices, including PFSs.

Q If a biopharmaceutical company has already started its clinical program with a 12.7 mm staked needle PFS, would switching to an 8 mm needle still be possible and, if so, what would that switch entail?

BA Health authorities recommend using the final marketing presentation for Phase III clinical studies; in cases where this is not feasible, the same authorities recommend an appropriate bridging strategy.[25,26] From a clinical point of view, the 8 mm needle length has been demonstrated[11] to reach the targeted subcutaneous tissue when recommended injection techniques are maintained. However, even if the injection would occur in the same targeted tissue with 8 mm and 12.7 mm needles, which would mitigate the risk of finding different drug pharmacokinetic/pharmacodynamic (PK/PD) results, a bridging study with 8 mm needles may be required to leverage initial clinical data generated by a PFS with a 12.7 mm needle.

FDA draft guidance on bridging for drug-device and biologic-device combination products describes the potential impact of changes in needle penetration depth and rate of delivery on bioavailability PK/PD.[26] This is also the reason why bridging PK/PD studies are often needed when pharmaceutical companies introduce autoinjector presentations, even if no PFS change is involved. One simple way to introduce a PFS with an 8 mm needle would be to leverage the required bridging study for autoinjectors and complement it with an additional study arm for manual use.

A revealing example of this would be in the context of diabetes pen needles, where clinical studies are performed to support changes in needle length and/or gauge, with a focus on glucose control and leakage at the injection site, to determine the potential impact on glycaemia levels.[11] While those data were a requirement for development and approval of some pen needles, they are mostly informative for future product development and for supporting clinical decisions, including being used as a foundation for clinical practice guidelines.

> "BD Neopak™ XtraFlow™ technology provides a combination of staked-needle length, gauge and inner diameter that enhances the user experience[2] and helps patients comfortably and successfully perform their subcutaneous self-injections."

CONCLUSION

Improving the patient injection experience should be considered a priority, especially for patients with chronic conditions who must inject themselves frequently over an extended period of time.

BD Neopak™ XtraFlow™ technology provides a combination of staked-needle length, gauge and inner diameter that enhances the user experience[2] and helps patients comfortably and successfully perform their subcutaneous self-injections. This is particularly relevant for patients with reduced hand dexterity[7] and when injecting higher viscosity and/or higher volume therapies.[7] What's more, BD Neopak™ XtraFlow™ offers a platform that can be applied to manual injection, safety device and autoinjector applications.

With the benefits and evidence presented in this article and, more specifically, with their contribution to enhancing the patient self-injection experience,[2,7] there appears to be no reason to delay the transition to shorter, thinner-wall needles for therapies that require subcutaneous injection, especially for chronic diseases.

Complementing its large portfolio of delivery solutions for chronic injectable drugs, BD Medical – Pharmaceutical Systems will also soon be integrating BD Neopak™ XtraFlow™ syringes into both BD UltraSafe PLUS™ safety devices for the prevention of needlestick injuries and into the BD Intevia™ 2.25 mL autoinjector platform, with the intention of even further enhancing the patient injection experience.

** BD Neopak™ XtraFlow™, BD UltraSafe PLUS™ 2.25 mL and BD Intevia™ 2.25 mL are products under development; some statements are forward looking and are subject to a variety of risks and uncertainties.*
*** Bergenstal et al compared 4 mm (32G), 8 mm (31G) and 12.7 mm (29G) needles and found no statistically significant difference in preference between 4 mm or 8 mm pen needles, in the case of diabetes care.*
**** Based on mathematical modeling. Bench, preclinical and clinical testing not performed.*
***** According to US FDA 21 CFR part 3.2(e) in and EU MDR 2017/745 article 1(9).*

ABOUT THE COMPANY

BD is a large, diverse, global medical technology company. Its Medical Pharmaceutical Systems division is the world's largest syringe manufacturer. It offers prefillable syringes, self-injection systems, safety and shielding solutions, and needle technologies and associated pharma services.

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THE DIFFERENCE OF ONE DRUG DELIVERED

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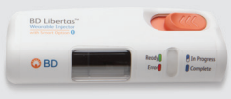

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APPLICATION OF CFD IN THE DEVELOPMENT OF A WEARABLE BOLUS INJECTOR

In this article, Marcus Hall, Senior Sales Representative, Validus Engineering; Björn Ullbrand, CFD Engineering Specialist, Validus Engineering; and Claus Schmidt Møller, Chief Technology Officer, Subcuject, describe the use of computational fluid dynamics (CFD) as the primary design and analysis tool in the development of a wearable bolus injector.

The Subcuject subcutaneous wearable bolus injector (WBI, Figure 1) is a small and very cost-effective alternative to the complex solutions on the market today and in development, without electronic components and based on a prefilled glass cartridge (e.g. 3 mL ISO standard). Due to the simple fluid mechanical principle, the device is suitable for cold storage and for one-time use.

REQUIREMENTS

Given the substantial dose volumes administered with WBIs, the delivery must necessarily be slow to avoid pain – thus requiring a long time to complete. At the same time, the drug may be highly viscous (resistant to flowing). Combined, these factors lead to a wearable device that needs to provide a low flow rate using a high force (or pressure) for a relatively long time. This can be achieved in complex and costly electronically controlled pump driven devices.

But a more cost-effective solution to meeting these requirements is an osmotically driven injector (Figure 2) as this offers high force, slow actuation

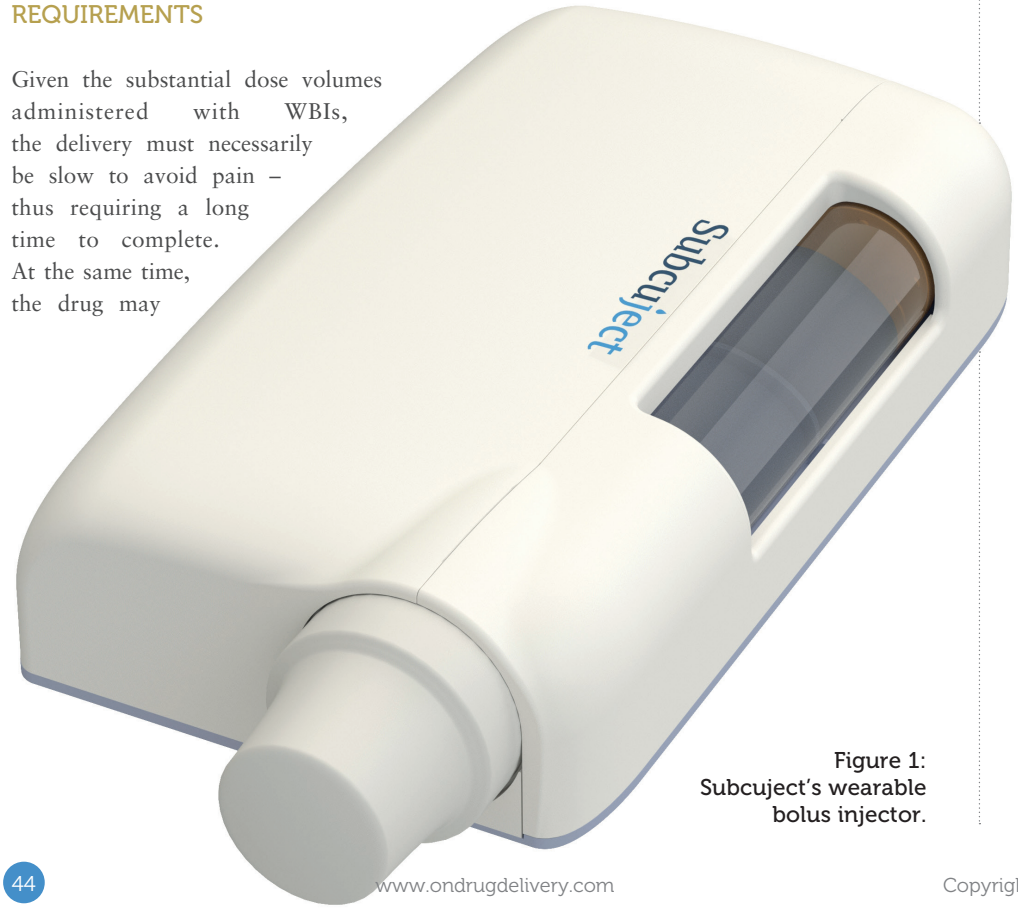

Figure 1: Subcuject's wearable bolus injector.

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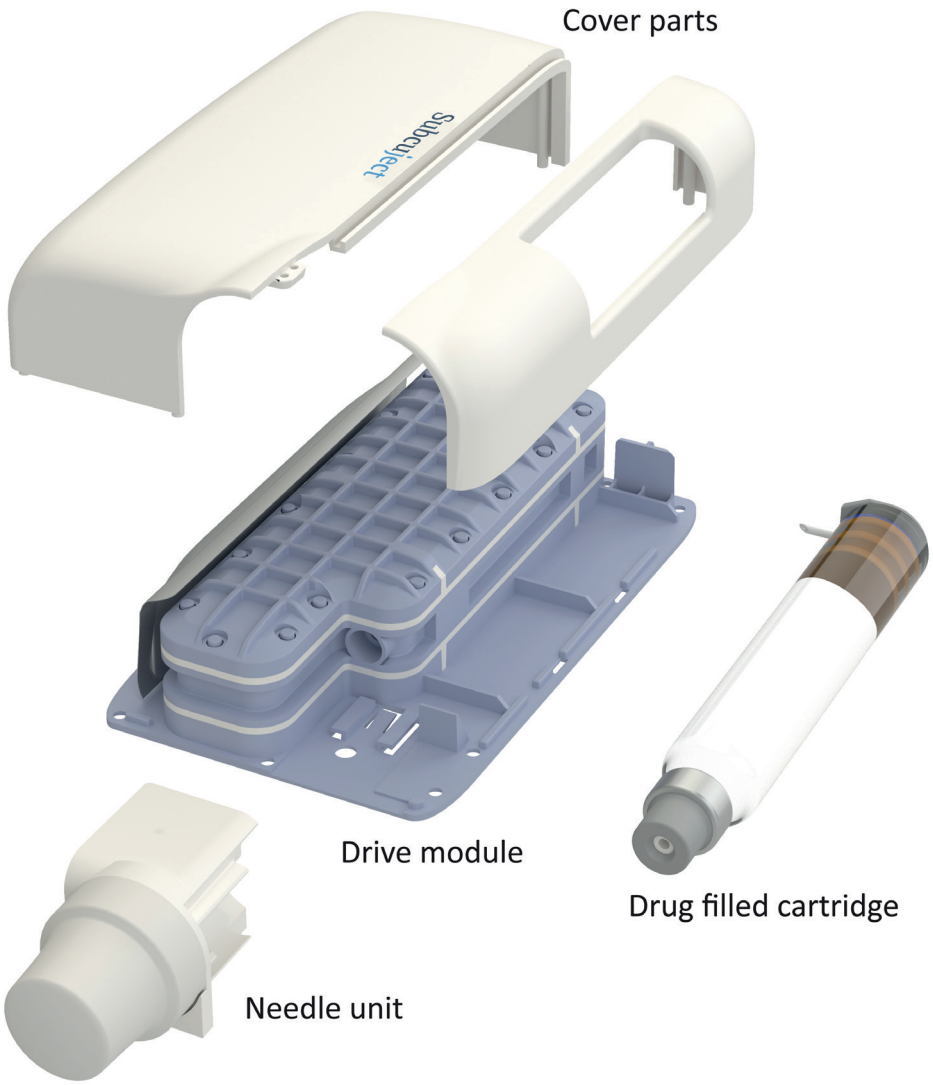

Figure 2: The wearable bolus injector components, including the drive module.

and a simple design at a low cost. Lacking electronics and batteries, an osmotic drive is also more environmentally friendly than electromechanical solutions when disposed of after single use.

Osmosis uses the principle that a solvent – normally fresh water – in a solution consisting of water with a dissolved salt, moves through a semipermeable membrane from the side with lower salt concentration to the side with higher salt concentration. This process takes place even though the fluid pressure on the side with higher salt concentration exceeds the pressure on the lower salt concentration side. The flow of water can then be used as the drive module in a WBI (Figure 3).

Prior to activation of the WBI, chambers on both sides of the membrane contain fresh water. The salt is stored in a container (pouch or glass vial) in the chamber on one side. The drive module is activated by rupturing the salt container, releasing the salt into the fresh water and thereby creating a saltwater solution. This initiates the osmosis and water moves from the freshwater side of the membrane to the chamber that now contains salt water. This inflow of water can generate a high pressure and moves a plunger in a cartridge which injects the dose into the patient.

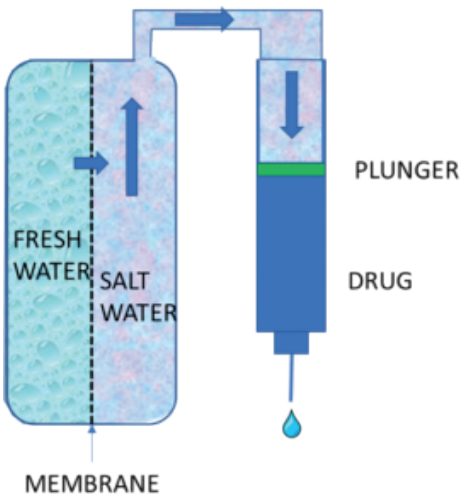

Figure 3: Principles of the osmosis drive module.

> "Lacking electronics and batteries, an osmotic drive is also more environmentally friendly than electromechanical solutions when disposed of after single use."

However, when using osmosis as a driving mechanism, some design challenges arise – such as designing the osmotic drive module in order to minimise the module's sensitivity to the membrane's physical orientation in relation to gravity. As the solvent dilutes the salt solution when it permeates through the membrane, it is not immediately mixed into the solution and thus a situation where there is mainly solvent and no salt close to the membrane on either side (concentration polarisation, Figure 4) may occur – significantly reducing the osmotic potential and thus the driving force.

This is particularly true if the patient places themself in a position where the membrane is horizontal and the salt solution is below the membrane, as in this case the fresh water acts as a barrier between the salt solution and the membrane. A non-flat membrane could potentially be used to circumvent this problem but, as this introduces difficulties in manufacturing of complete devices, it was decided that development of the WBI should focus on the use of flat membranes.

In addition, as part of normal operation, the solvent slowly dilutes the salt water and this, over time, reduces the rate of osmosis during the injection. For a simple, predictable and robust design, these challenges need to be overcome by the geometry and overall construction of the device.

CHALLENGE THE CHALLENGES BY USING CFD

Gaining pace in the late 1960s aircraft industry, computational fluid dynamics (CFD) is a numerical method for simulating fluid flow and thermal behaviour in and outside all forms of physical object, such as vehicles and devices – including medical ones. Among many things, CFD is used to predict phenomena such as the natural and forced convection of fluids, mixing, pressure drops, etc.

To aid in evaluating the WBI concept and optimise performance, Subcuject engaged specialist CFD consultant Validus Engineering, to employ CFD as the primary design and analysis tool in the development of the WBI from initial concept through to fulfilling the inventor's design goals – including robustness, behaviour and predictability.

METHODOLOGY AND CALIBRATION

Osmotic pressure can be defined as π = iMRT (Van't Hoff equation) where R is the universal gas constant, T is temperature, M the molar concentration of the solute and i the Van't Hoff index. The freshwater flux in forward osmosis is $Jw=A(\Delta\pi-P)$ where A is the semi-permeable membrane permeability, $\Delta\pi$ is the differential osmotic pressure across the membrane and P is the static pressure at the membrane.

In the CFD model, only the salt solution side of the membrane is modelled and the freshwater flux is defined as an inlet boundary condition depending on the salt concentration next to the membrane; there is no need to simulate the freshwater side as this is always only fresh water. Since the osmotic membrane is not part of the model but only the flux through the downstream side, the model is regarded as semi-empirical and requires calibration of two model constants using experimental data. The membrane permeability and the solution diffusivity, which depends on the properties of the salt, are the two constants which need to be calibrated.

Initial calibration analyses were performed for various orientations since gravity plays an important role in how the fluid moves inside the chamber. This is because the salt water is heavier than fresh water and tends to sink to the bottom. Hence, as previously mentioned, in order to provide a robust product, it is essential that the device performance is unaffected by gravitational orientation.

However, an early-concept calibration model displayed a high degree of susceptibility to concentration polarisation, as shown in Figure 4, Pos 2.

In addition, for other orientations it was seen that the flow rates were quite high during the start of the process but then were quickly reduced as the salt was diluted and – most importantly – lost out of the driven module chamber and therefore no longer in contact with the membrane.

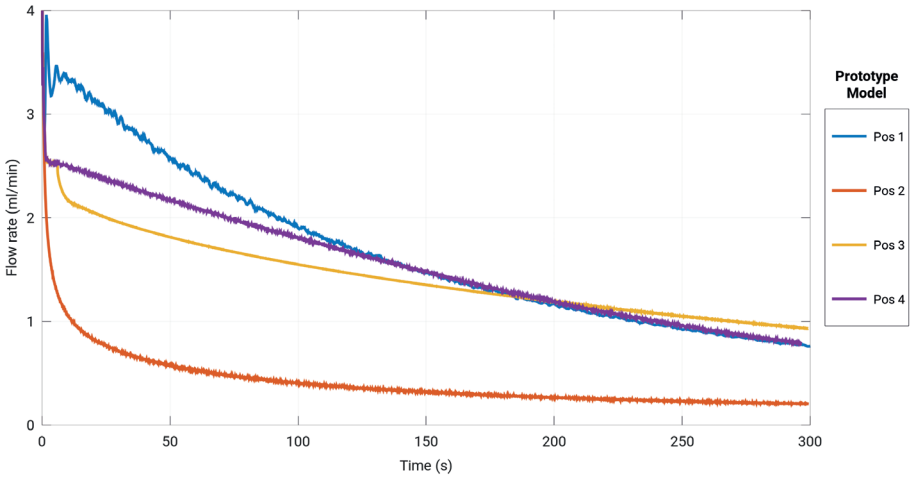

Figure 4: CFD – initial model flow rate showing, for example, a high degree of concentration polarisation.

"Much of the development effort was focused on identifying geometry and solutions that would prevent a barrier effect with low osmotic potential over the membrane and maintain a high concentration of salt in contact with the membrane."

OPTIMISATION PROCESS USING CFD

Much of the development effort was focused on identifying geometry and solutions that would prevent a barrier effect with

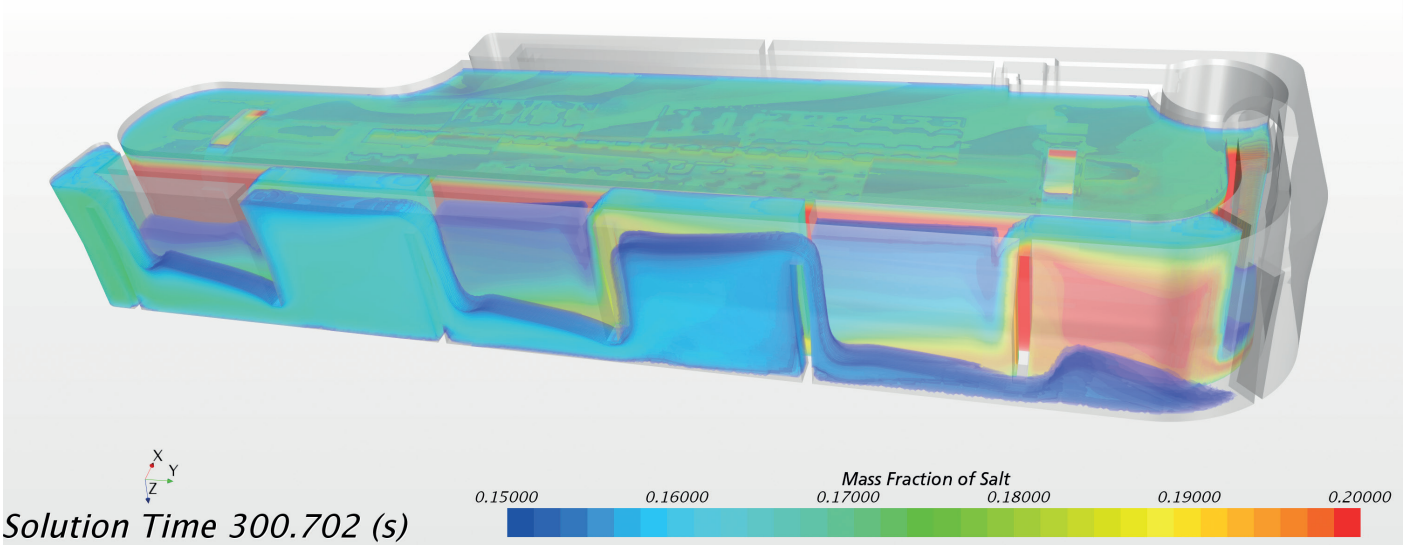

Figure 5: CFD – salt concentration in chamber plus meandering labyrinth concept.

low osmotic potential over the membrane (concentration polarisation) and maintain a high concentration of salt in contact with the membrane. Secondly, since the permeation rate in, for example, mL/min is ideally linear to the salt concentration multiplied by the membrane area, it is highly important not to "lose" salt out of the drive module as it moves the plunger. Losing too much salt solution would further worsen the already unavoidable slowdown of osmosis due to the dilution of the salt.

Each new concept was analysed for different orientations and the performance evaluated in order to optimise for a high output volume with as constant mass flow rate as possible. The simulation process complements prototype testing by means of virtual testing (digital twin) with fast turnaround times. A new or updated 3D CAD model from Subcuject was typically evaluated, with regards to performance, by Validus Engineering the following day, ensuring a high pace in the development process. In addition, and equally important, a deeper understanding of the physical processes involved was obtained as the flow could be visualised in great detail.

MITIGATING CONCENTRATION POLARISATION

Early prototypes, as seen in Figure 4, displayed a significant concentration polarisation, where the flow rate was more than halved with the drive module placed in an unfavourable orientation. This was outside the goals set for the WBI and thus required attention.

"Each new concept was analysed for different orientations and the performance evaluated in order to optimise for a high output volume with as constant mass flow rate as possible."

Initially various concepts were conceived and simulated, such as:

- Non-flat membrane – discarded due to manufacturing obstacles
- Mechanical stirring/mixing of the salt solution using a water wheel, impeller or Archimedes screw in various directions in relation to the membrane; driven by the outflow from the drive module
- Use of the outlet from the salt chamber to induce mixing in the chamber
- Dual membranes.

The CFD results revealed that, although some of the concepts using mechanical stirring of the salt solution to prevent concentration polarisation did offer a better-performing drive module, the improvement was too small to justify the complex mechanics required. Adjusting outlet positioning did not improve mixing in all orientations either, mainly due to the flow speeds in the saltwater chamber being exceptionally slow (only a few mm per second).

Based on numerous simulations of all proposals, the preferred approach offering the best performance in relation to the complexity of the design was to use two membranes with the salt solution in a centre chamber, flanked by freshwater chambers on both sides. If the flux through one membrane falls because of the orientation, the other membrane simultaneously compensates.

MITIGATING SALT LOSS

Early prototypes also allowed for the salt solution to immediately escape the drive module (as it drove the plunger) thus leaving less salt solution for the continued osmotic process. CFD studies of various locations of the outlet from the saltwater chamber found that all placements had drawbacks of inconsistent behaviour when the module was placed in specific (gravitational) orientations. In some orientations, mostly low-concentration solution escaped, whereas in other orientations, high-concentration salt was escaping – leading to very different osmosis rates as time progressed.

Instead, a concept using a labyrinth – making it "harder" for the solution to escape through the chamber outlet – was conceived. The basic idea behind this is for the salt container to be ruptured in a main chamber in the drive module (Figure 5, chamber is in the middle with the labyrinth on the outside. The labyrinth minimises salt water loss from the drive module). Initially this results in a smaller membrane area being in contact with salt solution but instead at a high concentration.

As the fresh water permeates through the membrane, the salt solution is pushed

from the main chamber into the labyrinth outlet. While this dilutes the salt water in the main chamber, reducing the flux here, it simultaneously increases the membrane area which is in contact with salt – thus increasing the flux in this area. Various design options for the labyrinth outlet concept were evaluated and optimised using CFD and the optimal design and ratio between initial membrane area and labyrinth membrane area was chosen.

REQUIREMENTS HAVE BEEN MET

Combining the dual membrane solution's insensitivity to gravitational orientation with the meandering labyrinth outlet part that increases the contact area between salt and membrane as the process proceeds, was proven to be the ideal balanced solution, as seen in the mass flow graph (Figure 6). Thus the WBI offers injection flow at 1 mL/min up to 10 mL while maintaining high orientation insensitivity and optimal flow rate profile.

ABOUT THE COMPANIES

Subcuject is developing an innovative and proprietary device platform for wearable bolus injection. It is a virtual organisation, working closely with external experts and specialist organisations. The management team and board of directors has decades of experience and a track record in medical devices, pharma and drug delivery. Located north of Copenhagen, Denmark, Subcuject is privately held.

Established in 1987, **Validus Engineering** is an ISO-certified organisation specialising in numerical simulation services within finite element analysis, CFD and multiphysics. These fields combined include structural, thermal, fluid flow, particle and electromagnetic simulations. In addition, the company develops custom software for use within the aforementioned fields. Among its main areas of expertise are medical devices, where applications include respiratory drug delivery, moisture ingress and desiccants, bolus injection and heat sealing. Validus Engineering also assists customers in fields such as offshore engineering, pulp and paper, automotive, electronics, wind power, food tech and heavy industry.

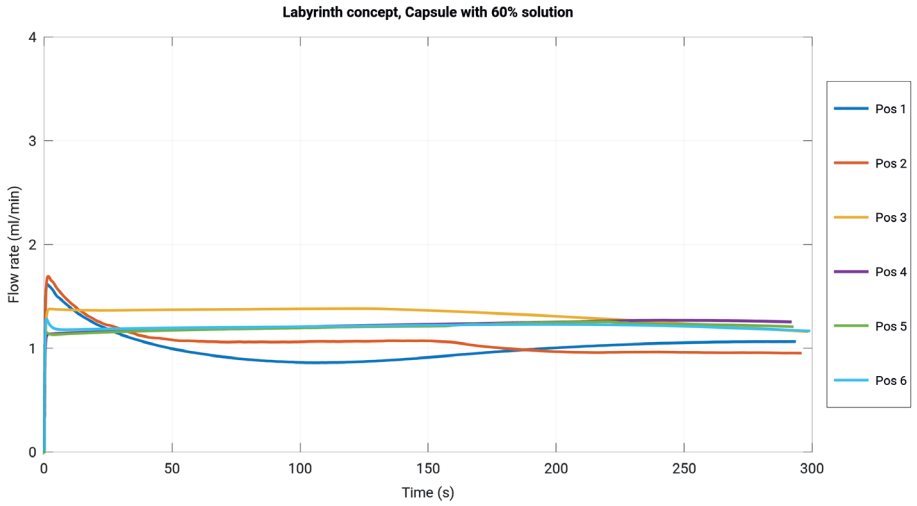

Figure 6: CFD – meeting the device flow rate goal.

ABOUT THE AUTHORS

Marcus Hall is a Sales Representative of Validus Engineering with a background in hands-on numerical simulations as well as CFD software sales and support. He has practical knowledge having worked on the development and analysis of medical devices since 1998, while later efforts have extended also into electronics and LED cooling, pulp and paper, flow control and food tech. Closely related to the service provided by the company, Mr Hall also has long-term experience in the management of high-performance computing equipment for use in the simulation industry. He holds an MSc in Mechanical Engineering.

Björn Ullbrand is the Head of CFD at Validus Engineering. His professional career, since 1994, has been dedicated to fluid flow, thermal and particle analyses in a wide range of fields. These include medical devices, aeronautical engineering, offshore engineering, pulp and paper, and Formula 1 aerodynamics. His major focus is the development of innovative ways to combine commercial CFD software with new academic findings, with the aim of resolving customer challenges in the most efficient way possible. Mr Ullbrand holds an MSc in Aeronautical Engineering.

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

ON drugDELIVERY

2020/21 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
June 2020	Connecting Drug Delivery	PASSED
July 2020	Novel Oral Delivery Systems	Jun 25, 2020
August 2020	Industrialising Drug Delivery	Jul 16, 2020
September 2020	Wearable Injectors	Aug 6, 2020
September/ October 2020	**NEW TOPIC - INAUGURAL ISSUE! Drug Delivery & Environmental Sustainability**	**Aug 20, 2020**
October 2020	Prefilled Syringes & Injection Devices	Sep 3, 2020
November 2020	Pulmonary & Nasal Drug Delivery	Oct 1, 2020
December 2020	Connecting Drug Delivery	Nov 5, 2020
January 2021	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Dec 3, 2020
February 2021	Prefilled Syringes & Injection Devices	Jan 7, 2021
March 2021	Ophthalmic Drug Delivery	Feb 4, 2021
April 2021	Pulmonary & Nasal Drug Delivery	Mar 4, 2021
May 2021	Delivering Injectables: Devices & Formulations	Apr 1, 2021

THE NEXT GENERATION OF COATED PLUNGERS

In this article, Carina Van Eester, Global Platform Leader, Prefilled Syringes and Cartridges at Datwyler Pharma Packaging, explores the benefits of fully coated plungers for prefilled syringes and cartridges.

These days, it is difficult to avoid the topic of COVID-19. In the healthcare industry, we are seeing the implications of the disease play out not only from a world health perspective but also in the work we do on a daily basis. When our new coated plungers, NeoFlex™, were launched back in February at Pharmapack, we were aware of the crisis our Chinese colleagues were facing but did not expect the global scale that this pandemic would reach only two months later.

With the knowledge that many pharmaceutical companies are developing medication to either treat the effects of or vaccinate people against COVID-19, we are aware that the packaging components accompanying these drugs will be an important factor in delivering these life-saving medications in a safe and reliable way to patients in need.

The common delivery applications for these medications will be sure to involve prefilled syringes and cartridges, which means it is essential to have a robust plunger solution offering exceptional reliability and functionality. Datwyler's solution for this drug delivery challenge is its NeoFlex coated plunger (Figure 1).

> "While many coated plungers on the market are only partially laminated, the NeoFlex plunger is fully spray coated, offering several advantages."

ADVANTAGES OF FULLY COATED PLUNGERS

With the rise of therapeutic biologics, as well as autoinjectors and wearables that facilitate self-administration, there are more drug delivery challenges than ever before. In these prefilled syringe and cartridge applications, plungers must meet strict requirements for drug compatibility, functionality and machineability. The best way to achieve these standards is through a complete fluoropolymer coated plunger.

Figure 1: NeoFlex coated plungers are the ideal solution for sensitive drugs in prefilled syringe or cartridge applications.

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While many coated plungers on the market are only partially laminated, the NeoFlex plunger is fully spray coated, offering several advantages:

1. The fluoropolymer coating is naturally lubricious, so no silicone is required to avoid stickiness of the plunger to the barrel or to other plungers. The absence of added silicone oil also reduces particulate levels
2. There is no ring of uncertainty where the partial fluoropolymer laminate ends and the siliconisation begins. The ring of uncertainty poses a risk that the drug will come into contact with the non-coated part of the product, negating its effectiveness. NeoFlex plungers are fully coated so the drug runs no risk of touching uncoated rubber
3. Processing of the plungers in vibratory bowls is easier due to the uniformly reduced surface friction and the smoothness of the plunger surface
4. The trim edge is at the bottom, undercut and coated. There is no shedding of particulates from the trim edge and no influence on the break-loose and gliding forces.

SPRAY COATING VERSUS FILM COATING TECHNOLOGY

NeoFlex plungers are made with Datwyler's proprietary fluoropolymer spray coating technology. Laminates that are used on some plungers on the market are typically made with polytetrafluoroethylene (PTFE) or ethylene tetrafluoroethylene (ETFE) film. Both the spray coating and laminate technologies have barrier properties. However, many other characteristics are quite different:

1. **Flexibility of the coating**: Datwyler's NeoFlex plunger coating is very flexible and is, in fact, a fluoro-elastomer. As a result, the coated component is able to seal against inherent glass surface imperfections. Under compression, no wrinkles occur which could potentially lead to leakage
2. **Compatibility with gamma irradiation**: while some fluoropolymer films cannot be gamma irradiated, the NeoFlex coating can be, and is not negatively impacted
3. **Uniformity of the coating**: Datwyler's fluoropolymer spray coating is applied in conjunction with a tumbling technology that guarantees uniform coating. In the case of film coating, the film is stretched onto the moulded product, which means there is a higher risk of small holes in the coating and variation in the film thickness across the moulded component.

"Analysing extractable and leachable substances is a significant step in guaranteeing the safety of the drug to the patient."

EXTRACTABLES AND LEACHABLES EVALUATION

Extractables and leachables analysis is a significant step in guaranteeing the safety of a drug to the patient. The rubber compound needs to be assessed in the fully assembled prefilled syringe, including the barrel siliconisation, the needle and the needle adhesive. Extractable studies evaluate compounds which have been forced out from the rubber components into the drug product under laboratory conditions. Similarly, leachables studies test for the migration of rubber into the drug product which has been forced out under laboratory conditions. These tests help to determine drug and rubber compatibility – and serve as an initial determinant for whether the rubber should be coated or uncoated.

It is known that fluoropolymer coatings act as a barrier between the rubber and the drug product. Depending on the rubber formulation, the type of coating and test conditions (e.g. extraction solvent, extraction temperature and sterilisation conditions), the list of potential extractables will vary. The extractables are generally grouped into different categories: metal ions, volatile organic compounds, non-volatile organic compounds and semi-volatile organic compounds. All the various coatings on the market – film and spray coating – considerably reduce extractables.

> "The compression of the plunger and the design of the sealing ribs is optimised to ensure that the break-loose force remains low enough for manual injection while maintaining complete seal integrity and limited plunger movement in the presence of air space."

FUNCTIONAL PERFORMANCE

The main characteristics to be taken into account to assess the acceptable functionality of a plunger include: break-loose and gliding forces, seal integrity and plunger movement under pressure fluctuations.

While designing the NeoFlex plunger, Datwyler developed a standard between the various performance criteria in order to make sure that the plunger can be used in a wide range of applications. The compression of the plunger and the design of the sealing ribs is optimised to ensure that the break-loose force remains low enough for manual injection while maintaining complete seal integrity and limited plunger movement in the presence of air space. In order to make sure that the plunger is suitable for secondary devices, the consistency of the break-loose and gliding force over the product shelf life is essential.

To preserve sterility, the plunger and the barrel must have an appropriate interference fit. The NeoFlex plungers are designed with a minimum compression of the first sealing rib of 3% during worst-case conditions (e.g. large barrel, small plunger). Due to the flexibility of the coating, there is no negative effect on the performance of the plunger: the coating does not wrinkle, which guarantees seal integrity and no substantial increase of break-loose and gliding forces.

All sealing rib dimensions are controlled by the mould, which guarantees that they are produced with narrow tolerances, with a minimum process capability of 1.33. The trim edge is undercut which prevents contact of the trim edge with the wall of the barrel, giving a better consistency in gliding forces over multiple batches.

BREAK-LOOSE AN GLIDING FORCES

The break-loose and gliding forces of a plunger depend on many factors: barrel siliconisation, needle size, viscosity of the drug, drug formulation, sterilisation conditions, etc.

The plunger force is measured on empty syringes to characterise the interaction between the barrel and the plunger – and to avoid interference from the fluid or the needle size. The gliding force in empty syringes can be substantially different from the gliding force in filled syringes. However, the break-loose force will remain relatively the same.

In order to have data available with regard to interference from the sterilisation on the final break-loose and gliding forces, a test was done with both gamma and steam sterilised plungers. The break-loose and gliding forces were tested in multiple syringes – both glass and plastic/cyclo-olefin polymer – with standard siliconisation, low siliconisation, and cross-linked siliconisation.

Most biological drugs are stored in refrigerated conditions, although in some cases room temperature may be acceptable. While not necessarily representative, accelerated studies at 40°C have been completed to assess the functional performance.

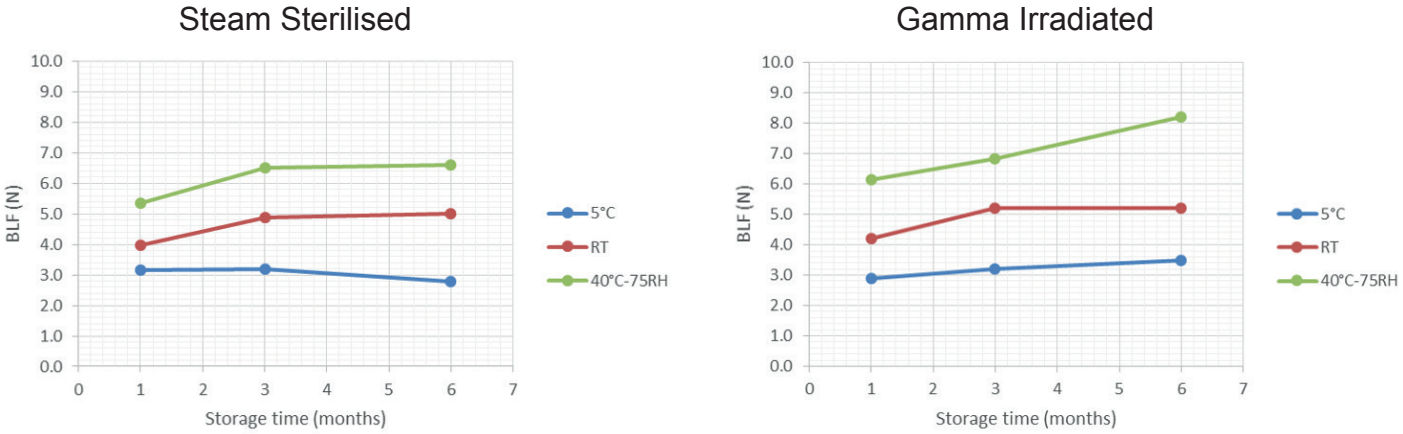

Figure 2: Break-loose force (BLF) at one, three and six months for steam sterilised (left) and gamma irradiated (right) NeoFlex 1.0 mL long plungers in a low siliconised barrel stored at different temperatures.

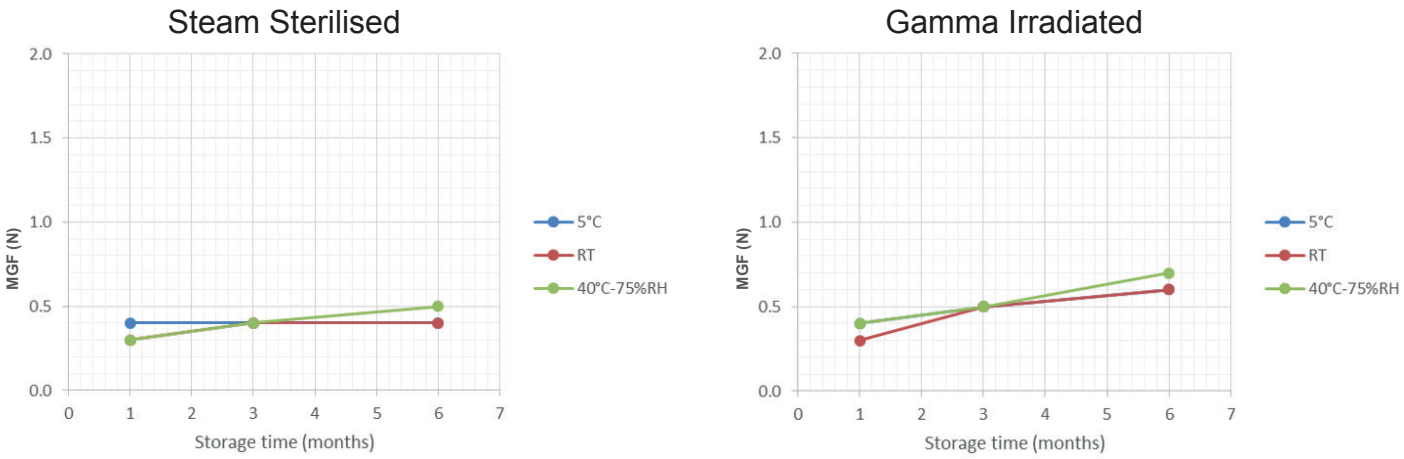

Figure 3: Maximum gliding force (MGF) measured at one, three and six months for steam sterilised (left) and gamma irradiated (right) NeoFlex 1-3 mL plungers in a standard siliconised barrel stored at different temperatures.

The data show that, within a specific temperature range, the break-loose and gliding forces remain low and consistent during storage, even in worst-case conditions – e.g. small barrel, big plunger (Figure 2 and Figure 3).

SEAL INTEGRITY

The sealing ribs of a plunger have two functions:

1. **Guarantee the sterility of the drug:** it is important that no microbes pass the rib farthest from the drug
2. **Prevent loss of content through leakage:** the drug must not pass the first sealing rib and enter the space between the first and second rib. Although all designs have three ribs, Datwyler considers leakage as occurring as soon as the drug passes the first rib.

> "Seal integrity has to be maintained during storage, transport and use."

The rib in contact with the drug is the most important one and, therefore, was tested by means of Helium leak testing, as well as blue dye testing, in both nominal and worst-case conditions – e.g. large barrel, small plunger (Figure 4).

To assess the performance of the seal during use, syringes are filled with blue dye and tested with a pressure of 6 N on the plunger. When no liquid passes the first rib, the plunger seal is guaranteed in dynamic conditions. All NeoFlex designs meet this requirement.

PLUNGER MOVEMENT

Seal integrity has to be maintained during storage, transport and use. In certain instances, the plunger can move under the influence of a change in pressure during air transport. The plunger movement will be limited or zero when there is no air bubble between the plunger and the drug. When there is headspace, the plunger will move if the headspace expands (Figure 5).

Two limits were specified:

- **Warning limit:** the distance between the second and third ribs. If the plunger travels less than this warning limit, it means the third rib is moving into the non-sterile area but the first and second ribs stay in the sterile area and will assure the integrity of the drug
- **Outer limit:** the distance between the first and third ribs. If the plunger travels more than this outer limit, it means all ribs go into the non-sterile area and there is a high risk of contamination of the drug.

In the case of the 3 mL cartridge, it can be concluded that it is safe to have an air bubble of up to 7 mm.

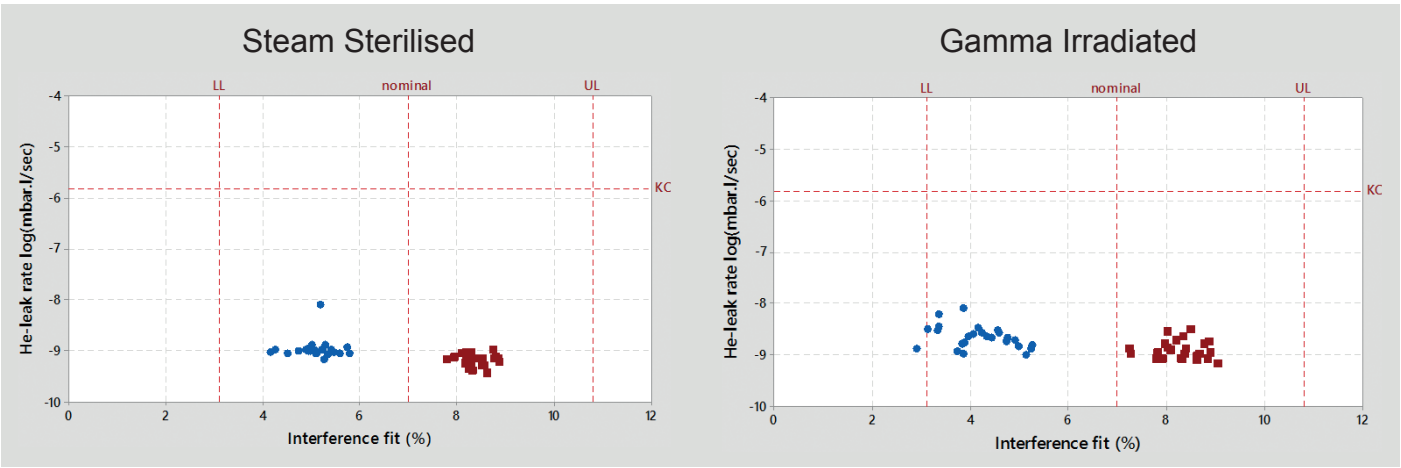

Figure 4: Helium leak rate against interference fit for steam sterilised (left) and gamma irradiated (right) 0.5 mL Neoflex plungers. All cases easily meet the Kirsch Criterion (1.6 x 10^{-6} mbar.L/sec).

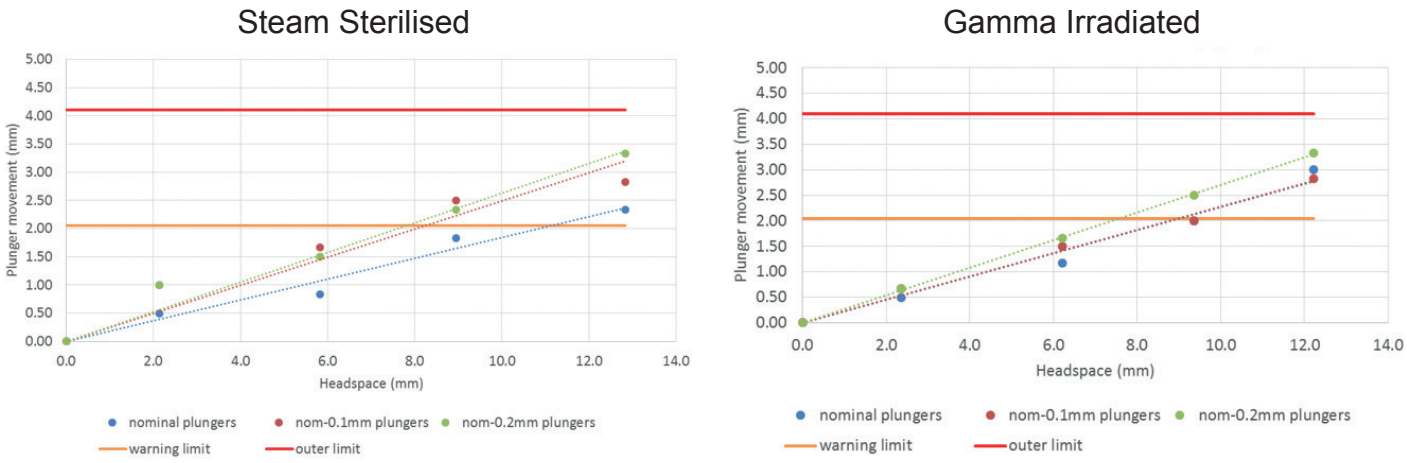

Figure 5: Plunger movement of steam sterilised (left) and gamma irradiated (right) NeoFlex plungers in 3 mL cartridges with different headspaces. Plunger movement is tested in a vacuum chamber at 752 mbara (=8000 ft) at room temperature. This condition is typical of the pressure decay in a pressurised cargo jet.

A ROBUST COATED PLUNGER FOR SENSITIVE DRUGS

Datwyler's NeoFlex plungers are proven to provide reliable drug compatibility, superior functionality and excellent machineability. The fluoropolymer spray coating provides a barrier to extractables and leachables, while ensuring smooth delivery in the field. NeoFlex plungers meet the demand for quality and performance for highly sensitive, large-molecule drugs.

ABOUT THE COMPANY

Datwyler is focusing on high-quality, system-critical elastomer components and has leading positions in attractive global markets such as healthcare, mobility, oil and gas, and food and beverage. With its recognised core competencies and technological leadership, the company delivers added value to customers in the markets served. It has more than 20 operating companies, sales in over 100 countries and more than 7,000 employees. Within the healthcare solutions business area, Datwyler develops, designs and manufactures solutions for injectable packaging and drug delivery systems.

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.

INTRODUCING DATWYLER'S NEXT-GENERATION COATED PLUNGER: **NEOFLEX™**

Datwyler's range of NeoFlex™ plungers offers a robust packaging solution for the prefilled syringe and cartridge markets, taking into account the need for superior functionality and exceptional compatibility. Coated with Datwyler's proprietary spray coating technology, NeoFlex™ plungers are the ideal solution for your drug product needs.

At Datwyler, we help to improve patients' lives – because we care.

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DATWYLER

SaferMed Technologies

SMPFS: A NOVEL PREFILLABLE SYRINGE WITH A GLASS PRIMARY CONTAINER BUT NO NEED FOR EXTREME THERMAL REFORMING

In this article, Stephen Shue, MD, MSc, President, SaferMed Technologies, introduces the company's proprietary prefillable syringe, the SMPFS, whose novel glass-tube-plus-plastic-sheath design enables the use of a standard glass tube primary drug container, but avoids the need for the extreme thermal reforming process that conventional glass prefillable syringes must undergo.

The global market for prefilled syringes (PFS) was valued at US$4.9 billion (£3.9 billion) in 2018 and is expected to exceed $9.7 billion by 2025, according to Global Markets Insights.

The increasing prevalence of chronic diseases such as diabetes and rheumatoid arthritis – which need prolonged drug administration in accurate doses – is one of the reasons behind the growth. PFS can be used to enhance patient compliance and dose accuracy. The emergence of biologics, which often need to be injected, has been another key driver. As well as ease and accuracy of use, benefits of PFS include increased product lifespan, minimised drug wastage – and elimination of the task of transferring a drug from a vial to a syringe, along with a corresponding decrease in the risk of drug contamination.

More than two billion PFS are used worldwide each year – with at least 60 drugs and vaccines available in a prefilled format for use across more than a dozen therapeutic categories. With analysts predicting that, by 2024, sales will reach around 12.4 billion PFS each year, there's never been a better time to focus on producing a world-class PFS.

STANDARD GLASS PFS DRAWBACKS

Almost all the drawbacks of the conventional glass PFS originate from the extreme thermal reshaping process that they must go through, which reforms a segment of standard glass tubing into a glass syringe. The drawbacks include:

- Higher manufacturing cost
- Destabilised stored drug due to drug-container interactions induced by fume deposits
- Lamellae, leachables and extractables associated with reshaped glass syringes
- Fragility issues arising from reshaped portion of glass.

SaferMed has designed the SaferMed Prefillable Syringe (SMPFS), a novel proprietary PFS design comprising two main parts:

- A primary drug container consisting of a glass tubing segment made from the direct cutting of original long glass tube, in combination with suitable elastomeric components
- A plastic syringe, made using standard precision mould injection mass production processes, which functions as a protective sheath fixed around the glass tube.

Together these components form the function orientated PFS. SaferMed has focused on eliminating the drawbacks of conventional glass PFS, which must be shaped from a segment of glass tubing heated to extreme temperatures.

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"The use of standard glass tubing, simply cut to size but with no thermal reforming, means that E&L can be dramatically reduced."

With the SMPFS, there is no need for the extreme thermal reshaping processes to be applied to the glass tubing drug primary container – and so no need for complex manufacturing facilities. All components are easily sourced from customised suppliers.

Easier and more efficient manufacturing means a lower overall cost for SMPFS – as low as one-third to half of the cost of conventional PFSs. The list of benefits also includes a reduction in the energy used during the glass manufacturing process.

The integrated plastic sheath protection of the SMPFS solves the fragility issues of conventional glass PFSs – providing safer transportation and stockpiling. The plastic component also provides the familiar syringe form and function (syringe barrel, finger flange and tip) required for assembling the additional components such as the plunger and needle hub with needle safety shield (see Figure 1).

The use of standard glass tubing, simply cut to size but with no thermal reforming, means that extractables and leachables (E&L) can be dramatically reduced or even eliminated, especially metallic ions and salts extracted by drugs, fume deposits, lamellae, and residual tungsten and glue often found in conventional glass PFSs. This confers the additional advantage of longer shelf life, including for vaccines, due to minimised or eliminated contaminants that are commonly found in traditional glass PFSs.

SaferMed's innovative technologies can be applied to produce devices in various volumes and configurations, all based on the current state-of-the-art technologies that provide physically and chemically stable elastomers, and within the paradigms of currently marketed glass PFS and cartridges with elastomeric components *in situ*.

For example, SMPFS can be configured with a detachable needle with front elastomeric stopper, and with a permanent needle, and in 1 mL and 3 mL volumes. Large-volume PFS for the delivery of antibiotics, and devices with volumes up to 25 mL are also possible.

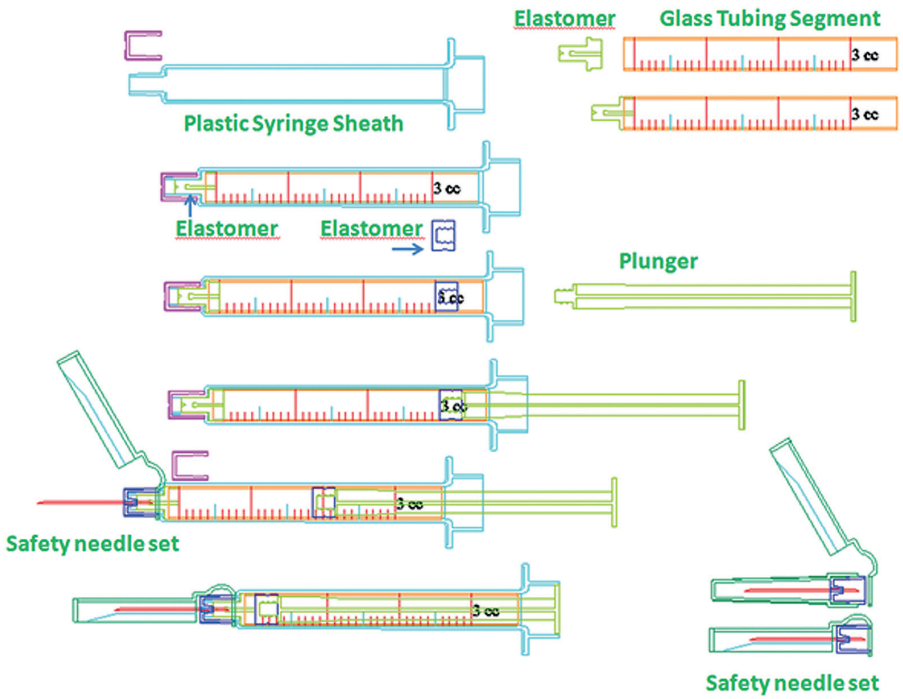

Figure 1: Main components of SaferMed's SMPFS (shown here is a 3 mL variant with detachable needle and front elastomeric stopper).

"The SMPFS, covered by several US and Taiwan patents, with patent applications pending in other areas, is currently at the concept stage and SaferMed Technologies seeks partners to advance its development."

More than two billion PFSs are used worldwide each year – with at least 60 drugs and vaccines available in a prefilled format for use across more than a dozen therapeutic categories. With analysts predicting that, by 2024, sales will reach around 12.4 billion PFSs each year, there's never been a better time to focus on producing an innovative, improved yet lower-cost PFS.

BUSINESS STRATEGY

The SMPFS, covered by US and Taiwan patents, with patent applications pending in other areas, is currently at the concept stage and SaferMed Technologies seeks partners to advance its development – an investor or device partner, to develop the device further, or a pharma partner to develop a pharmaceutical or biologic product that uses the devices.

In addition to the benefits around reduced E&L, reduced fragility, increased stability, longer shelf life, and reduced cost of goods described above, with its SMPFS SaferMed aims to reduce needle-stick injuries to needle-based delivery device users, to make the use of PFS easier and more convenient for patients and healthcare workers, and to enable a syringe application that is more environmentally friendly.

The ultimate objective is, in collaboration with a partner, to introduce this beneficial technology to the biopharmaceutical industry.

ABOUT THE AUTHOR

Stephen Shue, MD, MSc, is President of SaferMed Technologies. Having been a user and innovator of clinical needle devices for over 20 years, Dr Shue led his colleagues devoted to the innovation and evolution of clinical needle devices, to provide safer and more efficacious needle devices to front-line healthcare professionals, including prefilled syringes.

WHICH IS THE BETTER TOXICITY TESTING STRATEGY FOR COMBINATION DEVICES?

In this article, Mark Turner, President of Medical Engineering Technologies, explores the issue of toxicity testing for combination devices and asks which is the better testing strategy – ISO 10993 or extractables and leachables?

You have a prefilled drug delivery system and you are wondering how to demonstrate its biological safety. Your product is the pharmaceutical but you are now delivering it in a ready-to-use syringe or transdermal patch, an inhaler or maybe an implant.

> "The pharmaceutical approach still needs the extractables study to examine potential contaminants that could migrate into the formulation over a longer period."

A pharmaceutical manufacturer needs to demonstrate that a packaging system is suitable for its intended use and that is does not introduce extraneous materials (of toxicological concern) into the formulation or degrade the formulation's performance. The formulation must also be free from process equipment related leachables at levels of toxicological concern. A medical device manufacturer needs to demonstrate that their device does not cause toxicity in its mode of use.

The US FDA definition serves both camps well: "Drug product containers and closures shall not be reactive, additive or absorptive so as to alter the safety, identity, strength, quality or purity of the drug beyond the official or established requirements."[1]

Significant progress towards the satisfaction of all these requirements can be made in a single extractables and leachables programme. A range of solvents and extraction conditions for the purposes of targeting a variety of potential leachables can be applied for both the device and the formulation packaging.

ON-BODY DEVICES

Taking an on-body insulin pump as an example, there will be the external components of the cartridge and pump that are in contact with the body. The contact is with skin in this case, whilst only internal components will contact the formulation. A leachables study can be conducted on the fluid path to obtain information on what is likely to leach into the formulation. This same information can form the "simulated use" chemical characterisation of leachates required by ISO 10993.[2]

The pharmaceutical approach still needs the extractables study to examine potential contaminants that could migrate into the formulation over a longer period. Similarly, the medical device approach will be missing information on cytotoxicity[3] and local irritation.[4] Some extra work is required in each case. Additionally, according to ISO 10993, the biocompatibility of the outside (skin contact) surface should be considered. Therefore, an extractables study should include the entire device – not just the fluid path.

EXTRACT MEDIA

A choice of media – such as 50% water / 50% ethanol – will give good information for the pharmaceutical extractable analysis and the device mid-polar leachables. The medical device extraction requires polar

> "When considering leachables from a pharmaceutical container, the nature of the formulation should be taken into account."

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and mid-polar extracts to simulate the lipid and aqueous environments within the body (a third more polar extract must be included for invasive devices). Both study sets could use either saline or water as the polar extract medium.

When considering leachables from a pharmaceutical container, the nature of the formulation should be taken into account – is it aqueous and, if so, what is the pH; does it contain compounds that will influence migration of substances; is it non polar? To overcome this, in part of the study the leachables will need to be examined using the actual formulation. This is compatible with ISO 10993, which contains suggestions of which solvents to use but does not dictate them.

Post-extraction concentration and digestion for inorganic testing is also acceptable for both routes. For a pharmaceutical container, there may be more concern about the leachables concentration varying over time and the need for testing multiple batches. This would also be prudent for medical devices but it is not usually applied. Other additional questions for pharmaceuticals relate to bioavailability at the end of the shelf life.

ANALYTICAL METHODS

The analytical methods are also largely the same. For the extracted materials, inductively coupled plasma mass spectrometry (ICP-MS), gas chromatography–mass spectrometry (GC-MS) and liquid chromatography–mass spectrometry (LC MS) are most commonly applied. These methods allow quantification of the majority of the organic materials (across a wide range of volatilities) that might be found and any associated inorganic elements. There can be many variances for other analyses such as infrared absorbance and surface chemistry/morphology on devices and USP monograph and physicochemical analysis for pharmaceuticals.

TOXICITY ASSESSMENT

In both the pharmaceutical case and the medical device case, the chemical information gained goes on to be analysed by a toxicologist. In the toxicity risk assessment (following the analytical study), the same principles apply to both routes. Items such as the application of analytical evaluation thresholds (AET) and safety concern thresholds (SCTs) are common.[5] The Product Quality Research Institute (PQRI, Washington, DC, US)[6] has recommended that the high-risk SCT is set at 0.15 µg/day, whilst the low-risk SCT is set at 1.5 µg/day, both having been justified from toxicological and safety perspectives. Under certain conditions, such as short-term exposure or in the treatment of a life-threatening condition, the SCT can be raised above 1.5 µg/day.[7]

> "The quick answer to the question of whether to follow extractables and leachables testing or ISO 10993 for a combination device is that both are required."

IMPLANT DEVICES

What if my drug-releasing product is an implant? ISO 10993 includes a biocompatibility matrix[8] which describes the information it is necessary to obtain in order to demonstrate compliance. The matrix cross references body contact with "toxicological end points". These end points are the modes of toxicity that must be considered within a biological risk assessment. For an implant, just about everything is included: implantation, geneotoxicity, mutagenicity and chronic toxicity, to name just a few. Again, this is similar to the requirements for a pharmaceutical agent.

The requirements for an implant are more demanding than those for the surface-contacting insulin pump. Also, the "simulated use" extraction needs to be more aggressive because of the long-term contact at 37°C. There are many parts to ISO 10993. ISO 10993-18,[9] the chemical characterisation part, tells us to use exhaustive or exaggerated extraction for implants. ISO 10993-12,[10] the sample preparation part, is due for an update. It currently defines exaggerated extraction as 24 hours in the solvent at 70°C (however, this process might dissipate volatile contaminants and therefore should be accompanied by lower temperature extractions). The most aggressive possible solvent should be used, as long as it does not degrade the device in a non-representative way.

In situ degradation should also be considered for implanted devices. ISO 10993 has three sections detailing this requirement. One each for metal,[11] ceramic[12] and polymeric[13] devices.

PHARMACOPEIA TESTING

There are a variety of areas in which the USP makes requirements of pharmaceutical manufacturers. Namely, USP chapter <1663>, Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems, which is the basis for the chemical safety assessment section of USP <661.2>. This will soon be supported by two documents which are currently in draft form, USP <665> the extractables profile, and the chemical safety qualification draft USP <1665>. The latter applies to manufacturing systems, where a greater range of extraction solvents should be considered.

STUDY DESIGN

There are well-defined components and structures to be used in analytical and toxicity study design and reporting. The first step is an assessment of the input materials and processes, which is used to define what chemicals might be available from containers, devices and production methods. In pharmaceuticals, this is framed as a justification of methods used. In the device world, it is called a biological risk assessment. This is the information that goes into the study design. It contributes to identifying:

- The extraction media to be used
- The extraction conditions
- The analytical methods to be applied as well as:
  - method development
  - method quantification standards to be included
  - method validation
  - defining the sensitivity needed.

Again, the principles of study design and reporting are largely common between medical devices and pharmaceuticals.

CONCLUSION

The quick answer to the question of whether to follow extractables and leachables testing

or ISO 10993 for a combination device is that both are required. You need to prove the safety of the pharmaceutical agent and the medical device. The practical solution is that a well-designed extractables and leachables study will cover most of the requirements for medical device biocompatibility. In the pharmaceutical case, it is necessary to show that the formulation is still active to the extent expected without the addition of extraneous materials. For the medical device, we don't want to put extraneous materials into the body – whether they come from the formulation or parts of the device not in contact with the formulation.

Some additional work will be required to cover both sets of requirements but there is also a lot of overlap. Both systems have hierarchy of risk related to intimacy of body contact, although low-risk surface or transient contact devices could still be delivering into high-risk environments such as ophthalmics or intravascular.

ABOUT THE COMPANY

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

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ABOUT THE AUTHOR

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

MITSUBISHI GAS CHEMICAL

UPDATE ON OXYCAPT MULTILAYER PLASTIC VIAL AND SYRINGE

Here, Tomohiro Suzuki, Associate General Manager at Mitsubishi Gas Chemical Company, gives an update, including new oxygen barrier data, on the development of the OXYCAPT™ multilayer plastic vial and syringe.

Mitsubishi Gas Chemical (MGC) is one of Mitsubishi's companies and one of the leaders in the field of oxygen barrier and absorbing technologies. Our special polymer, Nylon-MXD6, has been used for the middle layer of multilayer beverage bottles for many years to prevent oxidation and carbon dioxide evaporation. Also, our oxygen absorber AGELESS has been used for more than 30 years for intravenous solutions and prefilled syringes to prevent oxidation of injectable drugs.

> "Although about 70% of UV light of 300 nm transmits through glass and COP, only 1.7% of UV light transmits through OXYCAPT."

Based on these technologies and experiences, we have developed a multilayer plastic vial and syringe called OXYCAPT (Figure 1). It consists of three layers – the drug contact layer and the outer layer are made of cyclo-olefin polymer (COP), and the oxygen barrier layer is made of our novel polyester (Figure 2). OXYCAPT possesses excellent oxygen barrier, high water vapour barrier and ultraviolet (UV) barrier properties, very low extractables, high pH stability, low protein adsorption and aggregation, a silicone-oil free barrel, high transparency, high break resistance, easier disposability and lighter weight.

Figure 1: The OXYCAPT multilayer plastic vial and syringe.

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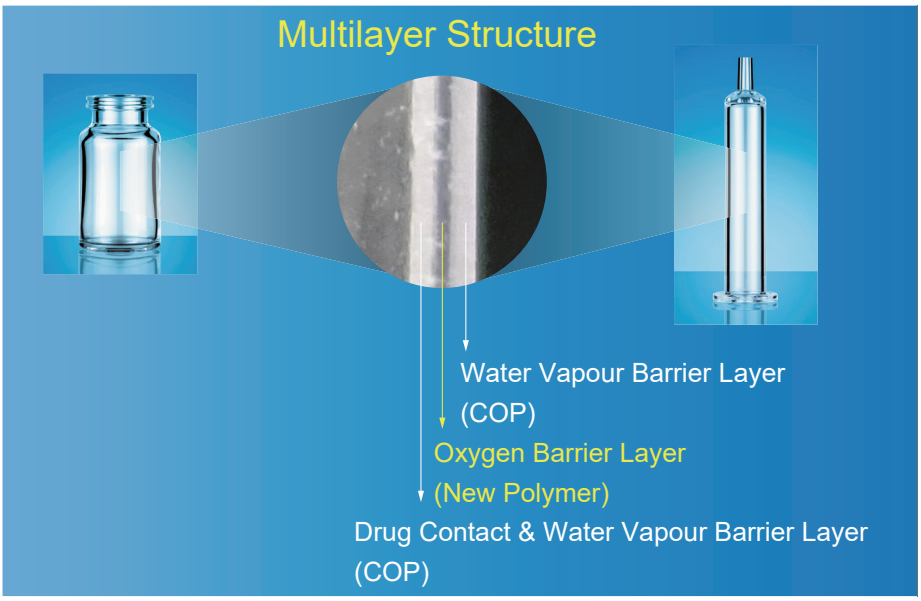


Figure 2: The multilayer structure.

There are two types of OXYCAPT multilayer plastic vial and syringe – OXYCAPT-A and OXYCAPT-P. OXYCAPT-A has achieved a glass-like oxygen barrier (Table 1). According to some internal studies, thanks to its oxygen absorbing function, OXYCAPT-A can maintain lower oxygen concentrations in the headspace than Type 1 glass. OXYCAPT-P has also achieved an excellent oxygen barrier, although there is no oxygen absorbing function. For example, the oxygen barrier of the OXYCAPT-P vial is about 20 times better than that of a COP monolayer vial. OXYCAPT-A is particularly suitable for oxygen-sensitive drugs and OXYCAPT-P is recommended for all drugs.

OXYCAPT is an excellent UV barrier. Although about 70% of UV light of 300 nm transmits through glass and COP, only 1.7% of UV light transmits through OXYCAPT (Table 2). We have confirmed this feature also contributes to the stability of biologics.

Regarding the water vapour barrier, OXYCAPT cannot reach the performance of glass. However, it is similar to COP, which has been used for injectable drugs for a long time, and easily meets the requirements of a water vapour barrier in ICH guidelines.

"The OXYCAPT syringe consists of a tip cap, a barrel, a polytetrafluoroethylene-laminated stopper and a plunger rod."

"The OXYCAPT vial and syringe are produced by co-injection moulding technology."

Studies have shown extremely low extractables from OXYCAPT. One study was conducted to confirm volatile, semi-volatile and non-volatile impurities from OXYCAPT. Water and four solutions (50% ethanol, NaCl, NaOH and H_3PO_4) were selected, and impurities were measured by gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-UV spectroscopy-mass spectrometry (LC-UV-MS) after 70 days at 40°C. Compared with the blank, impurities were not detected in OXYCAPT containers. A second study confirmed that inorganic extractables levels from OXYCAPT were

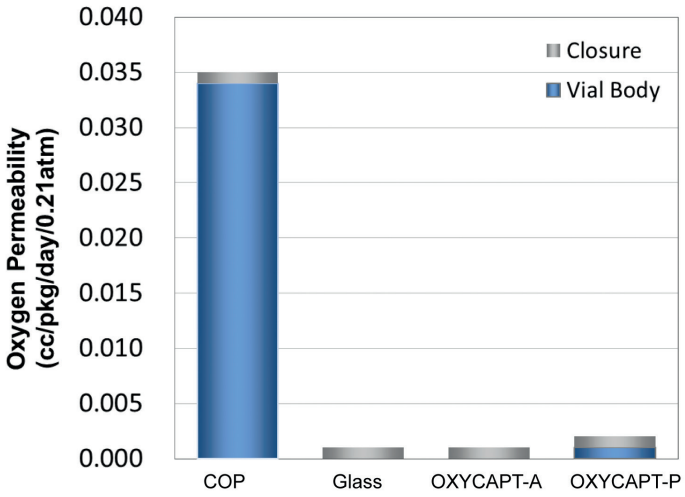


Table 1: Graph of oxygen barrier.

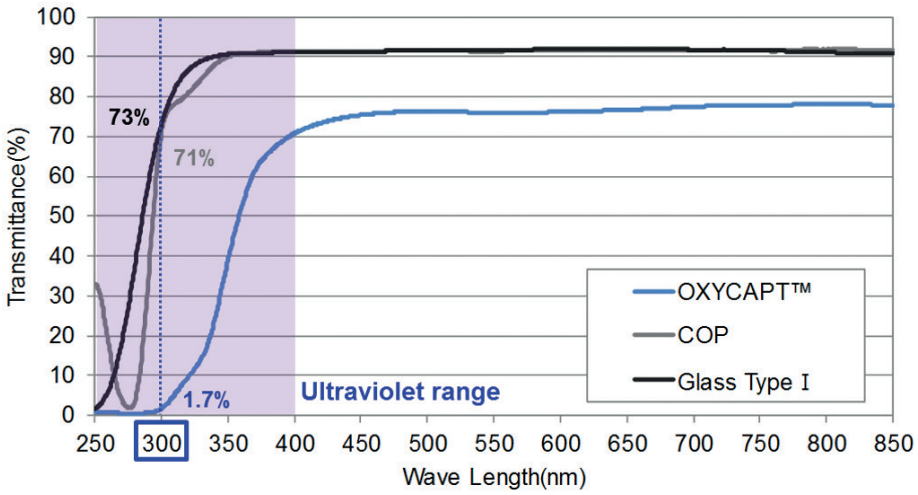


Table 2: Graph of ultraviolet barrier.

"We are the first company that has succeeded in developing multilayer plastic syringes."

similar to those from COP, which is well known as an extremely pure polymer, and with a better extractables profile than Type 1 glass. Lower levels of inorganic extractables are known to contributes to better pH stability in drug products (Table 3).

The OXYCAPT syringe consists of a tip cap, a barrel, a polytetrafluoroethylene-laminated stopper and a plunger rod. Although a very small amount of silicone oil is sprayed on the stoppers of OXYCAPT syringes, no silicone oil is baked on the barrel. According to our internal studies using existing antibodies, we have found this feature leads to much less protein aggregation compared with existing Type 1 glass syringes.

The OXYCAPT vial and syringe are produced by co-injection moulding technology. Although this technology has been applied to beverage bottles for many years, we are the first company that has succeeded in developing multilayer plastic syringes. We have also developed the inspection methods for the oxygen barrier layer. All the containers are 100% inspected by state-of-the-art machinery.

MGC can offer bulk vial, ready-to-use (RTU) vial and RTU syringes. Regarding the RTU products, vials and syringes are provided in ISO-based nest and tub formats (Figure 3). The nest and tub are mainly sterilised by gamma ray. There are 2 mL, 6 mL, 10 mL and 20 mL for vials, and 1 mL long and 2.25 mL for syringes

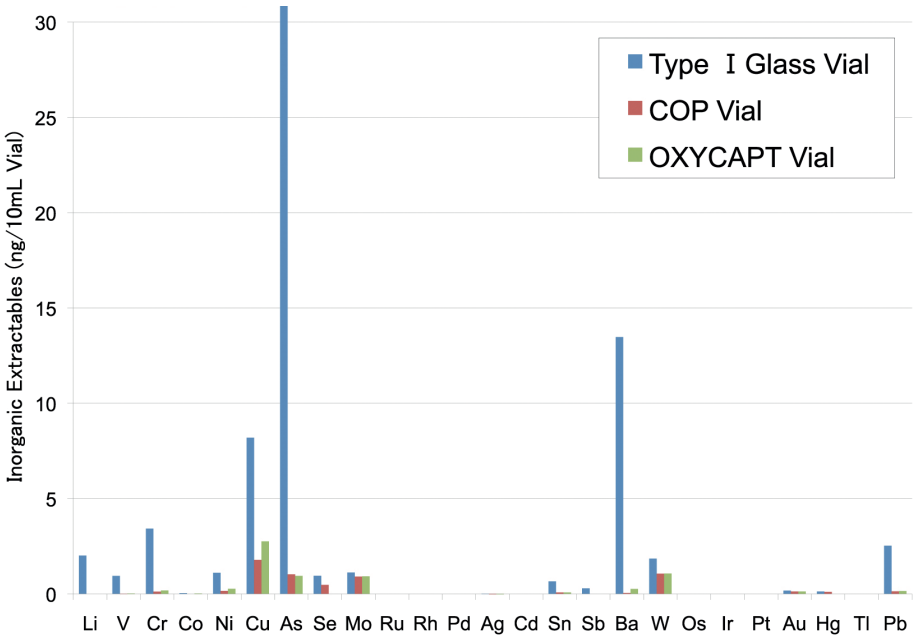


Table 3: Graph of inorganic extractables.

Figure 3: The nest and tub.

(Table 4). We are willing to provide samples for initial testing free of charge.

Each polymer meets the requirements of USP 661, USP87, USP88, EP, and has been filed in the US FDA's drug master file (DMF). The vials and syringes are also compliant with each pharmacopoeia and have been filed in the DMF. The syringes are produced and controlled in accordance with ISO 13485.

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 4: Product portfolio.

COLD STORAGE RESISTANCE

We have conducted some studies of cold-storage resistance. OXYCAPT vials and a competitor's COP monolayer vials were stored at approximately -180°C in a gas phase of liquid nitrogen, and then dropped from a height of 150 cm. Although some COP monolayer vials were broken, no breakage was observed in the OXYCAPT vials (Figure 4). As liquid nitrogen storage has become popular, thanks to the spread of regenerative medicine, OXYCAPT is expected to be used for this new field.

Finally, we would like to share some of our latest data. We are often asked if the oxygen barrier of OXYCAPT-A is better than Type 1 glass or not. In addition, some customers have informed us that the oxygen barrier of COP must be improved at lower temperatures. To answer such questions, we measured oxygen concentration in vials after storage at 25°C and 5°C. We confirmed that the oxygen concentration of OXYCAPT-A was better than that of Type 1 glass at 25°C (Figure 5). Also, we found that the oxygen concentration in COP vials at 5°C climbed to 10% after four months' storage and OXYCAPT-A and -P could maintain very low oxygen concentrations at both 25°C and 5°C (Figure 6).

In conclusion, OXYCAPT has been developed to overcome some of the current problems conventional PFS face, and to meet unmet needs in the pharmaceutical industry. In addition to special features of COP such as a high water vapour barrier, high break resistance, very low extractables and low protein adsorption, OXYCAPT can offer a high oxygen and UV barrier. We believe OXYCAPT brings considerable benefits, not only to improve product performance but also to achieve meaningful product differentiation, in the rapidly growing pharma industry.

ABOUT THE COMPANY

Mitsubishi Gas Chemical (MGC) does business in a wide range of fields, from basic chemicals to fine chemicals and functional materials. MGC established its advanced business development division in 2012 as a centre for creating new businesses, and has developed the OXYCAPT plastic vial and syringe as an alternative to glass containers.

ABOUT THE AUTHOR

Tomohiro Suzuki joined Mitsubishi Gas Chemical in 1998. He worked in the oxygen absorbers division until 2011 before moving 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 the marketing of the OXYCAPT plastic vial and syringe.

OXYCAPT™ Vial is more durable than COP Vial at cryogenic temperature .

Samples and Test Methods

- Number of vial: 20 (OXYCAPT™-A 10 mL vial)
- Closure: brominated butyl rubber with aluminum seal
- Filled with 10 mL distilled water
- Stored: approximately -180°C (liquid nitrogen gas phase)
- Extremely frozen vials were dropped to a steel plate from 150 cm

Test Results

Number of Breakage	
OXYCAPT™-A Vial	COP Vial
0/20	8/20

Broken COP Vial

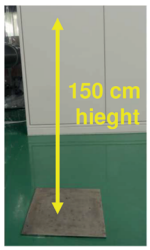
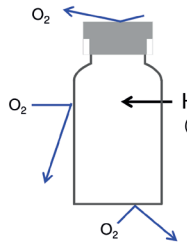


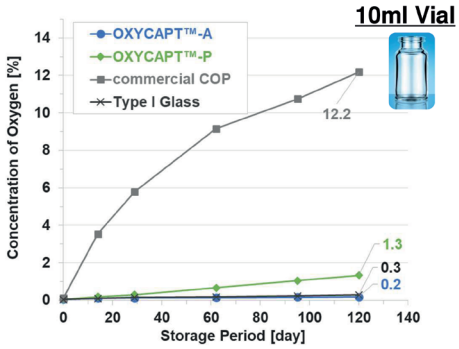
Figure 4: Break resistance at cryogenic temperature.

OXYCAPT™-A keeps better oxygen barrier than glass.
OXYCAPT™-P keeps much better oxygen barrier than COP.

Test sample
- OXYCAPT™-A & -P 10 mL vial
- Butyl rubber closure with aluminium seal

Test method
- Initial oxygen concentration: 0%
- Stored at 25℃ ・ 60%RH
- Analysis; oxygen analyzer





Calculated Oxygen Concentration after 2 years

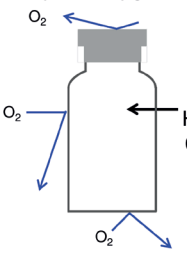
OXYCAPT-A	OXYCAPT-P	COP	Glass
0.7%	7.7%	21.0%	1.5%

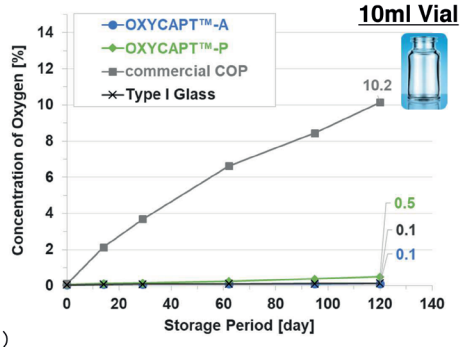
Figure 5: Oxygen concentration at 25°C.

OXYCAPT™-A keeps better oxygen barrier than glass.
OXYCAPT™-P keeps much better oxygen barrier than COP.

Test sample
- OXYCAPT™-A & -P 10 mL vial
- Butyl rubber closure with aluminium seal

Test method
- Initial oxygen concentration: 0%
- Stored at 5℃
- Analysis; oxygen analyser





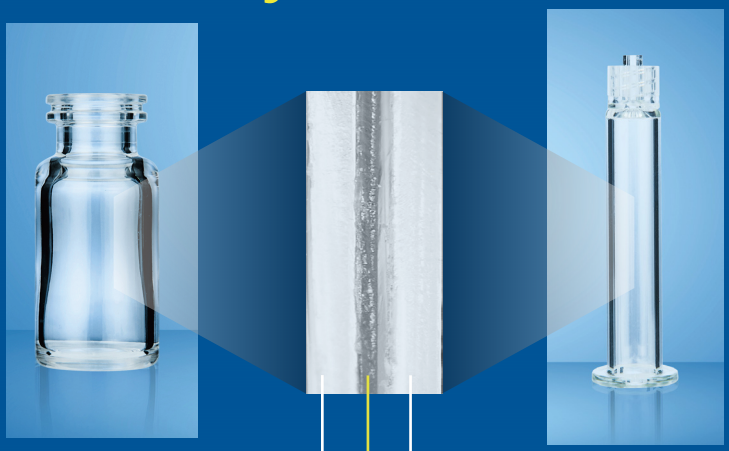
Calculated Oxygen Concentration after 2 years

OXYCAPT-A	OXYCAPT-P	COP	Glass
0.4%	2.6%	21.0%	0.5%

Figure 6: Oxygen concentration at 5°C.

OXYCAPT™ Plastic Vial & Syringe

Multilayer Structure



- Excellent Oxygen Barrier
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- Very Low Extractables
- Low Protein Adsorption
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- Gamma-sterilized Vial & Syringe
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SILICA RE-EMERGES AS POTENTIAL NUCLEIC ACID DELIVERY VECTOR

Nigel Theobald, Chief Executive Officer of N4 Pharma, looks at the challenges of oligonucleotide delivery and explores approaches to overcome them.

Rapid progress in molecular biology over the last three decades has led to nucleic acids, such as plasmid DNA (pDNA), messenger RNA (mRNA) and small interfering/silencing RNA (siRNA) being proposed for use as therapeutic agents. The market has seen significant research and development investment in this field by pharma and biopharma companies, with the pDNA market alone expected to see a growth rate of approximately 23% to 2024.[1]

It was reported that, at the end of 2018, the number of clinical trials in which oligonucleotides had been either tested as vaccines or used to inhibit specific cellular processes or replace faulty genes was close to 600 (in the period 2016–2018). These developments in the market highlight the increasing enthusiasm for the potential of DNA/RNA-based therapies.

However, while promising as potential prophylactic vaccines and treatments for cancer and other diseases, nucleic acids are difficult to formulate as drugs. It is widely accepted that an effective nanoparticle delivery system would be key in enabling them to be used successfully in a therapeutic setting. As such, research efforts have been focused on the significant challenge of nucleic acid delivery.

EARLY RESEARCH

When considering cancer therapeutics specifically, initial research focused on the delivery of small-molecule drugs, with encapsulation into a variety of liposome structures and pegylation among the favoured approaches. The objectives for successful drug delivery are today, as they were then, to protect the drug substance from early or rapid degradation in the body; to deliver it preferentially to the target site of action; and to offer a combination of high loading capacity, controlled release with extended half-life, no leakage and no interference with the stability of the encapsulated product.

"While promising as potential prophylactic vaccines and treatments for cancer and other diseases, nucleic acids are difficult to formulate as drugs."

In addition, good biocompatibility, low toxicity and biodegradability, as well as a clear understanding of the mode of action of the delivery system are critical factors. Nonetheless, multiple barriers need to be overcome in order to achieve successful delivery of nucleic acids – such as protecting nucleic acids against digestion by nucleases in extracellular and intracellular space; transporting a negatively charged, hydrophilic molecule across the negatively charged, hydrophobic cell and nuclear membrane; and ensuring immunogenicity of vaccine products.

CURRENT DELIVERY SYSTEM HURDLES

Initial attempts to deliver nucleic acids to target cells were focused on viral systems, which have high delivery efficacy – but their widespread use is limited by immunogenicity and toxicity concerns. Lipid nanoparticles (LNPs) then emerged

"Initial attempts to deliver nucleic acids to target cells were focused on viral systems, which have high delivery efficacy – but their widespread use is limited by immunogenicity and toxicity concerns."

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as a popular alternative and are considered to be the current standard for nucleic acid delivery. They can protect nucleic acid from digestion and can be produced with a catatonic outer membrane to facilitate cell entry.

However, there are several limitations to lipid systems. As a result of the liposome interaction with the lipid components of the cell membrane, issues such as cell toxicity – which leads to the release of systemic inflammatory cytokines – is a serious disadvantage. Liposomes can also accumulate in the liver and spleen, with the resulting possibility of hepatotoxicity.

Research has since been directed at silica. However, while inert and safe, most silica systems tested to date have been smooth mesoporous particles – meaning the nucleic acid is attached to the side of the particle, limiting the amount that would be successfully delivered into the cell. As a result, researchers are searching for an alternative, effective, non-lipid delivery solution that protects the nucleic acid, delivers enough of it into the cell for the required immune response and ensures safety and immunogenicity.

"The goal of an ideal gene vector is to deliver pDNA intracellularly and achieve transfection efficacy."

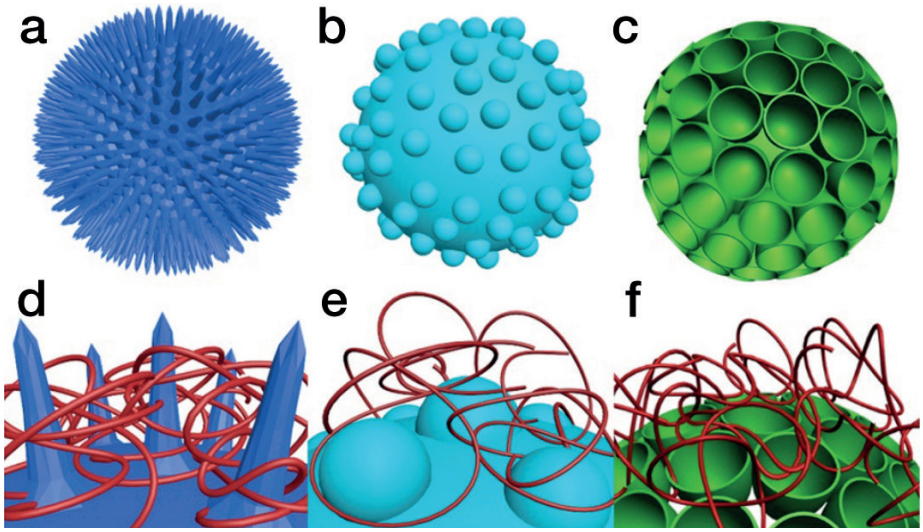


Figure 1: 3D model images displaying silica nanoparticles featured with spiky (a), raspberry (b) and flower-like (c) morphologies and spike (d), hemisphere (e) and bowl (f) type subunit nanotopographies conjugated with plasmid DNA at the interface.

Approaches using 're-engineered' silica nanoparticles (SNPs) that have been adapted to have a high surface area and high capacity are being considered as suitable alternatives to LNPs.

NOVEL SNPS SHOW PROMISE

By functionalising silica to alter its topography, researchers are now demonstrating how it can be considered a viable delivery system for nucleic acids. In a recent comparative study, scientists at the University of Queensland (UQ, Australia) investigated how the structure of SNPs impacts their performance as a nucleic acid delivery system.[2] SNPs with spiky, raspberry and flower-like morphologies were constructed with spike, hemisphere and bowl type subunits, respectively (Figure 1). To facilitate successful binding of each particle type with pDNA, negatively charged bare SNPs were modified with branched polyethylenimine (PEI) with a molecular weight of around 10 kDa, and plasmid DNA expressing enhanced green fluorescent protein (pDNA-EGFP) was loaded on the PEI modified SNPs (SNPs-PEI).

Scientists at UQ found that the spiky type subunits exhibited stronger binding affinity towards pDNA molecules and allowed effective protection against nuclease degradation when compared with the other morphologies and a commercial transfection agent. Out of the three, the spiky nanoparticles were shown to facilitate efficient cellular uptake, endosomal escape and delivery of pDNA to the nucleus most effectively, leading to successful intracellular gene expression and the highest transfection rate. The spiky SNPs also achieved high pDNA loading capacity up to 133 ng/µg. In comparison, flower-like SNPs-PEI (Flw-SNPs-PEI) showed a loading capacity of 114 ng/µg, slightly lower than Spiky-SNPs-PEI, and the raspberry-like SNPs-PEI (Ras-SNPs-PEI) and smooth-surfaced SNPs (S-SNPs-PEI) displayed a significantly lower loading capability (89 and 38 ng/µg respectively) (Figure 2).

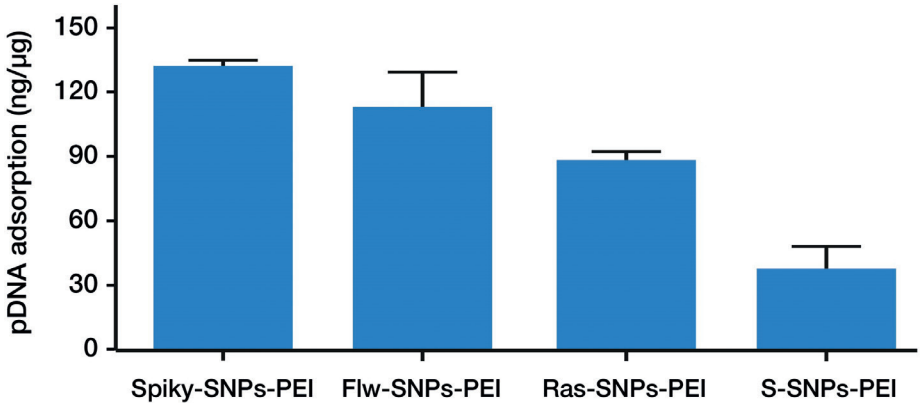


Figure 2: Loading capacity of pDNA-EGFP on Spiky-SNPs-PEI, Flw-SNPs-PEI, Ras-SNPs-PEI and S-SNPs-PEI.

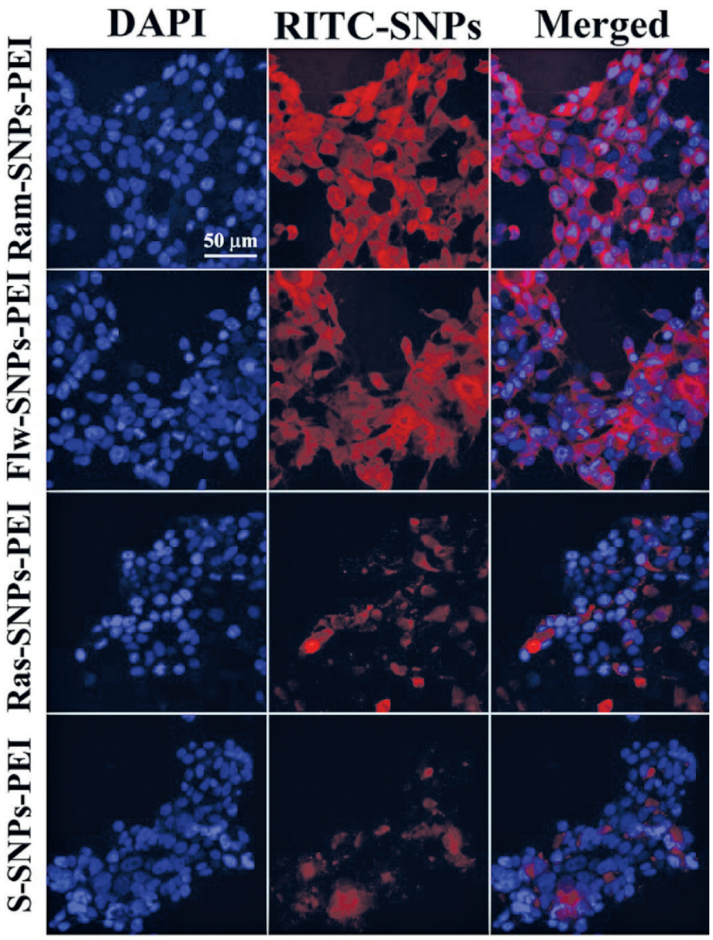


Figure 3: Cellular uptake analysis of pDNA/SNPs-PEI formulations in HEK-293T cells at a nanoparticle concentration of 40 μg/mL. Confocal images of cells incubated with pDNA loaded RITC-labelled SNPs-PEI (red fluorescent) for 4h.

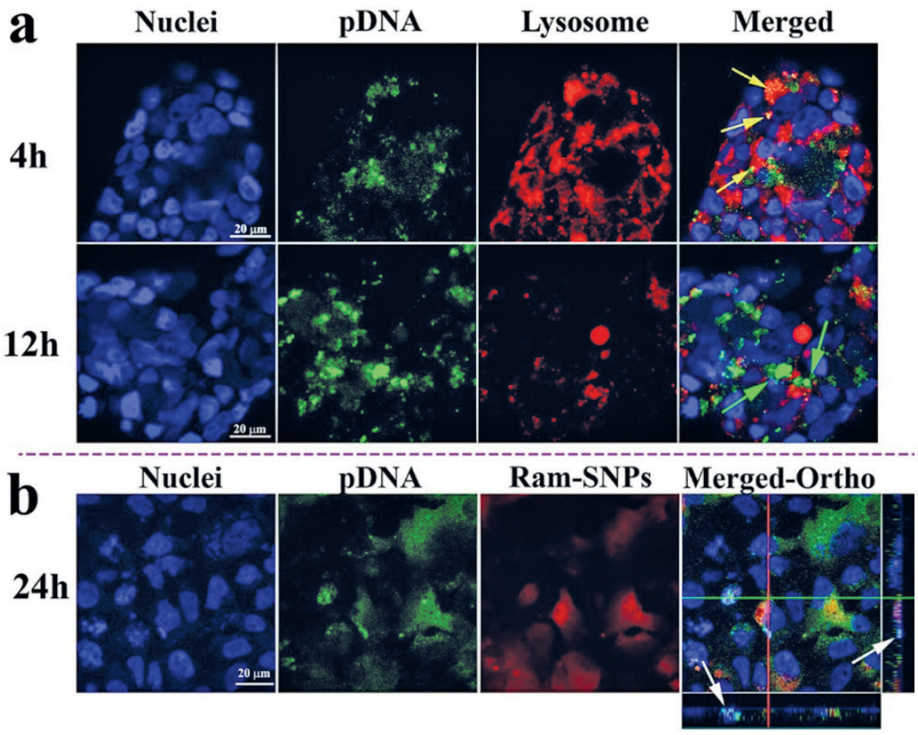


Figure 4: Intracellular tracking of fluorescein labelled-pDNA (green) in HEK-293T cells delivered by Spiky-SNPs-PEI at a nanoparticle concentration of 80 μg/mL. (a) Confocal images of cells incubated with pDNA/Spiky-SNPs-PEI for 4 and 12 h (a) and 24 h (b).

CELLULAR UPTAKE

The goal of an ideal gene vector is to deliver pDNA intracellularly and achieve transfection efficacy. Each of the pDNA/SNPs-PEI formulations were compared for their cellular uptake ability in human embryonic kidney cells 293T (HEK-293T). SNPs-PEI were firstly labelled with rhodamine B isothiocyanate (RITC) and then loaded with pDNA. Formulations were incubated with cells for four hours, followed by nuclei staining using 4',6-diamidino-2-phenylindole (DAPI). The cellular uptake was evaluated by confocal microscopy and flow cytometry. As shown in Figure 3, the nuclei show in blue fluorescence, while silica nano-formulations taken up by the cells are red. Judged by the intensity of red fluorescence, the Spiky-SNPs-PEI formulation exhibits the highest cellular uptake, followed by Flw-SNPs-PEI, Ras-SNPs-PEI and S-SNPs-PEI formulations. Quantitative analysis by flow cytometry revealed the same trend judged from the median fluorescent intensity (MFI).

TRANSFECTION EFFICIENCY

Early experiments visualised the intracellular transportation of only the pDNA/Spiky-SNPs-PEI formulation. This was tracked by labelling pDNA with fluorescein (green) and Spiky-SNPs-PEI with RITC (red) and the results are highlighted in Figure 4. The yellow arrows indicate that when pDNA and Spiky-SNPs-PEI were conjugated at four- and 12-hour (a) time points, pDNA was entrapped in endo/lysosomes (stained by lysotracker, red), while green arrows indicate successful endo/lysosomal escape of pDNA. At 24 hours (b), orthogonal side views from z-stack confocal images reveal the successful delivery of pDNA into nuclei, as indicated by the white arrows (b).

Subsequent experiments evaluated the gene delivery efficacy of all variants of the SNP complexes by transfecting pDNA-EGFP into HEK-293T cells. Spiky-SNPs-PEI demonstrated a significantly higher transfection efficacy compared with the other three complexes at all dosages. The transfection efficacy of Spiky-SNPs-PEI was 88% at a nanoparticle concentration of 80 μg/mL.

FURTHER TESTING ADDS WEIGHT

A range of further studies and experiments has been conducted to help characterise

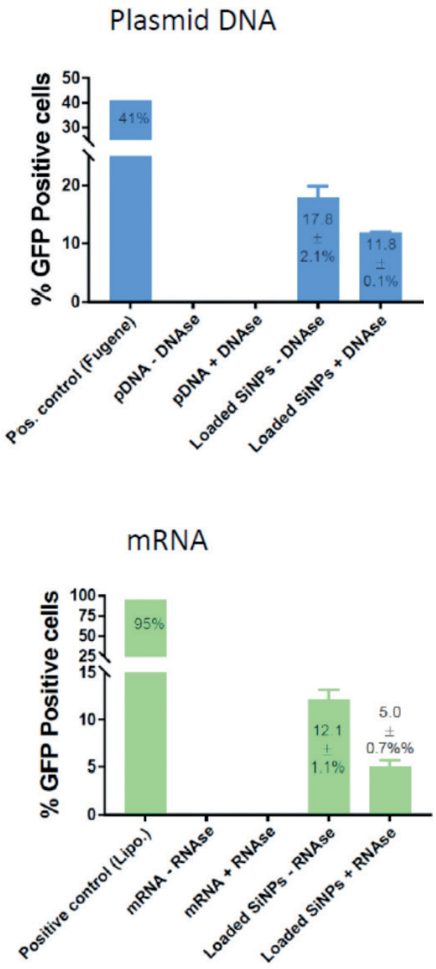
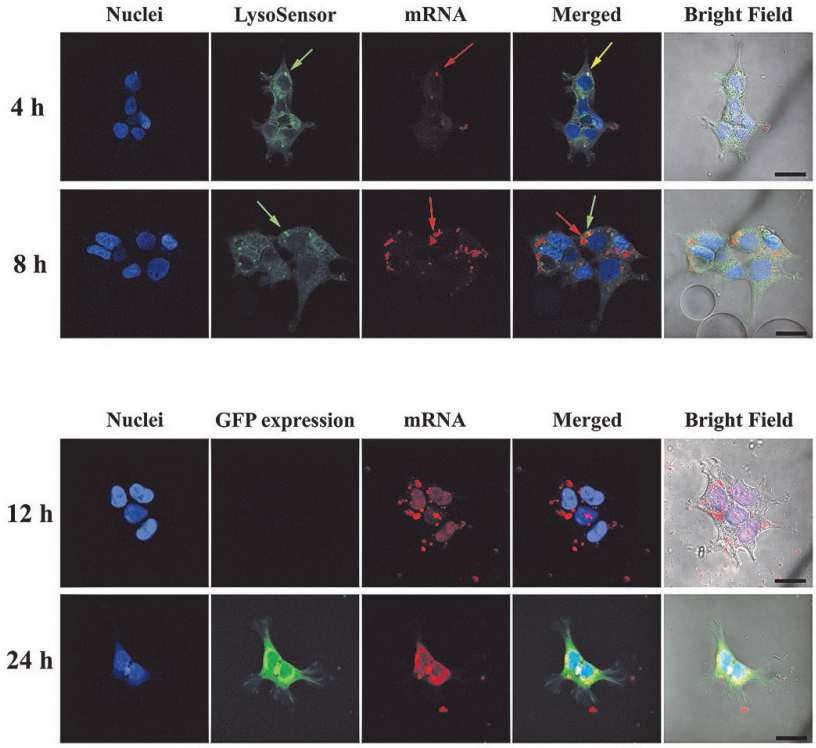


Figure 5: Spiky SNP affords both DNA and RNA protection from nuclease.



- At 4 hours, mRNA (red) is associated with lysosomes (green)
- At 8 hours, some mRNA has escaped the lysosomes
- At 12 hours, mRNA is within the cytoplasm, but no GFP expression is seen
- GFP expression is visible after 24 hours

Figure 6: Confocal microscope images of spiky SNP-mediated delivery of mRNA into the nucleus and gene expression.

the spiky SNP and its performance. For example, a study was conducted to assess SNP protection against endonucleases using HEK293 cells. The spiky structure was shown to afford both DNA and RNA significant protection from nuclease digestion, at around 67% for DNA and 41% for RNA (Figure 5).

The study, done in parallel with RNA, has provided important insights into the delivery of SNPs. For example, confocal microscopy studies have shown mediated delivery of mRNA into the nucleus and gene expression. Figure 6 summarises these findings, showing that at four hours, mRNA is associated with liposomes, at eight hours, some mRNA has escaped the liposomes and at 12 hours, mRNA is within the cytoplasm but no gene expression is seen. At 24 hours, gene expression is visible.

DEVELOPMENTS IN SILICA

The specific properties of a new functionalised SNP, such as increased surface area, have refocused attention on to silica as a potential drug delivery vector. The unique surface of the particle traps and protects the looped structure of nucleic acids and is designed to deliver the cargo directly into the cells. Compared with other topographies, the spiky structure of the SNP has proven to be best at facilitating efficient cellular uptake, endosomal escape and delivery of the payload to the nucleus. The safety profile of silica is well documented, with it being converted into silica acid in the body and naturally passing out, with no accumulation in the liver.

COVID-19 DEVELOPMENTS

N4 Pharma is currently undertaking a proof of concept research project using a COVID-19 spike DNA plasmid to explore the ability of Nuvec® to be used as an alternative delivery system by those developing COVID-19 DNA or RNA vaccines.

The proof-of-concept work will show how Nuvec® is capable of loading the COVID-19 plasmid and transfecting cells with the plasmid *in vitro* and *in vivo*. The research work is looking to demonstrate to those developing nucleic acid COVID-19 vaccines how Nuvec® could be a beneficial, alternative and safe delivery system for subsequent vaccines they may be looking to develop for COVID-19 or other viruses that may well surface in the future.

> "Silica is now being seriously considered as a drug delivery vehicle to improve efficacy and overcome the significant drawbacks of current nucleic acid delivery systems such as LNPs."

Although cancer therapy has improved and survival rates increased,[3] innovative approaches such as gene therapy and RNA/DNA vaccines are emerging with great excitement about how they could transform cancer treatment. Silica is now being seriously considered as a drug delivery vehicle to improve efficacy and overcome the significant drawbacks of current nucleic acid delivery systems such as LNPs.

ABOUT THE COMPANY

Established in 2014, N4 Pharma is a specialist pharmaceutical company developing a novel silica nanoparticle (SiNP) delivery system that is initially being directed towards pDNA/mRNA delivery in oncology. The business is built around a strong intellectual property portfolio that is licensed from the University of Queensland (Australia). N4 Pharma listed on the AIM (London, UK) in 2016 and is managed by an experienced team of scientists and business executives with significant know-how gained both in big pharma and other smaller, specialist pharma/biopharma discovery and development enterprises.

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ABOUT THE AUTHOR

Nigel Theobald has more than 25 years' experience in healthcare and in building businesses, strategy development and its implementation – and a strong network covering all aspects of pharmaceutical product development and commercialisation. He was the head of healthcare brands at Boots Group in 2002 before leaving to set up a series of successful businesses, including Oxford Pharmascience Group, which he grew over five years into an AIM-quoted company with a market capitalisation of £40 million upon departure. Mr Theobald formed N4 Pharma in 2014.

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