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

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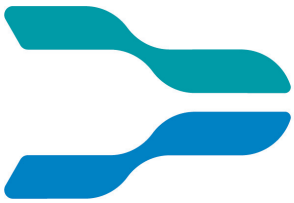

SHL GROUP

SOLUTIONS FOR HIGH-VOLUME DRUG DELIVERY

In this article, SHL Group introduces the high-volume variation of its Molly® family of products, the Molly® 2.25, and discusses more broadly the advantages that the Molly® business model offers to pharmaceutical and biotech clients.

In 2010, SHL introduced a new business model to the autoinjector industry with its Molly® platform, offering pharmaceutical companies the opportunity to launch their combination products in a much shorter timeframe. In response to the challenges of large-molecule drugs,[1] SHL has answered with a higher-volume solution based on the original Molly® platform – the Molly® 2.25.

Molly® 2.25 represents SHL's response to the growth of biosimilar products, providing its customers with a drug delivery device that enables high-volume injections and a faster development timeline. As biologics are expected to make up more than half of the world's 100 top selling drugs by 2020,[2] pharma and biotech companies are seeking ways to deliver these often highly viscous or high-volume drugs for self-treatment in a timely manner.

Injections can be of great discomfort to the patient. When injection discomfort exceeds a patient's pain tolerance, they run the risk of low adherence to their medication in the long term.[3] Pharmaceutical companies and device manufacturers must meet the challenge of producing a combination product that will, ultimately, deliver the formulation effectively without compromising patient comfort. After all, whilst a combination product is produced by a pharmaceutical company and device partner, it is the end user – the patient – who determines its fate.

Because biologics are large, complex molecules, a monoclonal antibody may consist of more than 1000 amino acids and weigh around 150 kDa.[4] These molecules often aggregate in high concentrations, resulting in highly viscous formulations. Delivering such formulations can require more power, and therefore impact the size of the device.[2]

Another factor that impacts the device size comes from drug makers adding diluents into highly viscous formulations to provide better syringeability.[2] This is a challenge to traditional subcutaneous autoinjectors as drug makers prefer to avoid extending the injection time, and increased volume often leads to increased delivery time. There is also a growing demand for larger-capacity devices that can deliver higher drug dosages per injection, due to a patient preference for less frequent administrations[5] of their existing treatments.

Magnus Fastmarken, Global Marketing Director at SHL, says, "Over the past few years, we have seen an increased interest in disposable autoinjectors providing doses above 1 mL. The larger volume allows new drugs to be delivered in autoinjectors, and it allows launched products to be dosed less frequently."

> "Recognising pharma's need to accelerate drugs to market, SHL introduced the Molly® line in 2010, revolutionising the business model of the autoinjector industry with its preconfigured infrastructure."

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SHL Group has long been a leading solutions provider in the drug delivery industry, with nearly 30 years of experience in developing self-injection products. Coming from a strong background in design, development, manufacturing, quality control and regulatory compliance, SHL understands the challenges that arise when developing a combination product and it is therefore capable of presenting top quality injection products to its customers.

Years in the industry have put SHL in a position to foresee market trends and recognise what biopharmaceutical clients lack, need and want. While fully aware of the need for device customisation designed specifically for original therapeutic drugs, SHL's R&D and business team also understood that pharma needed products with faster development timelines that deliver reliable, high-quality performance. Thus, the Molly® project was born.

Figure 1: SHL's first preconfigured autoinjector line, the Molly®, was launched in 2010.

THE MOLLY® MODEL

Recognising pharma's need to accelerate drugs to market, SHL introduced the Molly® line in 2010, revolutionising the business model of the autoinjector industry with its preconfigured infrastructure (Figure 1). Through years of observation and in-depth research, SHL experts created a superior investment strategy for its customers with the preconfigured autoinjector, which reduced product development time and eliminated many hurdles that regularly occur in the early stages of the design process. Designers rose to the challenge of developing an intuitive, functional, ready-made device that still considers the patient's comfort, resulting in a compact, portable, robust autoinjector.

Determined to simplify the treatment experience, SHL has also made advancements in the autoinjector's mechanisms, providing patients with the option to activate the injection by simply pressing the needle cover against the injection site. Patients no longer need an additional step of the button-press to activate injection, but can complete the injection via a two-step process – uncap and inject – that was specifically designed and built by SHL designers and engineers.

The Molly® technology reduces the number of components that must be packed inside an injector, but it still maintains balance between simplicity and functionality. This compact mechanism can deliver the desired injection speed and force for both 1 mL and 2.25 mL prefilled syringes, while still offering key design features, such as a two-click audible feedback to indicate the beginning and end of injection. SHL's Molly® family product offerings include Molly® FNS, Molly® RNS and Molly® 2.25.

> "SHL's in-house automation capabilities drive a robust assembly line for production scale-up, which leads to faster product delivery times."

PRECONFIGURED TO DELIVER

The Molly® business model requires SHL's customers to only make minor investments, thus cutting down major individual investments in tooling, assembly and/or testing equipment. Customers can be offered a selection of colour preferences for branding purposes and optional spring adjustments depending on the prefilled syringe, filling volume and drug formulation before launching the device for market.

The speedy development timeline Molly® enables is mostly from its preconfigured technology. However, an additional factor that expedites the process comes from SHL's vertical integration of key manufacturing capabilities, which facilitates automation and assembly systems to be developed in parallel. SHL's in-house automation capabilities drive a robust assembly line for production scale-up, which leads to faster product delivery times (Figure 3).

Commenting on SHL's automation systems, Lucy Chung, SHL's Director of Automation, says, "Years of dedication to developing our own automation capabilities have enabled us to produce fully automated assembly and testing systems that will upgrade Molly's production."

INTRODUCING MOLLY® 2.25

Offering volumes up to 2.25 mL per injection, Molly® 2.25 can now satisfy an even wider range of patient needs, while still shortening timelines in the

Figure 2: The Molly® 2.25 is a high volume variation of the Molly® autoinjector.

development process with its preconfigured settings. To coincide with demand as more pharmaceutical companies continue to develop and manufacture a growing number of biologics that are naturally large in volume, SHL is offering the high-volume variation of Molly® as a solution for high-volume injections (Figure 2).

Joshua Gonzalez, Director of Business Development at SHL, says, "Supported by our strongest ever manufacturing capabilities, Molly® 2.25 is an example of our commitment to delivering the most efficient solutions to our partners in the increasingly competitive space of combination products."

As numerous usability trials reveal that users prefer smaller devices,[2] SHL has managed to keep the slightly larger Molly® 2.25 handy and lightweight, ensuring an intuitive handling experience without sacrificing on patient preference. The bigger Molly® 2.25 has a design similar to the Molly® 1 mL, but a slightly larger body in order to accommodate the 2.25 mL syringe. The larger size, however, is far from bulky, maintaining the original Molly's design intent of being "portable and compact."

Molly® 2.25 comes with a rectangular, easy-to-pull cap that prevents the device from rolling, as often occurs with many autoinjectors with round caps. This strategic design was aimed at preventing autoinjector breakages from accidental drops, contributing to the safety requirements of the device.

The autoinjector is also built with a viewing window that clearly shows the plunger rod movement and finishes with an audible click at the end of injection. Users are sure to know when the injection has been completed, ensuring that the intended drug dose has been injected.

"As numerous usability trials reveal that users prefer smaller devices, SHL has managed to keep the slightly larger Molly® 2.25 handy and lightweight, ensuring an intuitive handling experience without sacrificing on patient preference."

With the combined forces of a strong team of designers, engineers, project managers and business developers, SHL now presents an extremely versatile preconfigured device to the industry. Andrew Moore, Director of Research and Development at SHL's US site, comments, "The Molly® 2.25 has a new industrial design and supports fully-automated assembly, all while keeping the reliable performance that makes Molly® so popular."

In launching Molly® 2.25, SHL has again taken into consideration customer demands and patient needs, delivering faster development timelines and higher volume injections. With the "less is more" approach to design, Molly® 2.25 aims to transform markets and shape the future of autoinjector development.

ABOUT THE COMPANY

SHL Group is a world-leading solution provider in the design, development and manufacturing of advanced drug delivery devices, such as autoinjectors, pen injectors and advanced inhaler systems. The company also offers core competencies and services in the fields of medtech and patient care solutions. With locations in Taiwan, Switzerland, Sweden, China and the US, the company's experienced engineers and designers develop product enhancements, as well as breakthrough drug delivery and patient care solutions for pharma and biotech clients globally. Significant investment in R&D has enhanced SHL's broad pipeline of next-generation drug delivery systems that support ongoing innovations in drug development and digital healthcare. This includes advanced reusable and disposable injectors that can accommodate high volume and high viscosities, which can be enhanced through digital implementations.

With over 4,000 employees worldwide, SHL Group consists of several distinct group companies:

- SHL Medical designs, develops and manufactures advanced drug delivery devices, as well as providing final assembly, labelling and packaging services for leading pharmaceutical and biotech companies across the globe.
- SHL Healthcare develops and manufactures equipment solutions for home, hospital and long-term care use.
- SHL Technologies provides contract manufacturing and engineering services for the production of complex medtech and industrial products.

Figure 3: SHL's in-house automation capabilities offer a robust assembly line for Molly®.

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CONNECTIVITY USING CONSUMER TECHNOLOGY TO CREATE REAL VALUE FOR PATIENTS

In this article, Napoleon Monroe, Managing Director, New Directions Technology Consulting, presents the case for the C-Container, a collective term for a theoretical class of consumer product designed to work with various drug delivery combination products, to provide the benefits of connectivity to the patient and sidestep the regulatory and development challenges that surround fully integrated connectivity, to the benefit of all stakeholders. While the article is US-centric, many of its conclusions relate well to international markets.

PREFACE

This article covers the potential for connecting drug delivery products, especially combination products, to the internet in ways other than designing them from the ground up to have integrated connectivity, making the device fully a "connected combination product". Combination product development is already difficult, and connected combination products face even more challenging, sometimes tortuous, regulatory and corporate paths. Pharmaceutical companies and their supply chain partners (hereafter referred to simply as "pharma"), regulators, payers, healthcare providers (HCPs) and patients are five of the most important stakeholders in drug delivery. In the current environment and given the immature state of connected combination products, the goals of these stakeholders are different, sometimes irreconcilably so. Our premise is that providing truly patient-centric information to meet patient needs should be the primary aim of connecting a combination product. The following is a discussion of a theoretical connected container for a combination product, which we shall refer to as a "C-Container".

> "A C-Container is an internet-connected consumer communications product, medical device data system or any truly patient-centric means of connectivity which can be used in association with various drug delivery or healthcare products."

A C-Container is an internet-connected consumer communications product, medical device data system (MDDS) or any truly patient-centric means of connectivity that can be used in association with various drug delivery or healthcare products. A C-Container may be for a pen injector, autoinjector, inhaler or any other dosage form, and would usually include appropriate apps for use with a consumer communications device such as a smartphone or tablet computer. Ideally, no C-Container should require extensive regulatory involvement for use.

The C-Container itself may or may not be a medical device, may physically contain or cover (in whole or in part) its associated combination product (or other dosage form) or may take another form not discussed in the scope of this article. A C-Container and its related software ought to be regulated in the least restrictive way legally and ethically feasible, preferably as a consumer product, or another type of product which is not regulated in an unduly restrictive manner. An expertly designed C-Container could provide greater value to patients than a sophisticated, industry-centric, highly-regulated connected combination product.

PRIMARY STAKEHOLDERS IN DRUG DELIVERY

Pharma, Payers, Healthcare Providers

While an HCP can diagnose a patient's ailments and then recommend the best therapy for their care, they generally do not have the time, workflow systems, information, training or payment incentives to deal with a patient's ongoing compliance

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"Pharma is typically risk averse and product introductions are highly time sensitive. To speed drug approval and for other reasons, pharma may wish to exclude connectivity in their early drug filings, or entirely."

with their treatment, or most of their other day-to-day needs and frustrations.

Pharma, HCPs and payers want to generate revenue and limit cost. Even with all the talk about models for creating shared value, ultimately all three of these stakeholders have to remain cost conscious and revenue driven. This can sometimes slow innovation in pursuit of patient-centric connected combination products.[1] The culture of pharma and healthcare administrative practice tends to be very cautious and slow-moving, whereas consumer culture is quick and agile by nature. Ideally, product lifecycles for pharma and medical device products take the course of several years. Compare this with the product lifecycle for a consumer software product. It may be years for the brand, but with constant evolution and updates to adapt to shifting markets, or even requests from individual users, the lifecycle of a specific software product (or product version) is often only months or days.

Pharma is typically risk averse and product introductions are highly time sensitive. To speed along drug approval, and for other reasons, pharma may wish to exclude connectivity in their early drug filings, or even entirely. When a connected combination product is filed, the US FDA considers the entire product, which could put a connected combination product in a never-ending loop of regulatory inquiries and change management. Consumer medication telemanagement software can be flexible and can be modified often, and in some cases the software may even be patient specific, which does not mesh well with the way regulators examine product filings. Furthermore, mergers, acquisitions and new entrants into the pharma space are bringing new conflicts and disruptions, which may necessitate software changes during a connected combination product's development.

"Regulators are mandated and expected to ensure safety and efficacy. They do not want to be blamed for failure, and thus a large part of a regulators' self-interest lies in staying out of trouble."

Some consultants may say it is best to avoid developing combination product injectors for emergency use because such a product must deliver the dose in the therapeutic range with near 100% reliability. Exactly how near can be a difficult question, especially when human factors are considered. Whilst it is true that preventive therapy would be better for patients than treating an emergency, emergencies do happen, and patients often need more assistance in an emergency than in non-emergency situations. Therefore, the benefits conferred by connectivity can be especially important for emergency products, whilst the task of developing a connected combination product for emergency use is even more daunting than for those used in preventative therapy.

Healthcare will not, in the foreseeable future, eliminate the need for direct patient interaction, nor should it. Access to mobile patients is difficult. However, providers, payers and pharma want select, automated, near real-time, clinically based information they can use as and when they want it. Selecting what is needed and desired is difficult and varies situationally. Even when other stakeholders have virtually unrestricted access to a patient, for example when they are in hospital, the quality of collected patient data is often poor. In the real world, the use of many poorly co-ordinated electronic medical record (EMR) systems for a single patient limits the usefulness of their data. On top of which, gathering, recording, screening and accessing all appropriate clinical information results in greater regulatory and administrative scrutiny, which can present an extreme burden.

Regulators

Regulators are mandated and expected to ensure safety and efficacy. They do not want to be blamed for failure, and thus a large part of a regulators' self-interest lies in staying out of trouble. One way to do that is to approve products in an extraordinarily cautious way, or not at all, in order to avoid becoming responsible for the unanticipated problems that may occur.[2] Regulatory issues go a long way towards explaining why pharma cannot easily execute on the various business cases that advocate for a connected combination product. As with most bureaucratic institutions, regulators may not move quickly.

Pharma regulators have difficulty dealing with combination products and even more difficulty dealing with the greater number of "what-ifs" associated with connected combination products. Legacy regulatory systems were not structured to deal with the frequent changes typical of consumer software systems. Add to this the fact that there are divergent definitions in various countries of what constitutes a combination product and how to regulate software, and it becomes clear that getting a connected combination product approved by the regulators may well end up becoming a very difficult task indeed.

Patients

Patients, on the other hand, do not particularly care about regulations; pharma, HCP or payer revenue or cost; or about HCPs' time. Patients care far more about treatment availability, quality, expense and, most importantly, outcomes. Patients are suffering ever-higher co-pays and are confused about the complicated payment, coupon and rebate schemes foisted on them. Patients also have become far less trusting of the other stakeholders, especially the non-HCP stakeholders, which limits the ability for pharma and payers to influence patient behaviour. Patients want real-world, actionable information that they can easily put to use.

The successes of many consumer internet-connected products demonstrate that consumers are willing to pay for what they perceive as real value in these products. The rapid uptake of smartphones by older populations shows their openness to technology when it is clearly in their interest. Older patients consume more healthcare and medications so, as with all segments, keeping the technology simple and focused on their needs is key to success.

Patients have quality-of-life-based personal incentives to make better choices about how they manage their own behaviour and spending towards improved healthcare outcomes. This need for patient education is being increasingly recognised. Outcome measurements, such as patient reported outcome measures (PROMs), enhance a patient's ability to judge which products improve their quality of life. Unlike with HCPs, immediacy of information and instant gratification are important to consumers. When patients or payers come to see the value of a C-Container, and perceive the cost to be appropriate, they will be more likely to buy it. Some HCPs and payers are already using C-Containers to help patients meet their individual, day-to-day needs.

Patients are concerned about misuse of their health data and other personal information. Breaches of personal data security are occurring regularly, and security costs are escalating. A vision of extreme data abuse is detailed in the novel "Cell" by Robin Cook.[3] Fortunately, such systematic, extreme abuses by payers have not occurred. While the possibilities for such abuse should be less than with a connected combination product, privacy and security concerns regarding C-Containers are still real. These concerns, along with the need for patient privacy and data security, have been one of the most intransigent obstacles to the flow of healthcare data and information to areas where it is most needed. Patient ownership and control of their own health data can help avoid the complex issues of data privacy by putting the data directly in the hands of the patient to use and reuse as they see fit.

When data is owned and controlled by patients themselves, it can encourage patient-directed data use and reuse to create the information needed for them to make healthy choices. Patients can make important behavioural and clinical information available when and where it is needed. Having the patient be the primary custodian of their health data, streaming from multiple sources, can reduce the complexity of data transfer and lower costs. Patients control access, ensuring that their data is used how and by whom they want. Additionally, in terms of data security, aggregated information from multiple sources on one patient is far less a target for theft or abuse than information on thousands of patients in a corporate database.

The stated primary objective of combination products is often patient-centricity, i.e. making pharma products more useful for the benefit of patients. Using a separate consumer product for connectivity as proposed here may benefit all stakeholders, but will benefit patients more than any of the others. The patient benefits of consumer software and C-Containers should not be unreasonably withheld.

> "The extremely low cost which stakeholders would like for a connected combination product or C-Container may never be met. Costs for both are driven by technical, manufacturing and logistical realities for creating and distributing a functioning product."

Many patients have already adopted consumer healthcare products (most frequently by purchasing them themselves). Regulators and other stakeholders are wrestling with how to approach the use and regulation of consumer software. Pharma and many others may benefit from embracing the use of truly patient-centric software and C-Containers without the various risks, complexity and costs of a connected combination product.

THE COST OF C-CONTAINERS

The extremely low cost that stakeholders would like for a connected combination product or C-Container may never be met. Costs for both are driven by technical, manufacturing and logistical realities for creating and distributing a functioning connected product. The factors that drive the cost of a C-Container include design, component costs, validations, range, battery life, power consumption and user support. The addition of high overheads, multiple regulatory costs, legacy margins and other costs unrelated to the final product may be factors which limit the growth of connected combination products.

RECENT EVENTS AND PRESS

Many concerns about connectivity were voiced by pharma at the October 2018 Parenteral Drug Association (PDA) Universe of Pre-filled Syringes and Injection Devices conference (Orlando, FL, US), as well as in the associated Combination Products Workshop P/L Biomedical President Lee Leichter's course "Technical and Regulatory Challenges of Drug Delivery Combination Products". The topic was also covered in a Cambridge Design Partnerships (Cambridge, UK) webinar on October 31, 2018, and in a November 20 announcement from Apple about co-operation with the US Veterans Administration on healthcare software. Many of the concepts discussed are generally understood, however content from some presentations and press contributed to some of the conclusions drawn in this article. As with all these types of events, much of the valuable information was exchanged in Q&A, personal conversations and follow-ups.

In his presentation and conversations at PDA, Paul Jansen told of his personal experiences with connected combination products, discussed the criticality of the supply chain and briefed on ISO 20069, "Guidance for assessment and evaluation of changes to drug delivery systems", the development of which he chairs.

Lee Leichter provided regulatory histories and definitions, an analysis of recent regulatory changes (for example the 21st Century Cures Act), discussed the importance of standards in development and covered emerging issues and discussions of tactical and strategic regulatory possibilities. He did not advance the consumer product approach, but a number of his insights reinforced the conclusions drawn in this article.[4]

FDA executives engaged with the combination products also presented at PDA. A key point was that they advised of plans to issue a mobile medical device guidance, although no estimated timeframe was provided in response to an audience question.[5] Subsequently, on November 19, 2018, FDA issued a notice of the establishment of a public docket for comments on software for prescription drug-related use. The notice states, in part, that "FDA recognises that digital health has the potential to offer new opportunities to improve patient care...".[6] This docket gives industry some information on FDA's position and provides an opportunity for all stakeholders to help clarify the status of, and perhaps improve access to, C-Containers.

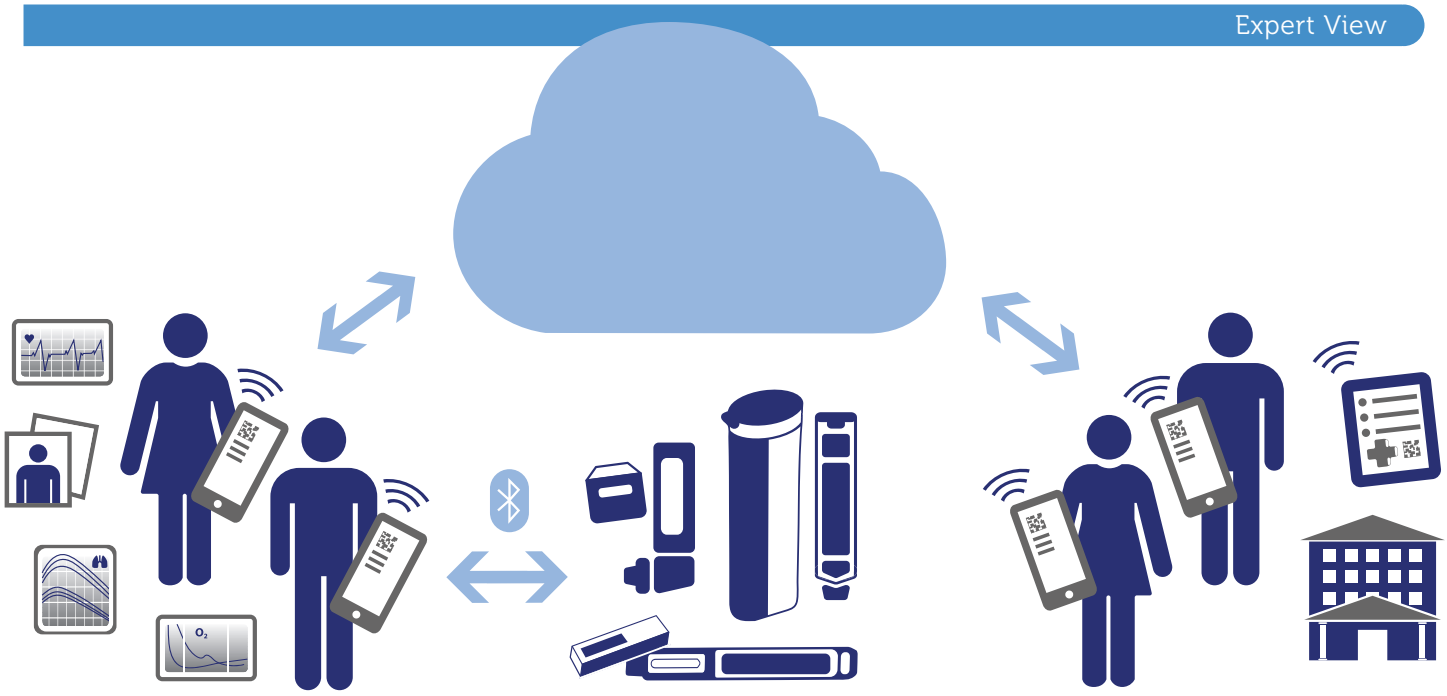

Figure 1: The B-C-B model, whereby connected drug delivery products provide their data directly to the patient, who is then free to use and share that data according to their wishes.

In his talk at PDA, Genentech's Paul Upham said that "Failures of connectivity are due to not having a strong business reason", and made the points that "Almost nobody's apps have good retention" and that "Consumer behaviour is hard to change, so why not just give them what they need?"[7]

Pharma organisations often confound attempts to define their business rationales and thereby contribute to their own failure. Each silo in a pharma company loads on new requirements to a given project, creating super-complicated technical and regulatory challenges. Apps connecting combination products fail to survive in the market when they are developed according to the desires and needs of pharma companies rather than users.[8]

Two posters at PDA, "What Plastic Bags Can do to our Devices: Something You Might Never Have Heard Before", by Hemanth Amarchinta of Roche, and "Aging of Complex Systems: Fundamental Theory and Implications…", by Nestor Rodriguez of Becton Dickinson, were remarkable for content about the known influencers of device performance which might not yet have been fully considered.

In the Cambridge Design Partnership webinar, Head of Drug Delivery Uri Baruch discussed "unknown unknowns".[8] The managerial revolution has led to the proliferation of experts, all of whom are well trained but few of whom have personal experiences in the unknown unknowns of combination product development and manufacture. An analogy is that well-respected quantitative financial analysts failed to see the black swans in the 2008 housing loan market prior to its collapse. Pharma experts are generally not versed in the unknown unknowns of devices or consumer software. Smaller companies, which includes many app developers, often fail because they do not have adequate resources.

BENEFTTING FROM PUBLIC INITIATIVES

Large and small companies have historically failed with developments outside their core competencies and have instead turned to market-tested consumer products. Consider that the US Department of Defense (DoD), the largest employer in the world with 3.2 million employees[9] and the inventor of military technologies that changed civilian life,[10] is now adopting consumer product-based technologies to boost the performance and reduce the price of military equipment.[11]

The setting of healthcare standards, potential (as yet not fully realised) benefits of EMRs and sensor-based medical products are examples of industry benefitting from public initiatives. Learning from the pioneering healthcare work that comes from the DoD and the US Department of Veterans Affairs (VA) is nothing new, but it may be especially important for healthcare software and related products. Public organisations have long led in healthcare due to their aims and structural needs.

I discussed these matters at length with Dr Stephen Ondra, founder of North Star Healthcare Consulting and formerly a senior official in the US Federal Government. The DoD and VA are among the largest providers of healthcare in the US, with taxpayers taking on the role of payers. Over the past several years, the DoD and VA have shared the goal of making their

> "This is a B-C-B model, where the patient is educated and given the data from potentially multiple Blue Button or other enabled sources to aggregate into a composite record. That data can then be used to power healthcare software application tools, share with the caretakers they want or with whomever and for whatever other use the consumer feels would be helpful to them."

electronic medical records interoperable. As a result, when each chose to re-platform their ageing healthcare IT infrastructures, it was no surprise that they eventually picked the same EMR platform to simplify the task. Even with this however, true interoperability will remain a challenge due to different instances of their respective EMR implementations.

This is an example of why a single EMR platform or format is not a realistic way to solve the problem of interoperability nationally. Additionally, such an approach is not even desirable for the commercial market. Such a move would not only raise anti-trust concerns, it would limit the innovation that is needed in a fast-moving space such as IT, which is spurred by private sector competition. Also, to be as robust and extensible as possible, healthcare data should come from multiple data sources and platforms. As such, interoperability will best be accomplished through approaches that allow the aggregation of data from multiple sources, alongside engines that can reconcile the various data streams and then pre-process it for downstream applications.

An example of this was seen in an innovative approach that the Federal Government took in 2010 known as "Blue Button". Led by VA, this application is an open-source and publicly available IT platform to allow individual consumers to aggregate their own personal health data from VA's EMR, as well as other sources, in a simple ASCII file. This is a B-C-B (healthcare business to patient/consumer to patient-selected business) model, where the patient is educated and given the data from multiple Blue Button or other enabled sources to aggregate into a composite record. That data can then be used to power healthcare software application tools, share with the caretakers they want or with whomever and for whatever other use the patient feels would be helpful to them (Figure 1).

As a federal programme, Blue Button is available to anyone or any company in the US public or private sectors. Blue Button has been made available to beneficiaries of not only public health programmes, such as those of the DoD and VA, but more generally through the Centers for Medicare & Medicaid Services (CMS). The benefits of Blue Button have also been made available to private healthcare consumers from many payer and provider organisations.

In contrast to this data platform-agnostic approach, the recent announcement by Apple is an example of a proprietary model approach.[12] In this model, there is a B-B-C (healthcare business to healthcare business to consumer/patient) approach. By placing another business between the healthcare generated data and the consumer, concerns of privacy and security resurface, along with concerns of data being harvested for means that the patient may not want. Whilst benefits may certainly come from a large corporate entity managing health data, the use of a B-B-C model, as compared with a patient-centric, patient-owned data B-C-B model, should be looked at with some caution.

Large conventional retailers' brands are already falling prey to small companies that use innovative technology designed and positioned to meet individual consumer needs. Companies attuned to this personalised consumer service, once seen as interesting curiosities, are now profoundly shifting the consumer goods sector.[13] Readers will already know that standards developers have published lists of procedures and diagnosis codes, and that FDA has recently mandated the use of automated information and data capture symbologies for prescription pharma and high-risk medical devices, which provide language sets for use in EMRs. Consumers can already use their smartphones to capture some product information, so it is no great leap to assume that some company, small or large, will empower patients to use some version of procedure codes, diagnosis codes, and standardised drug and medical device symbologies.

BENEFITS OF PATIENT ACCESS TO C-CONTAINERS

Whilst this article has thus far primarily discussed the benefits of C-Containers and their associated B-C-B model to patients, there are of course also benefits to pharma, including:

- Separating the C-Container from the drug regulation can improve time to market and reduce regulatory and product liability risks. Such separation can eliminate the need for pre-launch regulatory approval, so long as regulators exercise regulatory discretion towards consumer products or affirmatively declare policies enabling their use.
- Multi-product platforms and personalised versions of products are more easily achieved with consumer products.
- C-Containers can still enhance the pharma revenue stream and patient loyalty.
- C-Containers can help ensure regimen compliance and even combination product reliability by having experts in patient needs and device manufacture design them according to the requirements of patients and their devices.
- Approved digital therapeutics allow patients to self-diagnose, enabling home treatment. More such therapeutics are emerging, which will expand the potential appropriate use of C-Containers .
- C-Containers can be designed, tested and documented as though the C-Container were a medical device to allow ongoing future development of more highly regulated medical devices with added claims.
- Contracts can allow appropriate oversight of the C-Container by a pharma company without it becoming a connected combination product.
- Differentiated C-Containers can be platforms for multiple combination products from a given company, thereby bringing economies of scale and lower costs.
- Sequential, not simultaneous, development of connectivity is often more appropriate for emerging products. As with the automotive and other consumer industries, pharma can learn from consumer industry techniques using C-Containers as it moves into customer digitisation, to assisted intelligence and subsequently to automated intelligence.

SUMMARY

As shown, connecting combination products for drug delivery to the internet in ways other than fully integrated connected combination products can improve patient outcomes and provide benefits to other stakeholders. C-Containers could be just the tool to provide those benefits more quickly and efficiently. C-Containers can even help ensure that pharma products are safer and more effective. Public healthcare IT initiatives which will further enable the use of C-Containers being implemented.

This article reflects the author's personal opinions and analysis. It is not a professional interpretation of any medical, regulatory or legal requirements. The author, licensees to his intellectual property and his clients have interests in healthcare with a focus on medication telemanagement.

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ABOUT THE AUTHOR

Napoleon Monroe, Managing Director of New Directions Technology Consulting, has a diversified background that extends from developing and producing pharmaceutical product delivery systems, to managing thousands of private brand products for a Fortune 500 company, to building and managing the IP portfolio for a company that is now part of Pfizer. His expertise includes product development, licensing, regulatory processes as business opportunities, risk management and international marketing, with experience managing business relationships in more than 30 countries. Mr Monroe has led teams that have invented and commercialised major products, such as the (pre-Mylan) EpiPen, and nerve agent antidote autoinjectors for the US and allied countries. New Directions holds patents related to medication telemanagement.

The topics covered in this article will be discussed in more detail by the author in his upcoming presentation at Drug Delivery Partnerships. Mr Monroe's presentation, also entitled "Connectivity Using Consumer Technology to Create Real Value for Patients", will take place on Monday January 28th, 2019, at 4pm, DDP 2019, Palm Beach Gardens, FL, US.

TECHNOLOGY SHOWCASE: teamtechnik's LED Cannula Gluing Process

team technik
PRODUCTION TECHNOLOGY

The increasing amount and complexity of healthcare taking place in outpatient contexts is presenting pharmaceutical companies and drug manufacturers with major challenges. Self-medication, home based diagnosis and acute immediate treatment in emergency situations, together with a general trend towards greater convenience for patients, are leading to a growing demand for prefilled syringe (PFS) systems that are precise and 100% reliable. The driving forces in this continually changing segment are quality, safety and cost efficiency. This affects drug manufacturers and the suppliers of systems for series production of medical products in equal measure.

HIGH-PRECISION ASSEMBLY AND FUNCTIONAL TESTING PROCESSES

Systems specialist teamtechnik can demonstrate extensive engineering experience and outstanding process knowledge in the field of injection pens and autoinjectors. Thanks to its focus on the assembly and functional testing of medical products, the company can manufacture these production systems for its international customers with a high level of quality.

STRONG INNOVATION IN INJECTION SYSTEMS

teamtechnik responds proactively to the constantly changing needs of the market. A current example of this is the glass syringe. Containers used as primary packaging for medications must demonstrate a special pharma-resistance, be autoclavable and suitable for the standard filling systems already in place at pharmaceutical companies. In these respects, glass syringes satisfy the very high safety and quality standards prevalent worldwide thanks to the functional properties of the material. During assembly and functional testing it is important to prevent the build-up of particles, impurities, potential glass breakage, damage to the cannulas and numerous other potential flaws.

NEW GLUING PROCESS BETWEEN CANNULA AND GLASS

A great deal of attention is focused on the cannula, as it is the only component of a PFS that, along with the medication itself, comes into direct contact with the patient. Attaching the cannula to the glass body is achieved solely by means of adhesives which have been approved by the US FDA. In order to comply with the increasing demands on primary packaging, teamtechnik has established a new LED gluing process between the cannula and the glass to optimise PFS production (Figure 1). It is exactly in this adhesive bonding between a stainless steel cannula and glass syringe body that specific process expertise is necessary.

The traditional curing process for FDA-certified adhesives with UV light does work, but it has a number of disadvantages:

- The process is highly energy intensive
- Environmentally harmful ozone must be extracted at high cost

Figure 1: New FDA-certified adhesive cured with LED process.

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- High cost of conventional UV mercury vapour lamps
- The amount of heat generated by the mercury vapour lamps is immense.
- Large system footprint
- Downtime of production machine due to repeated replacement of UV luminaires
- Reduced operating lifespan of UV lamps.

teamtechnik therefore based its new solution for gluing cannulas to glass syringes on modern LED curing, making it both economical and capable of application in serial production.

This technology combines many advantages:

- FDA-approved adhesives can continue to be used unchanged.
- Higher production outputs thanks to shorter process cycle times
- LED curing is almost maintenance-free
- It saves energy and is also highly efficient for high production outputs.
- The process is not harmful to health and does not require cost-intensive, space-demanding extraction systems.

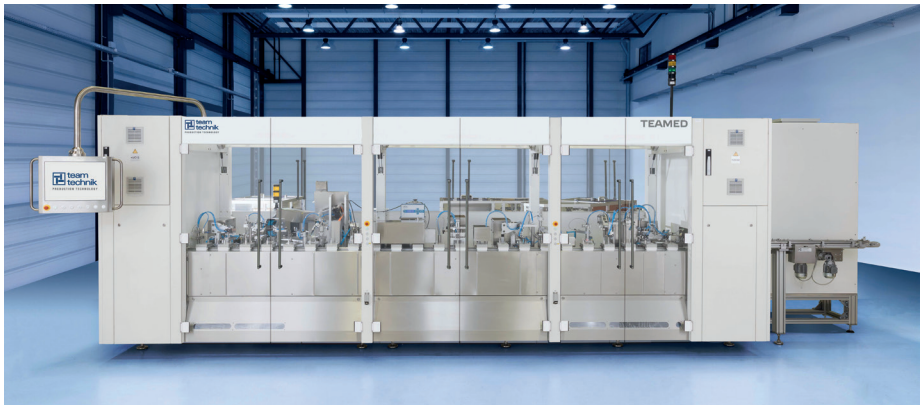

Figure 2: High volume assembly and test line for injection systems.

With its expertise in process technology and extensive engineering experience, teamtechnik is able to support manufacturers in meeting the challenge of preventing medication errors and producing safe products at high and, above all, consistent quality. The company's solutions for the assembly of glass syringes, pen injectors, autoinjectors, injection devices and point-of-care solutions are front runners in their segment (Figure 2).

ABOUT THE COMPANY

teamtechnik Group is an international market leader for production technology, assembly and functional test systems. Founded in 1976, teamtechnik has production sites in Germany, Poland, China and the US. With over 1000 employees worldwide, teamtechnik achieves an annual turnover of €170 million (£153 million).

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PHARMACEUTICAL SOLUTIONS

DEVELOPMENT OF PREFILLABLE SYRINGES TO MITIGATE THE RISK OF PARTICLE FORMATION IN BIOPHARMACEUTICALS

In this article, Hideaki Kiminami, Research Manager, Core Technology Group, Terumo Corporation, and Philippe Lauwers, Director Technology Development, Terumo Europe, discuss the problem of particle formation in biopharmaceuticals packaged in prefilled syringes.

INTRODUCTION

In recent years, the safety of drugs has become a topic of significant importance. To enable patients and healthcare professionals to use drugs comfortably and safely, it is necessary to assess their safety at each phase of the manufacturing process,[1] from active pharmaceutical ingredients to finished formulations, and to verify the safety and efficacy of the drug product as marketed within its primary container and secondary packaging.[2] A major concern is that therapeutic proteins may denature or aggregate by physical or chemical stimulation to form particles,[3] leading to the development of immunogenic responses and, consequently, adverse reactions in patients.[4] This article discusses the main factors responsible for particle formation in biopharmaceuticals and also describes a conceptual and technical approach for the reduction of particle formation in prefilled syringe (PFS) systems.[5,6]

> "A major concern is that therapeutic proteins may denature or aggregate by physical or chemical stimulation to form particles, leading to the development of immunogenic responses and, consequently, adverse reactions in patients."

> "Proteins used as active ingredients in biopharmaceuticals are generally chemically unstable, and therefore likely to undergo denaturation or aggregation due to stresses such as heat, vibration, and impurities introduced during the manufacturing process."

ISSUES AND MEASURES IN BIOPHARMACEUTICALS

A variety of drug products has been developed for many therapeutic applications, from small-molecule drugs produced by chemical synthesis, to biopharmaceuticals produced by biotechnological processes, such as genetic recombination and cell fusion.[7]

Proteins used as active ingredients in biopharmaceuticals are generally chemically

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unstable, and therefore likely to undergo denaturation or aggregation due to stresses such as heat, vibration, and impurities introduced during the manufacturing process.[8–16] Protein aggregation poses an important risk, including reduced drug efficacy and an increased risk of immunogenicity.[17–20] In response to this, the US FDA issued a guidance for industry on the risk management of biopharmaceuticals in August 2014.[4] Manufacturers are required to assess particles in biopharmaceuticals appropriately, and to reduce the risk of protein aggregation.

A variety of particle sizes may be present in biopharmaceuticals, from the nanometre scale up to the order of micrometres. In the US Pharmacopeia (USP), European Pharmacopeia (Ph Eur) and Japanese Pharmacopoeia (JP), the test for insoluble sub-visible particulate matter is listed as USP<788>, Ph Eur 2.29.19 or JP<6.07> respectively, and assesses the number of particles with a size ≥10 µm and ≥25 µm. The assessment of insoluble particles in biopharmaceuticals must be performed in compliance with USP<787>. In addition, recent studies have emerged to indicate that particles between 0.1 and 10 µm in size have an immunogenic potential. The relationship between sub-visible particles (SVPs) and immunogenicity has been determined from experiments in mice,[12,21] and fatal adverse events that may have been triggered by the presence of SVPs in biopharmaceuticals were reported in March 2016 by the FDA.[22] Thus, assessment of SVP-sized particles should also be performed.

USP<788>, Ph Eur 2.29.19, and JP<6.07> (Insoluble Particle Matter Test) include the use of the light obscuration (LO) particle count test for counting the number of particles. The LO method is a highly reliable analytical procedure that determines the attenuation of light energy (i.e. the blockage of transmitted light) by particles passing through channels and thus the size and number of particles based on the frequency of blockage. In addition to the LO method, there are various analytical procedures to measure particle size, with some of these analytical procedures shown in Table 1.

"Terumo's core R&D group has analysed and considered containers that are more "biopharmaceutical-friendly" to mitigate many of the shortcomings of PFS."

Analytical Procedure	Abbreviation	Detectable Range (µm)
Dynamic Light Scattering	DLS	0.001 – 10
Asymmetrical Flow Field Flow Fractionation	AF4	0.001 – 100
Analytical Ultracentrifugation	AUC	0.001 – 0.1
Hollow Fiber Flow Field Flow Fractionation	HF5	0.001 – 100
Size Exclusion Chromatography Multi Angle Light Scattering	SECMALS	0.001 – 0.1
Nanoparticle Tracking Analysis	NTA	0.02 – 1
Resonant Mass Measurement	RMM	0.1 – 5
Flow Cytometry	FCM	0.2 – 200
Quantitative Laser Diffraction	qLD	0.15 – 10
Flow Imaging	FI	1 – 200
Light Obscuration	LO	1 – 200

Table 1: Analytical procedures by particle size.

As these analytical procedures use different methods of detection and have varying levels of sensitivity, a wider detectable size range does not necessarily indicate a better analytical procedure. Additionally, the current research and development efforts of analytical instrument manufacturers have led to the emergence of instruments that provide highly accurate particle analysis over a wider detectable range. There is currently no single procedure that provides absolute quantification of the number of particles present in biopharmaceuticals, and therefore particle assessment using multiple types of analytical procedures is required.[23]

The recently increased interest in PFS is largely driven by their advantages compared with traditional ampoules and vials, such as allowing quick and accurate dosing; minimising dosing errors; reducing the risk of biological contamination; enhanced convenience and ease of use; preventing of overfill; and so on. With the increasing number of biological drugs becoming available, the demand for PFS has increased considerably in recent years.

It has been reported that silicone oil (SO) applied to the inner wall of PFS or tungsten oxide residues resulting from the glass forming process can cause the oxidation or aggregation of biopharmaceuticals.[14,16] Furthermore, it has been suggested that SO itself may adversely affect the human body.[24]

Terumo's core R&D group has analysed and considered containers that are more "biopharmaceutical friendly" to mitigate many of the shortcomings of PFS. The approach proposed in this article focuses on the following three aspects:

1. An SO-free (SOF) PFS system
2. A polymer-based primary container
3. Establishing measures against protein oxidation.[5,25-27]

To minimise the risk of immunogenicity, a major concern for therapeutic proteins, this study investigated whether the formation of aggregated particles, a major cause of immunogenic responses, could be reduced by the construction of the PFS system. Also tackled is how the application of SO lubrication and the method of sterilisation of ready-to-fill syringes may affect protein aggregation.

DEVELOPMENT OF THE PFS FOR BIOPHARMACEUTICALS TO REDUCE PARTICLE FORMATION

Effects of the Presence of Silicone Oil

Physical stimulation of therapeutic protein products in PFS has been reported to cause aggregation, leading to particle formation.[28] Prof John F Carpenter and Prof Theodore W Randolph, both from the University of Colorado (US), proposed a model to account for the particle formation in which, after the adsorption and gelation of proteins on the SO

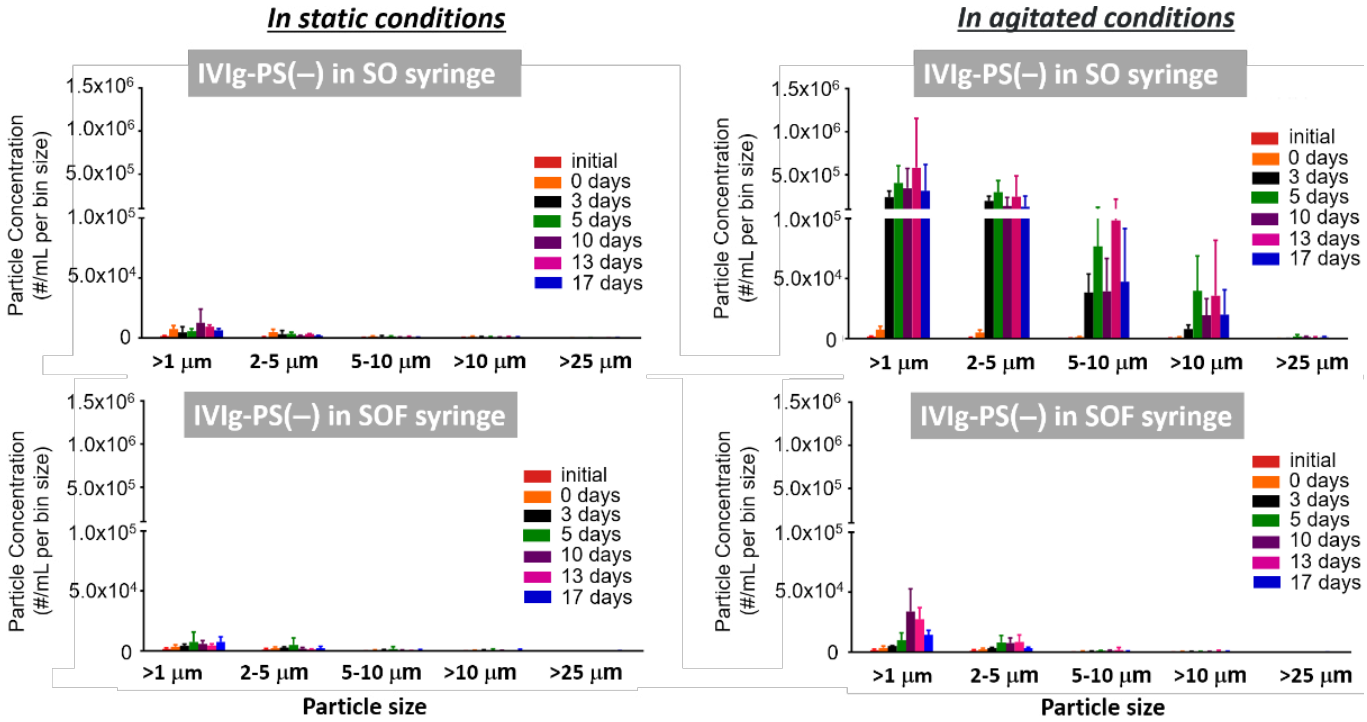

Figure 1: Results of particle assessment of IVIg products with and without SO in static and agitated conditions.

layer of the inner surface of a PFS, the layer of air remaining in the PFS is moved by physical stimulation, such as agitation, to remove the SO protein.[16] Terumo performed a particle assessment using the flow imaging (FI) method to determine the effect of SO on the aggregation of biopharmaceuticals under agitation, simulating physical stress during transportation, or during manipulation and administration procedures. The systems compared were PLAJEX™, a cyclo-olefin polymer (COP) ready-to-fill SOF system, and a siliconised PFS (Figure 1). This assessment used intravenous immunoglobulin (IVIg) as a model protein.

Under the conditions of static storage, the number of particles was only slightly increased in the SO PFS compared with that in the PLAJEX SOF PFS. However, with agitation, simulated transportation, and use, the number of particles was markedly increased in the SO PFS, while this increase was clearly minimised in the SOF PFS. These results indicate that the use of the SOF PFS system for biopharmaceuticals mitigates particle formation caused by physical stimulation in biopharmaceuticals.

Effects of Drug Composition

Proteins applied in biopharmaceuticals are composed of approximately 40–1000 amino acids (with the mean number of amino acids estimated to be approximately 300) which have a molecular weight of approximately 100 Da.[29] These amino acids contain both hydrophobic and hydrophilic groups, which makes many protein drug products poorly soluble in water. Many biopharmaceuticals therefore have polysorbate (PS), added as a surfactant to the drug formulation. Although the addition of the surfactant has been shown to reduce protein aggregation, recent investigations have suggested that additives may cause protein aggregation and SO particle formation, depending on the conditions of use.[30]

Therefore, Terumo performed a particle assessment of IVIg products containing PS by using the FI method for SO and SOF PFS under conditions that simulated actual drug formulation (Figure 2). In the PLAJEX SOF PFS, no increase in the number of particles was observed, despite the addition of PS. In the SO PFS, in contrast, the addition of PS caused a marked increase in the number of particles. As the particles observed in this assessment were either protein aggregates or SO, a particle image analysis was performed based on the FI analysis (Figure 3).

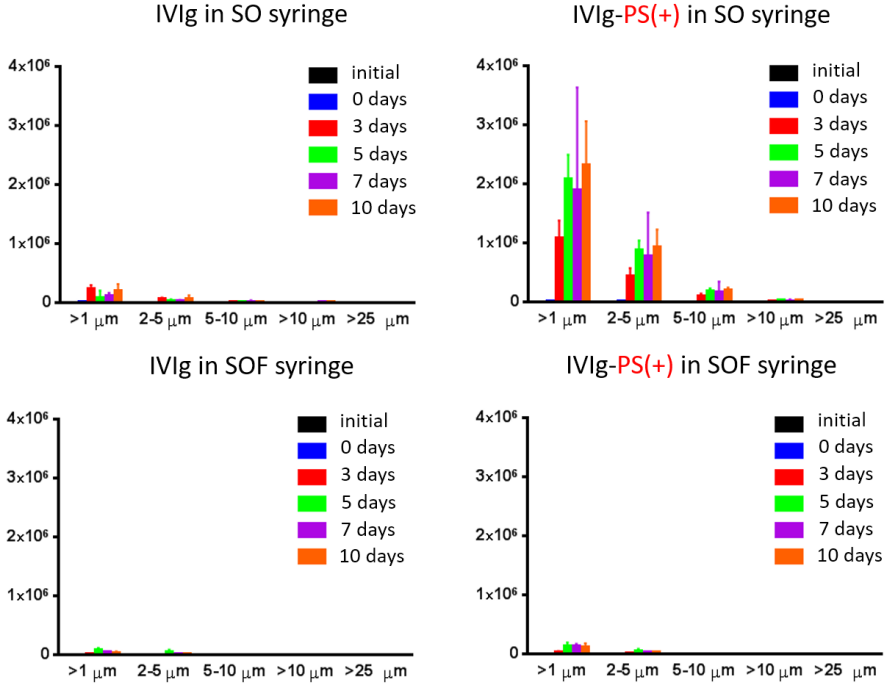

Figure 2: Results of particle assessment of IVIg products with and without PS80 in SO and SOF syringes.

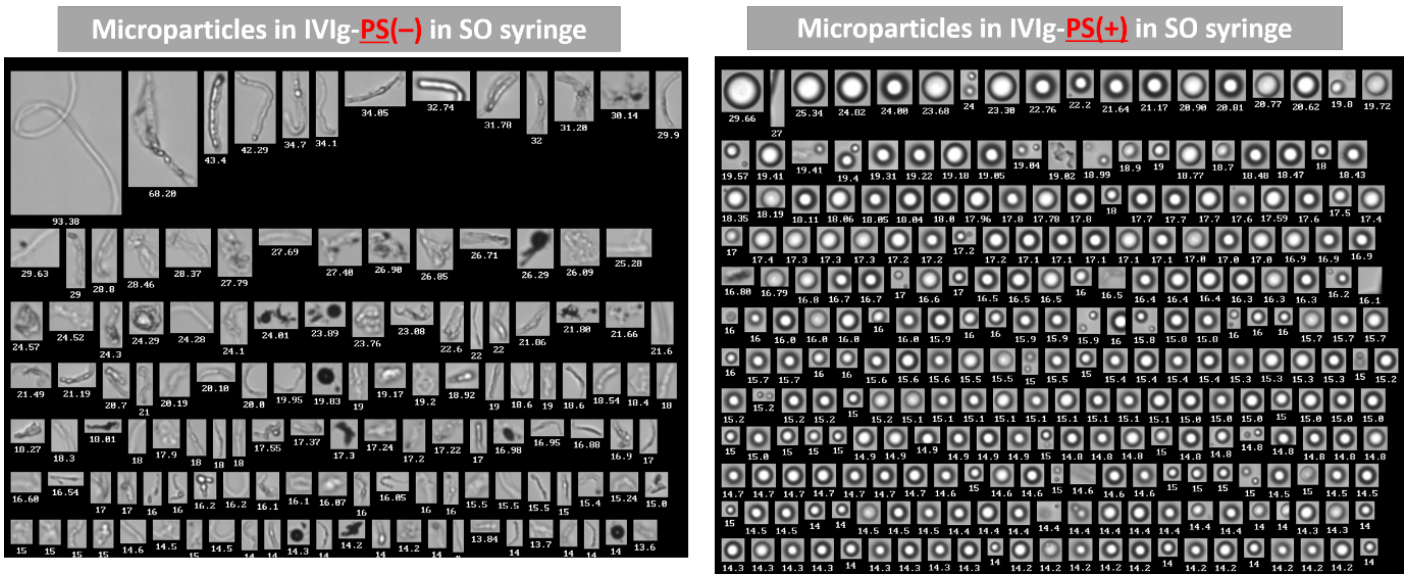

Figure 3: Results of the particle image analysis of IVIg products with and without PS in the SO syringe.

The analysis of images of particles in IVIg products showed that IVIg products filled in the SO PFS contained an abundance of long and thin filamentous particles, i.e. protein aggregates. In contrast, IVIg products containing PS were found to contain an abundance of spherical particles, i.e. SO. These results suggest that the clear increase in the number of particles in the SVP size range observed in the system with PS may be triggered primarily by an increase in SO particles rather than protein aggregates. In addition to the SO particles, as shown in the right panel of Figure 3, the IVIg product with PS was found to contain protein aggregates, shown in the left panel of Figure 3. These findings suggest that the PLAJEX SOF PFS may be effective in reducing particle formation when PS, an essential formulation component in biopharmaceuticals, is present.

Effects of the Sterilisation Method

Medical devices and prefillable ready-to-use primary drug containers are sterilised using various methods, those shown in Table 2 are commonly applied to PFS. Several of these sterilisation methods may result in some chemical or physical effects on prefillable syringes, for example radiation sterilisation causes the generation of radicals[25] and ethylene oxide (EtO) sterilisation leaves EtO residuals.[6]

Such effects and residuals may lead to the denaturation of biopharmaceuticals and radiation-sterilised PFS may lead to protein oxidation, as has been discussed in other publications.[5,25] Therefore, to determine the effects of various sterilisation methods on the denaturation and aggregation of biopharmaceuticals, Terumo assessed particle formation in erythropoietin (EPO) filled into PLAJEX SOF PFS, by examining aggregation using size exclusion chromatography with multi-angle light scattering (SEC-MALS), shown in Figure 4, and particle measurement using the FI method, shown in Figure 5. This assessment used non-sterilised PFS as a reference.

Method	Radiation Sterilisation		Ethylene Oxide Gas (EtO) Sterilisation	High-Pressure Steam Sterilisation
	Electron Beam Sterilisation	Gamma Sterilisation		
Instrument	Electron beam accelerator	Radiation source	Gas steriliser	Steam steriliser
Parameter	Dose	Dose	Time, temperature, pressure, etc.	Time, temperature, pressure, etc.
Permeability	Yes	Yes	No	No
Material	Radiation-resistant	Radiation-resistant	Gas permeability	Heat- and pressure-resistant
Treatment method	Continuous	Continuous	Batch treatment	Batch treatment
Duration of treatment	Several seconds to several minutes	Several hours to several days	Several hours	Several hours
After-treatment	Not required	Not required	Gas purging	Drying

Table 2. Sterilisation processes used for PFS.

The SEC-MALS profile of the EPO product in the steam-sterilised PFS was similar to that in the non-sterilised PFS, which indicated that no aggregation of EPO occurred in steam-sterilised PFS. In contrast, high molecular weight components tended to increase over time in the radiation-sterilised PFS, which suggest that the residual radicals induced the aggregation of EPO. Also, an increase over the components detected in the steam-sterilised PFS was seen at approximately 5.3 minutes in the EtO-sterilised PFS.

The FI measurement showed that particles in the EPO product considerably increased in the radiation-sterilised PFS at least four weeks after filling. In contrast, no remarkable increase in the number of particles was found in the steam-sterilised or EtO-sterilised PFS, with the number of particles similar to that in the non-sterilised PFS over time.

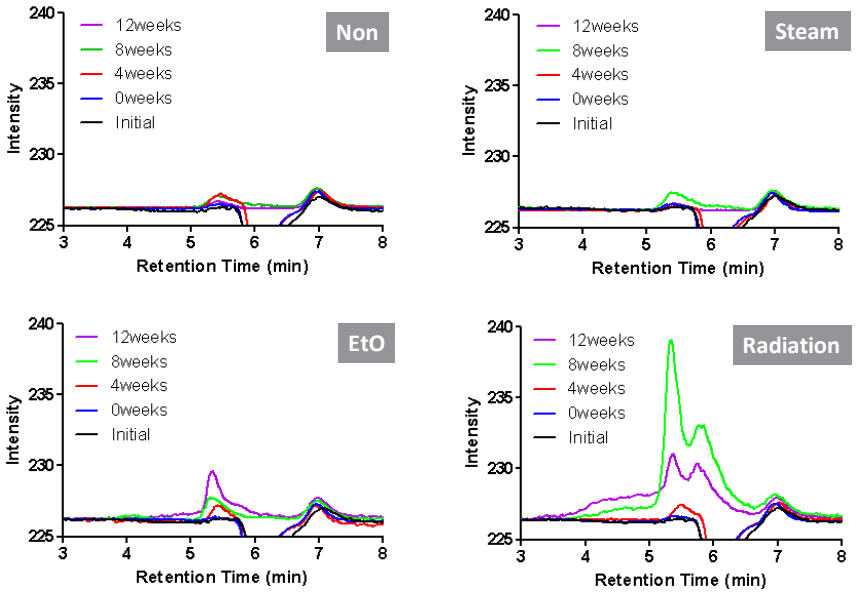

Figure 4: Results of the SEC-MALS measurements after storage of EPO products in sterilised and non-sterilised PFS.

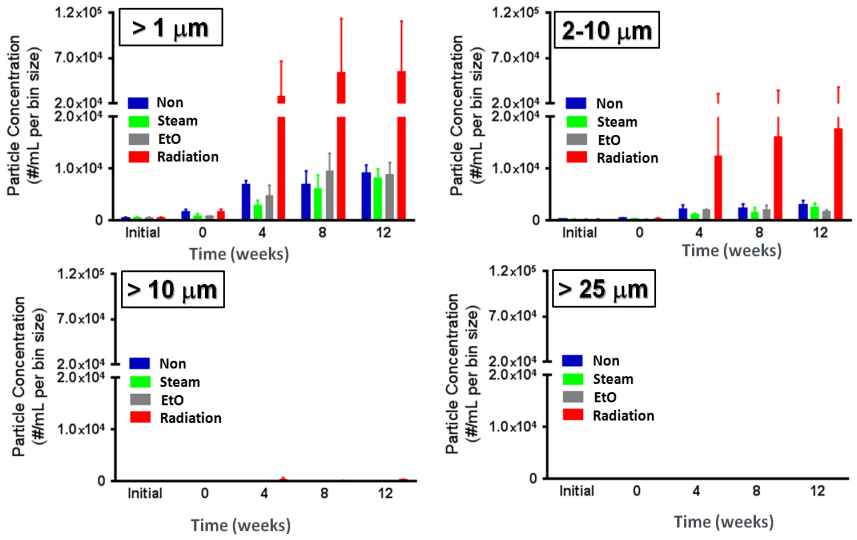

Figure 5: Results of the particle measurement by FI after storage of EPO products in sterilised PFS.

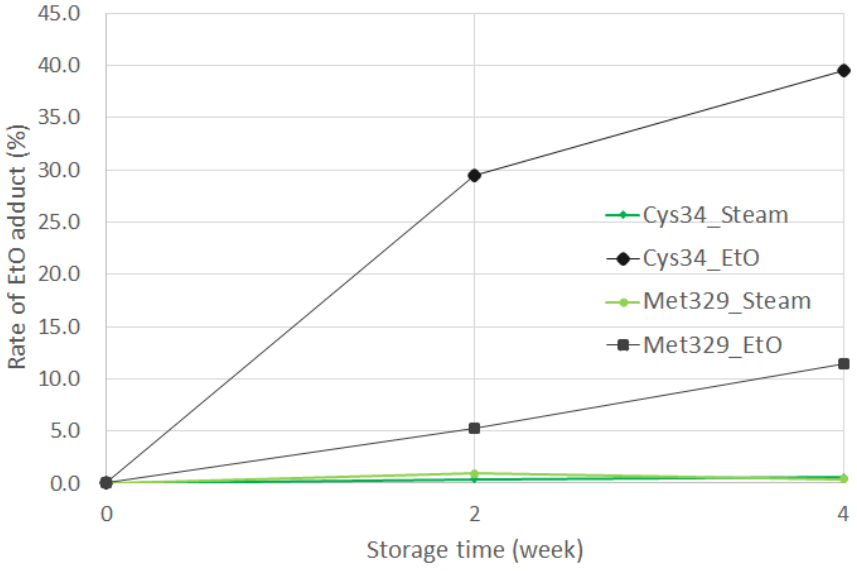

Figure 6: Rate of EtO adduct to HSA in the EtO-sterilised and steam-sterilised PFS.

Therefore, Terumo determined the effect of EtO molecules remaining in EtO-sterilised PFS on biopharmaceuticals (Figure 6).[6,31] After EtO sterilisation, an SOF PFS was left alone for four weeks, allowing for the period from sterilisation to filling and the period from filling to use, then filled with human serum albumin (HSA) solution and then stored at room temperature for four weeks. Terumo determined the rate of formation of EtO adducts with HSA. The results showed that approximately 39.5% and 11.5% of EtO molecules were added to Cys34 and Met329, respectively, in HSA. These results indicated that residual EtO molecules formed adducts with HSA, which resulted in structural changes to the drugs.

CONCLUSION

This article has discussed how, in comparison with an SO PFS, PLAJEX mitigates particle formation in biopharmaceuticals. As such, PLAJEX may be considered as a preferred primary container for biopharmaceuticals, owing to the SOF system and good response to steam sterilisation, which will help to minimise protein aggregation and the formation of particles in biopharmaceuticals, a problem that may be associated with a reduction in drug efficacy and the development of immunogenicity.

ACKNOWLEDGEMENTS

The authors would like to express their great appreciation to Yoshihiko Abe and Kaori Funatsu of Terumo Corporation, and William Dierick of Terumo Europe for their contribution to this study and the preparation of this article.

ABOUT THE COMPANY

Terumo develops alliances with pharmaceutical companies on a global scale, using the company's technology to develop, manufacture and supply carefully crafted solutions to customers' injectable drug delivery challenges. Terumo prides itself on offering a full portfolio of products and services for the pharmaceutical industry, backed by unrivalled scientific expertise and know-how. By anticipating new trends and maintaining a constant dialogue, the company provides a first-class customer experience.

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THE ROAD TO PREFILLED DEVICES IN NOVEL COMBINATION PRODUCTS

In this article, Lior Shtram, Senior Director, Design & Engineering, Flex, discusses three approaches to delivering novel combination products – user-filled, user-loaded and prefilled – through the lens of sterilisation processes and requirements at the industrial manufacturing scale.

INTRODUCTION

In recent years, developments in pharmaceutical markets have been driving the introduction of novel drug delivery methods. Biologic products are presenting new challenges that mean they cannot be delivered conventionally. These challenges are presented by technical requirements such as high viscosity and large volume. Considering volumes of ≥3 mL, a prefilled syringe (PFS) solution becomes cumbersome and inconvenient. The high frequency of the therapy exacerbates the problem, creating the desire for a patient-centric device to deliver therapy at home. To meet these requirements, we are seeing the development of novel combination products such as electromechanical autoinjectors and on-body injectors.

Potentially these types of injectors could be offered in either user-filled, user-loaded or prefilled configurations. The first two configurations require user involvement and are prone to use errors and interface (leakage) issues. The prefilled option eliminates most of these potential use errors, providing a simpler and more effective experience for patients.

One of the key challenges created by these novel combination products is sterilisation. While sterilisation is a key factor for every medical device and drug delivery product, previous-generation combination devices already have established solutions that are well accepted in the industry by all parties. However, when introducing new drug delivery methods, sterilisation presents a unique challenge as it involves not only the device designer, but also the pharmaceutical company, the fill/finish CMO, automation suppliers and quality engineers.

It is possible to look at this challenge as a meeting point between two industries with conflicting processes – medical devices and pharmaceuticals. The device industry is accustomed to manufacturing sterile devices by producing and assembling the device in a clean environment and then sterilising the product after assembly. The pharmaceutical industry, however, follows a different process, in which the primary container of the drug is delivered pre-sterilised and the drug product is filled in an aseptic setting. The finalised product cannot withstand another sterilisation cycle, as that affects the drug product and can introduce additional risks. The two processes described are obviously incompatible and present a major challenge in providing novel integrated combination devices, such as a prefilled autoinjector.

"When introducing new drug delivery methods, sterilisation presents a unique challenge as it involves not only the device designer, but also the pharmaceutical company, the fill/finish CMO, automation suppliers and quality engineers."

USER-FILLED

The immediately obvious solution is to keep each industry separate, each continuing with its own established and respected processes (Figure 1). This solution leads designers to offer products that are user-filled. Here, the drug and the device are presented to the user in separate packages and the user is required to fill the drug product into the delivery device. Products that follow this principle already exist on the market, most notably in disposable devices for insulin. Doing so means that processes for sterilisation are already in place; the supply chain of each manufacturer is maintained; the device

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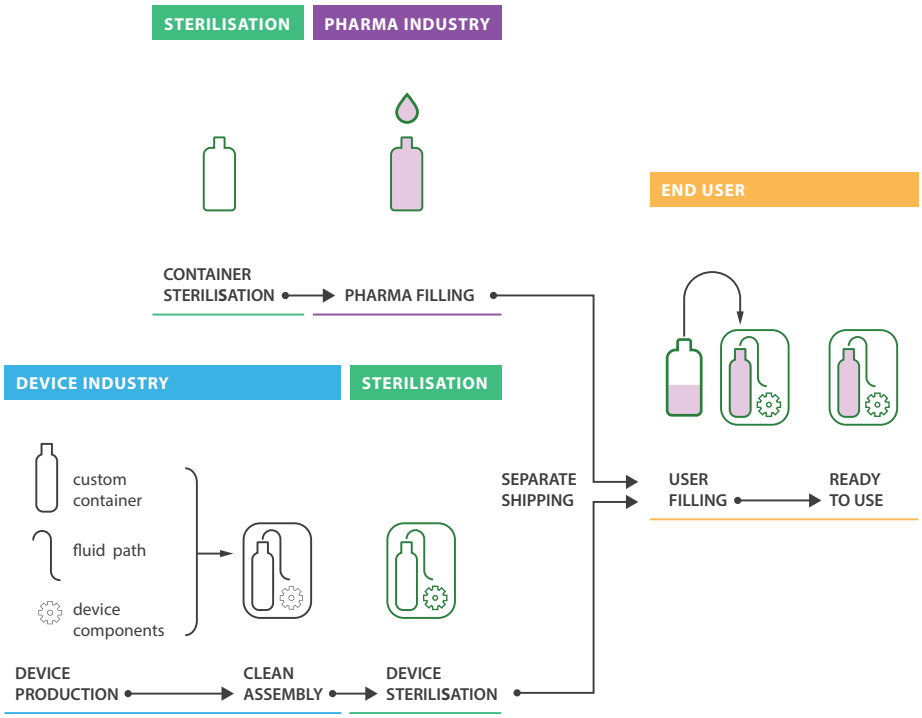

Figure 1: Assembly process for user-filled products.

manufacturer is not requested to handle the drugs and the drug filler is not requested to perform assembly operations. The advantages of this solution are significant to the commercial parties, not only from a technical perspective, but also from those of quality, liability and risk management.

Yet, from a human factors point of view, the solution of a user-filled device is severely lacking. The user is requested to utilise either an external vial and syringe or a PFS to inject the drug into the device. In certain cases, the drug is supplied in a vial and needs to be first drawn from the vial before injecting into the device.

In very specific use cases and requirements, the healthcare market might find this solution suitable. Consider the case where one would like to preserve the role of the healthcare provider (HCP) in the process of injection, while still avoiding IV injection and shortening the hospitalisation duration. This model is already employed in certain oncology applications with great success. However, these could be exceptions that prove the rule. In most cases, the need for device filling creates additional use steps that are considered demanding for a non-professional user/patient.

Several solutions have been suggested to address this problem and to simplify the operation from the user's perspective. With this type of solution, we can include devices such as automated filling stations. Strictly speaking, filling stations do not reduce the number of user steps, and therefore are not removing the burden from the user. Filling stations do overcome specific usability issues, such as reducing dexterity requirements. But more significantly, these solutions reduce possible errors and therefore try to limit the liability for the therapy provider. The attempt to solve a problem that is itself a by-product of a specific design problem with additional devices is far from ideal. The additional filling device is yet another device to design, ship and service, with its own specific costs, risks and liabilities.

USER-LOADED

A hybrid approach, that we shall refer to as user-loaded, has already been adopted in a few devices and could offer a small advancement towards improved usability (Figure 2). In this approach, the drug delivery device and the drug product are still delivered separately, however the drug product is provided to the patient in a custom container that fits as-is inside the drug delivery device. The custom container could be a custom primary container, as in the case of specific wearable devices, or else a custom secondary container, as is sometimes employed in smart electromechanical autoinjectors.

The assembly of the two components, delivery device and drug container, is still an extra step that is expected to be

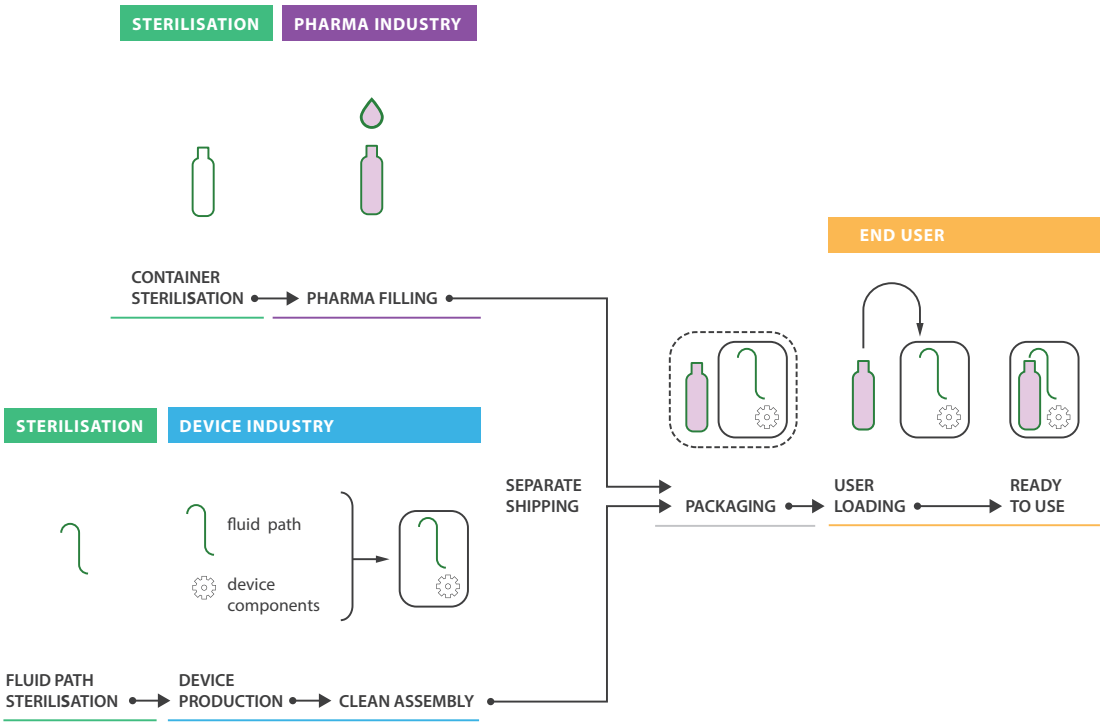

Figure 2: Assembly process for user-loaded products.

"While there is no necessity to use a custom container for the user-loaded device, in practice specific design considerations tend to drive designers toward these solutions."

performed by the patient. This solution is straightforward and sensible in reusable delivery devices (as could be the case in expensive electromechanical autoinjectors), but from a usability point of view could still be considered cumbersome in single-use disposable devices.

The advantages of the user-loaded approach are self-evident. From a provider point of view, the advantages previously mentioned of the user-filled solution are maintained – separate supply chain, each supplier works with well-established processes and maintains the presently known liability, quality control and risks. From the patient point of view, it is obvious that a simple insertion of a primary container into a designated slot in the delivery device could be much simpler than handling a syringe. Still, in most cases, the patient will be requested to perform quite a few actions.

Overall the approach is still inferior to prefilled devices, considering the design and manufacturing implications of a custom drug container; non-standard containers increase the complexity of the development and validation of the solution with key issues such as materials compatibility and drug stability. While there is no necessity to use a custom container for the user-loaded device, in practice specific design considerations tend to drive designers toward these solutions. User-loaded devices that employ completely standard drug containers are a rare breed.

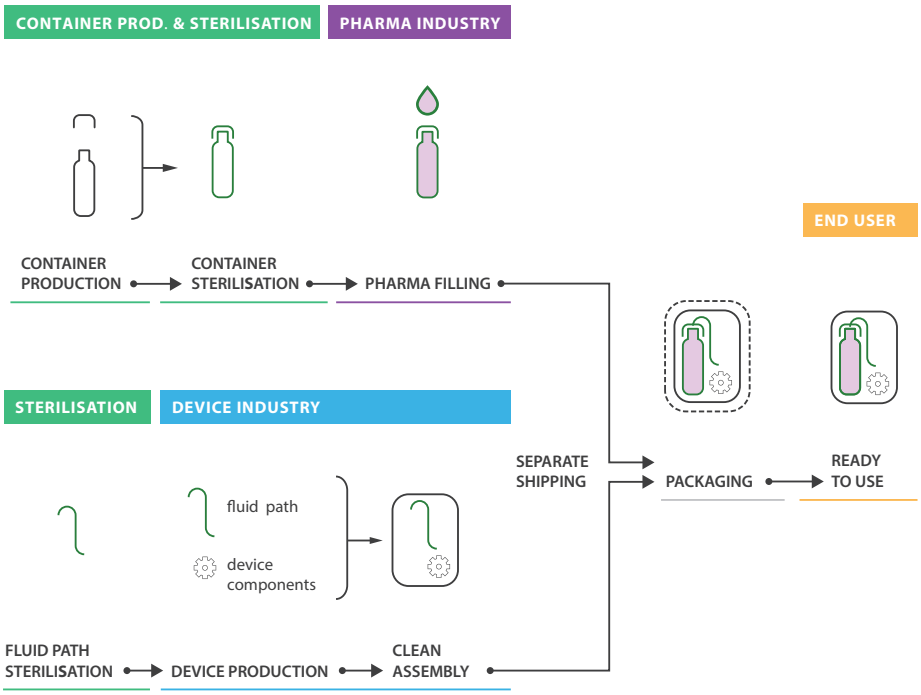

Figure 3: Assembly process for prefilled products.

"While the user-filled and user-loaded solutions provide current viable solutions, there is still a pressing need for a better design."

PREFILLED

While the user-filled and user-loaded solutions provide current viable solutions, there is still a pressing need for a better design. With ever more products requiring regular delivery at home, human factors become central to the design of the device. A desire to simplify and reduce the number of steps for the patient will likely eventually drive the market towards prefilled solutions. In this sense, once achieved in the market, prefilled solutions would set the bar for future products. It is therefore interesting to explore in depth the possibilities of such prefilled design options (Figure 3).

> "In the future, it might be possible to simplify the sterilisation challenges as new sterilisation processes are being developed that show promise in avoiding degradation of the drug product."

The immediate solution one could suggest would be to integrate the device and drug container at the filling site. Sterilised items are received into the aseptic core and could potentially be assembled into a complete unit. However, such secondary operations are expensive from the filling line perspective. These manufacturing lines require major investments into capital expenses, time to deploy and validation efforts. The approach might be technically feasible but strong business cases are required to justify the significant investments and thus, in most cases, the approach will be rejected by the relevant parties. It is important to note at this point that existing solutions that require device assembly after filling, such as PFS, do not require the assembly to be performed in the aseptic core. This is a major difference that presents a unique challenge, especially in the case of on-body injectors.

Another approach would take only essential elements into the aseptic core. These include the primary container and any element of the fluid path that would be in contact with drug. Keeping the rest of the delivery system external to this process does somewhat simplify the adjustments required of the aseptic core and filling line. Any modification of the primary container also impacts the way in which containers can be filled. Consider the addition of a fluid path in the case of an on-body injector, such a fluid path is required, at a minimum, to provide means of delivery perpendicular to the length axis of the tube. Fitting this bulky fluid path into a nest & tub setup requires adjustments and reduces the efficiency of the filling line.

Additionally, the two components of the design, the sterile container-fluid-path and the non-sterile device, require a box level assembly step. If the box level build is to be done at the device contract manufacturer, that manufacturer would need to handle drugs and comply with the relevant quality requirements. Thus, the disadvantages of the approach include a custom primary container, some modification to the filling process as well as drug handling requirements at the top-level assembly.

Yet another design approach would keep both device and pharma processes as they are. In this case, the fluid path that is part of the device would be sterilised after device assembly but before the assembly of the sterile primary container filled with the drug. Here, the connection between the container and the device becomes the key challenge of the design. This connection needs to guarantee sterility from the container and throughout the fluid path, and yet keep sterility after device sterilisation, through drug container assembly and up until the injection occurs.

A specific variant of the previously mentioned solution would solve the connection sterility problem by local real-time disinfection. A disinfection solution would emulate the current practices of injections by an HCP. Apart from the challenge of coming up with a viable real-time disinfection method, the major implications of real-time disinfections would revolve around transferring the liability of the disinfection process to the pharmaceutical company and placing the onus of validation on the device designer.

In the future, it might be possible to simplify the sterilisation challenges as new sterilisation processes are being developed that show promise in avoiding degradation of the drug product. Several suppliers have already made claims that their newly developed sterilisation process reduces risk and allows for the sterilisation of a combination product after filling. Considering the time scales the pharmaceutical industry tends to work on, we can expect adoption of these methods to take several years.

FINAL THOUGHTS

There are several key challenges to providing an effective solution to the market need for prefilled injectors. Solving these challenges is key to enabling the continued and successful expansion of home-based, patient-centric delivery systems that promise to deliver on the promise of ease of patient compliance, reduction of dosing and usage errors, and ultimately better and cost-effective care for patients.

In addition to the challenges presented by the development of a prefilled smart injection system concerning sterilisation, there are other areas to be fully developed. These are outside the scope of this article – and include considerations such as human factors, regulatory, certification, liability of the individual contributors in the supply chain and organisational challenges. However, a tight collaboration between all the stakeholders in the industry (device manufacturers, pharma company, fill finish CMOs, automation suppliers) will unlock the full potential of this category of devices.

Selection of the right partners is key to success by defining and addressing critical considerations from the beginning, so the right solution can be developed with full visibility to the challenges and the requisite experience can be employed to solve those challenges proactively. The clear need for the device category is present, and companies are responding with innovative solutions demonstrating the path to overcome the challenges that have been discussed in this article.

ABOUT THE COMPANY

Flex is the Sketch-to-Scale™ solutions provider that designs and builds Intelligent Products for a Connected World™. With approximately 200,000 professionals across 30 countries, Flex provides innovative design, engineering, manufacturing, real-time supply chain insight and logistics services to companies of all sizes in various industries and end-markets.

ABOUT THE AUTHOR

Lior Shtram is a Senior Director of Technology Management at Flex, which provides design, development, and manufacturing services for medical devices deploying the expertise of design teams and subject matter experts around the world. He has more than 10 years of experience designing and developing novel medical devices, helping to bring to market many diagnostic and therapeutic devices and drug delivery systems. Mr Shtram is based in Israel.

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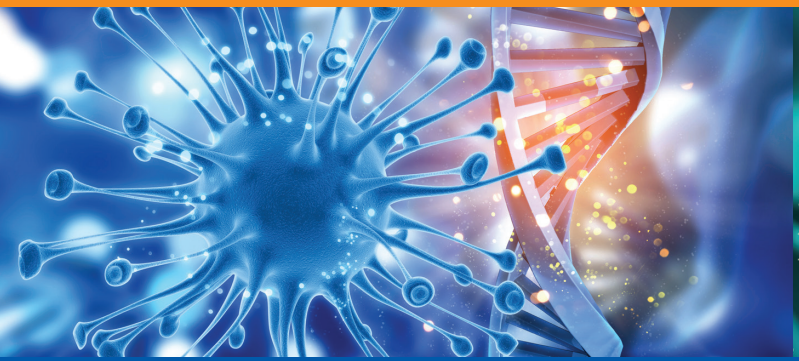
- Transit /Altitude Testing
- Design Validation Testing
- On Body Delivery Systems
- Extractables and Leachables



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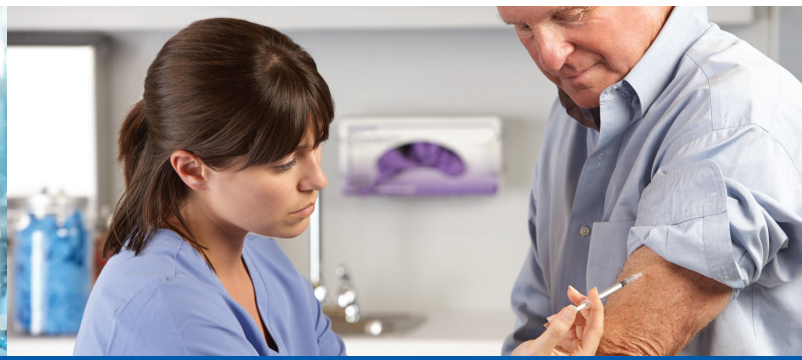

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ALICE MADEN & LIONEL MARITAN, BD

Alice Maden is Associate Director Regulatory Affairs at BD Medical – Pharmaceutical Systems. She has 13 years of regulatory experience in pharma and container closure system environments. Dr Maden has been with BD since 2007 and is in charge of the Global and Strategic Accounts & Prefillable Syringes Regulatory Affairs team. She is a Doctor of Pharmacy, from Université Joseph Fourier (Grenoble, France) and holds a Double Master's Degree in Health and Medicinal Product Engineering from IPIL Lyon, and in Business & Management from Emlyon Business School.

Lionel Maritan is Associate Director Research & Development at BD. He is responsible for design, development and lifecycle management activities for autoinjectors and safety solutions. He joined BD in 2005 and held roles of increasing responsibility within R&D. Mr Maritan has deep experience in drug delivery systems design and development from the innovation stage to commercialisation.

BD's long history and experience in combination products has allowed it to develop deep domain knowledge to support the development of more robust, well-designed systems. Pharma company partners reduce the risk by selecting an integrated system of multiple components that work together to deliver the drug formulation safely and effectively.

In this interview with *ONdrugDelivery Magazine*, Dr Maden and Mr Maritan discuss with detailed expert knowledge the benefits of using integrated systems for sophisticated drug device combination products with multiple device subsystems, and the crucial role that BD can play as systems integrator, delivering manifold advantages to its clients.

Q What does systems integration mean, and how important is it?

LM Generally speaking, systems integration is combining different subsystems into one functional system. For drug-device combination products it is the assembly of the drug with a primary container such as a prefillable syringe and, particularly in self-administration, with an add-on needlestick safety guard, an autoinjector, or a wearable injector.

The primary container and other device subsystems are delivered to pharma companies for final assembly. The subsystems are available from multiple vendors and must operate perfectly once assembled together.

To meet new drug delivery challenges we have seen the rise of complex delivery systems with automated functions. This has definitely raised the bar when it comes to providing robust integrated systems, due to the number of functional interfaces.

> "The systems integration engineering process starts at the innovation stage and it's a critical and indispensable part of bringing a safe and effective drug-device combination product to patients with reproducible performance across millions of units."

The systems integration engineering process starts at the innovation stage and it's a critical and indispensable part of bringing a safe and effective drug-device combination product to patients with reproducible performance across millions of units. To ensure this seamless interaction between the various subsystems throughout the entire product lifecycle, a large range of competences and capabilities is required. For example you need product development technical excellence; requirements and specifications management; the scientific experts across different fields such as chemistry, mechanics, fluid dynamics; and manufacturing engineering capability from preclinical and clinical through to large scale.

Our goal is to minimise and prevent issues that our pharma customers face during the early stages of a combination product's launch in order to reach the market on time. Getting to market on time is really a key driver and a key benefit of systems integration. But the advantages also flow through to the patient. Of course, after launch and during commercialisation we have to provide a robust system that operates

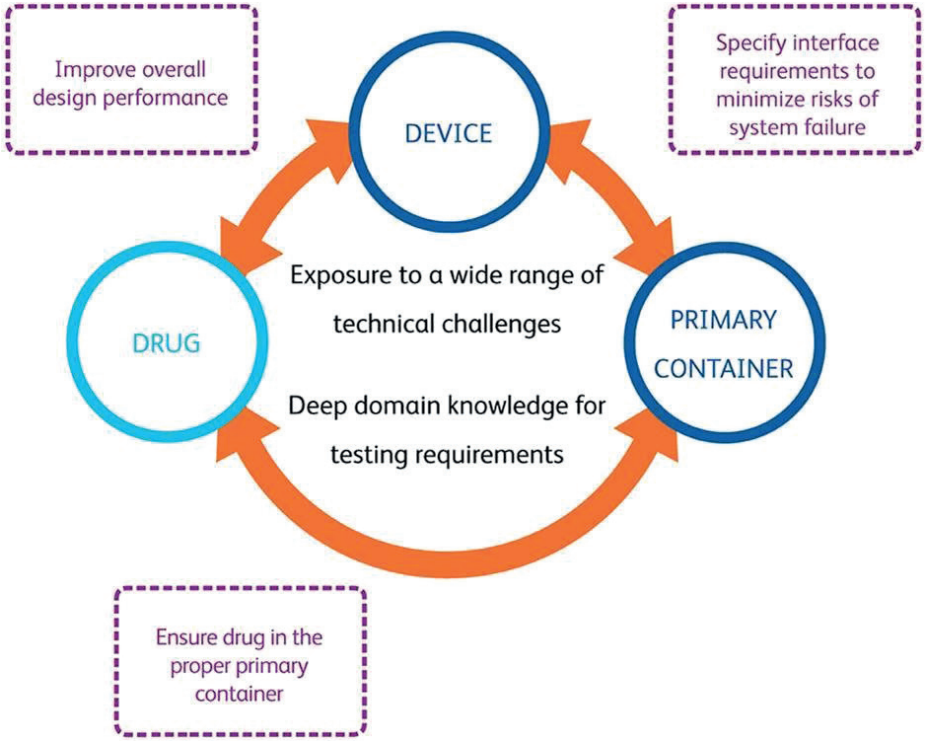

Figure 1: BD's experience with integrated systems enables robust and well designed combination products. BD has the primary container expertise, analytical tools and lab test capabilities to help predict interfaces and functionality.

perfectly in real life use conditions. This is why we cover human factors aspects. It's also important that we anticipate all of the use-related hazards that could arise (Figure 1).

AM The importance of systems integration data is increasing all the time as drug-device combination products are becoming more and more advanced. The demand for more sophisticated systems arises because it is becoming increasingly important that the patient is comfortable with their treatment, that their treatment is easy to use.

It's far more complex now than simply having a vial on one side and the syringe on the other. For this reason there are more regulations covering combination products, especially around the integration of different subsystems, and for good reason. It has been demonstrated that while sophisticated devices with multiple integrated subsystems are more expensive, there is an added value for the user who gains more benefit from their treatment and so at the end of the day the effect on total cost is positive.

This is all related to healthcare economics. When devices are easy to use and comfortable for the patient it means they are more likely to be compliant with the treatment. If they're compliant, there is definitely a cost saving for the payer.

At the other end of the process – at the initial design and innovation stages there are substantial clear benefits from having a single supplier of the device subsystems, with a single coherent viewpoint. When a pharma company is sourcing, for example the primary container, secondary packaging other device subsystems such as a safety add-on from a single supplier, they don't have the complexity of dealing with multiple different suppliers and integrating products from multiple different sources. There is a de-risking effect. The accompanying technical and regulatory data is also key – there are again clear benefits from receiving all of the relevant data covering the different device subsystems in one co-ordinated package from one supplier.

Q How does BD position itself to offer an integrated systems approach?

LM Filing and launching a drug-device combination product is a long and expensive journey for pharmaceutical companies. To make sure that BD's customers succeed and excel in this process, we are positioned as an advanced drug delivery solutions partner. We take care to assure and demonstrate the performance of the combined delivery system comprising the prefilled syringe together with the device subsystems. We assure performance throughout device technical management.

Ultimately, when developing an advanced delivery system with multiple device subsystems, a delivery system integrator is required. We are able to assume this role, and this differentiates us from other companies. Specifically, it means that we manage all of the iterative event loops and requirements through the cascading process from delivery system requirement definitions, sub-system requirements, component requirements, manufacturing process requirements during the definition and development phases.

AM There are specific guidances that deal with systems approaches, both from the ISO organisation and regulators. We can demonstrate that we have supporting documentation that is in line with what all relevant authorities and standards organisations expect from us and our customers. For example, design control is regulated in the US by the FDA's 21 CFR 820 so at BD we have included this in our product development methodology. We control all elements of the delivery system. FDA highly recommends to pharma companies leverage information at the supplier level. So the fact that we have the whole system is a definite advantage.

Our integrated systems approach is supported by a cross-functional team, meaning that not only are the technical aspects considered during development, but also the quality and clinical/medical aspects. So we're able to develop a very comprehensive, exhaustive data package thanks to the methodology that we apply and the variety of experience and capabilities in our cross-functional teams.

LM It covers all design control aspects including human factors, usability testing and preclinical and clinical evaluation. Also, later during the commercial phase which is also a critical phase, BD will define and implement all of the relevant routine inspections for the prefillable syringe and the device subsystem. This is where we're able to maintain product performance year after year and on millions of units. Additionally, we maintain and analyse post-market surveillance – feedback and reports of problems from our pharmaceutical partners after product launch. In this way we continually improve the performance of the full system by continually monitoring and improving the performance of each subsystem.

An example is our disposable BD

Figure 2: The BD Physioject™ disposable autoinjector, successfully launched eight years ago.

Physioject™ autoinjector (Figure 2), which we launched eight years ago. Today we have an extremely low level of reported problems regarding the critical functions including those functions at the interface of the syringe with the device subsystems, such as rigid needle shield (RNS) removal, syringe resistance, needle bending. On all of these issues we are below the one defective part per million (ppm) level on the market.

The coherent overview afforded to a systems integrator and to achieve this reliably high level of product quality is about more than being a large organisation. BD has to have the capabilities and also the organisation needs to be aligned appropriately to achieve this, not only technically to deliver the product but also the supporting data both at system level, and the whole cascade of requirements, specifications etc that I mentioned earlier at the subsystem level too.

This offering from BD is a key differentiator in the market today. It is a key differentiator. It might be possible to gather together different suppliers for different subsystems with capabilities at different points in the process – some early, some to launch and some post launch. However, it is very difficult indeed to gather together and co-ordinate all the different suppliers that cover all of the multiple subsystems at all the different points and stages of development and commercialisation. BD covers all the device subsystems all the way along – from concept to post market.

> "Our new generation of two-step, push-on-skin autoinjectors, called BD Intevia™, which is suitable for 1 mL and 2.25 mL syringes, leverages all of the lessons learnt over more than 13 years of experience developing, launching and commercialising BD Physioject™."

Q The advantages of having a single supplier are clear, but are there any disadvantages or circumstances where multiple suppliers would be preferable?

LM To be honest, we know that a weakness exists from having a single supplier, and we do not need to shy away from it. Some pharma companies prefer to double source their prefillable syringes and these companies would of course be less attracted to a single supplier of the integrated system. But to be clear, wherever systems and subsystems are sourced, at the end of the day you need a system integrator to make sure that the specifications are meaningful – dimensional specifications, functional specifications, cosmetic defects and so on. All of the specifications need to be applied to the prefilled syringe and device subsystems and the device integrator needs to do this job.

If a pharma company decides that it requires double sourcing for its prefilled syringes then they also have to position themselves and take the lead as systems integrator. It is entirely possible, but the pharma company takes on a substantial additional burden and it is a long journey. They will inevitably face the challenges we have faced internally and are now used to dealing with. There are invariably trade-off discussions. For example, what is the best design space between putting more burden on the syringe specifications or revisiting and redesigning an autoinjector to better accommodate a syringe? There are multiple back-and-forth discussions during the development process that are by their nature very iterative, so a pharma company assuming the role of systems integrator will have to undertake all of this. With multiple vendors, multiple stakeholders, with all of the different levels of IP protection to take into account, it becomes a major challenge.

AM Many pharma companies now have strong business continuity policies some of which will say that everything that can be double sourced should be double sourced. But what remains very true is they can still leverage systems integration from us for our prefilled syringes and secondary devices / device subsystems. With that completed by us, the challenge with double sourcing starts when it comes to validating and integrating the second supplier's syringe.

An organisation like BD can of course demonstrate very reliable production quality at extremely low part per million device fault rates, and this represents powerful evidence to support the case that only a single supplier is required if they are a very reliable supplier. However, it is a trade-off. It depends on the different strategies that different pharma companies have. Some will insist on double sourcing. Others might also prefer to develop their own device in-house. We have to acknowledge that and indeed BD still represents a good partner to supply individual subsystems to these pharma companies.

But many pharma companies really do not want to take on any burden with regards device system and subsystem integration and this is where BD is well positioned. We serve pharma companies that seek a true partner from whom they can source a robust entire integrated system.

Q Can you describe the most common issues that a pharma company can encounter when not opting for an integrated system? What can be the costs associated with not having an integrated system?

AM At BD we have worked on a modelisation which identifies all of the milestones throughout the development and commercialisation process at which poor integration could have an impact. This means that from device design through to launch and on into lifecycle management we have a cost case for integration.

We've had the opportunity to discuss this with customers in detail and we've found that some of these milestones are more impactful than others, and present challenges of a different nature. For example, at the early stages you're in development, you have an issue with poor integration, and during design control you realise that your product doesn't work. It's definitely an issue, but less painful discovering the problem early than discovering it later on. The further you continue through development with a poorly integrated system without realising, the greater the impact when the problem is identified.

We at BD recommend that pharma companies go to their suppliers as early as possible. It used to typically happen at around Phase III, but it is becoming more common now for first contact and consultation to happen earlier. Phase II is a suitable time. It seems early but this is really the right time to define the optimal system and again the earlier you identify problems the less painful it is, and less costly.

One of the reasons we're having these sorts of discussions today is that there are many autoinjectors out there on the market but a lot of them are facing issues. The industry is becoming increasingly aware of these issues, we're hearing about them often. Pharma companies planning to launch autoinjector-based products onto the market are increasingly seeking assurances that these issues will not arise.

At various stages during development you can discover that you don't have an optimal system because it is not fully integrated. It can happen just before launch during clinical studies or during human factors studies. This is already quite late because human factors studies are long and the cost is considerable so when you discover a problem at this stage this is a bigger and more costly problem.

But then going further through development you might be challenged by the regulatory authorities on the core integration during their review of the dossier containing the design control and human factors data. This could postpone launch and this has been identified by us and by our customers as the most painful milestone at which to encounter a problem. Postponing the launch of a blockbuster biotech product incurs really very high costs, due to loss of time on the market. This is the worst, most painful stage to encounter problems due to poor integration.

Then the next point a problem with poor integration might be discovered is post launch, during lifecycle management. This happens relatively frequently because you have large volumes of product reaching the market at this stage and a very large population using the product, with a wider variety of local / cultural habits, for example. This is costly because you might have to change something. Changing the primary packaging, for example, is most costly because each time anything is changed that is in direct contact with the drug you have to reconduct various studies that are time consuming and costly, such as stability studies. Changing secondary packaging, say for an autoinjector used for self-injection, is challenging in a different way. You're changing the look and feel of a product and altering how the patient is used to finding the product when they open the box. The identity and reputation of the product is at risk. Again, clearly the earlier such problems are identified and rectified, the better and less costly it is.

> "No matter where the customer is located, and no matter where the support they receive from BD is located, we know our customers have a worldwide target market and they can utilise our worldwide expertise to access that market. We leverage this global view and global experience and consolidate it into the recommendations we make to our customers."

The point I made earlier about the importance of making contact with a device supplier early links in with minimising systems integration problems even at the lifecycle management stage. Customers have various options at the early stages with regard to how they will approach lifecycle management. Some go with a sophisticated, multiple subsystem combination product from the outset. For example, this could be a syringe and an autoinjector or syringe and a safety system. In these cases BD can recommend the most appropriate system and we will have the data package that demonstrates that the suggested system is well integrated. Other customers start by launching a naked syringe and then consider a more sophisticated system as part of lifecycle management, perhaps to protect themselves from potential biosimilar or generic competition. In these cases, the more BD as systems integrator knows at the beginning, the better. If we know that they are planning, perhaps five or ten years from now, to add an autoinjector, for example, we are able to recommend the right syringe from the outset that is suitable for integration with the autoinjector at a later stage. Often customers themselves do not know the details of their lifecycle management from the outset, but if they do have a clear plan, and they communicate it to us, we can anticipate in the initial primary packaging all the future needs for the intended second step.

LM The chronic treatments market is definitely more competitive than it was ten years ago and we are seeing the arrival of biosimilars too. Patient adherence is crucial; the patient is now also the user and they are used to having numerous autoinjectors to choose from – autoinjectors are becoming more of a commodity today. Ultimately the quality of systems integration is what differentiates one product from another – not only from a purely functional standpoint but also from a human factors standpoint, and this will impact upon adherence and adoption. Today the end user has more choice than ever.

When we started work on BD Physioject™ 13 years ago, even before that time in fact, we were already talking about systems integration within BD. Eight years ago, when we started the commercialisation of BD Physioject™ and talked about systems integration with our pharma customers, some were not so receptive to that approach. But today systems integration is commonplace – it's a must have. As a result, we see customers coming to us very interested in BD Physioject™ and in particular our proven expertise, proven results, great post-market surveillance outcomes. The discussions we are having now with pharma partners are very different. Whereas eight years ago we were discussing specific features of the autoinjector, today we are talking about robustness, reliability at the commercial scale, hitting the market window, reliability of our production processes.

Figure 3: BD Intevia™ disposable autoinjector, the new generation of two-step, push-on-skin autoinjectors in 1 mL (a) and 2.25 mL (b) sizes.

Q What specific data can BD provide to customers to better control their development process and minimise development risks?

LM Using BD Physioject™ as an example again, we have a clinically proven and commercially available solution for which we have a rigorous clinical and supporting human factors data including post-market surveillance. We also have the full technical package, which means drawings, event verification, summary reports and customer product specifications. Additionally, we have what we call the customer design for manufacture guidance for customers, detailing how they should assemble BD Physioject™. We also provide validated instructions for use (IFU), the full regulatory package.

We also have a full documentation package covering the integrated solution – for example BD Physioject™ plus our BD Hypak™ for biotech syringe. All the interfaces are covered by these specifications.

To provide some idea of the extent of our experience with BD Physioject™, take as an example the fact that the syringe has to resist the stress exerted upon it when you activate BD Physioject™. Under the power unit's load, the syringe is stressed. Here we formed a deep and iterative engineering framework to work on the critical interface between the syringe and the BD Physioject™ to find the best design options and to define the right subsystem requirements, which means defining the target and acceptance criteria and the testing method.

To do this work we went through multiple design iteration processes, driven by a science-based approach to reducing the stress on the syringe. We ran simulations, we performed many designs of experiments with different syringe designs and different processing conditions. We performed more than 10,000 functional tests at limits on the syringe and on the BD Physioject™ device to support the robustness of the entire system.

For example, we created a specific requirement for flange resistance. We monitored flange resistance in routine, we built strong specifications, with specific testing methods and acceptance criteria and the result is that we added to our body of knowledge. We know that when you take this syringe and put it inside BD Physioject™, it works. And we know precisely why it works.

To undertake such testing, it helps to have experience with and access to the syringes at limits, and the subsystems for testing.

This also applies to our new generation of two-step, push-on-skin autoinjectors, called BD Intevia™ (see Figure 3). This platform, which is suitable for 1 mL and 2.25 mL syringes, leverages all of the lessons learnt over more than 13 years of experience developing, launching and commercialising BD Physioject™. For example, the excellent performance relating to RNS removal, usability studies, flange resistance, barrel resistance, completeness of injection.

Across all of these mandatory criteria we have integrated the lessons learnt from BD Physioject™ into BD Intevia™ and in this way we can demonstrate an extremely high level of robustness, even before commercialisation, which is scheduled to begin very soon.

Additionally, the substantial amount of knowledge and expertise we have allows us to better manage more conflicting requirements. Since BD Intevia™ is designed to accommodate higher viscosity ranges, this means that we require a stronger power unit, but a stronger power unit means more stress on the syringe. We had to design specific technical means to be absolutely sure that the prefilled syringe is not damaged by the forces exerted by the stronger power unit.

This is critical for this next generation of autoinjectors with higher power units. What was true in the industry yesterday – when we mainly had 1 mL autoinjectors for lower viscosity formulations – will be different tomorrow. With these additional stresses on the syringe and device subsystems, systems integration therefore becomes more important than ever.

Figure 4: BD Neopak™ glass prefillable syringes for biotech products.

Q How does systems integration play a role in the area of wearable injectors?

LM Certainly. Platforms such as BD Intevia™ and BD Physioject™ are integrated with more conventional syringes – our BD Neopak™ syringes (Figure 4) for example. But in the case of wearable injectors, during the development of our wearable platform and based on customer requirements, we designed a unique prefilled container in order to bring very specific,

differentiating features; the aseptic transfer function of the drug to the patient, for example.

To make it happen, to have this prefilled container within a specific form factor dedicated to our wearable injector, BD Libertas™ (Figure 5a), the internal technology is different from an autoinjector and to meet the specific requirements we had to create a new prefilled syringe. If we'd built the wearable device around a BD Neopak™ syringe, for example, we would not have been able to meet the specific form factor requested for a wearable injector. It's very different from a handheld device. Intensive engineering efforts led to the design of specific stoppers, a specific aseptic transfer area, and many other specific attributes.

It was possible to do this because we are the systems integrator so in this case we were able to orientate the design of a prefilled container to accommodate the target product profile of this specific device (Figure 5b). It's a unique prefilled container – you will not find it anywhere else – and it is supplied to patients embedded in the device, prefilled. We wanted to avoid filling at use, as this simplifies the steps for the patients.

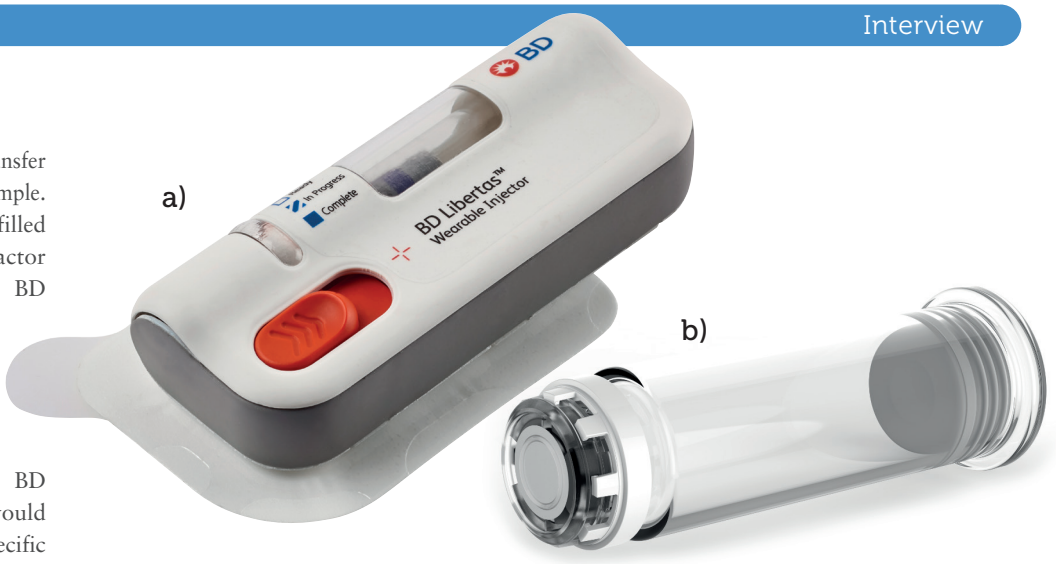

Figure 5: As systems integrator BD was able to design a new prefillable container (a) to accommodate the target product profile of the BD Libertas™ wearable injector (b).

Q Can you explain the difference between integrated system data and component specifications? What are the implications of choosing one versus the other?

LM Ultimately you need integrated system data for the registration of a combination product. You can't define reliable component specifications such as dimensions, functional interfaces etc, without a deep scientific understanding of critical parameters of the whole system itself. You do of course need to understand the impact of these critical parameters at the component level, but you must also understand their impact at the system level.

This is impossible without extremely detailed knowledge about all of the interfaces between all of the subsystems, and of what we call the transfer functions. For example, injection time is a transfer function and behind that information there exist a range of critical parameters – the viscosity of the drug for example, the needle diameter, gliding forces, size of the power unit, the length of the needle. So you see there are multiple critical parameters on the subsystem level that will have an impact at the system level.

The team that is assuming the responsibility of being the system integrator needs to know the transfer functions in order to be able to predict with the required level of accuracy what the injection time will be.

You also need to know the manufacturing capabilities behind each of the critical parameters. If we're talking about needle diameters for example, this not just an R&D consideration but also a question of manufacturing capabilities.

At BD, when we predict a transfer function such as injection time, we are able to factor in all of the correct manufacturing capabilities to our models precisely. It's true for a lot of functions – injection time, needle penetration depth, needle extension accuracy. We can be extremely accurate here, more accurate than other companies that are focused on one component, such as only the power unit or only the prefilled syringe.

We can of course provide all of this integrated system data to our customers, representing a clear and very important differentiation from component-specific suppliers.

Additionally, we are in a well informed and expert position to propose the optimal combination of subsystems to meet specific pharma customers' requirements optimally. We would not propose the same device, the same power unit, the same BD Neopak™ configuration for a pharma customer who has a product with a specific viscosity range and drug sensitivity, as we would for another customer with a different drug with different viscosity and sensitivity.

Systems integration is a long journey. At BD, our systems integration offering goes beyond the fact that we are a large organisation. Being large is important – the scale and range of the resources that we can deploy for our customers throughout development, commercialisation and lifecycle management is a significant factor. Regulatory services, clinical, technical services such as mechanics, chemistry analytics, testing labs – hundreds of world-class people working together. But size alone is not enough. Depth of expertise, the range of capabilities, and the amount and the quality of data at our disposal are all crucial.

It comes back to the fact that this work has to be done – without the integrated system data our pharma companies will not gain regulatory approval for their combination products. It really represents an added value point from BD's side that we can assume the systems integrator role and do this work on behalf of our customers.

We have to acknowledge that some pharma customers will prefer to do some device development internally, leveraging their own capabilities. That being said, when you're talking about more sophisticated devices with multiple subsystems – autoinjectors and wearable injectors, for example – BD remains one of the best device partners available where integration expertise is required across the prefilled container and subsystems.

Q What are the implications for combination product filing? How can this impact the filing process?

AM In terms of combination products regulation, the US FDA is the most familiar, with its 21 CFR Part 4 from 2013. But more regulators are focusing on combination products. In Europe, the EU's Medical Device Regulation (MDR) was published in May 2017 and will be implemented in May 2020. MDR, Article 117, specifically covers drug-device combination products and the fact that delivery devices

need to comply with a particular list of criteria, the General Safety and Performance Requirements (GSPR). It is similar to the Essential Requirements Checklist that is currently required; the demonstration of systems integration will be very similar but submitted in a different format under the MDR, and the level of scrutiny is expected to be substantially increased.

But further than the US and the EU, various other perhaps less known regulators, Malaysia's Drug Control Authority, for example, is also turning its attention to combination products.

The FDA has been very clear that, in terms of design control, everything that can be leveraged from the supplier should be. So if a pharma or biotech company has a systems integration design control data package from its supplier then that work done by the supplier does not have to be done again. The impact is obvious, and it's an important point. It's something that is not feasible if you have multiple suppliers. I've had the opportunity to discuss this with our customers and it is clear that this is something pharma recognises. They asked very clear questions – such as what happens if we source a rubber stopper from a different supplier. BD clearly can't supply the systems integration data for that because we don't have control over it.

As the systems integrator, thanks to our cross-functional offering, BD can provide a formatted document – not just the raw data but information of the type, level and format expected by specific local regulatory authorities. For example, it might be in the CDT format for the ICH regions such as the US, Europe and Japan. But BD supports hundreds of customers targeting the same markets with their various regulatory requirements – our experience is not limited to the major territories but is truly global, built over decades working with the largest regulatory agencies to the very smallest. No matter where the customer is located, and no matter where the support they receive from BD is located, we know our customers have a worldwide target market and they can utilise our worldwide expertise to access that market. We leverage this global view and global experience and consolidate it into the recommendations we make to our customers.

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TO SUBSTITUTE OR NOT TO SUBSTITUTE? THAT IS THE ANDA QUESTION

Here, Natalie Shortt, Senior Human Factors Specialist; Maija Smith, Human Factors Specialist; and Venetia Dickinson, Human Factors Specialist; all of Emergo by UL, discuss the US FDA's Draft Guidance on how human factors relate to the ANDA process, and how its encouragement to stay close to the reference product may result in some negative consequences.

Regulations within the medical field are continually being refined with an emphasis on improving the protection and wellbeing of all users and patients. The history of medical industry regulation stretches back just over 100 years, thus a multitude of regulations and procedures curtail poor design and ensure device safety and usability. In 2017, the US FDA provided a draft formal guidance document in relation to the human factors (HF) associated with the Abbreviated New Drug Application (ANDA) process: FDA draft guidance UCM536959 – "Comparative analyses and related comparative use human factors studies for a drug device combination product submitted in an ANDA".

The guidance states that when submitting a generic combination product, manufacturers should also consider replicating as closely as possible the user interface (UI) of the reference listed drug (RLD) or "seek to minimise difference from the UI for the RLD".[1] The reasoning is that a patient should be able to switch from the RLD to the new generic without having to undergo additional training or input from a healthcare professional (HCP). This reflects reality as they may be prescribed the generic in place of their usual medication without input from an HCP.

This new guidance explicitly does not replace the usability engineering process outlined in ISO 62366-1:2015,[2] as it states that "FDA does not consider the comparative use human factor studies… to demonstrate the safety or effectiveness".[3] However, it does state that by replicating the UI of the RLD, or by minimising the differences between the UI of the RLD and new generic, applicants may avoid conducting comparative use HF studies.[4]

On the one hand, if manufacturers copy the RLD, they should not need to perform a comparative study. If the RLD itself has HF shortcomings in its design, a usability validation study could lead to a situation whereby the generic device is not determined to be usable by intended users, even if it perfectly mimics the RLD. On the other hand, if a manufacturer changes the design of the generic, for example to address known HF problems with current devices, this may introduce critical design differences which would require a comparative study, which may be costly and time consuming. Therefore, generic manufacturers face a dilemma. Should they copy the RLD design, in which case the generic could be considered by regulators to be "substitutable but not usable"? Or should they innovate, and thus risk the generic being "usable but not substitutable"?

"Generic manufacturers face a dilemma. Should they copy the RLD design, in which case the generic could be considered by regulators to be "substitutable but not usable"? Or should they innovate, and thus risk the generic being "usable but not substitutable"?"

DECIDING TO REFLECT THE RLD CLOSELY

Avoiding the time and expense of comparative HF studies might not be the only appealing reason for a generics manufacturer to follow the design of the RLD closely. The guidance outlines that an ANDA applicant can rely on the FDA's previous finding that the RLD is safe and effective.[5] UCM536959 intends to apply this thinking to the user interface of the generic combination product.

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"The assessment of design differences is subjective, and it is possible for manufacturers to underestimate the differences in the UI design and class them as minor when they should, in truth, be classed as "other differences"."

Another positive for manufacturers is that if they follow the guidance recommendation that potential applicants should seek to minimise the differences "in the early stages of development",[6] they will have a less complicated design development process overall. In most cases, taking this route will be less time consuming and more cost effective, as the design team has a clear exemplar available to follow, although it should be noted that on some occasions it could be costly to replicate the RLD.

UCM536959 recommends the manufacturer to employ threshold analysis to identify the UI differences of the generic combination product when compared with the RLD.[4] The analysis may identify a number of outcomes:

- **No design differences** that would likely mean that FDA will not request "certain information and/or data, such as data from comparative use human factors studies"
- **Minor design differences** if the identified differences "do not affect an external critical design attribute" and FDA view these minor differences as acceptable
- **Other design differences** if the differences in the UI design "may impact a critical external design attribute that involves administration of the product". In this case FDA "may request that applicants provide additional information and/or data, such as data from a comparative use human factors study".[7]

In cases where the threshold analysis outcome determines there are "no differences" or acceptable "minor differences", there may be no need for a HF comparative study, again potentially saving time and costs. It certainly would appear to be a less risky approach regarding the potential approval from the FDA, as it has approved the RLD already.

Furthermore, if the design of the generic is close to the RLD, end users might already be familiar with the UI and therefore some may be more accepting of it. This would satisfy the desired recommendation that the switch from the RLD to the generic should not require additional training or intervention from an HCP.[4]

Keeping the design of the generic combination product as close as possible to the RLD design to avoid "other differences" when conducting the threshold analyses might also be seen as a low-risk strategy. However, the assessment of design differences is subjective, and it is possible for manufacturers to underestimate the differences in the UI design and class them as minor when they should, in truth, be classed as "other differences". Another possibility is that they may acknowledge the difference but argue that the difference improves the usability of the product. Although the generic manufacturer could be right, it can be difficult to argue that a specific difference does not affect or improve the usability of the generic combination product if there is no evidence present to demonstrate this. This can result in submitting the ANDA application without conducting a comparative HF study that the FDA recognise as being necessary evidence for the approval of the generic combination product, which may set back timelines. This could be considered too great a risk for some manufacturers.

However, maintaining similarity with the RLD's UI raises a question as to whether this approach to HF in an ANDA submission might negatively affect the potential improvement of the generic product's usability. Technology and manufacturing capabilities tend to progress and can lead to new design opportunities that would not have been possible at the time when the RLD product was developed. It could be that by choosing to minimise design differences, the potential improvement of the product (and possibly improvement to patient safety) is disregarded.

ADDRESSING RECOGNISED CONCERNS OF THE RLD'S UI

In principle, ANDAs allow a manufacturer to launch a generic combination drug product "to provide a safe, effective, lower cost alternative" to the RLD.[8] By using an ANDA, products can, in theory, get to market more quickly, and give HCPs a wider variety of treatment options. However, does the new HF guidance impede innovation in the design and usability of generic combination products?

The rate of technological advancement is important to consider. Technology is constantly in development to improve usability, function and even compliance with respect to device use. Due to the ANDA HF guidance, a company could look to replicate old technology currently on the market, that may have been designed before usability engineering even became accepted as a necessity. Taking these steps would minimise differences and the likeliness of comparison testing, but it would inhibit the adoption of new technology.

In instances where manufacturers follow the design of the RLD, predicate devices on the market are becoming not just the building blocks for new devices, but the entire structure. This could lead to the same post-market adverse events occurring as companies look to reduce the time and testing it takes to get their product launched.

Over the past two decades, the British Standards Institute (BSI) has found that there have been "alarming trends"[7] in post-market events for medical devices that can be attributed to UI design issues. This suggests that usability needs to be continuously advanced – not impeded.

"A generic combination product that has had few interface alterations would have a positive threshold analysis, but fail to reduce the known use errors of the reference product. A concern is that companies may find it an easier route to copy a product that users know, rather than looking to innovate safer solutions."

Combination products, such as autoinjectors and inhalers, have a known history of use errors due to poor use-related design. These use problems cause improper drug delivery, poor symptom control, delays in treatment and overdoses.[9] Figure 1 illustrates just one possible user error and the consequences thereof.

The guidance states that the proposed generic product may develop a user interface that has certain differences, however these differences may only be accepted by the FDA if they are "adequately analysed" and "scientifically justified".[10] A company may choose to improve a design to remove known UI concerns. However, in doing so they are at the risk of altering the design to the point where a negative threshold analysis outcome becomes a distinct possibility. Without appropriate analysis, the guidance states that in this case the generic manufacturer could be required to perform comparative use HF studies, adding to the cost of the project and delaying the time to market.

In this sense the regulation might dissuade companies from making necessary changes to a device. A generic combination product that has had few interface alterations would have a positive threshold analysis, but fail to reduce the known use errors of the reference product. A concern is that companies may find it an easier route to copy a product that users know, rather than looking to innovate safer solutions. The requirement to perform a comparative study gives making changes to the UI a negative connotation that requires time and money to justify, rather than highlighting the improvements or innovation.

CONCLUSION

Medical device regulations are clear in their desire to mitigate risk and improve device safety. However, at what point do known use errors become accepted into a design? This is a question that regulatory agencies, as well as medical device companies, need to think carefully about for not only the future of the industry, but the wellbeing of users.

ABOUT THE COMPANY

EMERGO by UL's human factors research & design (HFR&D) team is a highly-experienced, global team that specialises in early-stage user research, product design, usability testing and user interface design. With a primary focus on medical devices and combination products, the team has extensive experience helping clients bring safe and effective products to market and ensuring best-in-class user experiences. The team includes over 60 specialists and has offices in the US, UK, the Netherlands and Japan.

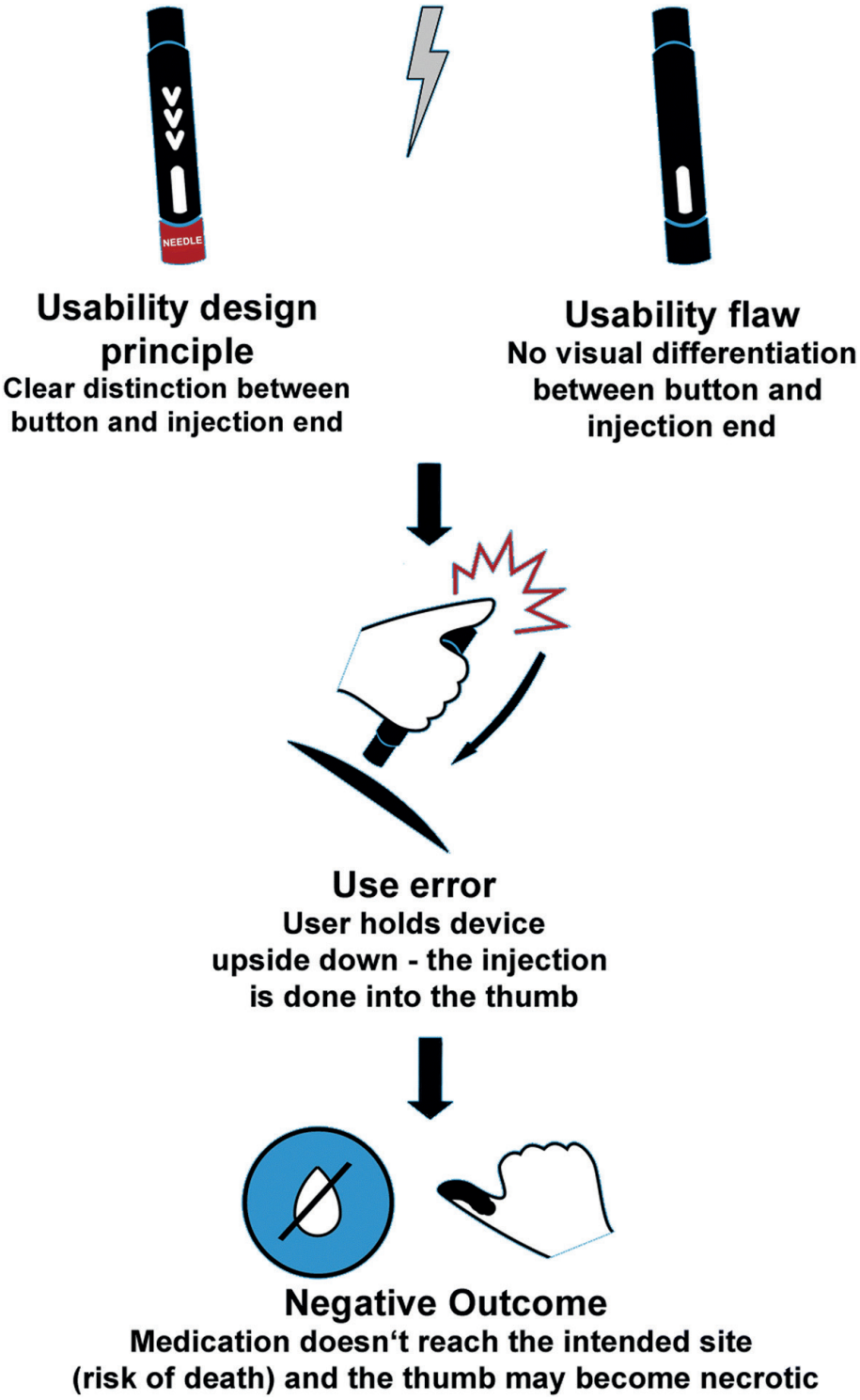

Figure 1: Schematic representation of the cause-and-effect chain between a use error and the negative outcome. Originally from Weinhold T et al, "Improving the safety of disposable auto-injection devices: a systematic review of use errors". AAPS Open, 2018 Vol 4(7). Reprinted under Creative Commons 4.0.

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Natalie Shortt graduated in 2014 from Loughborough University (UK) with a 2:1 in Ergonomics (Human Factors). Ms Shortt primarily provides consultation to clients on the usability engineering process inclusive of creating documentation, designing and performing usability studies in line with the usability engineering process.

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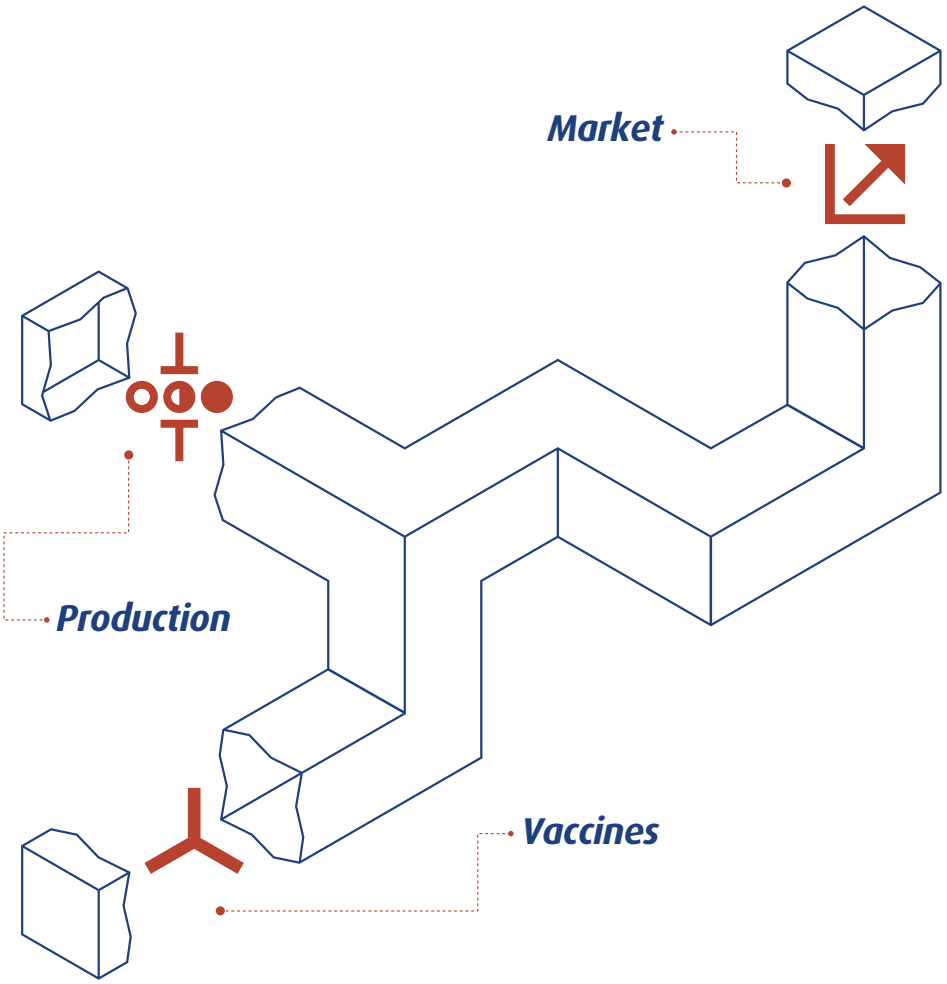

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DATWYLER

DURA COAT COMBISEALS – DATWYLER'S NEXT GENERATION IN ALUMINIUM

In this article, Carina Van Eester, Global Platform Leader, Prefilled Syringes & Cartridges, Datwyler Sealing Solutions, covers the advantages presented by the company's new abrasion-resistant material, Dura Coat, used for combiseals on cartridges.

INTRODUCTION

When it comes to the future of pharmaceuticals and medical care, the WHO pursues a clear vision in its operations: "A world where every child, man and woman has access to the quality essential medicines, vaccines and other health products they need to lead a healthy and productive life." Therefore, the ambition is to improve and maintain access to high-quality pharmaceuticals and medical products in order to achieve the best possible treatment for everyone. Indeed, an increase in average age worldwide is driving an increasing need for medical treatment.

Figure 1: Datwyler offers best-in-class packaging solutions compatible with all types of glass cartridges.

In addition to providing access to appropriate medicines, the WHO considers innovation and development, as well as improving the use of medicines, to be among the steps that are essential to ensure patients receive essential, high-quality medicines. The global healthcare industry strives to meet these expectations by investing in the continuous research and improvement of their products and collaborating on an international level.

The UK, US, Germany, France and Japan are among the leading nations driving global health efforts. Also, in China, there is enormous political will to invest in health. Thus, the Chinese government passed the concept "Healthy China 2030". As part of this, a drive towards health equality, improvements in the health insurance system and stricter standards in the healthcare industry can be expected.

To handle these circumstances, aside from developing new products and meeting new and extended regulations, companies need to rely on appropriate sealing solutions to provide the utmost protection for their products. For example, a variety of pharmaceutical and biotechnological therapies, such as dental care and insulin management, are becoming ever more important, resulting in a steadily growing need for the cartridges used for these therapies.

Datwyler's Role in This Time of Change

A drug therapy continuously improved to increase its effectiveness fits perfectly

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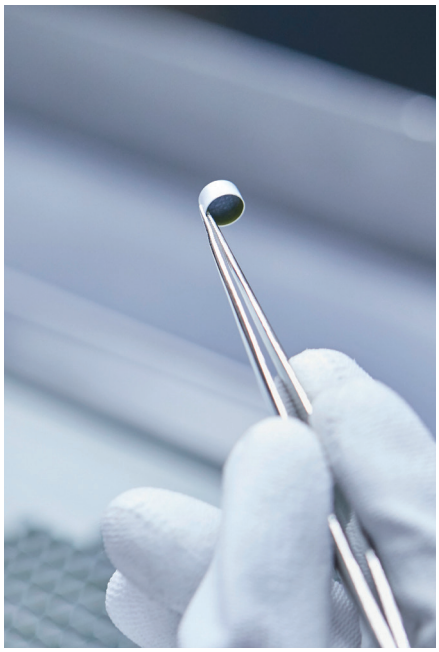

Figure 2: Datwyler aims to deliver the highest level of innovation, quality and safety in the industry.

with the ambitions of Datwyler Sealing Solutions. In a world where an abundance of innovation intersects with the opportunity to improve patients' lives across continents, there is an inevitable increase in complexity. Datwyler's healthcare offering rises to this challenge with the required market-specific product properties, highest quality and cleanliness (Figure 1). Datwyler combines long-standing experience and a history of innovation to better cater to its customers' needs and help them create a safer medical environment (Figure 2). In the company's portfolio of cartridges, two core components are included: a plunger and a combiseal.

IMPROVED COMBISEAL SOLUTIONS

Datwyler's plungers can perform a wide variety of functions to secure the integrity and efficacy of the drug. To ensure system integrity for cartridges, in addition to high-quality plungers, advanced combiseal solutions are needed.

It is important that combiseal components are multifunctional and offer multiple protection, a requirement which Datwyler's components meet. Even after multiple piercings, the combiseals maintain the integrity of the seal, while ensuring the lowest possible extractables and leachables profile for the application. For optimal usability and high resilience, the combiseals feature a dual-compound elastomeric liner inside the aluminium cap.

The components used in the combiseal must be produced with the utmost cleanliness. A zero-defect philosophy and sophisticated production technologies not only meet the qualitative and regulatory expectations of the pharmaceutical market, but also eliminate contamination risk for sensitive drugs. With highest chemical cleanliness, Datwyler develops some of the most complex and unique elastomeric compounds in the industry for medical use.

Different applications require tailored and specific solutions. Datwyler meets this challenge with components that offer a variety of possible combinations of type (monolayer or bilayer) and compound, including:

- **FM257:** A Type I bromobutyl formulation which can be used for a broad range of buffered solutions. It is used as the contact side of the combiseal.
- **FM457:** A modern Type I bromobutyl formulation based on a unique polymer that offers a very high chemical purity. It is used as the contact side of the combiseal.
- **H1-7-207:** A synthetic polyisoprene which is used for the non-contact side of the combiseal in order to improve sealing properties during multi-piercing.

Different liner compositions are selectable depending on the number of piercings that will need to be made. Monolayer liner are used for single piercing applications, such as dental care treatments. Bilayer liners are used for multi-piercing applications, such as biologics, including insulin. Depending on the intended use, Datwyler offers its customers suitable products, and supports them in choosing the right components (Table 1). These combinations have been tested according to ISO11040-3 (seals for dental local anaesthetic cartridges) and ISO13926-3 (seals for pen injectors for medical use) to ensure that sealing, resealability and fragmentation are guaranteed for the number of piercings for which it is recommended.

Monolayer Liner	Application	Liner Thickness
FM257 or FM457	<5 piercings	1,45 mm

Bilayer Liner (*contact compound)	Application	Liner Thickness
FM257* or FM457* + H1-7-207	>5 piercings <50 piercings	1,45 mm
FM257* or FM457 + H1-7-207	>50 piercings <100 piercings	1,95 mm

Table 1: Datwyler assists its customers in finding the most suitable combination of components to obtain a product tailored to their needs.

THE NEXT GENERATION OF ALUMINIUM: DURA COAT

To guarantee the durability and reusability of combiseals, they have to be extremely robust and of the highest purity. Datwyler continually improves its products and processes and tackles

"To guarantee the durability and reusability of combiseals, they have to be extremely robust and of the highest purity. Datwyler continually improves its products and processes and tackles this challenge with the next generation of aluminium: Dura Coat."

"When standard aluminium is used throughout various manufacturing processes naturally generate particles, which can contaminate combiseals."

this challenge with the next generation of aluminium: Dura Coat. A material newly developed by Datwyler, Dura Coat consists of an epoxy lacquer and polypropylene laminate which is applied to standard aluminium seals, meeting all the most stringent customer and regulatory requirements. Once these two layers are applied to a standard aluminium seal, the result is a durable and robust packaging solution (Figure 3).

This innovative product uses high-quality materials and therefore enables a clear reduction in particles during processing and handling. Furthermore, combiseals that use Dura Coat are more abrasion resistant than standard aluminium seals. Datwyler's testing showed that the product guarantees flawless processability in both production and usage. Utilising this proprietary material for combiseals helps to improve product robustness while also reducing the risk of drug product contamination. Dura Coat combines a high-quality alloy with a protective laminate, providing the customers with the cleanest product currently available on the market.

When standard aluminium is used throughout various manufacturing processes, such as deep drawing, assembly, washing, and crimping, naturally generate particles, which can contaminate combiseals. The cutting of standard aluminium, without strict specifications for earing, also results in aluminium particles. Epoxy based lacquers can also cause impurities, as they are not really robust with respect to flaking during production, transport and filling. When it concerns a silver cap, the transparent lacquer will also shed particulates, which are hardly visible. In case of other colours like blue, green or red, flakes can be created which finally end up on the liner and as such can contaminate the drug product.

Dura Coat reduces this particle generation up to 10 times more than lacquered alloy. The aluminium alloy used for the manufacturing of Dura Coat material conforms to ISO 8872, and the aluminium used is lacquered with epoxy based lacquer. Datwyler purchases aluminium with strict specifications for earing in order to avoid the need to cut the aluminium after deep drawing.

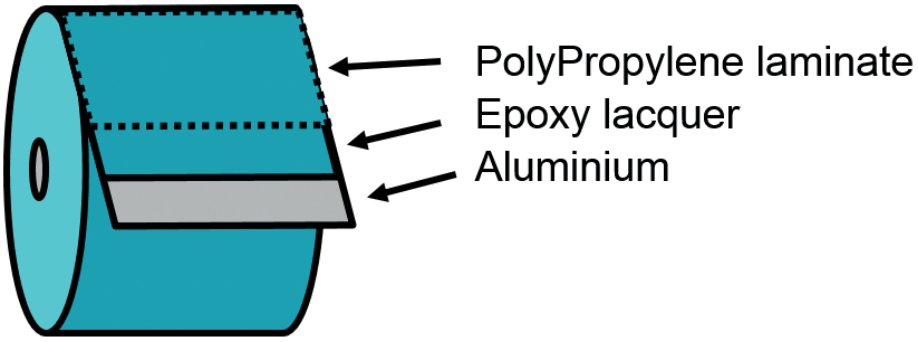

Figure 3: Once the epoxy lacquer and polypropylene laminate are applied to a standard aluminium seal, the end result is a durable and robust secondary packaging solution.

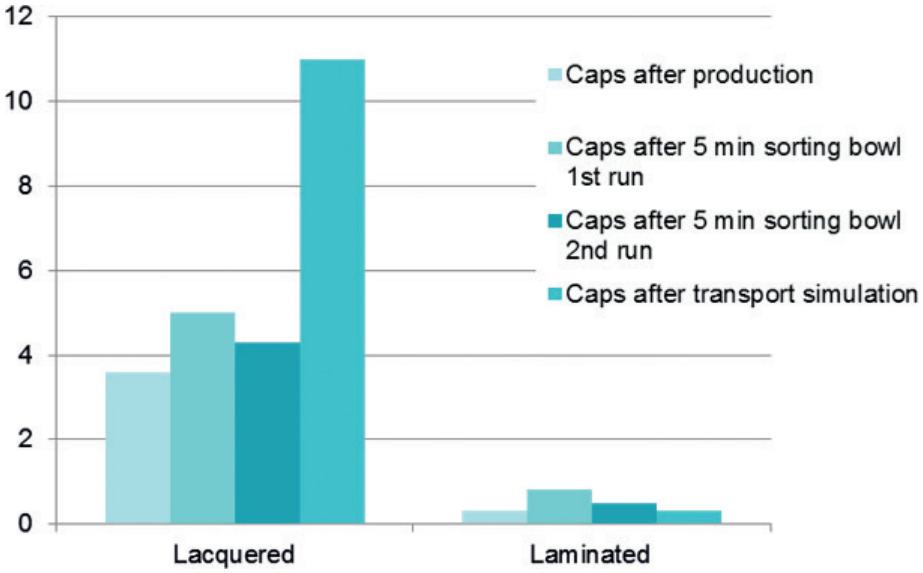

Figure 4: Dura Coat provides a protective barrier to external forces and thus significantly reduces the risk of abrasion during manufacturing and handling.

"The proprietary abrasion-resistant coating also provides a protective barrier to external forces, reducing the risk of abrasion during manufacturing and handling. In detail, Dura Coat combiseals contribute to the reduction of particles."

The protective laminate completely eliminates the issue. This allows an overall reduction in the number of particles produced during production due to the protective polypropylene liner.

Tested to Meet Highest Expectations

The proprietary abrasion-resistant coating also provides a protective barrier to external forces, reducing the risk of abrasion during manufacturing and handling (Figure 4). In detail, Dura Coat combiseals contribute to the reduction of particles. Abrasion can again result in flakes ending up in the drug product, which creates a high reject rate of the filled cartridges, but it can also result in visual defects, such as scratches, which, particularly for high-end products and certain markets, are not acceptable. For combiseals made of Dura Coat material, Datwyler offers a very low AQL (Acceptable Quality Limit) for this type of visual defect.

An extensive series of tests were undertaken to examine the robustness of the material and to assess the effectiveness and functionality of the laminated aluminium. For example, a Taber abrasion test, which measures how resistant an object is to wear over time, was performed in accordance with ASTM D1044-08. The results showed a significantly different wear resistance of the aluminium surface between non-coated (only epoxy lacquered) and Dura Coat-treated aluminium. While the Taber abraser wears completely through the lacquer layer on the non-coated samples during 500 cycles, the colour layer of the laminated material remains intact (Figure 5). This visual impression is also confirmed by the measured weight loss.

In order to provide every customer with unlimited functionality and flawless processability, according to their specific requirements, a combiseal can undergo various steps before treatment. There is a number of worst-case tests to make sure that the material withstands different pre-conditioning processes like washing, sterilisation and drying before filling and post-sterilisation. This proof of quality ensures that the material is as durable as promised and that the customer receives a high-grade end product.

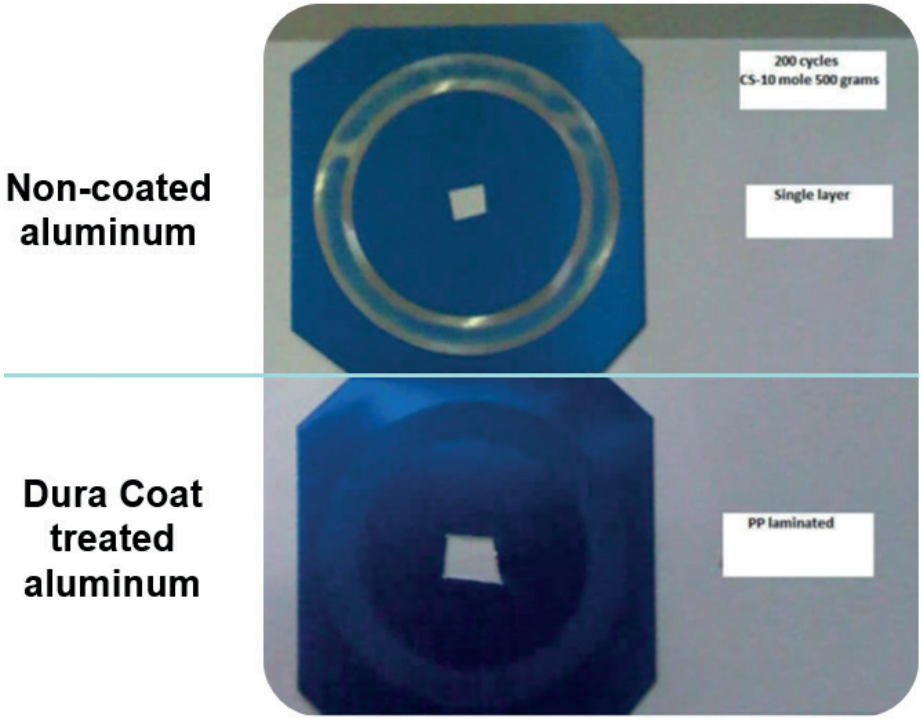

Figure 5: By applying a polypropylene liner to the aluminium prior to processing, Datwyler has found a way to create a cleaner and more effective aluminium seal.

THE FUTURE OF CARTRIDGES HAS BEGUN

The Dura Coat material used for cartridge applications offers a very robust combiseal with a low particulate level, low level of visual defects, flawless processability and a seamless container closure. In combination with Datwyler's compounds, this product is the best solution to handle the growing demand for cartridges and to meet the expected increase in dental and insulin therapies. Datwyler is thus taking an important step towards the development programme set out by the WHO, which aims to achieve universal access to safe and quality-assured health products and general healthcare by 2030.[1] This required change necessitates progress, including efficient and safe delivery systems and advanced drug packaging. With its components for cartridge applications, Datwyler Sealing Solutions keeps pace with these challenges.

ABOUT THE COMPANY

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

ABOUT THE AUTHOR

Carina Van Eester is Global Platform Leader, Prefilled Syringes & Cartridges at Datwyler Sealing Solutions. She has a Master's degree in Chemical Engineering and has been working in the pharma industry for 15 years as a packaging engineer. After several years of experience in Technical Key Account Management and Validation, Ms Van Eester's current position as Global Platform Leader for Prefilled Syringes and Cartridges includes managing strategic initiatives related to Datwyler's components for various applications.

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SCHOTT
glass made of ideas

INNOVATIVE SOLUTIONS FOR PACKAGING BIOLOGICS

In this article, Florence Buscke, Global Senior Product Manager, Bulk Solutions, Nicolas Eon, PhD, Global Product Manager, syriQ®, and Tom Van Ginneken, Global Product Manager, SCHOTT TOPPAC®, all of SCHOTT Pharmaceutical Systems, outline the company's offering across both glass and polymer primary containers for pharmaceuticals, emphasising their advantages in the rapidly growing biologics market.

Today, innovative pharmaceuticals and approaches to cell and gene therapies are creating new treatment options for severe and hard-to-treat diseases. Collectively referred to as biologics, these molecules are particularly sensitive, and prone to interact with packaging material due to their complex structure. Such interactions can limit their efficacy and purity and consequently require extensive risk analyses and staking tests before regulatory approval. Hence, biologics require especially high-quality packaging in order to ensure drug stability throughout the product's shelf life, and to simplify the administration process for the patient.

PRIMARY PACKAGING MATERIALS FOR BIOLOGICS

In order to ensure that the packaging fits the individual requirements of both the drug and the application, SCHOTT Pharmaceutical Systems takes a holistic approach together with its customers and considers the three "Ps": the product, the process and the patient. This is done by analysing the specific requirements of a drug, such as if it needs particularly inert packaging; evaluating process requirements, for example considering how the product will be integrated into existing manufacturing lines; and focusing on the patient and how the drug will be administered.

Borosilicate glass has been the first choice for parenteral packaging for drug manufacturers since its development in 1911, due to its excellent barrier properties and ease addressing regulatory requirements. Nevertheless, there is another material garnering interest: polymer. The physical stability of polymer, as well as the diverse design options it enables, make it an attractive alternative for some drugs, including biologics. With over 130 years of glass knowledge and 20 years of polymer expertise, SCHOTT is able to support pharma companies with a broad range of both glass and polymer packaging solutions suitable for biologics.

"With over 130 years of glass knowledge and 20 years of polymer expertise, SCHOTT is able to support pharma companies with a broad range of both glass and polymer packaging solutions suitable for biologics."

NEXT GENERATION OF VIALS

The next generation of vials from SCHOTT combine a number of modular features,

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leading to unmatched drug stability, even for so-called low-fill applications, and an efficient, cost-competitive fill and finish. The superior chemical resistance and extractables and leachables (E&L) profile, as well as low leaching out of the bottom of the vial, make the vials highly suitable for sensitive biologics, high potency drugs and vaccines. The vials are made of an improved, highly inert Type I FIOLAX® borosilicate glass and include the company's validated delamination-controlled production process. Both aspects ensure improved resistance of the inner surface. For pharma companies, this means that no change in registration files is required as the interior surface will remain unchanged from its known borosilicate Type-I form.

Improved Total Cost of Ownership

SCHOTT's offering also enables pharma companies to improve the total cost of ownership (TCO) by using more efficient processing on fill and finish lines. This is achieved by ensuring flawless glass quality from tube to container, utilising optimised processes that increase vial strength. Improved dimensions lead to perfectly shaped geometry and, ultimately, optimised filling-line yields. Lastly, a low-friction outer surface reduces any sticking or climbing effect on the filling lines, ensuring smoother operations.

SYRIQ BIOPURE®

As part of its prefillable syringe (PFS) portfolio, SCHOTT has developed syriQ BioPure® glass syringes especially for highly sensitive formulations, such as biologics (Figure 1). The syringes are designed to keep sensitive drugs stable over their full shelf life, shorten time to market and make administration more convenient for patients. As such, they are manufactured using improved processes to lower tungsten and adhesive levels and to ensure a uniform silicone layer – all validated and documented according to US FDA regulations.

High-End Materials for Improved E&L Profile

syriQ BioPure® syringes are made FIOLAX® borosilicate glass, the gold standard for packaging complex drug products. Thanks to its strong track record, the suitability of this glass type for sensitive drugs is well researched and understood.

In addition, syriQ BioPure® syringes use the latest polymers as rubber plunger stoppers to limit interaction with elastomer coating compounds. The plungers and various closure systems, such as Aptar 4800, Aptar 4900, West 7025 and West 7028, are tailored for sensitive applications. More than 48 combinations have been validated. The use of high-end materials further contributes to the superior E&L profile of syriQ BioPure®.

Seamless Autoinjector Integration

These new glass syringes are designed to work with leading safety and autoinjector devices, meeting market demand for products suitable for home administration, improving patient comfort and convenience. Seamless integration into these devices is achieved thanks to high dimensional accuracy, with each single glass tube used for the manufacture of the syringes closely inspected using lasers, cameras and infrared systems, also known as SCHOTT's big data perfeXion™ process. By collecting roughly 100,000 data tags per minute, an integrated IT system registers imperfections with such precision that it can later differentiate corresponding individual tubes, which can then be discarded. Additional dimensions beyond ISO requirements and new geometrical tolerances for the syringes are achieved by cutting-edge forming technology and online inspection systems. This ensures device compatibility by design, and therefore leads to superior functionality.

> "SCHOTT TOPPAC® syringes are particularly break resistant, lightweight and feature excellent barrier properties, as neither ions nor heavy metals are used in the production."

The syringes are documented according to the latest design controlled guidelines (accurate to FDA 21CFR Part 820) to support combination product requirements. This leads to a short time to market for pharma companies, as all required documentation is fully and readily available.

POLYMER CONTAINERS FOR SPECIAL APPLICATIONS

In addition to glass, polymer is becoming increasingly popular as a primary packaging material due to its diverse properties, and as such the market for polymer PFS has grown continuously in recent years. This growth has been driven in part by existing markets, including emergency pharmaceuticals, infusion therapies and highly viscous medications, such as dermal fillers, but also by a broader range of applications, including sensitive biologics.

Figure 1: SCHOTT's syriQ BioPure® glass syringe.

Figure 2: SCHOTT is leveraging its expertise in processing COC to co-develop customised polymer containers with customers for novel drug delivery devices.

SCHOTT is one of the pioneers in the field and manufactures its SCHOTT TOPPAC® syringes out of cyclo-olefin copolymer (COC), which offers a number of advantages for producing pharmaceutical containers. SCHOTT TOPPAC® syringes are particularly break resistant, lightweight and feature excellent barrier properties, as neither ions nor heavy metals are used in their production. The particle level is also lower than for glass syringes. Due to the strong moisture barrier provided by COC, injectables can be stored for longer periods in small containers.

The SCHOTT TOPPAC® sensitive syringes are especially well suited for the sensitive-drug and biologic markets, having a particularly low E&L profile. This is due to the use of a special elastomer as the material for the plunger stopper, cross-linked silicone inside the syringe body and ethylene oxide (EtO) sterilisation. These properties enable the polymer syringes to ensure higher stability for storing sensitive pharmaceuticals.

Individualised Polymer Containers

Besides its transparent glass-like appearance and physical stability, COC offers new possibilities due to its high design flexibility. As ever more biologics are administered in combination with a specific device, with the aim of making the drug delivery process as simple and comfortable for the patient as possible, the compatibility between the primary container and the device is becoming increasingly important. However, novel drug delivery device design has thus far been restricted by the need to fit with primary containers already available on the market. SCHOTT is now using its extensive expertise in processing COC and is taking a new approach towards co-development of customised polymer containers (Figure 2). This means the cylindrical container is created specifically to ensure a perfect fit with the device, without the need to compromise on the device's design. This allows device makers to focus on device development without having to cater to pre-existing primary containers.

ABOUT THE COMPANY

SCHOTT Pharmaceutical Systems is a leading supplier of primary packaging for pharmaceuticals and analytical lab services. The company provides quality solutions while meeting the highest demands. SCHOTT's product portfolio includes ampoules, syringes, cartridges and vials as well as various polymer solutions. Its production facilities and products comply with the highest international standards for pharmaceuticals.

ABOUT THE AUTHORS

Florence Buscke heads product management for bulk ampoules, cartridges and vials at SCHOTT Pharmaceutical Systems as Senior Global Product Manager. She holds a French and German diploma in economy and business administration from Johannes Gutenberg Universität (Mainz, Germany) and Université Paris X Nanterre (Paris, France). In 2001, she joined SCHOTT and has since worked in several business units in various fields.

Dr Nicolas Eon is Global Product Manager, syriQ®, at SCHOTT Pharmaceutical Systems. He graduated from the University of Nancy (France) and the University of Nantes (France) and holds an engineering degree in Fluid Mechanics & Energy Science, a Masters' in Energetics and Heat Transfer and a PhD in Biomechanics. In 2012, he joined SCHOTT AG as Business Development Manager for Glass and Polymer Prefillable Syringes (PFS). He is now in charge of the Glass PFS Strategy, Innovation and Technology Roadmap as Global Product Manager for the syriQ® brand.

Tom Van Ginneken is Global Product Manager, TOPPAC®, at SCHOTT Pharmaceutical Systems. He studied chemical engineering in Antwerp (Belgium) and holds a MBA from the University of Sankt Gallen (St Gallen, Switzerland). After working in the chemical and pharmaceutical sector in Belgium for three years, Mr Van Ginneken joined SCHOTT in 2008. Following different positons in the pharmaceutical product development department, he joined the product management team as Global Product Manager for SCHOTT TOPPAC® polymer syringes.

SCHOTT Pharmaceutical Systems

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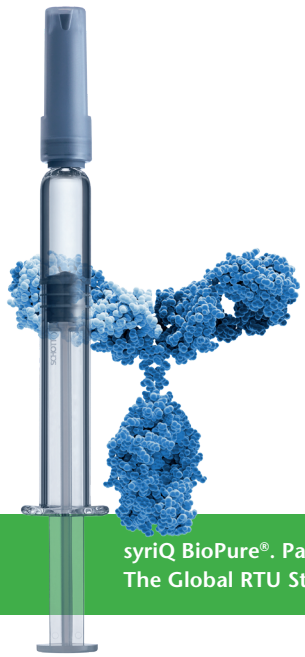
Improve the safety of self-injection with syriQ BioPure®.



syriQ BioPure®. Part of iQ™.
The Global RTU Standard.

The new glass syringe syriQ BioPure® is designed for highly sensitive biopharmaceutical drugs. Dimensions beyond ISO requirement and tighter geometrical tolerances ensure the device compatibility by design, and therefore lead to superior functionality. Your benefit: a safe and easy patients experience. **What's your next milestone?**

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SCHOTT
glass made of ideas

SAFE, CONVENIENT AND EFFICIENT: INDIVIDUALISING PREFILLED SYRINGES

In this article, Ursula Hahn, Team Leader, Product Management, Sanner, discusses the value of individualised prefilled syringes and explains how small changes in design or components can make a huge difference for doctors, patients and pharmaceutical manufacturers alike.

The market for prefilled syringes is growing steadily. Although forecasts vary significantly depending on the issuers of market reports and the respective interpretations, they share one common conclusion: the prefilled syringes market is projected to expand at a rapid pace over the coming five to 10 years.[1,2] A key driving factor is the ongoing boom in the development of biopharmaceuticals, as well as rising life expectancy and an increasing move towards self-medication for the treatment of chronic diseases.

In this context, prefilled syringes allow patients and physicians both a more accurate dosage and a more convenient way of handling drugs. Prefilled syringes are also used in ophthalmology, orthopaedics and cosmetic medicine, for example in therapies based on botulinum neurotoxin (e.g. Allergan's Botox®) or hyaluronic acid. In these sectors, a rapidly growing trend towards individualisation can be observed. This trend is not just about designing prefilled syringes to make them attractive and the brand recognisable; easy handling and safe usage are just as important.

The increasing demand for individualised solutions leads to pharmaceutical manufacturers employing different procuring strategies. Many companies no longer purchase prefilled syringes as system solutions, but instead combine the glass or plastic syringe with individually adapted components to increase both customer and patient orientation. With small changes such as individually adapted piston rods or backstops, manufacturers manage to differentiate themselves from the competition both visually and in terms of user comfort.

CONVENIENCE AND SAFETY FOR DOCTORS AND PATIENTS

For Botox or hyaluronic acid therapies, convenient handling and dosage safety are both very important, both during administration by a doctor and during a patient's self-medication. Particularly in highly sensitive therapeutic areas, such as ophthalmology, ensuring the maximum possible precision and accuracy are essential when it comes to injected treatments. In strabismus and blepharospasm (dystonia of the eyelid), injections with Botox are good alternatives to eye surgery. During this treatment, the doctor injects the neurotoxin into the target muscle close to the eye. However, neurotoxins might migrate from the target muscle to other eyeball-engaging muscles or into the eyelid muscle, resulting in undesirable side effects, such as transient double images. Individualised syringes facilitate a more convenient injection procedure for the physician by sustaining a flexible range of motion and at the same time a clear view of the puncture site.

The same need for accuracy and precision applies to the treatment with Botox or hyaluronic acid in cosmetic medicine. It is easy to come by pictures of people after inaccurate (self-) treatment of Botox. Such is a nightmare scenario – but also a very plausible one. As a highly viscous substance, hyaluronic acid is particularly challenging to administer, especially because its viscosity changes with acting mechanical

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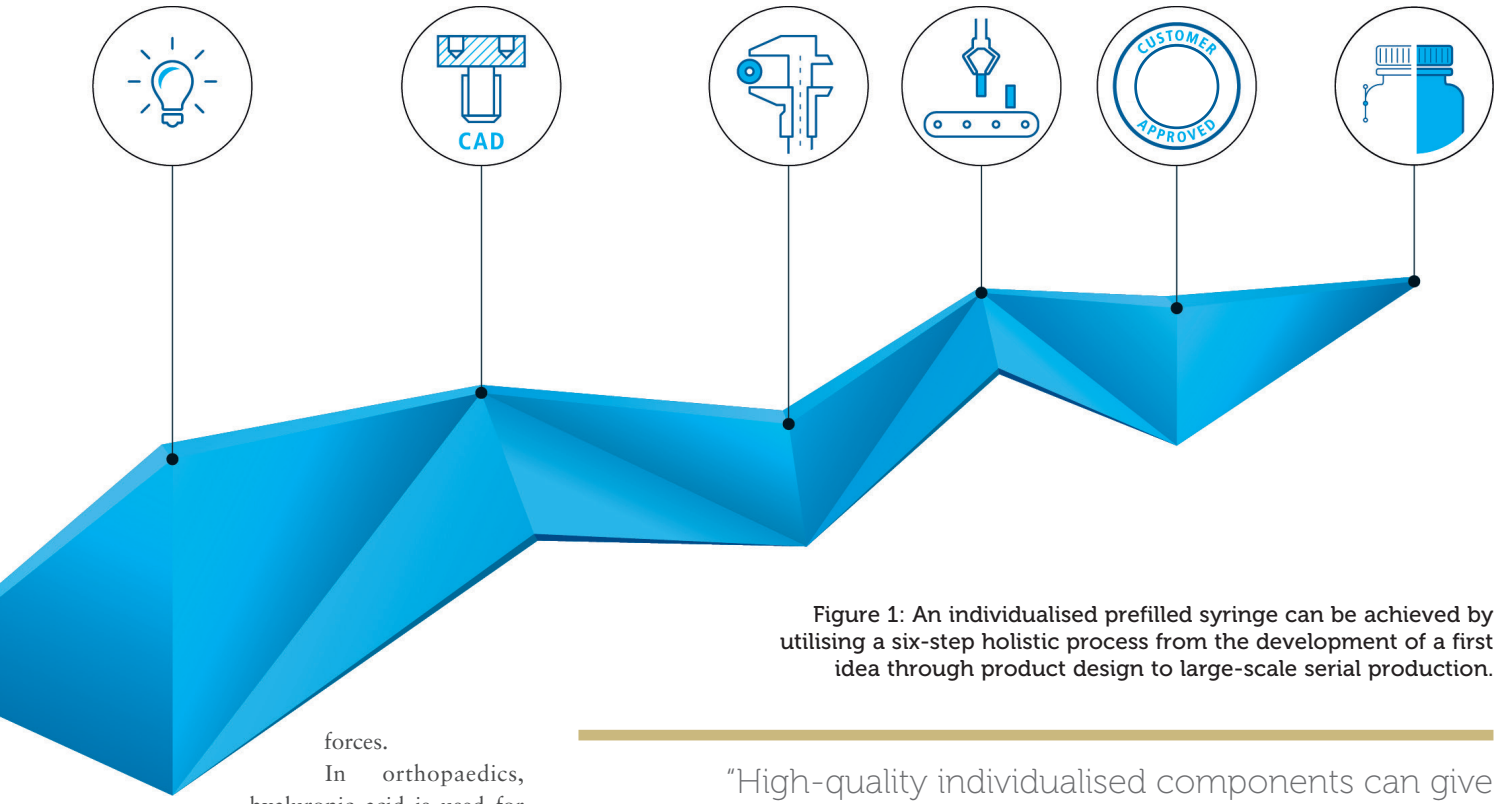

Figure 1: An individualised prefilled syringe can be achieved by utilising a six-step holistic process from the development of a first idea through product design to large-scale serial production.

forces.

In orthopaedics, hyaluronic acid is used for treatments in rheumatology or arthritis, as it is the main component of synovial fluid and acts as a lubricant in all joint movements. Most often, orthopaedic injections are performed by physicians. To avoid injuries during treatment despite the high viscosity of the substance, they require devices that are designed to be both as simple and as safe as possible, allowing for easy administration.

INDIVIDUALISATION WITH VISUAL AND TECHNICAL BENEFITS

The possibilities to individualise prefilled syringes are manifold. Most importantly, individualisation not only benefits the end users, but also the pharmaceutical manufacturers. As far as safety and handling aspects are concerned, the design of individualised syringe components focuses on ergonomics. However, how a device looks also plays an important role for both parties involved: while end users, especially in the cosmetic field, prefer to undergo their expensive treatment by means of a high-quality and visually appealing device, pharmaceutical companies want to make their products distinctive and thereby gain a competitive advantage.

High-quality individualised components can give prefilled syringes a distinctive appearance – from applying the brand name or logo to the use of different colours or the indication of dosage strengths. International and country-specific traceability, safety and information requirements can be met with simple, but effective, means. To simplify complicated logistics in delivering the same product with different dosing strengths to different markets, the syringes can be distinguished in terms of colour, shape and labelling.

"High-quality individualised components can give prefilled syringes a distinctive appearance – from applying the brand name or logo to the use of different colours or the indication of dosage strengths."

From the technical point of view, a sophisticated design of syringe components, such as the thread, can ensure fast processing on filling lines and simplify the packaging procedure. Thousands of prefilled syringes can be filled and assembled on high-speed lines – provided the single components, such as backstops and rods, are perfectly compatible. An exact design and compatibility with common filling systems is crucial for high process efficiency which, in turn, is decisive for pharmaceutical manufacturers, especially in view of the high time and cost pressure in the pharmaceutical market.

AN INDIVIDUALISED PREFILLED SYRINGE IN SIX STEPS

Component manufacturers with long-term experience in different markets and with varying regulations are uncommon when it comes to prefilled syringes. However, individualised solutions require a high level of packaging and processing expertise, combined with industry knowledge and design know-how. In addition, a component manufacturing partner should not only have a specific process installed that enables detailed product specification, conception and development of individual solutions, but one that does so under competitive conditions.

How can all these requirements be reconciled? Which characteristics must a prefilled syringe solution fulfil to be both convenient and efficient, without sacrificing patient or physician safety? The answer lies in a holistic development process that encompasses several phases: from the development of a first idea through product design to large-scale serial production (Figure 1).

Step One – Concept Phase

At the beginning of the multi-stage development process, different approaches are developed based on customer demands, whilst already considering the criteria for subsequent serial production. This phase

should also include a first, rough cost estimate, as well as a detailed examination of the regulatory requirements and the patent situation. Moreover, first sketches of the proposed solutions are created, giving pharmaceutical companies the option to choose between several possibilities, all of which fulfil the given requirements (Figures 2 and 3).

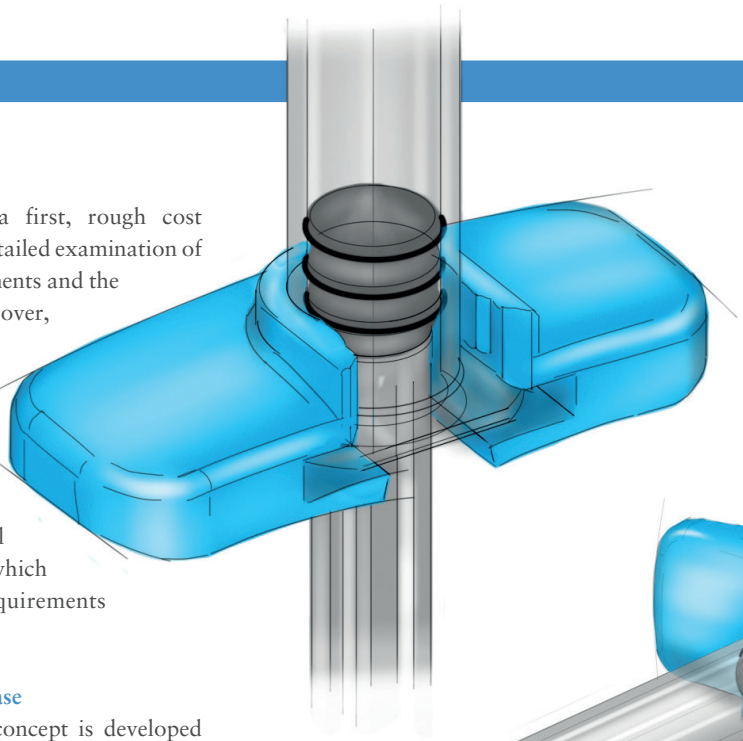

Figure 2: Different approaches are developed based on customer demands, whilst already considering the criteria for subsequent serial production.

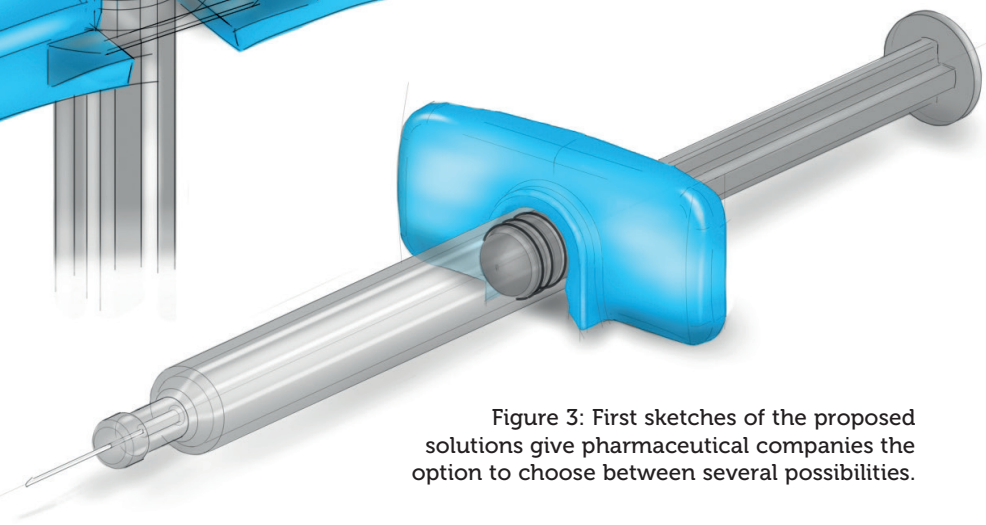

Figure 3: First sketches of the proposed solutions give pharmaceutical companies the option to choose between several possibilities.

Step Two – Design Phase

The selected product concept is developed in further detail during the design phase, while the manufacture of close-to-production product samples is prepared. A physical 3D model as well as detailed elaboration of the data help demonstrate the basic functionalities of the concept (Figure 4). In parallel, the materials are selected in line with regulatory requirements and long-term availability.

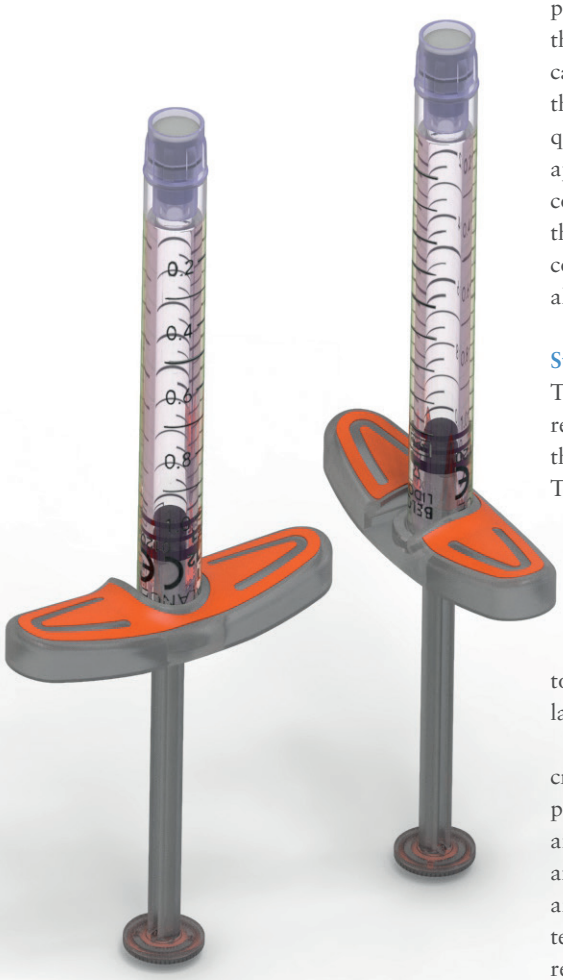

Figure 4: In the design phase, a physical 3D model demonstrates the basic functionalities of the concept.

Tool engineering for near-serial product samples is particularly important during this phase. By means of mould-flow simulation, the engineers analyse the filling of the cavities and the temperature conditions in the planned tool to achieve an optimum quality. This way, the number of subsequent approval loops can be reduced, leading to considerable time and cost savings. During this phase, the basis of the production concept for later serial production should also be established.

Step Three – Prototype Phase

The third phase of the process contains the realisation of the necessary equipment for the manufacture of near-serial prototypes. This equipment forms the basis of the fabrication tools later required for large-scale production. In this phase, final changes to equipment and design can still be carried out without major costs and time loss. The actual production tool will only be manufactured during a later phase, once series maturity is reached.

The prototype phase is also the most critical and complex phase of the entire process as all requirements must be finalised and tested. Good project management and close co-operation with the customer are crucial during finalisation. Quality tests can only be performed if all quality requirements and deadlines are adhered to. This results in a tested and approved product design for successful transfer into serial production.

Step Four – Industrialisation Phase

The industrialisation phase mainly consists of the production, installation and qualification of serial production equipment, as well as the definition of parameters for a smooth and efficient production process, under cleanroom conditions if required. The manufacturing tool is subjected to a comprehensive qualification process in accordance with cGMP guidelines.

Step Five – Implementation Phase

Next, it is necessary to validate the production processes and finalise all necessary documents for approval and registration. According to a testing plan especially developed by quality management, all relevant functionality parameters are inspected. If the final inspection is successful, constant product quality, and consequently a timely market entry of the pharmaceutical product, is ensured.

Step Six – Roll-Out and Monitoring Phase

To ensure the quality of product and processes during, and especially after, market launch, continuous control of serial production is indispensable. An individual in-process control inspection plan defines test criteria and intervals. In addition to the attributive and variable tests, it is also necessary to test the functionality of the syringes and components and to monitor and safeguard the functions of all production equipment continuously through preventive maintenance.

CREATING TAILOR-MADE SYRINGE COMPONENTS

Throughout the entire product life cycle, a multi-phase process can provide for the highest quality, especially in large order volumes. Integrating all test results, as well as the operating data, into a manufacturing execution system ensures continuous traceability. Thanks to this kind of close-knit quality control and professional process and production management, complaint rates can be kept under 0.5 complaints per ten million delivered parts, while "On Time In Full" (OTIF) levels are high, with a rate of over 98% of all deliveries arriving complete and on time.

The close involvement of the drug manufacturer in the entire development process is extremely important to achieve satisfying and efficient results. High transparency and open communication in all project phases keeps everyone informed about the project's current status at any time. Thanks to professional project management and profound expertise, this multi-stage development processes is able to create successful tailor-made prefilled syringe components with the required focus on ergonomic handling and patient safety, as well cost-effectiveness.

ABOUT THE COMPANY

Based in Bensheim, Germany, the Sanner Group was founded in 1894 and is now in its fourth generation as a family-owned enterprise. Sanner develops and produces high-quality plastic packaging and drug delivery systems for pharmaceutical, medical and healthcare customers. The group gained international recognition for its desiccant know-how and moisture protection solutions. With more than 500 employees, Sanner is present all over the world, including in Germany, China, India and the US. The company produces over two billion plastic units each year for standard and customised packaging and drug delivery solutions.

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ABOUT THE AUTHOR

Ursula Hahn started her career in quality management after graduating in Material Science and Surface Engineering from the University of Applied Sciences (Aalen, Germany) in 1992. She joined Sanner in 1995 and has since held a variety of positions in quality management, engineering/packaging development, innovation management and product management, gaining a wealth of expertise in packaging development. Ms Hahn has been Sanner's Team Leader, Product Management, since 2017 and, amongst other tasks, is responsible for patent management.

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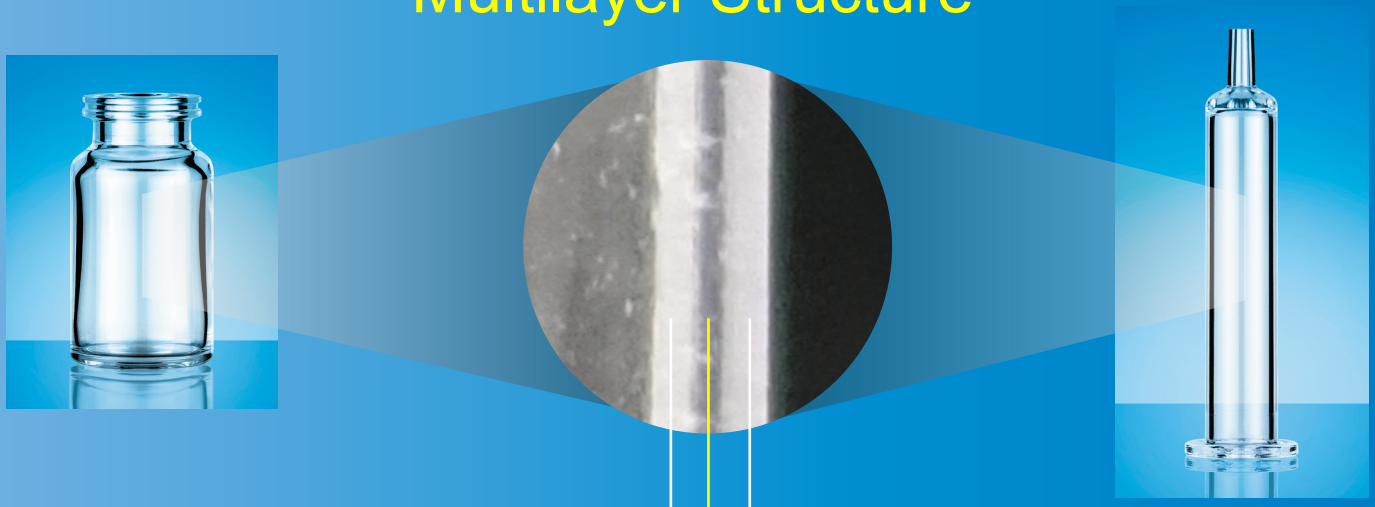
OXYCAPT™ Plastic Vial & Syringe

Multilayer Structure



Water Vapor Barrier Layer
(COP)

Oxygen Barrier Layer
(New Polymer)

Drug Contact & Water Vapor Barrier Layer
(COP)

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

MITSUBISHI GAS CHEMICAL

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MITSUBISHI GAS CHEMICAL

MULTILAYER PLASTIC VIALS & SYRINGES FOR BIOLOGICS

In this article, Shota Arakawa, Researcher, and Tomohiro Suzuki, Associate General Manager, both of Mitsubishi Gas Chemical, discuss OXYCAPT™ Plastic Vial and Syringe, the company's proprietary material, made of multilayered cyclo-olefin polymer and a novel polyester, which provides a product with all the advantages of plastic, coupled with strong oxygen and UV barrier properties.

Although essential for humans, oxygen is basically unnecessary for processed foods and drugs. Over 40 years ago, Mitsubishi Gas Chemical (MGC) developed an oxygen absorber called AGELESS® which prevents the oxidation of foods. Since then, AGELESS® has been used for in a variety of food products worldwide and MGC has been a leading company in the oxygen-absorber field. AGELESS® has also been used for

> "The COP layers give OXYCAPT™ the traditional characteristic advantages of polymer syringes while the new polyester plays a role as an oxygen and UV barrier to address the weaknesses inherent to using COP alone."

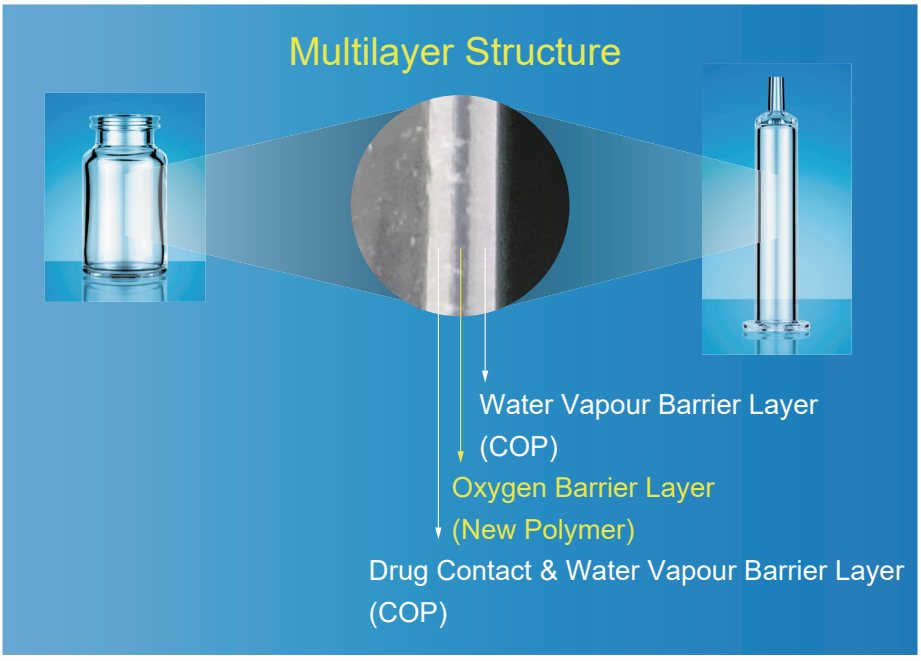

Figure 1: Multilayer Structure of OXYCAPT™.

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	Glass	Cyclo Olefin Polymer (COP)	OXYCAPT™
Oxygen Barrier	Excellent	Not Good	Excellent
Water Vapour Barrier	Excellent	Good	Good
Resistance to Breakage	Bad	Good	Good
Inorganic Extractables	Not Good	Excellent	Excellent
Organic Extractables	Excellent	Excellent	Excellent
Protein Adsorption	Not Good	Good	Good
pH Stability	Not Good	Good	Good
UV Barrier	Bad	Bad	Good
Weight	Bad	Excellent	Excellent
Disposability	Bad	Good	Good

Table 1: Comparison of the strengths and weaknesses of glass, COP and OXYCAPT™.

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

drug products, such as intravenous (IV) solutions, prefilled syringes, ampoules and tablets, for many years, especially in the Japanese market. It significantly contributes to stabilising the efficacy of drugs and extending their shelf-life. However, the use of an oxygen absorber is not common so much in the US or Europe, because additional items, including dispensing machinery, sealing equipment and secondary packaging with high gas barrier, are needed to apply the absorber.

Therefore, MGC began developing alternative technologies to the oxygen absorber. Firstly, MGC developed a new oxygen-absorbing polymer, which featured a very low level of extractables and demonstrated no degradation, even after absorbing oxygen. Secondly, MGC sought an improvement on the existing multilayer-moulding technology which has been used frequently in the beverage industry to enhance the oxygen and carbon dioxide barrier provided by the packaging. By combining these two technologies, MGC has successfully developed a multilayered plastic vial and syringe called OXYCAPT™.

OXYCAPT™ Vial & Syringe consists of three layers. The inner and outer layer are made of cyclo-olefin polymer (COP), the most reliable polymer used by the pharma industry. The middle layer is made of a novel polyester that has been developed by MGC (Figure 1). The COP layers give OXYCAPT™ the traditional characteristic advantages of polymer vials and syringes while the new polyester plays a role as an oxygen and UV barrier to address the weaknesses inherent to using COP alone.

Current syringe primary packaging materials all come with their own problems: glass suffers from breakage and delamination, whereas plastic is not a sufficient oxygen and ultraviolet light (UV) barrier. Particularly with glass, the US FDA has pointed out these problems, which have led to more than 50 incidents of recall. To address the problems associated with glass, some suppliers have launched plastic alternatives, however the oxygen barrier provided by these products has failed to meet the demands of customers. However, OXYCAPT™ has overcome both the weaknesses of glass and of COP (Table 1). MGC believes that OXYCAPT's achievements, including a strong oxygen barrier, very low extractables, good UV barrier and high break resistance will bring

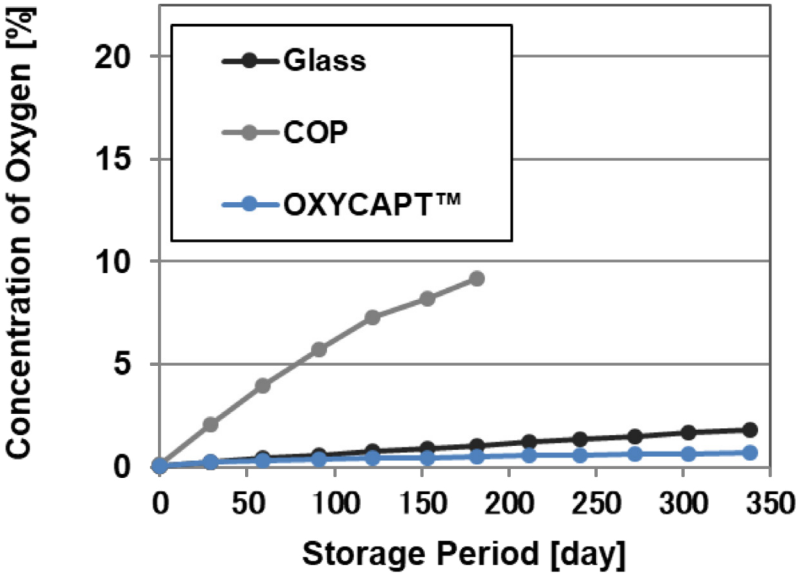

Figure 2: Concentration of oxygen over time inside vials of glass, COP and OXYCAPT™ originally filled with nitrogen.

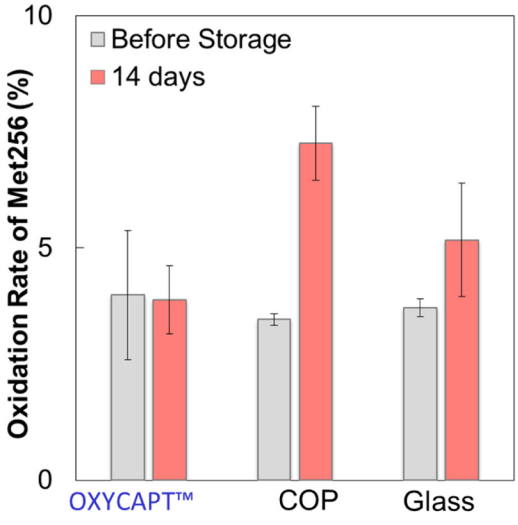

Figure 3: Oxidation rate of an antibody, stored in containers of glass, COP and OXYCAPT™ at 25°C, under a light source of 2000 lx for 14 days.

substantial benefits to the pharma industry.

A study showed that the oxygen barrier quality of OXYCAPT™ is superior to that of glass and far better than COP. The air in vials of glass, COP and OXYCAPT™ was completely replaced with nitrogen and were then stored at 25°C and 60% relative humidity (RH). The oxygen concentration in the COP vial immediately rose, because oxygen transmits through the wall of the vial and the surface of the rubber stopper. The glass vial with a perfect barrier property also rose up gradually, as oxygen transmits through the rubber stopper. On the other hand, OXYCAPT™ kept very low oxygen concentration for a long time, since OXYCAPT™ gradually absorbs the oxygen that permeates through the rubber stopper, as well as the vial itself (Figure 2).

OXYCAPT™ also provides an ultraviolet (UV) barrier. Although about 70% of 300 nm UV light transmits through glass and COP, only 1.7% transmits through OXYCAPT™. This further contributes to biologic stability. MGC conducted studies to confirm the efficacy of OXYCAPT™ as a UV and oxygen barrier. An antibody stored in containers of glass, COP and OXYCAPT™ was exposed to a light source of 2000 lx and stored at 25°C for 14 days. The oxidation rate of methionine 256 was measured by peptide mapping. The results show that the oxygen and UV barrier of OXYCAPT™ can contribute to the stability of antibodies (Figure 3).

"The OXYCAPT™ Syringe consists of tip cap, barrel, PTFE-laminated stopper and plunger rod. Although a very small amount of silicone-oil is coated on the stoppers, no silicone-oil is baked on the barrel."

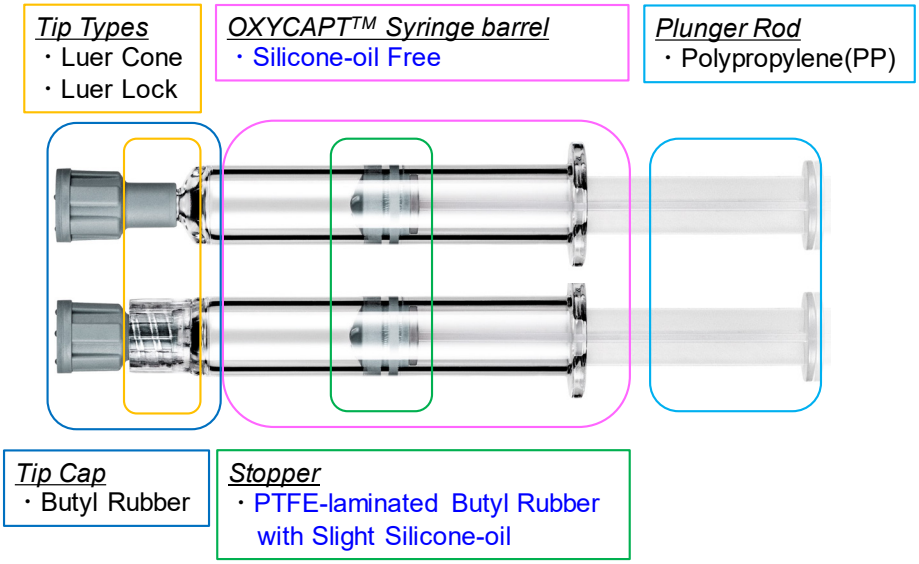

Figure 4: Components of the OXYCAPT™ syringe.

The OXYCAPT™ Syringe consists of tip cap, barrel, PTFE-laminated stopper and plunger rod (Figure 4). Although a very small amount of silicone-oil is coated on the stoppers, no silicone-oil is baked on the barrel. According to MGC's internal studies using antibodies, it has found this feature noticeably reduces instances of protein aggregation, compared with existing Type I glass syringes. In addition to Luer Cone and Luer Lock, MGC has tackled the development of staked-needle syringes.

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

MGC can offer bulk vials, ready-to-use (RTU) vials and syringes, provided in ISO-compliant nest and tub formats (Figures 5 and 6). The nest and tub are primarily sterilised using gamma rays. There are 2, 6 and 10 mL variants for vials, and 1 mL long and 2.25 mL variants for syringes.

Each polymer meets the requirements

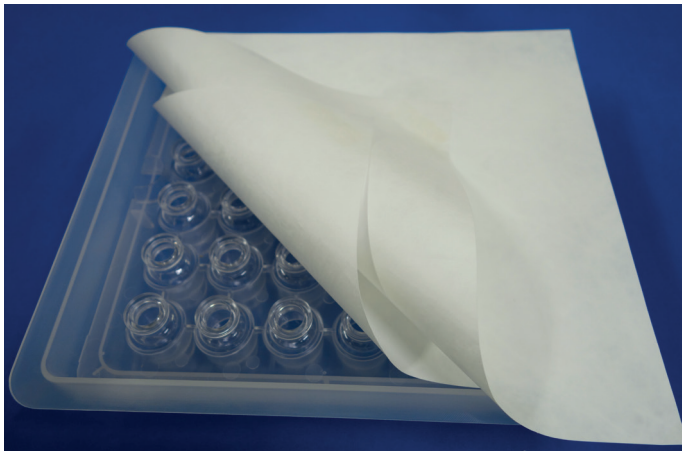

Figure 5: ISO-compliant nest and tub format for vials.

Figure 6: ISO-compliant nest and tub format for syringes.

of USP661, USP87, USP88, EP and has been filed in the 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.

In conclusion, OXYCAPT™ Plastic Vial and Syringe was developed to overcome the weakness of glass and plastic currently in use. In addition to the special features of COP, such as a strong water vapour barrier, high breakage resistance, very low extractables and low protein adsorption, OXYCAPT™ provides a strong oxygen and UV barrier. MGC anticipates that OXYCAPT™ will be used for oxygen- and UV-sensitive drugs, particularly in the rapidly growing biologics market.

ABOUT THE COMPANY

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

ABOUT THE AUTHORS

Shota Arakawa is a Researcher in the Advanced Business Development Division of Mitsubishi Gas Chemical. He gained a Diploma in Science in 2007 and a Master Degree of Science in 2009 from Osaka University (Japan). Since April 2009 he has been in charge of macromolecular science, especially the synthesis of polymers and material development, for MGC. In 2012 he joined the development team for OXYCAPT™.

Tomohiro Suzuki is an Associate General Manager at Mitsubishi Gas Chemical, having joined the company in 1998. He belonged to the Oxygen Absorbers division until 2011, and was transferred to the Advanced Business Development Division in 2012 to be a member of OXYCAPT™ development team. Since then, he has been in charge of marketing OXYCAPT™ Plastic Vial & Syringe.

ON drugDELIVERY

2019/2020 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
Apr 2019	Pulmonary & Nasal Delivery	Mar 7th 2019
May 2019	Injectable Drug Delivery	Apr 4th 2019
Jun 2019	Connecting Drug Delivery	May 2nd 2019
Jul 2019	Novel Oral Delivery Systems	Jun 6th 2019
Aug 2019	Industrialising Drug Delivery Systems	Jul 4th 2019
Sep 2019	Wearable Injectors	Aug 1st 2019
Oct 2019	Prefilled Syringes & Injection Devices	Sep 5th 2019
Nov 2019	Pulmonary & Nasal Drug Delivery	Oct 3rd 2019
Dec 2019	Connecting Drug Delivery	Nov 7th 2019
Jan 2020	Ophthalmic Drug Delivery	Dec 5th 2019
Feb 2020	Prefilled Syringes & Injection Devices	TBC

WEIBEL CDS AG

safer, easier and faster drug delivery

LYCAJECT: AUTOMATIC RECONSTITUTION PATCH INJECTOR

Here, Hans Peter Manser, Chief Executive Officer; Christoph Egloff, Chief Technology Officer; and Martin C King, Head of Quality & Regulatory; all of Weibel CDS, introduce the LyCaJect Patch Injector, the company's offering in the field of wearable injectors, with automatic reconstitution as a headline feature.

LYCAJECT

Following its mission to support safer, easier and faster preparation and administration of drugs, Weibel CDS has developed the LyCaJect Patch Injector, a wearable drug delivery platform with all functions and parts needed for a specific drug administration integrated into a single product (Figure 1). The user only opens one package and the complete handling of the drug is done wholly in a closed system, reducing the risk of contamination, handling errors and needlestick injuries, as well as proving to be a time-saving and convenient product.

> "The LyCaJect Patch Injector platform is a cartridge-based system and is designed to be ideal for self-use in a non-clinical environment."

Figure 1: Weibel CDS' LyCaJect Patch Injector.

LyCaJect features:

- Drug product integrated during final assembly, never touched by the user
- Automatic reconstitution of lyophilised drugs
- Safe, automatic needle insertion system.

The LyCaJect Patch Injector platform is a cartridge-based system and is designed to be ideal for self-use in a non-clinical environment. It includes a system for safe, automatic reconstitution of lyophilised drugs, independent of the device's orientation and not requiring the patient or caregiver to perform any handling steps (Figure 2).

LyCaJect is operated by a spring-loaded mechanism and includes a proprietary automatic needle insertion system (ANIS) for subcutaneous injections. The device uses a 27 gauge steel cannula, which is immediately retracted after the injection, leaving only the soft cannula in the

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"The user unpacks the device, which automatically starts the drug reconstitution process. After the patch is adhered to the body, on the thigh, abdomen or upper arm, the injection is executed by simply pressing a button."

tissue offering controlled, painless skin penetration and improved comfort during delivery of the drug. The design is very safe with respect to needlestick injuries, drug reconstitution and dosage accuracy. Additionally, the soft cannula provides maximum wearing comfort.

The slow injection technology used by LyCaJect offers painless drug administration to patients. The injection mechanism is completely mechanical by design, but electronic monitoring sensors provide status information and a display guides the patient through the three steps required for successful administration of the injection.

As LyCaJect is intended for use in both emergency situations and homecare, it was established early on that handling the device needed to be intuitive and all functions, including drug reconstitution, should be fully automatic and handled by the device itself, not requiring any further input from the patient.

Figure 3: LyCaJect can be customised to the intended use, needs and desires of pharmaceutical clients.

In practice, the user unpacks the device, which automatically starts the drug reconstitution process. After the patch is adhered to the body, on the thigh, abdomen or upper arm, the injection is executed by simply pressing a button.

The fluid path, designed for manufacture using gamma sterilisation and combined with a unique sterility concept, assures the full integrity of this combination product throughout its lifespan. As well as the reconstitution of lyophilised products, LyCaJect is capable of performing liquid-liquid mixture too.

The LyCaJect Patch Injector facilitates product differentiation, meeting the current needs and requirements of clients, including improved patient adherence via a holistic user experience. The final design can be customised according to a client's specific needs from functional, drug-related and design perspectives (Figure 3).

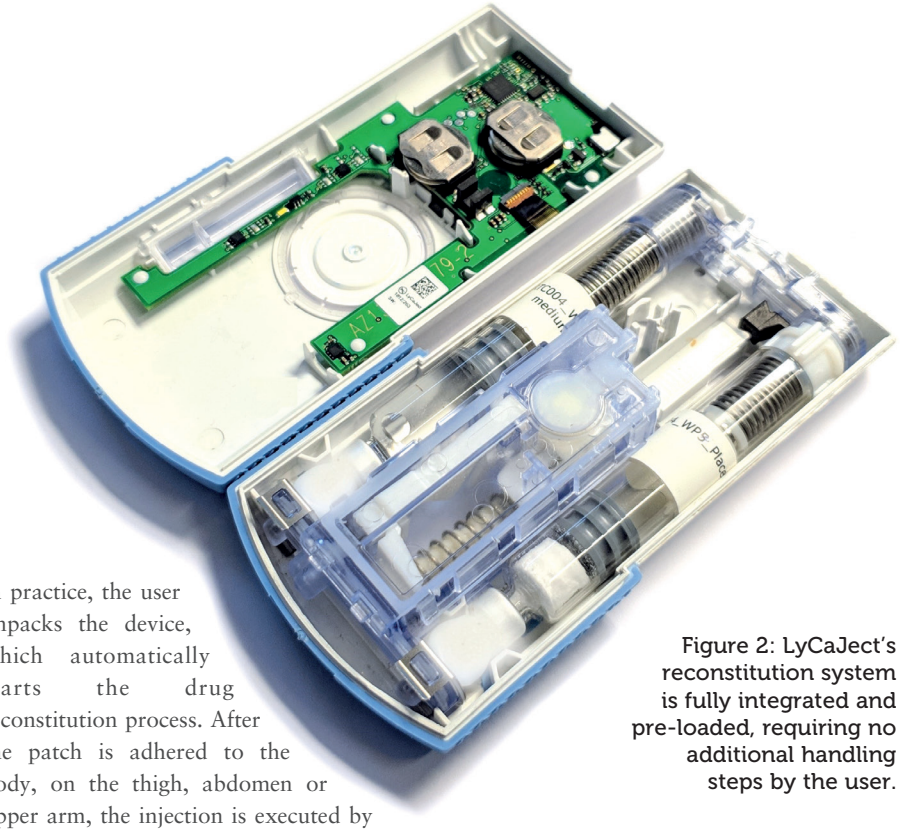

Figure 2: LyCaJect's reconstitution system is fully integrated and pre-loaded, requiring no additional handling steps by the user.

"The LyCaJect Patch Injector facilitates product differentiation, meeting the current needs and requirements of clients, including improved patient adherence."

For liquid drugs, a less complex version is available using a standard 3 mL cartridge, providing a true alternative to conventional autoinjectors. LyCaJect makes the whole self-injection procedure simpler and safer for patients and guarantees a high level of compliance.

WEIBEL CDS PORTFOLIO

Alongside LyCaJect, Weibel CDS offers the following drug delivery systems:

- Large-volume, high-viscosity DRUGDELIVERYSYSTEMS (LVDs) based on Weibel CDS' MiniBagSystem for micro infusion of up to 50 mL.
- Squeezer based on the MiniBagSystem, enabling fast and easy stability and preclinical testing.
- Standard cartridge-based DRUGDELIVERYSYSTEMS.

- The SuperCapSyringe® product family for upgrading a vial practically to a prefilled syringe. Based on a modular design, the syringe is fully adaptable to the needs of a given application. It is supplied in different sizes and with staked needles, including a passive safety device.
- The Reconstyringe® product family is first in offering a fully automated reconstitution system for lyophilised drugs. The drug is contained in its original vial and the solvent in Weibel CDS' MiniBagSystem. Using a spring mechanism and holder plates, the contents of the MiniBagSystem is emptied into the vial. Like a Swiss watch, it reliably runs through the full reconstitution cycle. Finally, the drug is drawn into the SuperCapSyringe® for injection.

Weibel CDS AG is holder of numerous international patents. SuperCapSyringe® and Reconstyringe® are registered trademarks of Weibel CDS AG, Switzerland

BOX 1: LYCAJECT SPECIFICATIONS

DIMENSIONS
- Approx. 158 x 75 x 30 mm

WEIGHT
- Full device with medication: approx. 170 g

CASING
- Biocompatible materials
- Shock resistant
- Resistant to pharmaceuticals
- All edges rounded

IP54
- Protected from limited dust ingress
- Protected from water spray from any direction, limited ingress protection

TEMPERATURE RANGES
(dependent on pharmaceutical)
- During operation: 5–40°C
- Storage in shipping case: 5–45°C
- During transport: 2–50°C

AIR HUMIDITY (Relative Humidity)
- During operation: 20–90%
- Storage in shipping case: 5–85%
- During transport: 5–95%

MAXIMUM DELIVERY PRESSURE
- 400 kPa (4.0 bar)

FLOW (Delivery Rate)
- Built in Cartridge size 2 x 3 mL
- Dead Volume 0.2 mL

ABOUT THE COMPANY

Weibel is a privately owned Swiss medical technology company, founded in 2010 and headquartered in Waldstatt, Switzerland. The company is specialised in customer-funded research and development of affordable, innovative, user-friendly injection systems and devices to ensure safer, easier and faster delivery of parenteral drugs for home, point-of-care and clinical users.

In 2018, the company opened a technology centre in Schaffhausen specialising in the development, manufacturing and supply of modern parenteral drug delivery solutions serving an international customer base. Weibel CDS is part of a unique medtech cluster in Switzerland that benefits from a high density of precision industry-specialised suppliers with significant medtech know-how.

ABOUT THE AUTHORS

Hans Peter Manser is the Chief Executive Officer at Weibel CDS, holds a diploma in Business Administration and Applied Technical Management. After perennial stays in the UK, Australia, US, France and Germany, he assumed sales management and executive functions in the communications industry with global responsibilities. Mr Manser transitioned to the pharmaceutical packaging industry in 2001 and subsequently joined Weibel CDS in May 2011 as Business Director, responsible for setting up and management of all administrative and commercial aspects of the company, taking over the overall responsibility of the company in October 2016.

Christoph Egloff is the Chief Technology Officer at Weibel CDS. His role covers innovation, technical design, management of the engineering department and project management. Mr Egloff worked on the manufacturing, installation and qualification of SuperCapSyringe®, and development, testing and production for the LyCaJect project.

Martin C King is Head of Quality and Regulatory at Weibel CDS. He has extensive experience in the fields of international medical device development and pharmaceutical management, encompassing all aspects of quality management and regulatory affairs. Mr King has served as a Deputy Swissmedic Responsible Person and Certified Lead Auditor under ISO 13485:2016, with specific expertise in ISO 62304, ISO 14971, 21 CFR 820 and MDSAP.

LyCaJect

Automatic Reconstitution Patch Injector

safer, easier and faster drug delivery

International patents pending

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DEBIOTECH S.A. Switzerland
Innovative Medical Systems

LOW-COST DISPOSABLE WEARABLE INJECTOR PLATFORM FOR LARGE VOLUMES OF VISCOUS DRUGS

In this article, Eric Chappel, PhD, R&D Project Manager, Dimitry Dumont-Fillon, R&D Engineer, and Laurent-Dominique Piveteau, PhD, Chief Executive Officer, all of Debiotech, discuss Debiotech's novel wearable injector technology, which utilises a propellant vapour system to drive the injection, making the device both space- and cost-efficient.

There is a wide variety of device types available for injectable drugs. Pen injectors, jet injectors and others, including piston syringes or mechanically operated injectors, are designed to inject single or multiple doses of drug, contained in a cartridge or reservoir, via an automatically or manually inserted needle, or through a high-velocity jet. Depending on the application (acute intervention, prevention or long-term treatment) the intended user can be a healthcare professional, a caregiver or the patient themselves. Injectors can be generic or dedicated to a single class or family of drugs. The injection routes targeted include subcutaneous (SC), intradermal, intramuscular and intravenous.

Today, there is a growing interest in providing a wearable injector platform dedicated to the delivery of viscous formulations. Thousands of injectable drugs are currently in development.[1] Many of them are large-molecule biologics and the viscosity of the formulation is relatively high after concentration. The concept of syringeability (or injectability) is commonly used to characterise a drug formulation.[2,3] While pen injectors are generally preferred for injecting aqueous solutions up to 3 mL, wearable injectors become the more desirable option in the case of viscous solutions and/or a large volume. Particle characteristics are also an important factor to consider for syringeability. Specific SC formulations, such as for trastuzumab, comprise recombinant human hyaluronidase as an excipient to lower the resistance of the tissues during injection, via localised hydrolysis of the extracellular matrix.[4]

> "While pen injectors are generally preferred for injecting aqueous solutions up to 3 mL, wearable injectors become the more desirable option in the case of viscous solutions and/or a large volume."

The development of a wearable injector could also be driven by product lifecycle management considerations, a trend initiated by Amgen (Thousand Oaks, CA, US) and its product Neulasta® (pegfilgrastim). This drug stimulates the bone marrow to produce more white blood cells (neutrophils) in order to decrease the incidence of infection after chemotherapy. Since 2015, Neulasta has been combined with the Onpro® kit, a wearable injector which is an interesting solution not only to improve patient convenience, but also to stave off biosimilar competition.

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Many bolus injectors, such as Amgen's Pushtronex® and Onpro®, comprise a complex engine that moves a plunger inside a cylindrical barrel containing the drug, with the reservoir being either prefilled or filled by the user. In addition to the cost associated with the motor and its assembly, such technology limits the size ratio between the drug reservoir volume and the device volume, the maximum plunger displacement being limited to about half of the device length.

A fully disposable wearable injector platform should ideally utilise a low-cost, reliable engine to be compatible with reimbursement policies. It should be able to deliver a large range of viscous fluids in volumes from 1 to 10 mL. Finally, it should be reliable and exhibit a low dead volume as many biologics are expensive.

DEBIOTECH'S WEARABLE INJECTOR TECHNOLOGY

Debiotech has developed a new wearable injector with the following considerations:

- The device structure should be cost efficient by design.
- The reservoir should be semi-flexible and made with the same materials as previously developed JewelPUMP™ micropump patch insulin delivery system due to their well-proven drug stability.[5]
- The device shall be compatible with the state-of-the-art cannula available on the market.
- The standard version of the device shall contain no battery, no electronics and no software to speed up time-to-market and to alleviate both regulatory requirements and patient hazards.
- The dead volume of the device shall be equal to or lower than existing wearable injectors.

Figure 1: Wearable injector and its needle protection.

The device is a fully disposable wearable bolus injector made of two different parts:

- The drug reservoir and its fully mechanical engine and indicator
- The cannula patch and its automatic inserter.

Sequence of High-Level Steps to Start the Therapy

The device and the cannula are provided in the same package. The cannula patch is first affixed to the patient skin using the automatic inserter that retracts the inserter needle to prevent user injury after positioning. The user can then fill the drug reservoir with a syringe and verify that filling is complete by checking a visual indicator. The protective cap on the device's needle (Figure 1) is then removed and the user can slide the device onto the cannula patch, where it is permanently affixed, making the device ready to use. The infusion is started by pressing the activation button and can be monitored using a mechanical infusion status indicator, where the presence of an element visible through a window indicates that the full dose has been administered. Once the infusion is complete, the user can remove and discard the patch and device.

Filling Gauge

The device contains a semi-flexible drug reservoir that is initially collapsed against the rigid part, and user-filled with a syringe. This action inflates the reservoir membrane, which is thermoformed to prevent the generation of pressure onto the drug as filling is completed. The cavity surrounding the reservoir membrane is initially closed by a plug that covers the reservoir vent and the needle. During filling, a positive pressure generated inside this cavity will move a low-friction plug inside a transparent cylinder, equilibrating the pressure inside the container. The filling gauge, which is located on the bottom of the device, is only visible during the filling process. As shown in Figure 2, the fill volume is indicated by the position of a plug.

> "The injection is driven by a liquefied gas reservoir that is opened by the user after placement onto the patch. The vapourisation of the liquefied gas generates a large pressure differential that will push an elastomeric membrane against the flexible part of the drug reservoir."

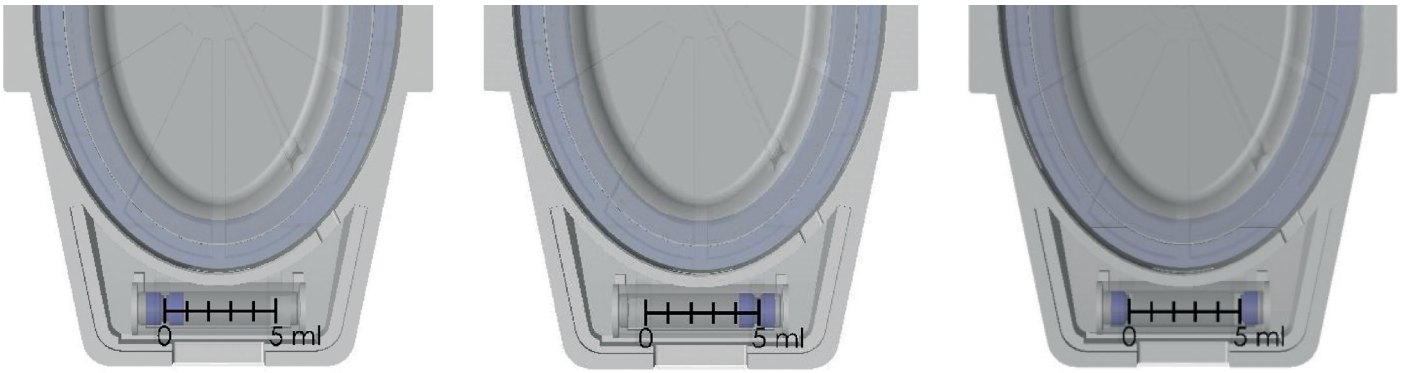

Figure 2: Back-side of the bolus injector showing the filling gauge before filling (left), just after filling of 5 mL (centre) and after the needle cap removal (right).

Figure 3: Infusion status indicator before activation (left), during infusion (centre) and after infusion (right).

Bolus Injector Engine

The injection is driven by a liquefied gas reservoir that is opened by the user after placement onto the patch. The vapourisation of the liquefied gas generates a large pressure differential that will push an elastomeric membrane against the flexible part of the drug reservoir. The cavity between the two membranes is vented to prevent any risk of infusion of propellant into the patient.

The pressure acting on the fluid is equal to the vapour pressure of the propellant since both membranes are flexible. At the bottom of the drug reservoir, a small cavity is used to connect an infusion status indicator, and the fluidic restriction used to limit the flow rate to a maximum of 1.5 mL/min.

Infusion Status Indicator

The status indicator is a transparent cylinder that contains one drilled plug and another solid one in contact with the drug. The pressure generated during infusion first moves both plugs towards the dead-end of the cylinder until pressure equilibration. When the full dose has been administered, the reservoir membrane can no longer transmit the propellant pressure to the fluid and therefore the solid plug comes back to its initial position, infusing the residual amount of drug that was located inside the indicator cylinder. The dead volume of the device is thus limited to a few tens of microlitres. Figure 3 shows a first illustrative version of this indicator as seen on the top shell of the device. Usability studies are on-going to refine the indicator and to make sure that the user interprets it correctly.

This purely mechanical infusion status indicator has three different states:

- One dot: Ready to inject
- Two dots: Injection on-going
- Three dots: End of injection.

The "end of injection" indication is only visible when the reservoir membrane is fully collapsed against the bottom of the reservoir shell. It is not visible in case of cannula occlusion.

For a specific medication volume and viscosity, maximum infusion duration will be indicated in the user manual, therefore the user can deduce that the full volume has not been administered (in case of total occlusion for instance) if the infusion status indicator is still showing "injection on-going" after this maximum duration. The high pressure generated by the propellant vapour will limit the occurrence of an occlusion in the cannula.

"Because a single dose of a biologic medication can cost up to thousands of dollars, it is highly undesirable to discard an injector filled with the drug solely based on a cannula failure."

Drug Preservation, Removable Injector and Cost Rationale

A common issue in insulin delivery is associated with a failure of the infusion set, due to issues such as cannula occlusion, cannula dislodging and leakage, amongst others.[6] The use of the cannula patch is a key asset to secure the connection to the patient. Other products developed by Debiotech share the same philosophy: after the placement of the cannula, the user is able to check visually, via a transparent window, that the cannula has been properly inserted into the skin.

Because a single dose of a biologic medication can cost up to thousands of dollars, it is highly undesirable to discard an injector filled with the drug solely based on a cannula failure. The user is therefore provided with an independent cannula that could be used to replace the defective one, thereby saving wasting the drug and limiting the cost to only a few dollars.

DEVICE CHARACTERISTICS

Volume Accuracy

Tests to confirm the volume accuracy were performed at 20°C using a mix of water and glycerol. The nominal volume of the reservoir is 5 mL. Volume accuracy was first estimated considering fill volumes of 1, 2, 3, 4 and 5 mL respectively (±2%), and fluid viscosities of 5 and 25 cP.

A mean dead volume of 32±6 µL was measured, which was independent of the fill volume and the fluid viscosity. Figure 4 shows the volume accuracy as a function of the fill volume. Considering all the data, the mean accuracy is better than 98%.

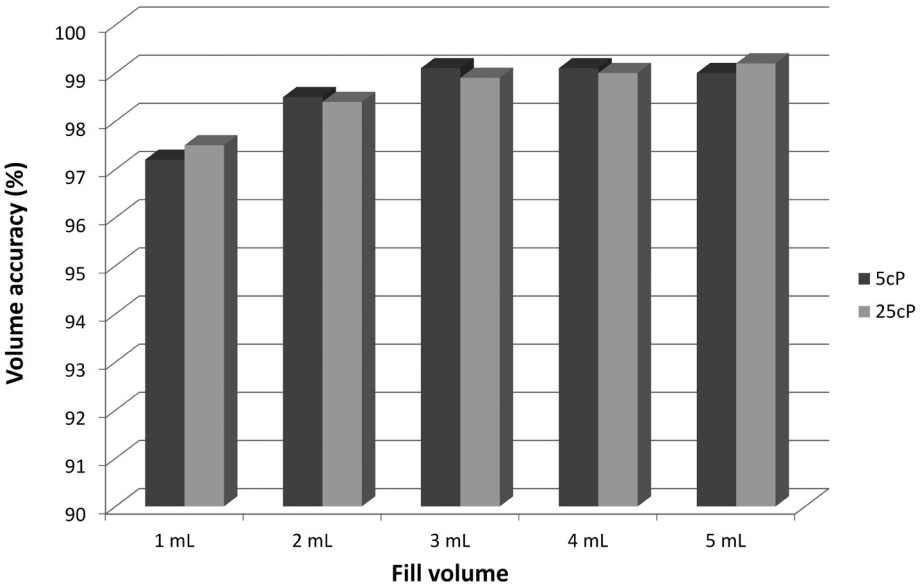

Figure 4: Mean volume accuracy at 5 and 25 cP, for fill volumes of 1, 2, 3, 4 and 5 mL.

Fluid viscosity (cP)	5	10	25	50	100
Volume accuracy (%)	98.7	98.7	98.9	98.9	99

Table 1: Volume accuracy as a function of medication viscosity for a fill volume of 3 mL.

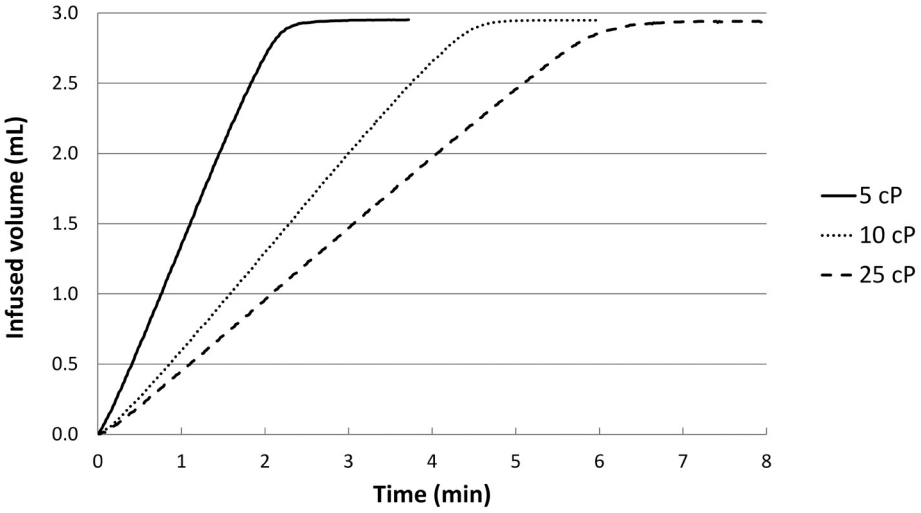

Figure 5: Infusion profiles of low viscosity device at 5, 10 and 25 cP. Fill volume = 3 mL

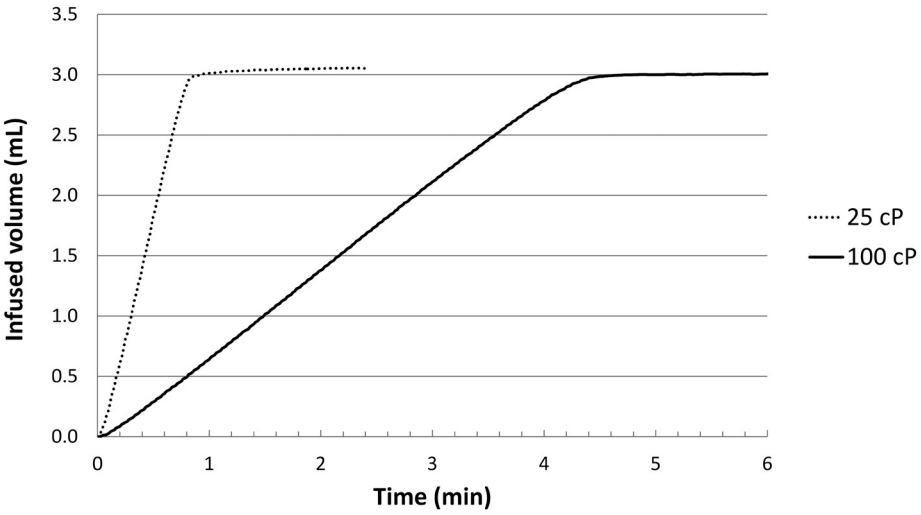

Figure 6: Infusion profiles of high viscosity device at 25 and 100 cP. Fill volume = 3 mL.

A specific test was carried out to measure, for a given fill volume of 3 mL, the effect of viscosity on volume accuracy considering fluids of 5, 10, 25, 50 and 100 cP. The results are shown in Table 1. Volume accuracy was again shown to be above 98%, independent of the fluid viscosity.

Delivery Profile

Two versions of the bolus injector designed for infusion of volumes up to 5mL were tested: the low viscosity (LV) version is dedicated to fluid viscosity up to 25 cP while the high viscosity (HV) version is adapted to viscous fluids up to 100 cP and above. The LV version is intended to deliver a minimum flow rate of 0.5 mL/min at 25cP, and the HV version at 100 cP respectively.

The fill volume was fixed at 3 mL. The LV version was tested using fluids of 5, 10 and 25 cP respectively. Viscous fluids of 25 and 100 cP were used to characterise the HV device. The measured flow rate profiles are provided in Figures 5 and 6. The linear slope indicates that the flow rate is constant throughout the infusion duration, as the propellant vapour maintains a constant pressure on the elastomeric membrane, which is fully transmitted to the fluid via the elastomeric and reservoir membranes.

The patch injector is in thermal equilibrium with the patient's skin and limited temperature variations are expected. However, should it be necessary, an add-on could be used to limit the variability of the flow rate in case of a large ambient temperature change which may modify the vapour pressure of the propellant and the fluid viscosity. A flow-control valve developed by Debiotech can be placed into the fluidic path to prevent any change of flow rate related to pressure condition changes, including the propellant reservoir or external conditions, for example altitude.

The add-on is a microfluidic chip, 1 mm thick with a typical surface of 1 cm^2. The functioning principle of the device is described elsewhere.[7] Two different designs are available depending on the target flow rate:

- One for intermediate to high flow rates (typically from 5 mL/h to 100 mL/h or more)
- One for very low flow rates (down to 1 mL/day or less).

This add-on is particularly useful for long-term infusion, to control the infusion duration better, and for the infusion of a drug requiring especially careful control of the flow rate, such as insulin or morphine.

CONCLUSION

The latest functional test results showed that Debiotech's design for a disposable wearable bolus injector is able to inject a large volume of viscous medication, up to 100 cP, at a minimum flow rate of 0.5 mL/min.

Future designs will include a dedicated compartment for optional high-end features that are already implemented in the JewelPUMP insulin micropump patch developed by Debiotech. Human factors studies are also planned in order to refine the actuator position and the indicator visibility.

In summary, Debiotech intends to drive collaboration with key partners, including pharmaceutical companies, to customise this new platform to their needs for a subcutaneous delivery system dedicated to large volumes and/or viscous fluids.

ABOUT THE COMPANY

Debiotech is a Swiss company with nearly 30 years' experience in developing highly

innovative medical devices, based on micro- and nanotechnology, micro-electronics and innovative materials. The company concentrates on both implantable and non-implantable systems, in particular for drug delivery and diagnostics, with a demonstrated competence in the identification of breakthrough technologies and their integration into novel medical devices. Devices developed by Debiotech are eventually licensed to major international pharmaceutical and medical device companies, with a track record of over 40 license agreements worldwide. Examples of successful products are the DebioJect™ microneedles for intradermal injections, the I-Vantage™ IV pump for hospital and home care, the CT Expres™ Contrast Media injector for CT-Diagnostic Imaging (acquired by Bracco Imaging, Milan, Italy), the JewelPUMP for diabetes care, the DialEase™ home dialysis equipment (licensed to Fresenius, Bad Homburg vor der Höhe, Germany) and the HemoXpress home haemodialysis machine developed in collaboration with the Dutch Kidney Foundation.

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ABOUT THE AUTHORS

Eric Chappel joined Debiotech in 2003 as an R&D Engineer and was appointed as an R&D Project Manager in 2004. Prior to Debiotech, Dr Chappel developed and industrialised the backend process of optical MEMS at Memscap. His research interests are innovative medical devices, including insulin micropumps, hydrocephalus shunts, implantable pumps and wearable injectors. He received an MSc in Physics in 1996 from the Université Grenoble Alpes (Grenoble, France) and achieved his PhD in Condensed Matter Physics at the French National High Magnetic Field Laboratory (Grenoble, France) in 2000.

Dimitry Dumont-Fillon joined Debiotech in 2013 as an R&D Engineer. His work focuses on microsystems, microfluidics and mechanics as applied to drug delivery devices. He holds an Engineer's Degree from the Grenoble Institute of Technology (Phelma, France) and a joint MSc in Micro- and Nanotechnologies for Integrated Systems from the Swiss Federal Institute of Technology in Lausanne (EPFL) (Switzerland) and the Polytechnic University of Turin (Italy).

Laurent-Dominique Piveteau joined Debiotech in 2005 and was appointed as Chief Executive Officer in 2015. Prior to this, Dr Piveteau held several positions in R&D and in business development. He developed a coating for bone implants in collaboration with the Robert Mathys Foundation, he was a researcher at MIT (Cambridge, MA, US) working on contrast media for MRI, and worked in technology transfer at the Swiss Federal Institute of Technology in Lausanne (EPFL) (Switzerland). In parallel to his current position, Dr Piveteau also teaches Innovation Economics at EPFL. He holds an MSc in Physics from the ETH Zürich (Switzerland), a PhD from the University of Fribourg (Switzerland) and an MBA from INSEAD in Singapore and Fontainebleau (France).

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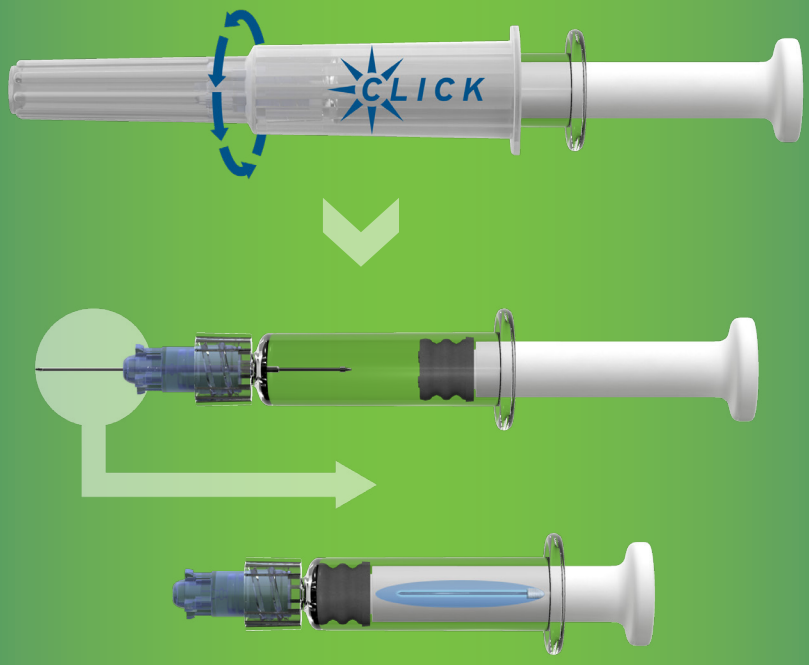

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HOW SAFETY FEATURES MAKE OR BREAK INFUSION PUMP DESIGN

In this article, Charlotte Harvey, Medical Sector Manager, and Tim Frearson, Senior Consultant, both of Sagentia, overview the safety systems required when designing an infusion pump system, with a focus on free-flow prevention, occlusion detection and air-in-line detection.

Infusion pumps are complex electromechanical devices used to deliver fluids into a patient's body in a controlled manner. They typically serve the needs of hospital-bound patients, where life-saving medication is normally delivered via intravenous infusion. With the desire for patients to be able to manage their own conditions outside of a hospital setting, together with the trend towards continuous drug delivery, the use of at-home, ambulatory and wearable infusion pumps is on the rise.

> "Many of the learnings from volumetric and syringe pumps are also relevant to ambulatory or wearable pumps, as they are typically based on the larger volumetric or syringe devices."

New entrants to the world of infusion pumps will find that safety features are a major driving force behind their design, as they control every aspect of a user's interaction with the device and have the potential to make it unusable when things go wrong. This article reviews different pump types, their typical safety features, and the implementation of three of the most important safety features in infusion pump design.

IDENTIFYING THE DIFFERENT TYPES OF INFUSION PUMP

There are several types of infusion device. The type of pump used is dependent on the patient's needs, such as the required volume and the speed of the desired infusion. And different types of pump are more or less suited to hospital, at-home or ambulatory usage.

In hospital settings, volumetric, syringe and gravity pumps are the most popular choices. Volumetric pumps (Figure 1), sometimes referred to as large volume pumps (LVPs), are the preferred choice

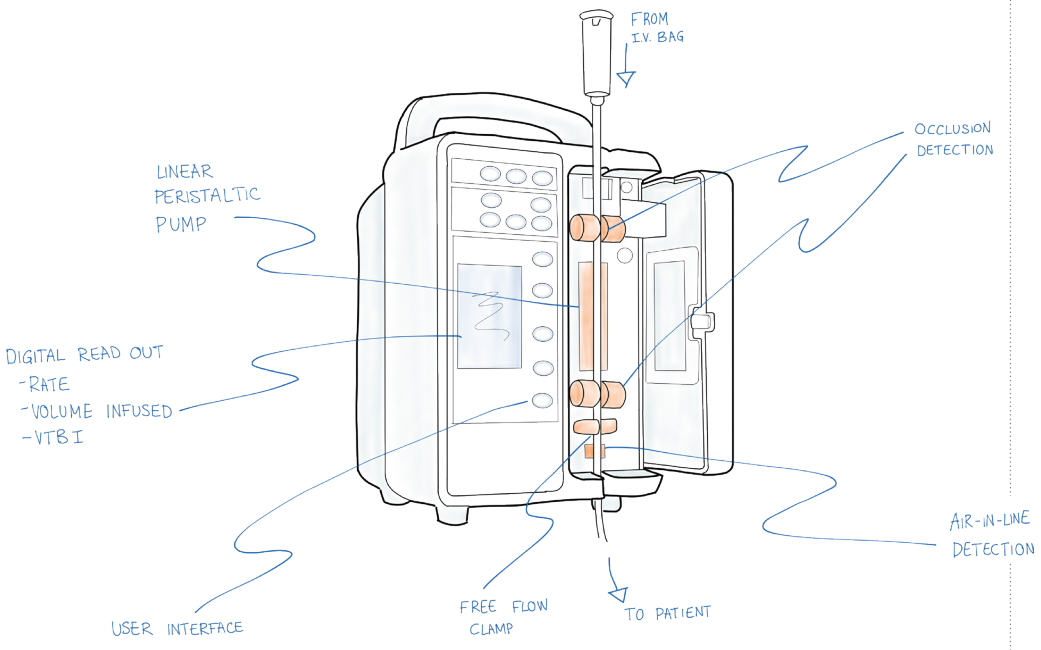

Figure 1: A typical volumetric infusion pump.

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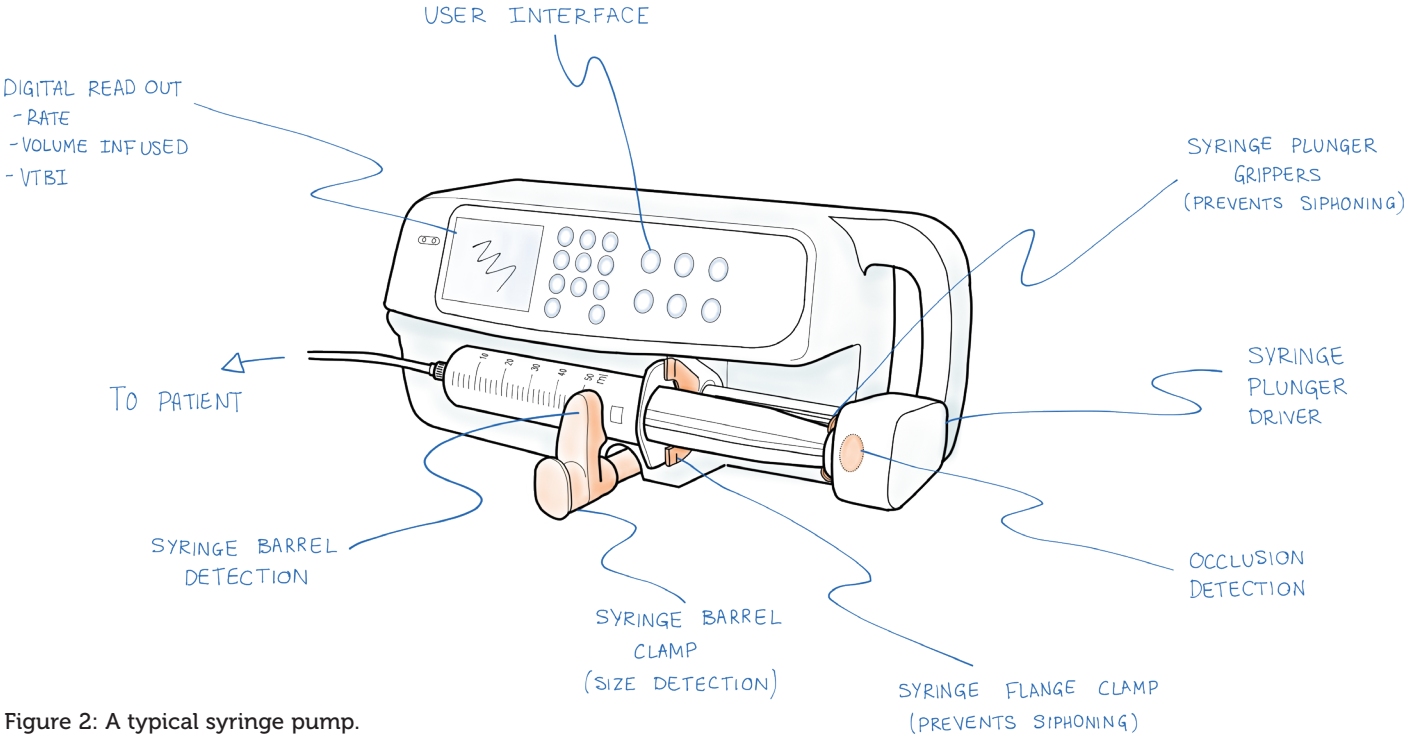

Figure 2: A typical syringe pump.

for medium and high flow rates and large volume intravenous or enteral infusions. They use a pumping action (typically linear or rotary peristaltic) to pump fluid into the patient under pressure and resistance. An IV bag can be used, or the device may employ a dedicated cassette.

For lower volume delivery and lower infusion rates, syringe pumps (Figure 2) are usually the preferred option. They work by pushing the plunger of a disposable syringe along at a predetermined rate. This rate can be continuous or in steps, delivering several boluses in a given time. Pumps for delivering anaesthesia for sedation are based on the syringe mechanism. They are specially designed so that the rate can be adjusted, and other functions accessed, during infusion. These pumps allow for a higher flow rate, so that the induction dose can be delivered quickly in a single operation.

Some infusions are given using gravity rather than a device to deliver the fluid. Gravity pumps rely on the head height of the fluid bag relative to the point of delivery to the patient. A gravity-controlled infusion employs a clamping action to vary the flow of liquid. The speed of delivery is dependent on pressure differential, which can be limited, but the volume is almost limitless. A gravity infusion would be employed when the rate of infusion can be imprecise and large volumes are required.

Pump types that are more suited to at-home or mobile use are elastomeric, patient-controlled analgesia (PCA) and "wearable" pumps. Elastomeric pumps are non-electronic single use pumps, with an elastomeric balloon reservoir that empties itself with a fixed pressure. They are generally designed for use by a patient at home as they are small, lightweight, easy to use and are easily portable. They are primarily intended to deliver antibiotics, chemotherapy and analgesics where a high degree of accuracy is not required. The downside to these types of pump is they have no built-in alarms or event log. Both temperature and the fill volume of the reservoir (under- or over-filling) can affect the intended delivery rate. Conversely, the fixed volume and flow-rate reduce the risk of user error.

Patient-Controlled Analgesia (PCA) pumps allow a patient to control the delivery of pain-relieving medication. Typically, the syringe pump design allows patients to deliver a bolus themselves. Protection against free-flow is especially important with PCA pumps due to the nature of the medication involved (pain relief) and risk of overdose, particularly if the patient may be unsupervised for some of the time.

There are also pumps specifically designed to allow patients to continue receiving treatment or therapy away from a hospital, thereby leading a normal life during treatment. These are usually referred to as ambulatory pumps and have a size and design that makes them wearable. Wearable solutions vary from ones that adhere to the skin, to ones supplied in a backpack or shoulder-bag. These pumps usually use the volumetric or syringe pump models as a basis for the technology, but are often designed to be more specific to a single drug. Size and usability become larger concerns and significantly impact the device design.

Other types of infusion devices not included here are pneumatic, clockwork and spring. However, these are significantly less common than volumetric and syringe pumps, which will be the focus of discussion in the rest of the article. Many of the learnings from these types of pumps are also relevant to ambulatory or wearable pumps, as they are typically based on the larger volumetric or syringe devices.

DESIGNING FOR SAFETY

The reliability of medical devices such as infusion pumps is extremely important because they are used on patients likely to be in a critical condition. For this reason, they typically incorporate warnings and alarms.

Many of the safety features common to infusion devices are particularly susceptible to tolerance variation of components and assembly processes. Therefore, a large part of designing these features must be dedicated to fully understanding their intended use, clinical environment and potential variations in manufacturing. Getting the design right upfront is critical to ensuring that the design is robust in the field. Some design issues may not present themselves until the product is released into manufacturing where the extreme of tolerance variation is encountered. Due to the adverse events that can occur in the field, there is heavy regulatory focus on their design.

Box 1 shows a list of typical safety features in descending order of importance. Note that a number of these safety features are usability based, to protect against misuse. Note also that the importance of these features does not always correlate with the ease of implementation during device design and development. In the rest of this article the focus will be on free-flow protection, occlusion detection and air-in-line.

ASSESSING FREE-FLOW PROTECTION FEATURES

Over-infusion is known to be a major cause of fatal adverse events when considering infusion pumps. There are a few key differences between free-flow in a syringe pump and in a volumetric pump. In volumetric pumps, free-flow may occur if the disposable tubing is not correctly fitted, or if the fluid is under the action of gravity without the tubing being correctly pinched or clamped. In either of these cases, there are device alarms which can be used to alert the user or caregiver. If free-flow becomes an issue in a syringe pump, the syringe plunger or barrel must not have been correctly loaded, with the pump at a height sufficient to generate a pressure that overcomes the venous pressure and the friction between the plunger and barrel. Warnings and alarms will typically be used to alert the user or caregiver to incorrect syringe loading. Other precautions may include positioning the pump level with the patient and use of an anti-siphon valve.

UNDERSTANDING OCCLUSION DETECTION

Perhaps a more complex system to consider when assessing its robustness in the field (when subject to manufacturing variation) is the occlusion detection subsystem. An occlusion is a common occurrence during an infusion, which occurs when there is an obstruction or closure of the fluid pathway or vessel. Clearly, an occlusion is an issue as it means a patient is not receiving their medication (or other fluid). In some critical applications involving the use of drugs which have a short half-life and result in an immediate pharmacological or physiological response (e.g. adrenaline, dopamine, dobutamine, dopexamine, insulin) the plasma concentrations of drug may drop rapidly following cessation of delivery. In the case of short half-life vasoactive drugs used to maintain cardiac output, it is known that the patient's condition can deteriorate rapidly if the infusion stops. However, occlusions also introduce the risk of a post occlusion bolus, where the pressure in the line builds behind the occlusion and releases suddenly when it clears. As previously mentioned, over-infusion is a major cause of fatal adverse events involving infusion pumps.

Infusion devices typically require high pressures, due to high resistance in the delivery system. This resistance to flow comes from both the body itself and elements in the fluid path, such as filters, anti-siphon valves, compliance in the tubing, the cannula and any potential kinking of the tubing. Additionally, more viscous medications increase the required delivery pressure. The active pumping mechanisms used in syringe and volumetric pumps generate high pressures to overcome this resistance, and therefore the pressure in the line will increase further when an occlusion occurs. Thus, occlusion detection devices typically use force measurement to detect this increase in pressure.

There are key differences in how this is implemented in volumetric and syringe pumps. In volumetric pumps, it is common practice to determine the occlusion status by coupling a force sensor directly to the wall of the disposable pumping segment. As the internal fluid pressure increases or decreases the tubing will exert more or less force on the sensor (Figure 3). To ensure adequate coupling, the disposable tube must be compressed to provide a pre-load force baseline for the sensor. This system can be used to detect a flow restriction either between the pumping mechanism and the administration site (downstream occlusion) or between the medication bag and the pumping mechanism (upstream occlusion). Depending on the pumping mechanism design, a single sensor can detect both.

This type of implementation can be very susceptible to manufacturing variance. However, proper calibration can remove variation in the assembly, signal processing, force sensor, mechanical parts, etc, and software algorithms can be utilised to manage drift and hysteresis. The greatest concern is variation in the disposable tubing (such as wall thickness), as this can lead to large differences in the force sensor output voltage. Batch-to-batch variation means it can be difficult to calibrate out this variance.

Many devices have predetermined occlusion pressure thresholds at which the

BOX 1: TYPICAL SAFETY FEATURES FOR INFUSION DEVICES

- Anti-free-flow device in administration set
- Free-flow clamp in pump when door opened (volumetric pump only)
- Air-in-line detection (volumetric pump only)
- Detection of an empty drug/fluid reservoir
- Occlusion detection
- Provision against accidental modification of settings
- Two distinct actions to change rate
- Two distinct and/or simultaneous actions to initiate bolus
- Syringe barrel clamp alarm, door open alarm or equivalent
- Syringe plunger disengagement alarm or equivalent
- Automatic switching to keep the vein open (KVO) rate at the end of infusion
- Pre-set control of the total volume to be infused and digital read-out of volume infused
- Patient history log and technical history back-up
- Battery back-up (automatic switching to battery when mains power fails)

"The active pumping mechanisms used in syringe and volumetric pumps generate high pressures to overcome this resistance, and therefore the pressure in the line will increase further when an occlusion occurs. Thus, occlusion detection devices typically use force measurement to detect this increase in pressure."

device will trigger an alarm, with this being adjustable by the user or caregiver. The positioning of this threshold is important. Set too high, the chance of harmful effects on the patient prior to the alarm sounding are increased (longer time to alarm resulting in a delay to medication delivery). Set too low, the number of nuisance alarms may go up, leading to customer complaints. Infusion pumps undergo vigorous testing of safety critical features (such as occlusion pressure, and time to alarm on occlusion) to ensure patient safety during administration.

On the other hand, measurement of pressure inside a syringe pump is typically performed by measuring the force needed to compress the syringe plunger. This will detect an occlusion in the infusion line or tubing between the syringe and administration site.

Force can be measured here in one of two ways. One implementation is to place a force sensor into the transmission of the drive mechanism to determine resistance as the mechanism pushes the plunger. However, this can be susceptible to manufacturing variation and design tolerance. A more common implementation involves placing a force sensor on the end of the syringe plunger, providing a much more direct measurement of the force required to compress the syringe plunger.

Regardless of implementation, the result is a force-pressure calculation which then requires set occlusion pressure alarm thresholds in the device. However, even with calibration there can be large variance due to the variation in the syringe itself, which is typically not controlled by the pump designer/manufacturer.

Above all, the greatest concern with syringe pumps is the variation in plunger friction. It typically does not influence volumetric accuracy, except at low flow-rates where slip-stick may cause poor flow uniformity, but it does affect pressure-reading accuracy. Higher friction means a higher operating pressure, and thus a shorter time to occlusion alarm for any given pressure alarm threshold. Conversely, lower friction provides a lower operating pressure reading and would result in a longer time to alarm following an occlusion. This problem is eliminated by users, as it is clinical best practice to use the occlusion system as a relative system and set the alarm threshold within a few selectable levels of the average operating infusion pressure. However significant friction variation is not always well accounted for, and users may perceive poor device performance.

EXAMINING AIR-IN-LINE SUBSYSTEMS

Small volumes of air injected intravenously are considered a hazard. Syringe pumps typically do not employ air-in-line detection systems, as they deliver medication from a prepared syringe, with it falling to the caregiver to ensure that air is removed from a syringe before use, or a prefilled syringe. Volumetric pumps, on the other hand, provide mechanisms for preventing the pumping of air into the patient's venous system or incorporate an air-in-line detection system where, if excessive air is detected in the line, the device stops the infusion and generates an alarm to alert the caregiver. Real air-in-line alarms are a result of unacceptable volumes of air detected in the infusion line.

Developing an air-in-line detection system within volumetric pumps is challenging as the robustness of the system is affected by many factors, including flow rate, manufacturing variance, clinical environment (head height of device relative to patient), medication properties (viscosity), detection technology employed, software and calibration, to name just a few! Typically, an air-in-line detection system utilises a pair of ceramic ultrasonic sensors in tandem with software algorithms to detect the presence of air in the infusion line. An alarm would occur when the sensor detects either a series of smaller air bubbles (that equate to a dangerous total sum of air) or a continuous/single air bubble that is of an unacceptable volume.

Nuisance air-in-line alarms are due to misdetection and may occur due to the device being too sensitive, which can lead to customer complaints. Nuisance alarms can also occur for other reasons:

- Tube decoupled from sensor (requires careful design of the interface between the disposable part and the device where the sensors are located)
- Bubbles bouncing within the infusion line (requires careful consideration on the type of mechanism and geometry around the sensors to prevent bubbles forming on the internal wall of the disposable tube, as well as the software algorithms employed in the detection of air).

Conversely, a device that is insensitive may not detect unacceptable volumes of air, which may lead to patient harm. It is important that these devices have a high level of accuracy, with the challenge coming from understanding and controlling those factors affecting robustness. Developing these complex systems requires a good understanding of all factors and systematic testing.

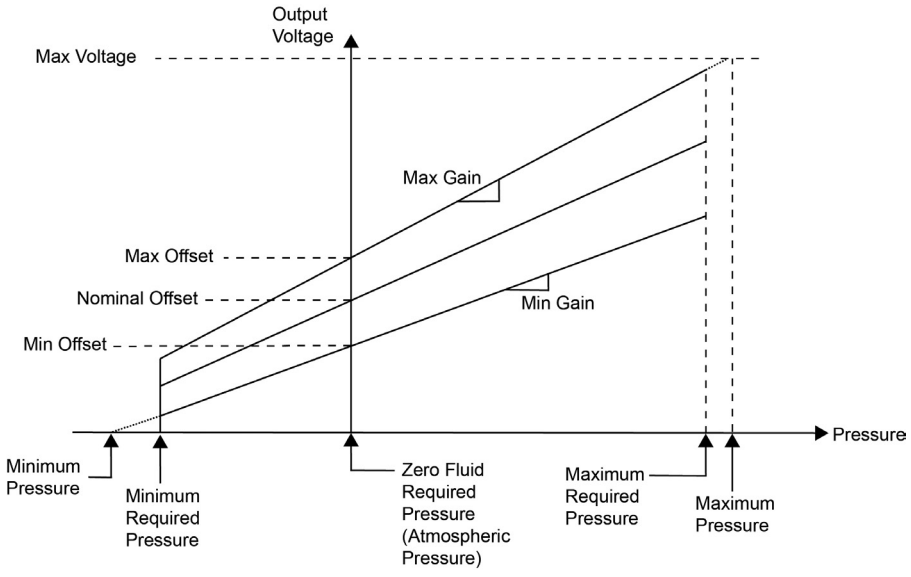

Figure 3: How the output voltage of a typical force sensor relates to pressure in the tubing set. This calculation would be performed by the infusion pump software and used to control certain occlusion alarm conditions. The force sensor can also be used to detect whether the disposable part is fitted correctly.

CONCLUSION

The technical issues outlined here are those which most commonly catch out first-time infusion pump designers. Each is

enough by itself to make an infusion pump unusable, either for safety concerns or for an abundance of nuisance alarms. These issues must be considered very early in the design process, and an approach must be taken that anticipates failure. Similarly, the stringent regulation of these devices warrants early consideration. Indeed, if these concerns are thoroughly understood, there are proven ways to design effective infusion devices.

ABOUT THE COMPANY

Sagentia is a global science, product and technology development consulting company that helps its clients maximise the value of their investments in R&D. Sagentia partners with clients in the medical, consumer and industrial sectors to help them understand the technology and market landscape, decide future strategy, solve complex science and technology challenges and deliver commercially successful products. Sagentia employs over 150 scientists, engineers and market experts and is a Science Group company. Science Group provides independent advisory and leading-edge product development services focused on science and technology initiatives. It has 16 European and North American offices, two UK-based, dedicated R&D innovation centres and more than 400 employees. Other Science Group companies include Leatherhead Food Research, TSG Consulting, Oakland Innovation and OTM Consulting.

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UV STERILISATION & THE CASE FOR PREFILLED & PRELOADED DRUG DELIVERY SYSTEMS

This article reviews the different fill form configurations of drug delivery devices, outlining the importance of the prefilled and preloaded device configuration for self-administering patients. Mindy Katz, Director of Product, and Ori Ben-David, PhD, Director of R&D, both of Sorrel explain the challenges associated with these devices; along with how Sorrel Medical's prefilled wearable drug delivery platform uses innovative UV technology for disinfection at point of care, bringing both patient-centric design and partner-focused strategy to the spotlight.

Recent advances in technology are positively influencing how we take medications and manage our health. This can be seen across multiple aspects of healthcare, and in drug delivery specifically. Drug development is changing due to advances in biotechnology research, allowing new medications to be developed, symptoms to be better managed and diseases to be cured. Accordingly, we see biologic medications filling the pipelines of pharma companies, overtaking traditional oral medications and small-molecule injectable drugs.

Connected drug delivery devices are enabling patients to become more engaged in their treatments and to better manage their diseases. Smart and intuitive devices allow patients to self-administer, adhering to their prescribed therapies in the comfort of their own homes. Technology advances in various areas are positively influencing the world of drug delivery, and we can expect to see further innovation in the coming years for the benefit of patients worldwide.

> "Wearable drug delivery devices, or wearable injectors, are one category of drug delivery device designed for self-administration of injectable medication. These devices align with several trends in the drug delivery market, offering a solution for the administration of large volume and high viscosity medications into the subcutaneous tissue in a smart and user-friendly drug delivery device."

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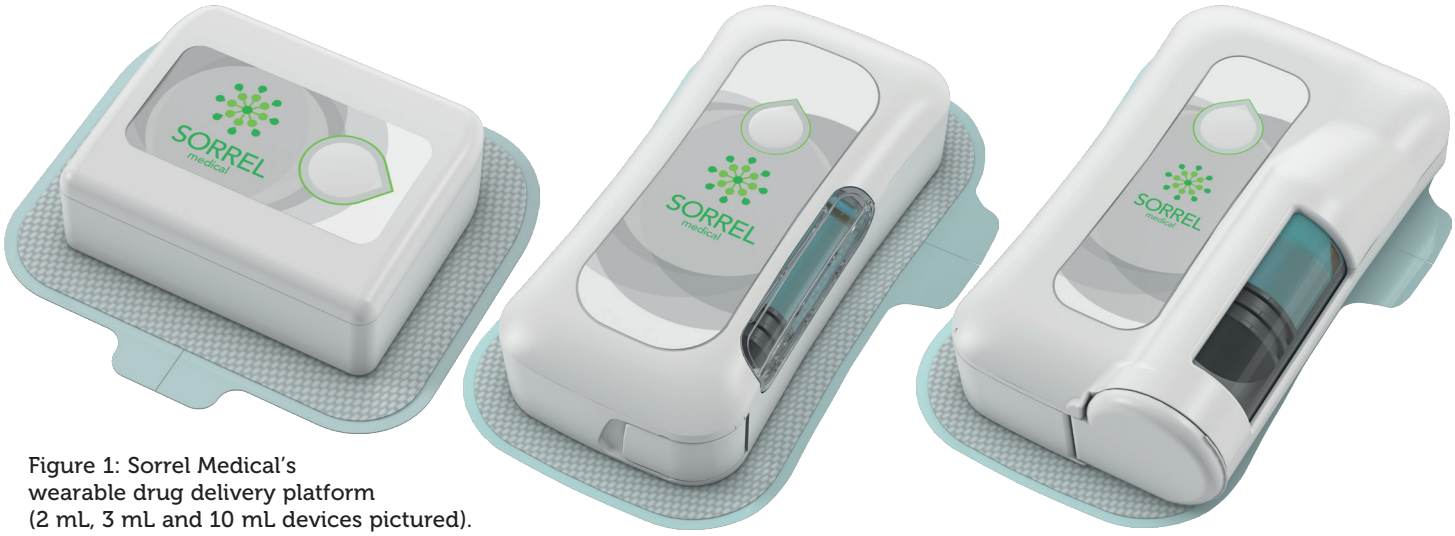

Figure 1: Sorrel Medical's wearable drug delivery platform (2 mL, 3 mL and 10 mL devices pictured).

DEVELOPING WEARABLE DRUG DELIVERY DEVICES

Wearable drug delivery devices, or wearable injectors, are one category of drug delivery device designed for self-administration of injectable medication. These devices align with several trends in the drug delivery market, offering a solution for the administration of large-volume and high-viscosity medications into the subcutaneous tissue in a smart and user-friendly drug delivery device.[1] Sorrel Medical is focused on the development, manufacturing and commercialisation of a wearable drug delivery platform (Figure 1), utilising the company's experience in medical devices and innovative technology solutions.

Guidelines for Developing the Platform

Two primary customers for Sorrel's wearable platform were identified, which helped determine the definition of product requirements and development guidelines:

- The end user – a patient receiving injectable medication, most likely in the home environment without the presence of a healthcare professional
- The partner – a pharmaceutical or biotech company, partnering with Sorrel to bring a drug/ biologic-device product to market.

Sorrel's development guidelines present a delicate balance between the distinct needs of both patients and partners.[2] Specifically, the device platform would need to adhere to the following:

1. Enable a primary container-agnostic system, allowing drug manufacturers the freedom to choose the primary container
2. Utilise proven and reliable technologies, avoiding exotic components and reducing product risk
3. Ease of use for the patient.

When needing to solve technical challenges throughout the product development cycle, it was imperative to adhere to the defined development guidelines, ensuring that the end product was a non-compromising, patient-centric and partner-focused system.

FILL FORM CONFIGURATION OPTIONS

Looking at drug delivery devices, there are three primary configuration options, which are differentiated by the way the medication is filled into the device. Accordingly, each configuration offers a different approach to how the patient interacts with the medication and the number of steps required for administration. The three configurations are:

1. The medication is filled at point of care into the device
2. A prefilled primary container is loaded into the device by the user at point of care
3. The device configuration is prefilled and preloaded.

These configurations vary according to factors such as complexity for the patient, ease of use, final assembly, supply chain considerations, regulatory status and more.

The first fill form requires the user to fill the device with the drug manually. With the second, the drug reservoir is prefilled, and the user is tasked with loading the prefilled reservoir into the drug delivery device. Where there are steps for the user, there is room for error and risk of non-compliance. Users can drop vials, place drug cartridges in upside down, incur needlestick injuries, leave device doors open or skip the mandatory disinfection of a cartridge septum.

The prefilled and preloaded device configuration is essentially a ready-to-use device, in which the user has no interaction with the medication itself, and the drug delivery device constitutes the entire user interface of the patient with the medication. Alongside the benefits of a prefilled and preloaded configuration come inherent challenges, which can be barriers to the development and commercialisation of such a drug delivery device.

THE BENEFITS AND CHALLENGES OF PREFILLED AND PRELOADED

The User Perspective

For self-administering patients, the assumption is that they are at home, without the presence of a healthcare professional. For such patients it is essential to provide the best experience possible, regardless of age or

"The prefilled and preloaded device configuration is essentially a ready-to-use device, in which the user has no interaction with the medication itself, and the drug delivery device constitutes the entire user interface of the patient with the medication."

health condition. This includes a simple user interface that reduces room for use errors, while promoting adherence to therapy. Ideally, the drug-device system would come as one single unit, preloaded with a prefilled primary container. In this scenario, the user would simply remove the device from its packaging, peel the adhesive liner, adhere to the body and initiate treatment (actively or automatically). The patient's experience would be as intuitive as putting on a plaster.

The Pharmaceutical/Biotech Company Perspective

For any injectable medication, it is important to recognise that the way the patient experiences the medication is through a drug delivery device. As a critical influencer in the interaction between their medication and their users, pharma companies often rely on external device manufacturers, putting the experience of their users in the device manufacturers' hands. A positive user experience is of highest importance for the pharmaceutical company, as it will influence the patient's level of adherence to the prescribed treatment. With medication non-adherence associated with 125,000 deaths in the US alone, costing up to US$289 billion (£225 billion) annually,[3] pharma companies are investing significant efforts into ensuring a positive experience.

The Challenge of Avoiding Infection

A critical challenge in the development of a prefilled and preloaded device is the process of integrating the aseptic drug filling process and the device assembly in a way that ensures a disinfected fluid path. Furthermore, doing this in a manner that is cost effective, with no user intervention and minimal disruption to established pharma processes, poses an additional barrier. The injectable medication is sterile in its primary container, and the drug delivery device can be sterilised. The challenge is to maintain a sterile path for the fluid to travel through, from primary container all the way to the subcutaneous tissue where it is therapeutically active. And there is an additional challenge of achieving this without disrupting established filling processes, while also allowing the device manufacturer to test the final assembled product prior to it leaving the manufacturing facility.

> "Throughout the search for an adequate technology that allows disinfection at point of care, UV technology was discovered to be ideal."

The point of engagement between the two separate and sterile entities is crucial. Creating a micro-organism-free fluid path for a prefilled and preloaded solution generally necessitates alterations to be made to the established pharma processes; for accommodating proprietary cartridges that contain the entire fluid path, or for loading the cartridge under aseptic conditions.

THE IDEAL THEORETICAL SOLUTION

The ideal solution envisioned by Sorrel (Figure 2) would have each party doing what they do best: the pharma partner handling the drug filling with or without the assistance of an external contract manufacturer, as they do today; and the medical device manufacturer fully assembling the device, and performing its final testing and sterilisation. The prefilled primary container (coming from the pharma partner) would then be assembled into the device (coming from the device partner) either at the pharma company, a contract manufacturer or at Sorrel. In some instances, a homecare pharmacy or clinic could even prepare the medication for a patient, loading the prefilled reservoir into the device before sending it home with a patient for self-administration.

Given the division of labour outlined above, the ideal solution would incorporate disinfection at the point of engagement between the primary container and the device's fluid path, right before delivery initiation, and would be independent of the primary container. In order to adhere to the development guidelines outlined above, a solution would need to be:

- Scalable to different primary containers
- Use a proven and reliable technology
- Maintain a fully disposable and easy-to-use, prefilled and preloaded wearable drug delivery device.

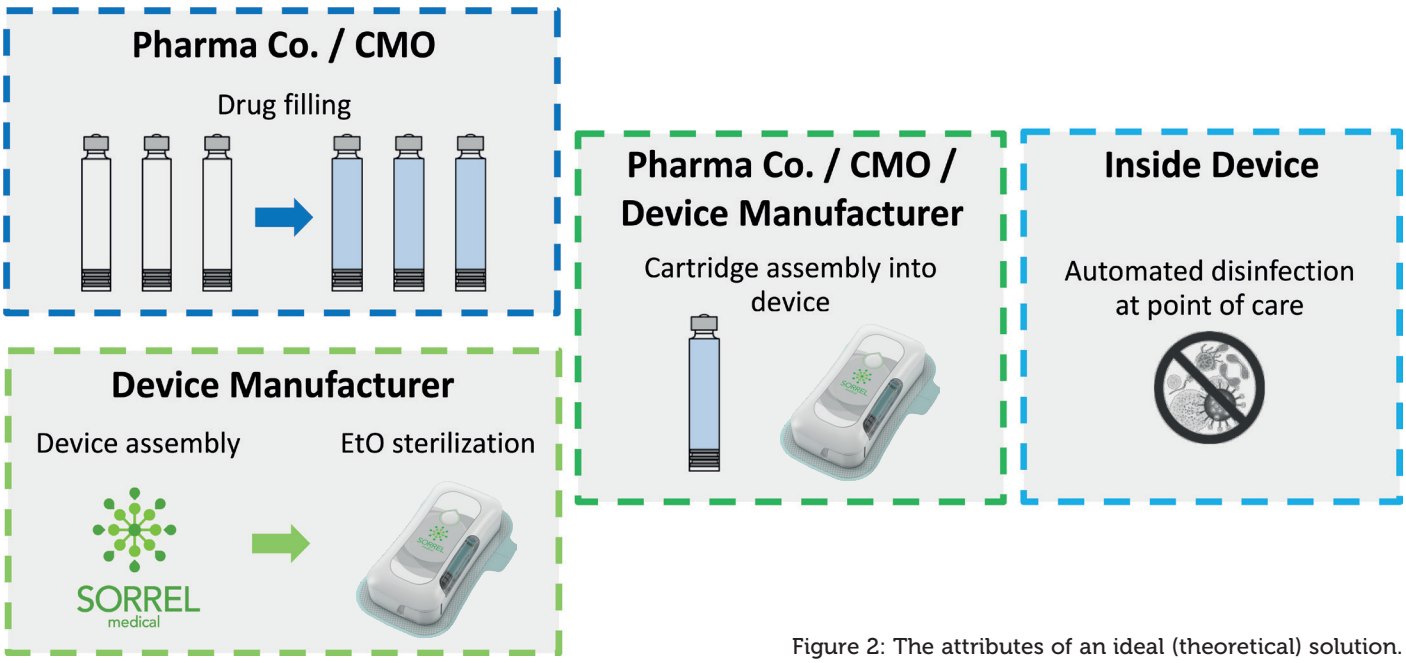

Figure 2: The attributes of an ideal (theoretical) solution.

THE SORREL SOLUTION: UV DISINFECTION AT POINT OF CARE

Throughout the search for an adequate technology that allows disinfection at point of care, UV technology was discovered to be ideal. The UV light can be activated inside a confined disinfection chamber prior to engagement between the device fluid path and the primary container, ensuring a completely disinfected fluid path (Figure 3). This enables a solution that can be automatic, verified and controlled, taking the responsibility of disinfection out of the patient's or pharma partner's hands.

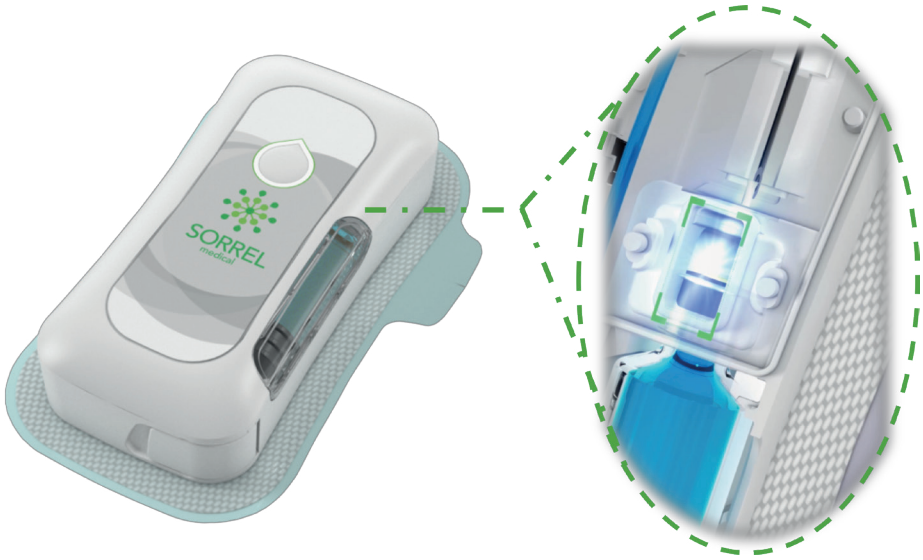

Figure 3: The Sorrel wearable injector disinfection chamber (3 mL pictured).

Track-Record of UV in Disinfection Applications

UV-C is a short wavelength ultraviolet light which is "germicidal"; having the ability to destroy nucleic acids and break apart the DNA of bacteria, preventing the ability of micro-organisms to function or reproduce.[4] UV technology has a long history and strong track-record for healthcare-associated infection control. In 1903, Niels Finsen was awarded a Nobel Prize in Medicine, for using UV to treat tuberculosis, and in 1910, UV was first used to disinfect water systems in France. By 1960, UV-C was being applied inside biological hoods in hospitals to ensure the sterility of drug-compounding workstations. In 2012, UV-C LEDs were introduced widely for water disinfection. Today, they can be found in commercial and hospital disinfection systems for mobile phones, tablets, keys and more.

As the technology developed over the years it has, like many technologies, become smaller and more cost effective, while its efficacy and reliability for disinfection have been proven time and again. The size and cost reduction reached today are what enable Sorrel to integrate UV-C LEDs within a disinfection chamber in a wearable drug delivery device, while allowing the device to be fully disposable for the benefit of patients.

Crucially for pharma partners, the integration of a UV-C LED allows the device to maintain its "primary container-agnostic" definition, with the solution being complementary to a variety of drug reservoirs, and not affecting the choice of primary container for the partners.

EXPERIMENTAL RESULTS

Working with internal resources and external laboratories, UV-C was put to the test. A significant amount of data was created in order to validate and verify the UV technology, and below is a summary to provide insight into two experiments conducted.

UV Disinfection

Several tests were designed to determine the efficacy of UV-C at eliminating bacteria from the disinfection chamber. The goal was to be comparable with the industry standard of manual ethanol swabbing, with the added benefits of the control and repetitive results. The starting point was planting a bacterial load of 5,000,000 *Staphylococcus aureus* (a representative bacteria; one of many strands tested) on a cartridge septum, aiming for 6 Log reduction of bacteria on the septum and total elimination of viable bacteria entering the cartridge. UV-C was tested using an 18G needle to penetrate the cartridge septum. Although a percentage of the bacteria were eliminated by the mechanical barrier from entering the cartridge's rubber septum, a significant number of bacteria were found to enter the medication if no disinfection method was applied, further proving the importance of finding a suitable disinfection solution. After UV-C LED exposure, the goal of 6 Log reduction in the number of bacteria on the cartridge septum was obtained, with no viable bacteria entering the cartridge, proving the technology's ability to properly disinfect the cartridge septum (Figure 4).

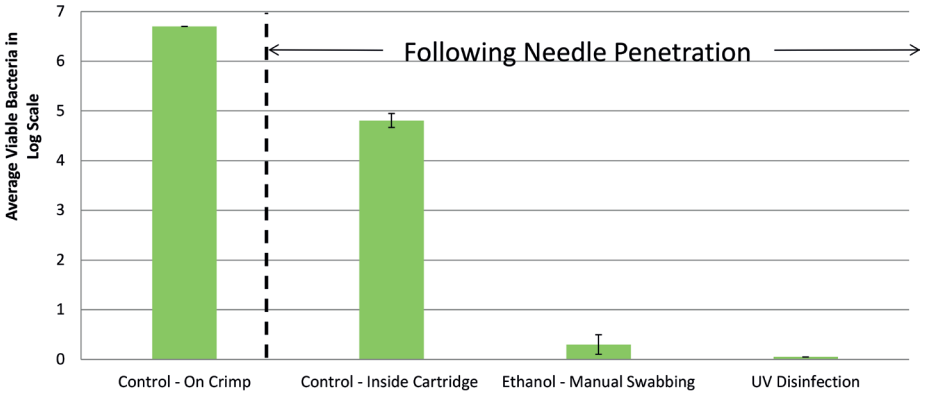

Figure 4: Bacteria elimination following application of various disinfection methods.

UV Reach

A second set of experiments was conducted to ensure UV-C was only disinfecting the chamber and would not have the ability to reach any area outside the disinfection chamber, including the medication, the patient, the environment or any other part of the device outside of the designated chamber. To test the UV reach, an experiment was designed using highly sensitive sensors encircling the disinfection chamber, with one under the seal of the medication cartridge to simulate medication exposure (Figure 5). As predicted, only the sensor inside the disinfection chamber registered UV readings, demonstrating that the UV cannot reach the medication or other external areas beyond the disinfection chamber (Figure 6).

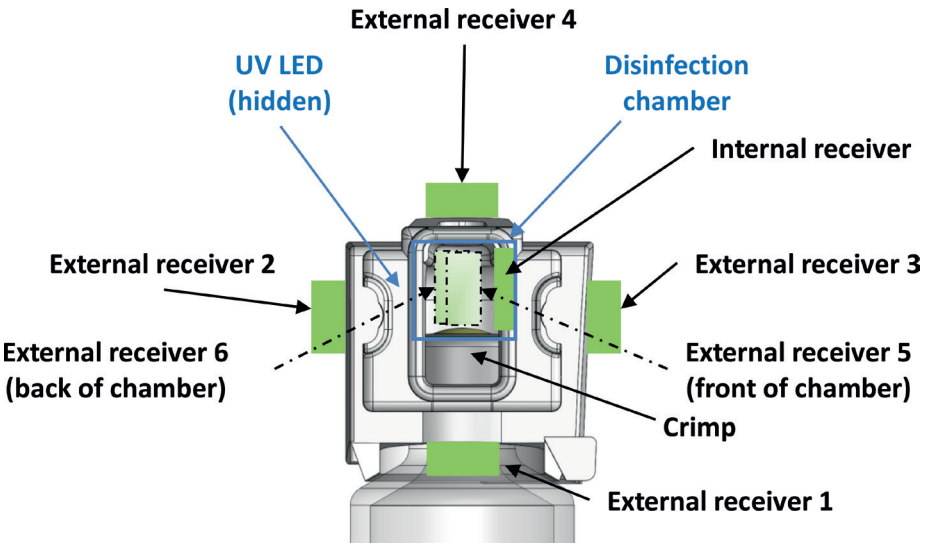

Figure 5: The experimental set-up to determine UV reach.

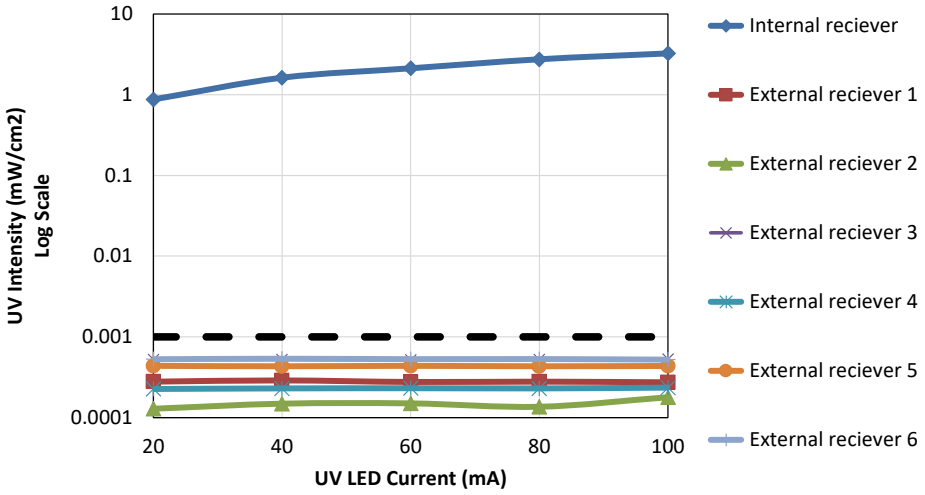

Figure 6: The results of the experiment showing UV reach.

SUMMARY

To provide a patient-friendly experience and partner-focused approach, Sorrel determined that the prefilled and preloaded device configuration was the optimal choice. UV-C LED technology enables this configuration in a proven and reliable manner, reducing risk and supporting treatment adherence. Harnessing the disinfecting power of UV-C results in automatic, verified and local disinfection at the point of care. Numerous experiments were conducted by Sorrel in order to verify and validate the solution, proving the efficacy of UV-C LED technology for disinfection in a fully disposable wearable drug delivery device. Widely available, time and scale tested and cost effective, the UV-based prefilled solution allows Sorrel to provide the optimal product configuration for patients, while meeting the needs of pharma partners.

ABOUT THE COMPANY

Sorrel Medical is a medical device company focused on prefilled wearable injectors. Sorrel is one of three privately held companies operating under the Eitan Group, all in the world of drug delivery devices, including Q Core Medical, Avoset Health and Sorrel Medical.

Q Core Medical develops and manufactures the Sapphire infusion system, on the market in both hospital and homecare environments. Avoset Health is developing a connected homecare infusion pump, available for pharmaceutical companies in a dedicated application configuration. The joint experience shared amongst the Eitan Group's three companies, includes commercialisation of drug delivery products across the continuum of care, multiple FDA approvals, market presence in over 20 countries worldwide and a team of R&D innovators who are experts in parenteral drug delivery, accuracy, flow control, human factors, cybersecurity and more.

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Mindy Katz is the Director of Product at Sorrel Medical, responsible for product management, marketing and business development. Ms Katz previously served as Program Manager at Q Core Medical, where she worked across multidisciplinary teams to build structured and collaborative partnerships between companies in the world of drug delivery. Mindy holds a BSc in Biomedical Engineering from the Technion – Israel Institute of Technology.

Ori Ben-David is the Director of R&D at Sorrel Medical, responsible for research and development of Sorrel's entire device platform, where he applies his extensive hands-on expertise in medical device innovation. Prior to joining the Sorrel executive team, Dr Ben-David served as Manager of Research and Mechanics at Q Core Medical, and R&D Director at Bmax. He holds a PhD in Energy, and an MSc and BSc in Mechanical Engineering, all from Ben-Gurion University of the Negev (Israel).

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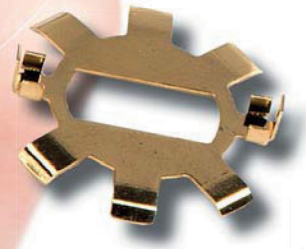

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SIX TECHNIQUES FOR RAPID EARLY-STAGE MEDICAL DEVICE DEVELOPMENT

Here, Stuart Curtis, Consultant Mechanical Engineer at Cambridge Design Partnership, runs through six techniques which, in his experience, are invaluable for accelerating the early development stages of drug delivery device design and can therefore be of great use when trying to accelerate a product's time to market.

INTRODUCTION

There has always been pressure in pharmaceutical companies to be first to market, thus gaining a key edge over competitors. In the so-called "Age of Impatience", this is more important than ever before. So, how best to achieve it? One approach, discussed here, is accelerating design development in the early phases of a device programme to get ahead of the normal timeline. Looking back at some recent programmes I've worked on, I've highlighted some of the techniques that have helped accelerate early-stage development.

SIX TECHNIQUES

One – Get the Project Scope Right from the Start

The crux of early development is that it's all about learning. The earlier in the process that learning can happen, the faster development can occur. Critical learning can start as soon as a project is initiated, long before any design work starts. Being able to collect information from a range of stakeholders, whether internal product owners or, best of all, from direct front-end user research, allows for building a solid foundation of evidence to support the rationale behind the development brief. Such a foundation communicates and validates the project vision throughout the team, and often provides new insights that can have a profound impact on the project's overall success.

"The crux of early development is that it's all about learning. The earlier in the process that learning can happen, the faster development can occur."

Two – Get the Team Right

I work in a team of multidisciplinary engineers who regularly work on projects from sectors outside healthcare, so we have the ability to cross-fertilise expertise and experience (Figure 1). Taking proven design solutions from other sectors, rather than developing them from scratch every time, is a great timesaver. For example, some of the manufacturing volumes that are encountered in the injection device space, mean that high-speed manufacturing techniques from the fast-moving consumer goods (FMCG) world can be a good point of reference.

Three – Use the 80/20 Rule to Your Advantage

Some of the many steps required in a regulated medical device development process can be time consuming, making it tempting to leave them until the number of concepts has been reduced. Considering the Pareto principle, which states that 80% of an effect comes from 20% of the cause, it can make sense to start some of these tasks early, intentionally leaving them unfinished until later phases. This can accelerate learning and reduce the effort required in subsequent phases. For example, just reviewing the potential failure modes in a design

"Taking proven design solutions from other sectors, rather than developing them from scratch every time is a great timesaver."

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Figure 1: Cross-pollinating ideas and expertise with team members who are active on projects outside of healthcare can open the way to interesting, and often time-saving, approaches to early-stage design problems.

failure mode and effects analysis (dFEMA) template (20% of the effort) and discussing where team members see major unknowns, allows you to address these in this early phase of development when concepts can still be easily adapted, compared with later phases. Formal dFMEA scoring can occur later (the remaining 80% of the effort).

The same is true of mathematical modelling. When working on a mechanism for an injection device, we might put together the first-pass of a dynamic model with just a subset of interfaces (20% of the effort) whilst multiple concepts are still being developed. This quickly delivers insights into the designs, such as the largest contributing factors to accurate motion and where the largest forces will occur. Not only does this help to refine the design earlier in the development process, but it allows for a more accurate estimate of the effort required to complete to model in later phases (remaining 80%).

Four – Build It Early

Getting designs into a physical form usually finds unexpected issues, as well as helping to present a more compelling case to stakeholders. With the explosion in 3D printing technologies and their ever-decreasing costs, a working model can be made overnight and tested the next day with relatively little investment. Model making is a key part of the learning and development process and should be used freely whilst the design is still in rapid development. The burden of costly and time-consuming design reviews can be kept low (remembering the 80/20 rule once again), as the impact of parts not working is low and it is almost certain something useful will be learnt. A model does not need to be feature complete, or even functional, for it to be worthwhile. Just getting a sense of size, forces and assembly steps is useful to guide the design forwards and can help mitigate some of the effects of computer-aided design (CAD)-eyes, where everything looks simple, perfect and tough on a computer screen. Making models early on can be particularly useful for picking up "unknown unknowns", providing valuable insights with very little time or resources.

"With the explosion in 3D printing technologies and their ever-decreasing costs, a working model can be made overnight and tested the next day with relatively little investment."

Five – Use Agile Methods

Setting regular short-term reviews helps focus the team and keep the development pace up. An agile approach, borrowing techniques from the world of software development, can be applied in early-stage development. This involves short-term sprints, with regular face-to-face team meetings to encourage an iterative design approach with rapid build and test cycles. This is a very effective method at a stage when design process lead times are conveniently short and it is important to make any big changes that may be required quickly. At the end of each sprint cycle, a review with the stakeholders allows time to reflect on the progress, direction and discussions, and assess if changes to the requirements or vision are needed.

Six – Knowing When to Pivot

As noted prior, the early design phases are all about learning quickly. Typically, a project will start with a wide number of early concepts that could work. As more is learnt about the individual concepts,

some of these are then dropped to get a shortlist of concepts that should work, usually determined by those that best fit the requirements. As the design of these mature, it often becomes apparent some aspects are more challenging than first thought, or that priorities on requirements have changed during the process. Ceasing development of an imperfect concept and pivoting, apparently jumping backwards to a previously discarded concept, may appear counterintuitive on the surface (Figure 2), but whilst it may look like a time-consuming process to bring previous designs up to the same level, it is likely that the majority of the learning gained so far is applicable, so the effort required may be less than it initially seems, and certainly much less than could be wasted trying to get a fundamentally flawed concept to work.

CONCLUSION

By using the techniques described here, in my experience it is possible to get from an initial brief to fully functional working models of miniaturised devices in around three months. Clearly it depends on the levels of innovation inherent in the device, but by introducing some of these practices into your device development programmes, especially at the early stages, you may be able to shorten development timelines and get ready-to-test prototype devices earlier than ever before.

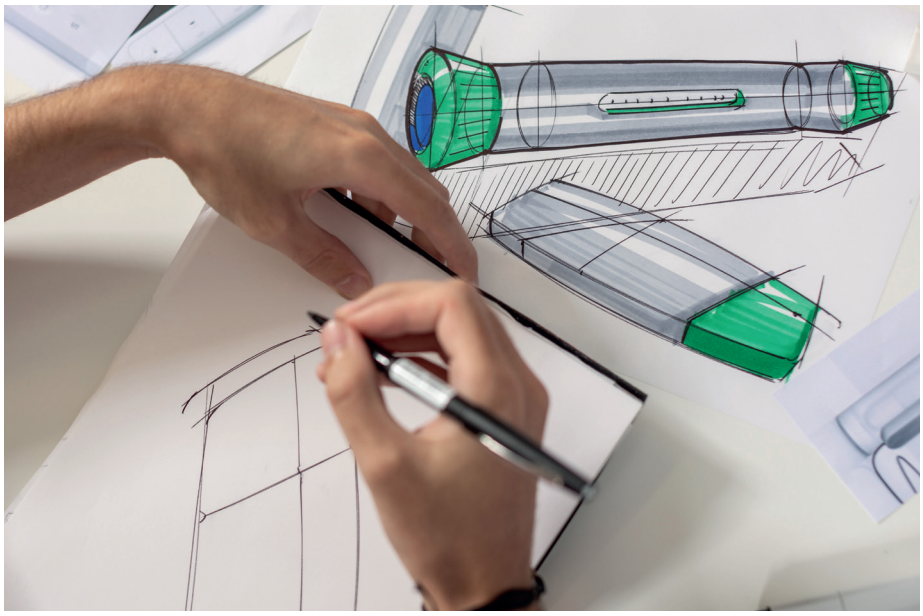

Figure 2: Pivoting from a matured design after a key flaw is uncovered to an older, previously discarded, one, may in fact save significant time and effort in the long term.

ABOUT THE COMPANY

Cambridge Design Partnership is a technology and product design partner focused on helping clients grow their businesses. Some of the world's largest companies trust CDP to develop their most important innovations. Located in both Cambridge (UK) and in Palo Alto (CA, US), CDP specialises in the consumer products, healthcare, energy and industrial equipment markets. Its multidisciplinary staff have the expert knowledge to identify opportunities and tackle the challenges its clients face.

ABOUT THE AUTHOR

Stuart Curtis is a Consultant Mechanical Engineer at Cambridge Design Partnership. He is a chartered mechanical engineer who has worked on product development across consumer, industrial, medical and FMCG markets over the last six years. As well as leading projects, he regularly works on the technical and creative aspects of engineering and has several successful on-the-market products to his name from a wide range of projects, from industrial printer design for manufacture through to hot chocolate dispensing. More recently, he has been concentrating on leading fast-paced projects involving early-stage medical devices.

DRUG-DEVICE CO-PACKING SOLUTIONS TO ENHANCE DIFFERENTIATION AND IMPROVE EXPERIENCE

In this article, Janice Adkins, Associate Director, Global Marketing, BD, discusses the benefits that co-packing, the practice of providing drug preparation and delivery systems along with a medication, can bring to pharmaceutical manufacturers, clinicians and patients.

A WELL-ESTABLISHED SOLUTION TO AID IN MEDICATION ADHERENCE

With medication nonadherence estimated at 50%,[1] packaging solutions have emerged as useful tools to help patients manage their therapies. Several studies have suggested an adherence benefit as a result of packaging interventions, such as calendarised blister packages.[2-6] In addition to adherence packaging, some manufacturers have employed co-packing strategies to facilitate improved adherence to medications that are co-administered. Examples include:

- Kisqali® (ribociclib) and Femara® (letrozole) Co-Pack for breast cancer by Novartis (Basel, Switzerland)
- Viekira Pak-RBV® (ombitasvir/paritaprevir/ritonavir, dasabuvir and ribavirin) for hepatitis C from AbbVie (Chicago, IL, US)
- Orkambi® (lumacaftor/ivacaftor) for cystic fibrosis from Vertex (Boston, MA, US).

Not all of these packaging configurations are complex, with some involving a simple "box within a box" design.

Co-Packing Medications With Devices

The growing number of self-administered, parenteral medications entering the market with large volumes, high viscosities, complex dosing regimens and/or reconstitution requirements has spurred innovation in packaging solutions as well. However, rather than drug-drug co-packing, as is the case with co-administered oral medications, parenteral medications often require packaging solutions where drugs are provided alongside delivery devices or other supplies to enable their preparation or administration. This is most apparent in areas where patients or caregivers are required to manipulate drug components, for example reconstitute a lyophilised product. In some of these cases, simple supplies, such as vial adapters, blunt fill needles or intravenous infusion sets, are co-packed with medications, while others involve specifically-designed devices to

> "Providing a vetted, co-packaged device alongside a drug product can put manufacturers at ease that their products are being used as intended and help prevent variability that may lead to product complaints."

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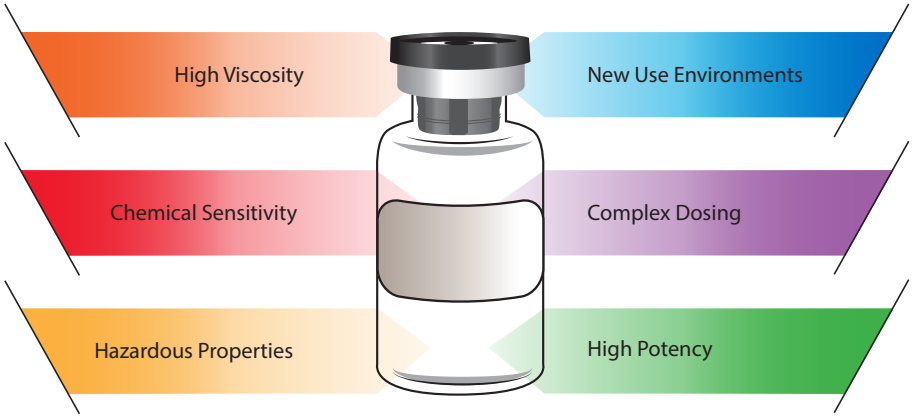

Figure 1: Complicating factors.

"As drug preparation and administration demands continue to increase, pharmaceutical manufacturers will require an even higher degree of quality control for device specifications and performance data."

aid in performing particular use steps.[7-15] Examples include:

- Genotropin Mixer® from Pfizer (New York, NY, US)
- saizenpro® from EMD Serono (Rockland, MA, US).

Increasing molecule complexity has also demanded a higher degree of rigour and consideration from drug manufacturers to ensure drug and clinical compatibility with their chosen drug delivery device (Figure 1). This is particularly true in areas where new devices are adopted and used in clinical practice without pharmaceutical manufacturers having a clear idea of exactly which devices are being used for what purpose. A recent study published in the PDA Journal of Pharmaceutical Science and Technology evaluated several chemotherapy vial spikes for their propensity to cause stopper push-in at the device-to-vial interface, and concluded that variability in device size, design and lubricity may contribute to primary container complications.[16] Providing a vetted, co-packaged device alongside a drug product can put manufacturers at ease that their products are being used as intended and help prevent variability that may lead to product complaints.

BD PROVIDES DRUG DELIVERY SOLUTIONS FOR CO-PACKING

BD brings its long history of device excellence and diverse product portfolio to co-packing engagements. With a wide range of best-in-class syringes, needles, vial adapters, catheters and hazardous drug solutions, pharmaceutical manufacturers partnering with BD have the flexibility to select the optimal product for their specific application. Moreover, BD's extensive experience in drug delivery and its global presence make it able to help customers understand market needs and make data-driven device decisions. BD has successfully partnered with manufacturers to accomplish this in several therapeutic areas, including rheumatoid arthritis, multiple sclerosis, haemophilia, short bowel syndrome, oncology and radiology.

Pharmaceutical manufacturers have integrated BD's drug delivery devices in their co-packing designs in various forms. One approach is a fully-integrated solution where the pharmaceutical manufacturer provides the appropriate device(s) within the same unitary package, directly alongside the drug product (Figure 2). This configuration ensures that patients uniformly have every component they need when they receive the drug product, and minimises complexity for other healthcare providers and prescribers. In a second configuration, pharmaceutical manufacturers supply the desired devices separately from the drug product as a

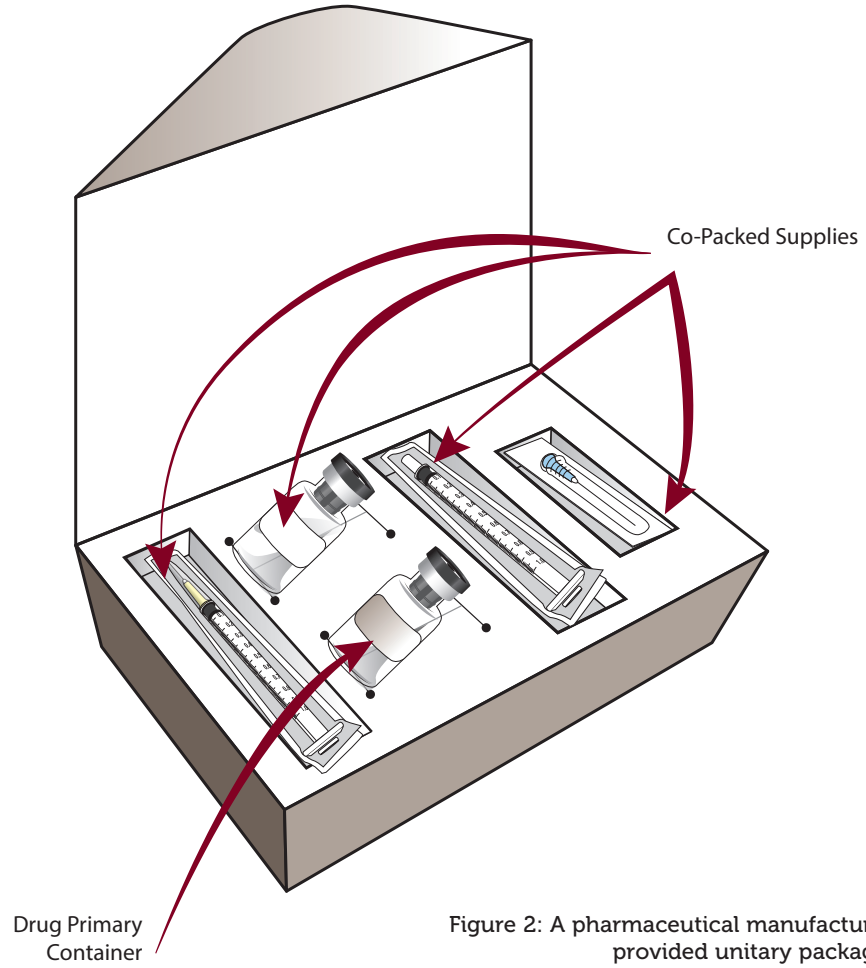

Figure 2: A pharmaceutical manufacturer provided unitary package.

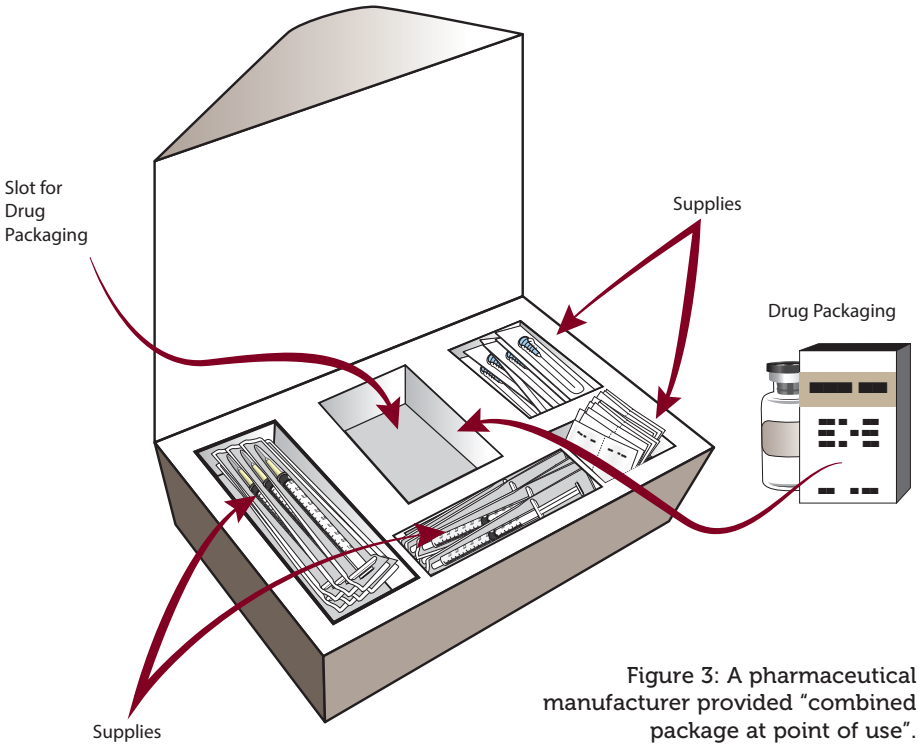

Figure 3: A pharmaceutical manufacturer provided "combined package at point of use".

discrete package, which is then combined with the drug packaging at the point of dispensing (Figure 3). This option minimises the burden on manufacturers and allows the drug product and devices to be treated separately in the supply chain.

Pharmaceutical Manufacturers – Quality Assurance and Consistency

As a partner in optimising drug preparation and delivery process, BD can be relied upon by manufacturers to provide performance quality assurance and supply assurance.

As drug preparation and administration demands continue to increase, pharmaceutical manufacturers will require an even higher degree of quality control for device specifications and performance data. When directly collaborating with pharmaceutical customers, BD can offer visibility on the product capabilities of its industry-leading devices to its direct partners. This becomes of key importance when specifications such as materials of construction and device performance are critical.

Finally, BD's broad portfolio of drug preparation and delivery solutions for co-packing can help pharmaceutical partners standardise clinical trial supply and ensure performance consistency as molecules progress towards commercialisation. Several organisations have reported challenges associated with managing clinical trial ancillary supplies, including difficulty sourcing the right supplies for each trial efficiently and cost-effectively, overlooked the make or manufacturer of supplies, and the need for expensive repacking.[17-19] A clinical trial strategy that utilises co-packing to guarantee the right devices are supplied with investigational drugs can mitigate these risks, and a partnership with BD enables manufactures to study their medications with the supplies that patients and clinicians may ultimately use upon approval.

> "BD's broad portfolio of drug preparation and delivery solutions for co-packing can help pharmaceutical partners standardise clinical trial supply and ensure performance consistency as molecules progress towards commercialisation."

End-Users – Intuitiveness, Confidence and Convenience

From a patient perspective, a co-packaged offering utilising BD devices can help to encourage proper use and ensure that the drug is prepared and delivered as intended by the manufacturer. This is especially important when patients are presented with unfamiliar use steps or when specific supplies are required. One representative example is Gattex® (teduglutide) from Shire (Lexington, MA, US), a medication that requires reconstitution with a supplied prefilled diluent syringe, withdrawal of very small dose volumes, and potential pooling of the contents of more than one drug vial before subcutaneous injection. To facilitate these use steps, patients are provided a kit that contains BD 22G 1.5" needles for attachment to the diluent syringe and reconstitution and BD disposable 1 mL graduated syringes with attached 26G 5/8" needles for dose withdrawal and injection.[20] Along with the product's instructions for use, co-packing of these two particular supplies (i.e. a fill needle and separate pre-attached needle and syringe) aids in the proper use steps to the user and may help prevent use errors, such as accidental injection with the incorrect needle and syringe.

Moreover, in situations where provided supplies are not standardised, device variation can have unintended implications. This may occur when a device is not co-packaged by the manufacturer but rather by another party, such as a specialty pharmacy, at the point of dispensing. In these cases, pharmacies may provide supplies that are intended to aid the patient in taking their medication but may not be ideal for the particular drug. Common examples of this include medications with complex preparation steps.

In addition to not necessarily being intended for use with particular products, pharmacy-provided supplies pose other challenges. First, because the devices are supplied in bulk, storage of such large quantities may be burdensome for patients. Second, there is likely a lack of standardisation of these provided supplies across pharmacies, or even within the same pharmacy, if purchasing is made solely based on product price. As a result, there could be differences in the particular device and associated training that patients receive, potentially causing unnecessary confusion.

For clinicians, the benefits of a BD co-packing strategy are two-fold: confidence and convenience. Due to BD's industry leadership, clinicians may be aware of BD products and may be already comfortable using these devices if provided

"Due to BD's industry leadership, clinicians may be aware of BD products and may be already comfortable using these devices if provided alongside drug products."

alongside drug products. Additionally, providing the appropriate devices at the point of use can increase convenience for clinicians, especially in acute clinical situations or those that require the use of special supplies, such as filter needles, filtered extension sets, closed-system transfer devices and vented vial adapters.

MAXIMISING THE VALUE OF PACKAGING SOLUTIONS

Although a BD co-packing solution offers a number of benefits, manufacturers can refer to the expected use environment characteristics to inform selection of which products would receive the greatest benefit from co-packing. Co-packing may add the most value when:

- Specific supplies are needed to support use steps, such as reconstitution, filtering, complex manipulation or large volume transfer.
- Dosing- or clinical practice-related circumstances require device standardisation, for example to protect the user from hazardous drug product and/or minimise device dead space.
- Use setting is a home or specialised clinic, rather than a general hospital environment, therefore favouring the convenience of co-supplied devices.
- Acute or emergency clinical situations demand that the correct devices are immediately accessible.
- Certain patient populations, for example psychiatric, paediatric or geriatric, mean that special device considerations are necessary.
- Required supplies are barriers to adoption into clinical practice.

BD is excited to work with the industry to navigate these factors and bring the highest-impact packaging solutions to market.

ABOUT THE COMPANY

BD is one of the largest global medical technology companies in the world and is advancing the world of health by improving medical discovery, diagnostics and the delivery of care. The company develops innovative technology, services and solutions that help advance both clinical therapy for patients and clinical process for health care providers. BD has 65,000 employees and a presence in virtually every country around the world to address some of the most challenging global health issues. BD helps customers enhance outcomes, lower costs, increase efficiencies, improve safety and expand access to healthcare.

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IMPROVING PATIENTS' SELF-INJECTION EXPERIENCE

Jeff Lettman, Senior Research & Design Engineer, and Josh Hopkins, Engineering Manager, Noble, explain how they worked with a client to develop a product that would function with the pre-existing drug delivery device to help rheumatoid arthritis patients with reduced dexterity. Through direct interaction with patients and a review of research, the team worked with engineers and the client to create an ergonomic sleeve that avoided the need for a push-button operation.

The rapid advancement of biologic therapies has created numerous opportunities for improving patient self injection. As a result, every year, more patients are being introduced to both established and new devices for home treatment.

However, studies have shown some patients find it hard to follow the required steps outlined in instructions for use (IFU) documents[1] while others struggle with a variety of physical and emotional factors that impact the injection experience and can even cause inconsistencies in treatment.

To help improve the patient experience, Noble provides drug delivery device trainers and onboarding solutions. Furthermore, it also provides a variety of customised solutions to address patient needs and works with industry leaders to bring these solutions to market. Its focus on expediting design solutions for a variety of clients results in a better patient experience.

> "The challenges patients face can be difficult to determine. Even with the benefit of direct interaction, recognising opportunities to improve the patient experience often relies on research-based insights as well as a bit of serendipity."

IMPROVING SELF INJECTION FOR PATIENTS WITH RHEUMATOID ARTHRITIS

The challenges patients face can be difficult to determine. Even with the benefit of direct interaction, recognising opportunities to improve the patient experience often relies on research-based insights as well as a bit of serendipity. If an unfulfilled need for a specific patient population is identified, Noble can help turn this insight into real products, which ultimately improve patients' use of drug delivery devices.

Noble was approached by a client to develop a product that would function with a pre-existing drug delivery device to improve rheumatoid arthritis (RA) patients' overall injection experience. The development process typically

> "Studying and understanding the patient self-injection process is paramount to Noble's core mission of improving the injection experience and overall patient adherence through training and support materials."

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Figure 1: The sleeve provides an ergonomic grip when used for an injection.

> "According to a multinational survey of 200 RA patients and 100 nurses, easy grip and ease of performing self-injections were the two most important attributes identified by both groups."

includes a research review that provides better insight into prioritising patient needs and wants. Grounding the investigation in research papers, market research and customer surveys provides a cornerstone when defining the patient problem and creating a streamlined solution to meet patient needs.

It was identified that patients with reduced dexterity may prefer an ergonomic grip when self-administering medication. According to a multinational survey of 200 RA patients and 100 nurses, easy grip and ease of performing self-injections were the two most important attributes identified by both groups.[2] Injecting without having to push a button is important for patients with RA, and the survey found that patients had clear personal preferences for which autoinjectors they found easiest to use.

Based on this conclusion, Noble decided to focus on understanding every aspect of the patient injection experience, including dexterity issues. Having identified potential for improvement in this specific area, a client-led targeted market research plan was developed to better understand patient needs. This led to the idea for a sleeve that would provide an ergonomic grip and eliminate the need for the user to press the activation button during injection (Figure 1).

DEVELOPMENT OF THE SLEEVE THAT MADE IT POSSIBLE

The client initiated the project with Noble during market research, which made it possible to hit the ground running on design and development of the sleeve.

When developing this new sleeve, Noble needed to define the product it intended to create to improve the self-injection experience for RA patients.

The requirements for our proposed solution, such as starting the injection without pushing a button directly, were created to define the functionality of the product without unduly restricting the engineering team when it came to implementation. Additional technical and measurable requirements, like removal and assembly forces (based on human factors studies), were also included.

For this project, a design that could strike a balance between several high-priority patient needs (easy to attach/remove, allow for autoinjector cap-removal, simple two-step activation, etc.) was a necessity. This also needed to be cost effective in order to maximise potential impact. Unfortunately, these goals can often be diametrically opposed. However, in this project, Noble was able to keep the part-count low and still improve the user experience.

The sleeve was designed to incorporate a soft rubber over-mould, and the careful design of the substrate allowed for much of the user and autoinjector interface to be incorporated into a single part, with the over-mould providing a clean exterior appearance. Early integration of finite element analysis tools (Figure 2) allowed for the accurate prediction of performance prior to prototyping, and a reduction of weight, material and cost during design optimisation. Similarly, mould flow analysis saved a tremendous amount of time by eliminating excess trial production runs and costly tool modifications.

Since the target patient population has reduced dexterity, creating easy-to-open packaging with contents that are readily removable was critical. As with other elements of the project, packaging costs also needed to be managed. To answer these challenges, a folded, single-sheet design was created, which minimised cost while still managing to incorporate an easy-open flap, and a raised platform which made the sleeve easy to grasp and remove.

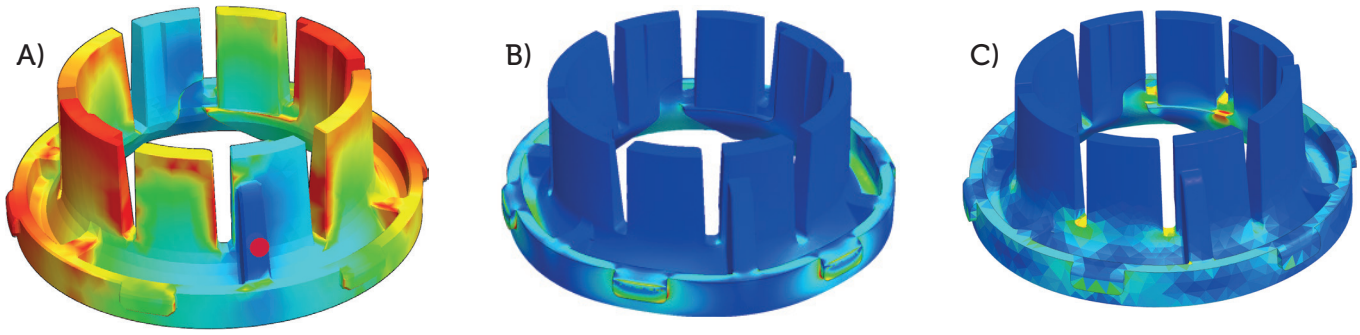

Figure 2: Engineering analysis in product development. (A) mould flow analysis during part fill; (B) von mises stress analysis during assembly; (C) the engineering strain analysis during cap removal.

This hard-won knowledge, combined with a design optimised for manufacturing, allowed for a fast-tracking of the sleeve which will be introduced into the commercial market this year.

THE DEVELOPMENT PROCESS PROVIDED BY NOBLE

In the earlier stages of a project, the team works with pharmaceutical and biotech companies in a creative and expansive mindset to maximise the opportunity. When developing a solution to best answer that opportunity, it is vital to the project's success that the purpose, features and functionality of the proposed solution are clearly and explicitly defined. However, it is often necessary to jettison some potential features or functionality to ensure that those key to the project's success are achievable – which can be challenging. Noble guides clients through this process, codifying project initiatives and prioritisation so that there is a mutual team understanding and goal.

Noble works closely with clients to transform commercial team initiatives and generic patient needs into specific user needs and marketing requirements. This leads to the creation of realistic and measurable goals early in the project, ensuring that client expectations are exceeded when trainers and medical devices are in patient hands.

In the exploratory stages, it is important to select – from the wide variety of proposed solutions – only those most in line with stakeholder needs. For this reason, Noble provides users and clients with prototypes as early as possible, which can be used to champion a project internally or be utilised in robust user studies and market research. Our on-site prototyping capabilities allow for rapid turnaround times to test early-stage prototypes. In this specific case, iterating through various form factors (Figure 3) for the sleeve project early in the design phase allowed Noble to understand how the sleeve would be utilised during the injection process.

Noble not only leads product development activities and documentation, but also provides unique and comprehensive support to pharmaceutical companies to meet their internal documentation and deliverables according to the nature and classification of the product.

As an example, our team leads and documents all development activities such as regulatory, human factors and risk management deliverables to guide programme development in the US, EU and any other global markets for commercial teams. It is imperative for Noble to provide services such as regulatory reviews, clinical evaluations, risk management activities (i.e. hazard analyses and failure mode analyses) and product benchmarking studies to its clients with the goal of providing a speed-to-market approach that is advantageous for clients and patients alike.

This, coupled with Noble's strategic intellectual property approach, means an idea can be transformed into reality quickly. Noble grants clients the opportunity to provide hundreds of thousands of medical devices and trainers to their patients to differentiate their brand and ultimately improve the patient injection experience.

Once design freeze occurs within the process, Noble manages all verification and validation testing for clients, leads formative and summative studies for US and global markets and drives design transfer activities for production. Speed-to-market is increasingly important due to the competitive pharmaceutical landscape, and Noble has global manufacturing sites and partners that are involved early in the design phase to expedite the design transfer process.

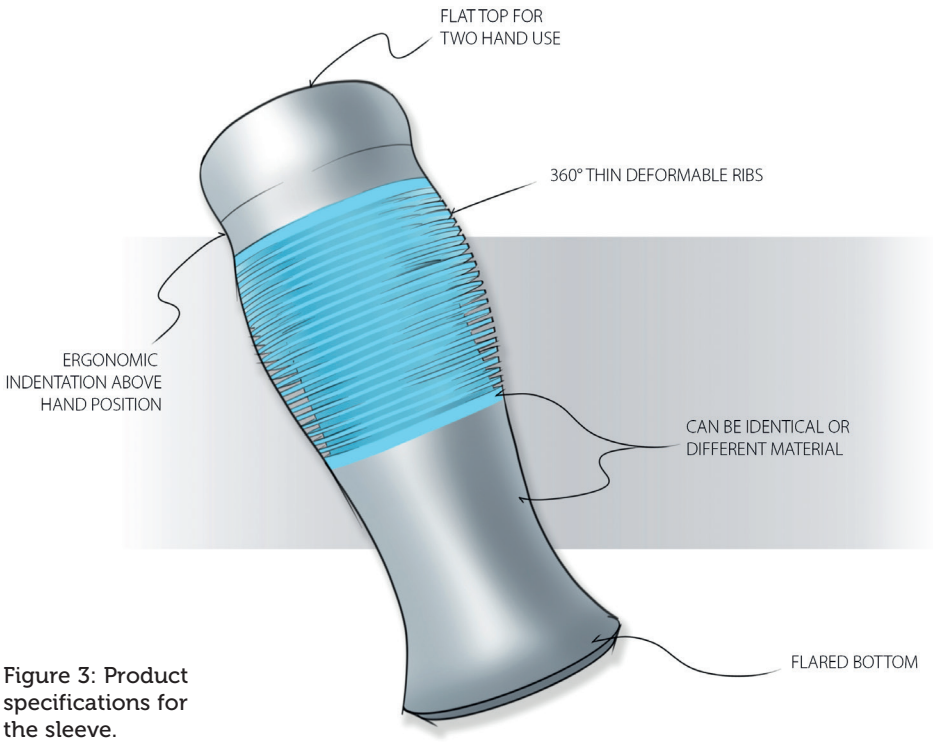

Figure 3: Product specifications for the sleeve.

SUMMARY

Noble manages the entire design transfer process for all trainers and medical devices, providing fully validated processes and finished goods for global markets with manufacturing capabilities to accommodate commercial team pipelines ranging from highly complex electromechanical and connected IoT devices to low- or high-volume mechanical trainers and devices.

Figure 4: A user simulates sleeve utilisation during an injection.

Early concept development through to the later stages of product development and production concludes with shipping impactful products to patients around the world to improve the patient injection experience (Figure 4).

Studying and understanding the patient self-injection process is paramount to Noble's core mission of improving the injection experience and overall patient adherence through training and support materials.

ABOUT THE COMPANY

Founded in 1994, Noble is the global leader in medical device training solutions, patient onboarding strategies and multisensory product development for the world's top pharmaceutical brands and biotechnology companies. Focused on driving innovation, Noble works closely with brand, device and commercialisation teams to develop turnkey solutions that improve onboarding and adherence, bringing value to clients and patients alike.

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ABOUT THE AUTHORS

Josh Hopkins, Engineering Manager, is responsible for design, engineering and development of regulated and non-regulated medical devices. He has over nine years of medical device and pharmaceutical development experience including a focus in product development, risk management, programme management and human factors engineering. Josh has earned a Bachelor of Science in Biological Engineering and a Master of Science in Biomedical Engineering from the University of Florida (FL, US).

Jeff Lettman, Senior Research & Design Engineer, has over 10 years of experience in applied research specialising in mechanism design, mechanical optimisation and finite element analysis. He is responsible for devising proof-of-concept projects to validate the feasibility and manufacturability of new products and features, as well as reducing Noble's intellectual property to practice. During his seven-year tenure in technical operations and applied research at Lockheed Martin, his diverse experience ranged from leading R&D teams to facilitating testing at LM locations across the US as the subject matter expert in thermal and vibration screening. Jeff holds a Bachelor of Science in Mechanical Engineering from University of Florida and a Master of Science in Mechanical Engineering from the Pennsylvania State University (PA, US). He is currently attending University of Central Florida for his PhD in Mechanical Engineering.

BIOLOGIC MEDICINES AND PATIENT-CENTRICITY – A NEW PHASE OF HOPE

In this article, Justin Schroeder, Senior Executive Director, Global Marketing and Design, PCI Pharma Services, discusses how the increasing biologics and biosimilars market has driven innovation and a trend towards self-administration and user-centricity in the injectable drug delivery device market.

INTRODUCTION

The global pharma industry has entered an exciting era of drug development, bringing new hope to patients around the world. Estimates suggest that close to 40% of all medicines in development are biologics. The world's top selling commercial biologic medicines cover a broad range of diseases, including autoimmune challenges such as various forms of arthritis and psoriasis, Crohn's disease, ankylosing spondylitis and ulcerative colitis, as well as other conditions such as multiple sclerosis and macular degeneration.

Biologic medicines have also transformed treatment and personal care for a significant portion of diabetics. Furthermore, biologics have provided breakthrough therapies in the advanced treatment for various forms of cancer, where more than 70 new therapies have entered the market within the past five years, many of which are biologic in nature.

Within the last few years, favourable incentives have also encouraged the use of biologics to treat rare and orphan diseases, bringing much needed hope to a significantly under-served population. The US FDA approved record numbers of new drugs in 2016 and 2017, and kept pace in the first half of 2018. Drugs with special designation, including "orphan" and "breakthrough" among others, have comprised approximately 40% of FDA new drug approvals over this 30-month period.[1] It is noteworthy that approximately 25% of these new drugs are cancer therapies.[1]

It is also worth noting that biologics represent big business potential for drug developers. The top ten biologic therapies have annual global revenues in excess of $71 billion (£55 billion).[2] Biologics represent seven out of the top ten best-selling medicines across all therapeutic categories.[3] There are currently more than 45 biologic medicines on the market that have reached blockbuster status (sales of more than $1 billion annually) and ten biologic medicines yield sales in excess of $5 billion globally. The total biologic market is expected to reach $390 billion by 2020.[4]

> "In fact, even the best and most effective medication would fail to garner FDA approval without a successful comprehensive human factors study showing that the average patient can administer the therapy effectively, easily and repeatably."

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The rise of biosimilars, or generic biologics, represents another attractive growth opportunity for the pharmaceutical industry, and is a perceived win for the patient population as decreased costs through market competition leads to increased access to medicines. Biologic medicines facing patent expiration represent significant biosimilar market opportunity for a multitude of developers. By 2020, biosimilars have the potential to enter the market for brand biologics currently representing more than $45 billion in global sales.[4]

CHANGES IN DRUG DELIVERY BRING NEW FREEDOMS

Biologic medicines require considerably different forms of drug delivery to traditional oral solid dose medications. In the early days, biologics were commonly delivered in traditional glass vials, requiring ancillary components for administration, such as syringes or needles of various gauges, depending on drug and patient tolerance, potentially paired with safety applicators or other devices. These medicines were sometimes self-administered by appropriately trained patients, but more commonly they were administered by healthcare professionals in clinical settings. The implication was that this method of delivery required frequent visits to a healthcare facility by patients to seek treatment, which, for some diseases, could be multiple times per week.

This continues to be the case for many institutionally administered medications. However, the increasingly competitive landscape and the healthcare industry's initiative to become more customer-focused, or "patient-centric", coupled with the payer community's desire to reduce the amount of time patients spend in clinical settings to reduce the cost burden, more focus and resources have been allocated to advancing drug delivery forms that enable easier administration. In some instances, this is driving development of better drug delivery systems in the clinical setting (Figure 1), but increasingly the focus has been to provide safe, reliable and convenient self-administration for patients, with the goal of minimising the impact on their everyday lifestyle and freeing them from the burden of receiving their medication in a formal healthcare setting.

Diabetes care is one area that has seen great benefits from this developing technology, with multi-use, and often refillable, injectable insulin pens spreading beyond developed markets in North America and Europe, and now making rapid progress into developing countries.

Figure 1: Patient receiving medicine.

> "As the market has progressed to consider safety and ease of use in the specific context of patient self-administration, new designs have sought to both aid the injection process and provide safety features to reduce the potential for needlestick injuries and other concerns."

This has generated new paradigms for patients, providing more freedom but also shifting the burden of responsibility for safe and accurate dosing from healthcare professional to patient. This considerably raises the stakes for the pharmaceutical company, which must ensure that the patient is best positioned for success. In fact, even the best and most effective medication would fail to garner FDA approval without a successful comprehensive human factors study, showing that the average patient can administer the therapy effectively, easily and repeatably.

THE IMPACT ON INJECTABLES

The popularity of prefilled syringes has grown considerably over the past few decades, with the current global market estimated to be between three and four billion syringes annually, with projected growth of 8–10%, year-on-year,[5] largely fuelled by the burgeoning Asian market.

The familiarity with and increasing use of injectable devices in diabetes treatment has provided significant economies of scale in the syringe market, as well as a platform for advancing syringe material and delivery technologies. As the market has progressed to consider safety and ease of use in the specific context of patient self-administration, new designs have sought to both aid the injection process

and provide safety features to reduce the potential for needlestick injuries and other concerns. Innovative approaches have been taken to engineering safety solutions, such as sheathing needles with protective covers that are triggered by use, or retracting needles into the housing of the prefilled syringe system. Likewise, patient comfort has been better addressed in advanced delivery systems with refined needle technologies, particularly impactful for large-volume injections.

Such advanced prefilled syringe delivery systems and safety features result in increased complexity in assembly and handling (Figure 2). Precise multi-part integrated assemblies with precision-moulded plastics and spring-based systems demand expert automated solutions, complete with multi-stage in-process inspection to ensure the accuracy of each sequential assembly step. This systematic, sequential approach to assembly provides consistency in mitigating risk and maximising safety, ensuring reliable delivery for every dose. Inaccuracy at any individual assembly point would likely result in a failure of the intended feature. PCI's investments in cutting-edge technologies have focused on robust multi-level inspections to ensure that safety and accuracy are consistently and reliably achieved for these complex assemblies (Figure 3).

PEN INJECTORS AND AUTOINJECTORS

The success of products such as Enbrel® (etanercept, Amgen), Avonex® (interferon beta-1a, Biogen) and Lantus® (insulin glargine, Sanofi) has paved the path for the advancement of autoinjector and pen injector technologies, rapidly progressing this as an important growth category for the biotech market. The sheer scale of the market has made it attractive for investment.

Whereas initial pioneers in the autoinjector and pen injector markets were once forced to create and engineer their own technologies, leading providers have now created portfolios of innovative "off the shelf" proprietary delivery systems built on standardised syringe or cartridge deliveries from sterile manufacturers. These solutions provide uniform volumetric-based platforms, taking into account other critical factors such as product viscosity. Medical advances are pushing the envelope for longer lasting medicines, reducing frequency of injection, but often by requiring larger volumes of liquid-based delivery. This has driven the industry to develop larger-volume injection systems, sometimes pushing wearable injectors as the more optimal solution when autoinjectors may not be conducive to the duration of administration for patients.

Figure 2: Autoinjectors on production line.

The wearable injector for Neulasta® (pegfilgrastim, Amgen) is a great example of how this can transform patient care and truly deliver freedom for patients. Innovative dual chamber technologies also provide for simple reconstitution, combining lyophilised drug with sterile water prior to injection, simplifying preparation and administration of these drug forms – further providing freedoms for patients looking to self-administer and minimise trips to the clinic.

Figure 3: Autoinjector assembly.

INJECTABLE DEVICES AND TERTIARY PACKAGING FOR DELIVERY

The move towards patient-centric solutions and enabling freedom from the clinical setting for administration creates a dynamic where it is crucial that pharmaceutical companies put considerable thought into the packaging in which the device is delivered. Furthermore, the premium nature of the medication warrants careful consideration to ensure successful navigation of the supply chain, as well as providing a user experience consistent with the expectations for a premium product.

Secondary packaging plays a vital role in ensuring the product navigates the complex supply chain safely and securely, and with consideration for end delivery to the patient (Figure 4). Product protection is paramount. Sophisticated drug delivery devices are often designed around combinations of glass, plastic and elastopolymers that are susceptible to breakage if mishandled. Furthermore, the complexity of these advanced drug delivery systems demands appropriate protections from shocks and vibrations that may occur in the distribution system, coupled with (sometimes exacerbated by) the refrigerated or frozen conditions required in a cold chain environment. Protective packaging must be both useful in its intended form, as well as elegant and sophisticated, marrying the advanced device with its other critical components in a cohesive and functional system.

Packaging must also be communicative. Through the process of human factors studies, careful and detailed analysis can identify the essential graphic elements and tools that form the basis for communicating key factors for success – instructions for use, as well as conditions for safe storage or other drug protections, potential side effects, and many others. Given the high value and critical nature of this category of medicines, compliance and adherence is vitally important for successful health outcomes.

> "Communication tools such as Bluetooth or NFC are simply the first stages in the ability of injectable medical devices being able to communicate proactively and reactively, generating valuable new opportunities for interactivity in healthcare."

Figure 4: Injectables kit.

Leading pharmaceutical companies leverage the packaging system as an opportunity to address compliance and adherence by incorporating valuable patient support tools. In addition to well-prepared packaging graphics, it is common to include patient support tools, such as brochures, leaflets and other included media, that provide a platform for patient education, support programme enrolment, prescription discount or reimbursement, or other tools to address common factors for non-adherence.

Given the high value of the drug product, and the inherent attractive nature of biologics for counterfeiters or other bad actors in the supply chain, thorough preparation must also be given to a robust serialisation and anticounterfeiting strategy. Taking a comprehensive approach in both the drug delivery device as well as the secondary packaging in a systems-based architecture provides an opportunity to orchestrate a multi-layered and nuanced strategy to ensure both product safety and authenticity, which is vital in today's global pharmaceutical market. This may require incorporating anticounterfeiting elements in various parts of the delivery, as well as a rotational approach to the use and administration of these tools, and thereby ensure a sophisticated strategy for staying ahead of criminal elements that may look to counterfeit or divert premium drug products.

CONNECTIVITY

Looking towards technologies such as the internet of things (IoT) and artificial intelligence (AI), there is tremendous excitement in the world of connected health. Communication tools such as

Bluetooth or NFC are simply the first stages in the ability of injectable medical devices being able to communicate proactively and reactively – both for data gathering and transmitting patient information, as well as prompting and communicating information to the user – generating valuable new opportunities for interactivity in healthcare. Benefits of such real-time connectivity include the ability to intervene when adherence issues begin to present themselves, as well as to deliver positive reminders and patient support in advance of bad habits being formed. Drug delivery devices can be interconnected with other health monitors, related diagnostic devices, healthcare providers and other touch points in the connected healthcare ecosystem.

CONCLUSION

The pharma industry is underway on an exciting journey, developing highly effective new drugs for long-term health issues such as diabetes, cancer and autoimmune conditions, demonstrating breakthroughs in combating these afflictions and improving quality of life for those who suffer with the daily struggles of their diagnosis. Furthermore, incentives have provided a pathway for the development of treatments for rare and orphan diseases, giving optimism to patients who may have otherwise lacked effective treatment, yet may now have therapy options that they never had before. There is optimism that biosimilars will level the playing field for a broad population of patients seeking impactful and affordable treatments.

Innovative drug-device combinations are making drug delivery increasingly safe and effective. Patients are provided with more control and independence, without being bound by the requirement to visit their healthcare provider constantly for frequent treatment. Such technologies allow them to live more normal and predictable lives and maintain a relationship with their providers without needing to be face-to-face. The advances in biotech medicine have transformed therapy and should provide hope and optimism to us all.

ABOUT THE COMPANY

PCI Pharma Services is an integrated full-service provider and a proven and trusted partner to leading companies in the global healthcare industry. The company offers unparalleled expertise and experience in taking compounds from the earliest stages of development through to successful commercialisation, delivering speed-to-market and commercial success for its customers.

PCI's core services support each stage of the product lifecycle, including drug development, clinical trial supply, commercial launch and ongoing commercial supply. The company partners with clients in providing innovative technologies, flexible solutions and an integrated supply network supporting lifesaving medicines destined for over 100 countries around the world.

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ABOUT THE AUTHOR

Justin Schroeder is Senior Executive Director, Global Marketing & Design at PCI Pharma Services, responsible for new account development, global marketing and creative package design with a focus on the development and commercialisation of unit dose and compliance-prompting packaging. He holds a Bachelor of Science from the School of Packaging at Michigan State University (East Lansing, MI, US), and a Master of Business Administration in Marketing from Northern Illinois University (IL, US). Mr Schroeder has been at PCI/Anderson since 2000, holding positions in Packaging Engineering, Project Management, and Marketing. Previously, he held package engineering positions with Hershey Foods Corp (Derry Township, PA, US) and JM Smucker Company (Orrville, OH, US). Mr Schroeder is also an IoPP Certified Packaging Professional.

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2018 UNIVERSE OF PRE-FILLED SYRINGES AND INJECTION DEVICES

Orlando, FL, US, October 8–9, 2018

By James Arnold, Assistant Editor, ONdrugDelivery Magazine

In October 2018, the Universe of Pre-Filled Syringes and Injection Devices conference, organised by the Parenteral Drug Association (PDA), was held in Orlando, FL, US. Over the course of a week, PDA hosted the two-day conference and exhibition, a combination products workshop and two days of courses. The conference was attended by 865 delegates from over 20 countries.

The conference programme presentations were organised in thematic pairs, followed by a Q&A, with ample breaks between sessions for delegates to attend the exhibition. Throughout many of the sessions there was a strong theme of connectivity and digital technology, reflecting the significant interest they generate in the present discussion of healthcare and drug delivery device design.

Directly following the opening remarks from Committee Co-Chair David Haase (Genentech), the first two talks both placed a strong emphasis on digital healthcare. Kai Worrel (Chief Executive Officer, Worrel Design) presented on how to design with respect to "Healthcare's 3 Masters", patients, payers and providers, followed by Paul Geevarghese (Vice-President, Market Access North America, mySugr) discussing value-based care in light of connectivity and digital health innovations.

"Throughout many of the sessions there was a strong theme of connectivity and digital technology, reflecting the significant interest they generate in the present discussion of healthcare and drug delivery device design."

It was not only the opening talks of the conference that veered towards digital healthcare however. Session A1, entitled "Drug Delivery within the Digital Health Ecosystem: Where do we Stand?" directly addressed the topic with a talk by Kevin Deane (Executive Vice-President, Front-End Innovation, Phillips-Medisize) candidly discussing Phillips-Medisize's experience developing the BETACONNECT™ and his perspective on the effects of connectivity on adherence and, subsequently, revenues. In the concurrent session, there was a presentation by Markus Bauss (Managing Director, SHL Connect) and Egmont Semmler, PhD (Director, Research & Development, Groninger), on smart packaging, with an emphasis on the role of the Internet of Things (IoT) in the future of drug delivery.

As is to be expected, a number of talks focused on regulatory issues, with the last talk pair of the conference dedicated to the new EU MDR. The speakers on the subject were Marc Rohrschneider, PhD (Head of New Technologies, Novartis Pharma), and Girish Kumar, PhD (Product Specialist, TÜV SÜD America). Even in the regulatory area the topic of connectivity raised its head, with a talk given by Chin-Wei Soo, DRSc (Global Regulatory Head, Combination Products and Devices, Genentech), entitled "Challenges and Opportunities with Applying Device Software Regulation in a Drug Setting".

"The mood on the exhibition floor was positive and lively, with the hall well attended across the two days."

Other talks of note included a presentation on patient personality profiling and how it can provide insights into non-adherence by Claire Everitt (Design Engineering, Lead, Pfizer), one on how to test products for emergency use in a stressful environment given by Allison Strochlic (Research Director, Human Factors Research & Design, UL), and another digitally themed talk covering artificial intelligence (AI) and machine learning in pharmaceutical inspection from Massimo Frasson, PhD (General Manager, Brevetti CEA).

The conference was also host to a busy exhibition floor. More than 110 companies exhibited, including major multinational CDMOs and device companies, manufacturing and assembly equipment providers, design consultancies and specialist service providers. The mood on the exhibition floor was positive and lively, with the hall well attended across the two days. Alongside the exhibitors there was a well-stocked poster display, with numerous research groups, including of the exhibiting companies, presenting their work.

ONdrugDelivery was pleased to attend this successful event and we are looking forward to this year's conference. The 2019 Universe of Pre-filled Syringes and Injection Devices will take place on the October 22-23, in Gothenburg, Sweden.

HAZARDOUS DRUG HANDLING AND INVESTIGATIONAL DRUGS: LESSONS TO LEARN

In this article, Marino Kriheli, Co-Founder of Equashield, discusses the need for closed-system transfer devices when handling hazardous drugs, particularly as they relate to investigational drugs, not only as key to patient and healthcare practitioner safety, but also in the context of upcoming US regulation.

Almost every drug contains some level of hazard, some are acute while others carry serious long-term risks. In the US, the National Institute of Occupational Safety and Health (NIOSH), a division of the Centers for Disease Control (CDC) under the Department of Health and Human Services, issued an alert in 2004, providing guidelines on how to identify and handle several specific categories of hazardous drugs (HD). According to NIOSH, a drug can be considered hazardous if it meets one of six health risk criteria:

- Carcinogenicity
- Teratogenicity or other developmental toxicity
- Reproductive toxicity
- Organ toxicity at low doses
- Genotoxicity
- Structure and toxicity profiles of new drugs that mimic existing drugs determined hazardous by the above criteria.

NIOSH maintains and updates its list of HDs every two years. NIOSH's 2016 list of HDs contained some 217 drugs, and NIOSH has proposed adding approximately 22 new drugs to the list in 2018. Although antineoplastic agents make up a large portion of the list, there are non-antineoplastic agents that constitute a significant part of it as well.

Within its listing, NIOSH divides HDs into three categories:

1) Antineoplastic agents with manufacturer's safe handling guidance
2) Non-antineoplastic agents with manufacturer's safe handling guidance
3) Non-antineoplastic agents that have reproductive risk.

> "Recent studies that have utilised NIOSH's original proposed CSTD testing protocols, which assess how well a device contains vapours, have found that devices which are fully contained achieved the best results."

CURRENT GUIDELINES FOR HAZARDOUS DRUG HANDLING

The US Pharmacopeia (USP) recently introduced an updated chapter on hazardous drug handling guidelines – USP Chapter 800. These updated standards around safe handling provide the guidelines by which healthcare facilities must abide when handling HDs.

USP 800, coming into full effect on December 1, 2019, provides several key recommendations around safe handling practice. These include the use of biological safety cabinets and cleanrooms when compounding HDs, the requirement to wear personal protective equipment (PPE) when compounding and administering HDs, a strong recommendation to utilise a closed system transfer device (CSTD) when compounding HDs, and the requirement to use a CSTD when administering HDs.

Why CSTDS?

NIOSH defines a CSTD as "drug transfer device[s] that mechanically prohibit the transfer of environmental contaminants into the system and the escape of hazardous drug or vapour concentrations outside the system". There has been a great deal of conversation around what constitutes a "good" CSTD. However, recent studies that

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"When investigational drugs reach Phase I, in which they are administered to humans for the first time, maintaining sterility from manufacturing through to administration is critical not only for worker safety, but especially for patients."

have utilised NIOSH's original proposed CSTD testing protocols, which assess how well a device contains vapours, have found that devices which are fully contained achieved the best results.[1] Effective CSTDs, those which fully contain hazards, are designed and proven to be able to:

- Prevent aerosol escape
- Prevent leakage
- Prevent microbial ingress
- Not contain acrylonitrile butadiene styrene (ABS) or polycarbonate
- Be used efficiently and backed by clinical data
- Be made with materials that are compatible with hazardous drug/solvents such as dimethylacetamide (DMA).

14 years since NIOSH's original alert, which recommended the use of CSTDs for safe HD handling, and approximately one year before use of CSTDs is mandated in the administration of HDs, it is estimated that approximately 55–60% of US healthcare facilities use a CSTD to handle HDs.

WHAT CAN THE DRUG DEVELOPMENT INDUSTRY LEARN?

Drugs in development, or "investigational" drugs, pose a challenge. The healthcare industry is still uncertain on how to handle new drugs that are in the clinical trial phase. Often, investigational drugs are handled like non-HDs, simply due to lack of data on whether the drug should be considered hazardous. However, as a precaution, investigational drugs that are designed to treat diseases traditionally treated by HDs are considered hazardous by staff in healthcare settings. With this being the case, healthcare institutions should use the same safety measures that they would use when preparing HDs.

However, the challenge is that while healthcare institutions may want to use CSTDs for handling investigational drugs, they are often unsure about the compatibility of the device with the new drug. This issue was also raised in a 2018 Institute for Safe Medication Practices (ISMP) safety alert on investigational drugs, suggesting that "the vials/containers [of investigational drugs] are compatible for use with a closed system transfer device (CSTD) if necessary", and stating that, "if use of a specific CSTD is required, the sponsor should provide it with the drug."

WHAT CAN DRUG DEVELOPERS DO TO ENSURE SAFETY FOR HEALTHCARE WORKERS?

Given the uncertainty in handling new clinical trial-stage drugs, it is vital that drug developers are partnering with reliable, clinically evaluated and proven safety equipment. Only those products that have proven their efficacy to the strictest standards will provide the protection to both healthcare workers and trial participants.

Those working in drug development can ensure they are achieving the highest safety levels for handling investigational drugs by partnering with CSTD-makers who are willing to work closely with the pharmaceutical industry early in the drug development process to understand system feasibility. Furthermore, drug developers should look for a partner willing to develop customised solutions to address their unique needs.

INVESTIGATIONAL DRUGS AND PATIENT SAFETY

When investigational drugs reach Phase I, in which they are administered to humans for the first time, maintaining sterility from manufacturing through to administration is critical not only for worker safety, but especially for patients. Patients utilising investigational drugs, either in trials, or through expanded access for those with severe health conditions that have exhausted other options, are often immuno-compromised. As such, adhering to current good manufacturing practices (cGMP) is key for all personnel involved in trial phase investigational drug handling.

To ensure aseptic drug processing, drugs should be handled under laminar flow hoods, biosafety cabinets or using isolators. Further, having appropriate air flow during compounding can help ensure that the drugs remain sterile and isolated from the environment. Microbial control is also a key component of drug sterility and safety. This is another element for which a clinically-validated CSTD may serve a key role in the future. CSTDs that mechanically prevent the transfer of environmental contaminants into the system can prevent microbial ingress and protect the sterility of the drug. Given the state of patients trialling such drugs, any introduction of an external contaminant could skew results of the drug's efficacy, and potentially harm the patient. As such, all available means of maintaining the drug's sterility should be implemented, from environmental controls to engineering controls, including CSTDs.

"With the uncertainty surrounding the safety of investigational drugs, regulations will only become stricter and healthcare professionals will continue to demand better and proven safety measures. As in the hazardous drug handling industry, the use of CSTDs looks set to become the norm."

THE FUTURE OF SAFE HANDLING FOR INVESTIGATIONAL DRUGS

With the uncertainty surrounding the safety of investigational drugs, regulations will only become stricter and healthcare professionals will continue to demand better and proven safety measures. As in the hazardous drug handling industry, the use of CSTDs looks set to become the norm. This means that now is the time to begin assessing current systems on the market. Just as drug developers must critically assess the safety and efficacy of the medications they are developing, so too should they look to select a closed system that has been rigorously tested and proven effective at minimising the risk of hazardous exposure. Doing so will allow developers to move past compatibility issues early, and find new, customised ways to offer an ideal drug delivery product that is safe for healthcare professionals and patients alike.

ABOUT THE COMPANY

Equashield is a leading provider of manual and automated solutions for the compounding and administration of hazardous drugs. Equashield's product suite includes EQUASHIELD II, its flagship closed system transfer device (CSTD), and EQUASHIELD® Pro, the first ever closed system-enabled automated pharmacy compounding system (APSC). Equashield's CSTD is clinically proven to protect healthcare professionals from hazardous drug exposure. EQUASHIELD II covers more routes of exposure than alternative systems and has passed the proposed 2015 alcohol vapour containment protocol from NIOSH, confirming that it can contain the harshest vapours and emissions. Studies have demonstrated that Equashield's CSTD is faster to deploy and easier to use than competing systems. Used by hundreds of hospitals and clinics around the world, EQUASHIELD II is CE marked and substantiated by the US FDA for preventing microbial ingress for up to seven days.

ABOUT THE AUTHOR

Marino Kriheli, Co-Founder of Equashield, has over twenty years' experience in industry project management, in both the industrial engineering and medical device manufacturing spaces. In 2010, he co-founded Equashield, a leading provider of a full range of manual and automated solutions for the compounding and administration of hazardous drugs. Prior to founding Equashield, he co-founded medical device manufacturer Plastmed, an original equipment manufacturer for Johnson & Johnson.

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SAGAR BEJALWAR, BD MEDICAL - PHARMACEUTICAL SYSTEMS

Sagar Bejalwar is a Global Marketing Manager at BD Medical – Pharmaceutical Systems, where his responsibilities include developing prefillable syringe solutions that most closely address drug, product manufacturer and clinician needs. Mr Bejalwar holds an MBA from Texas Christian University (Fort Worth, TX, US) and also a Bachelor's degree in Electrical Engineering from the National Institute of Technology, India.

Over the past three decades, BD has worked collaboratively with drug and product manufacturers to put solutions in place, avoid disruption to manufacturing and to ensure regulatory readiness. This approach has been highly successful and has earned BD a reputation for developing innovative technologies, which helps companies achieve ambitious time-to-market goals. BD's long collaboration with biopharmaceutical companies has allowed it to anticipate emerging needs, improve components and find solutions to complex delivery requirements.

In this interview, Mr Bejalwar discusses the product and clinician needs in delivering hyaluronic acid (HA) for cosmetic applications. He describes the problems that may arise when existing syringes are used to deliver HA, the substantial unmet needs, and what an optimal solution looks like.

Q Please could you give a brief overview of HA, what it is used for, and how and by whom it is typically administered?

A Hyaluronic acid is a naturally occurring substance in the body which is usually indicated to be used in dermo-cosmetics, intra-articular (IA), intra-ocular and vesico-ureteral reflux. HA in general is non-active and is not expected to have pharmacological and toxicological effects.

The viscosity of HA dermal fillers in cosmetic applications is found to be high. We are also observing that the viscosity of HA is increasing on an ongoing basis. Low reticulation dermal fillers may be used for hydration of skin and ageing prevention whereas a high reticulation may be used for dermal filling applications. Moreover, HA in cosmetic applications can have an effect in a week and may last for six to 12 months.

HA dermal fillers are usually administered by a dermatologist or a nurse depending on the country. It is normally delivered through a needle of around 27–30 G. Dermal fillers, being very viscous and having a gel type formulation, can exert a substantial pressure on the syringe tip and needle during administration. This pressure may challenge the connection of the syringe and needle leading to issues such as the needle popping off or leakage of HA.

There are different techniques for administering HA. For cosmetic applications HA may be delivered intradermally (ID) or through a subcutaneous (SC) route when the face or chin is to be restored and with a low angle of injection. The low angle of injection and high viscosity of HA makes administration of the product even more challenging.

Q What problems do users encounter when delivering HA dermal fillers with current devices?

A Current HA dermal filler products delivered through a syringe and needle may not be optimised to withstand the pressure that a viscous formulation such as HA exerts. One of the main problems that arises is rotation or disconnection of the Luer lock adapter (LLA). Rotation or disconnection of the LLA may lead to an insecure connection and may cause the needle to disassemble from the syringe. Rotating LLA and needle ejection can effectively lead to leakage of the HA product during administration.

45% of dermatologists have experienced leakage with HA syringes according to a recent international survey. The survey was conducted in February 2018 through a voice-of-customer (VoC) research survey of 87 dermatologists in the US, EU and Asia and was carried out by The MarkeTech Group (Davis, CA, US). Reducing the risk of this leakage thus represented a major unmet need. Ideally, we do not want leakages or spills in a clinical environment as this can expose a patient directly to HA and also cause disruption in the clinical work-flow. Leakages and spills may also portray an unprofessional image in a clinical setting adding to the patient's anxiety. In order to address the mentioned issues, it is necessary to ensure that the connection of the syringe with the needle is sufficiently robust and provides a secure delivery mechanism to the patient. A safely connected syringe and needle combination may enable the HA product to be injected optimally providing a safe and satisfactory experience to the patient.

> "45% of dermatologists have experienced leakage with HA syringes according to a recent international survey."

There is an increasing demand for more robust syringe delivery systems that can withstand the pressure the viscosity of HA exerts during administration.

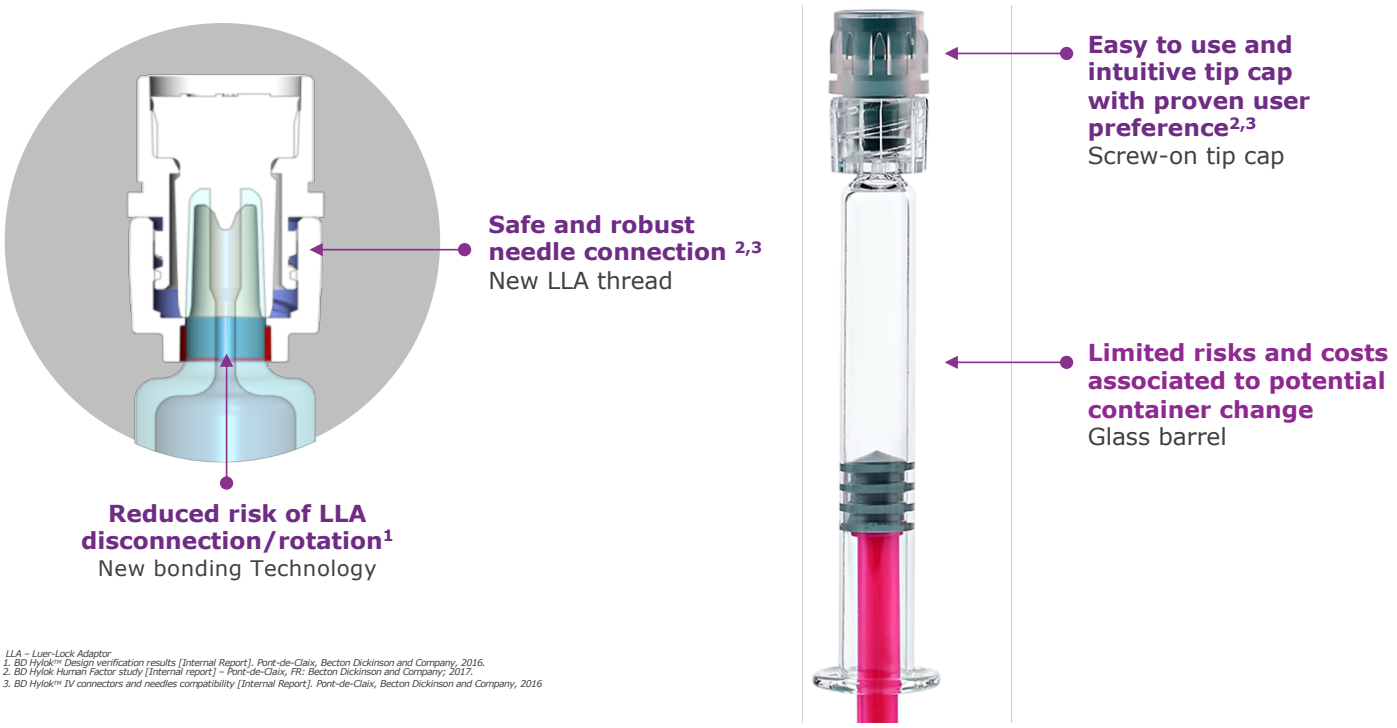

Figure 1: The BD Hylok™ syringe design.

Q Still focused specifically on the delivery of HA dermal fillers in cosmetic applications, what are the most important requirements HA product manufacturers have of prefillable syringes?

"Issues of leakage due to needle disconnection and LLA rotation are considered top priorities for HA manufacturers."

A Issues of leakage due to needle disconnection and LLA rotation are considered top priorities for HA manufacturers. This finding is based on VoC research conducted by The MarkeTech Group in November 2017 wherein 36 respondents including managers in manufacturing, quality, R&D, procurement, marketing and sales, and general management across the EU and Asia were interviewed.

We have come to realise that HA product manufacturers are primarily interested in sourcing a syringe that meets their filling and manufacturing requirements, and also addresses end-users' administration needs. Additionally, inertness of the syringe when storing and delivering HA has been found to be a need with HA manufacturers. In fact, 72% of decision makers in the HA industry expressed in an international study, a preference for glass over plastic. They favoured the material's inertness and resistance to steam sterilisation. The international study was based on the previously referenced survey conducted in November 2017.

Smooth and predictable gliding that is provided through a glass syringe is an attribute that is desired with the HA product manufacturers and end-users. Additionally, glass syringes are supplied by multiple suppliers with a large variety of configurations, enabling manufacturers to manage business-continuity risks. Glass may also appear aesthetically appealing when used in dermo-cosmetic applications.

Another requirement we have identified for HA manufacturers is syringe barrel resistance to steam sterilisation after the syringe is filled with the HA formulation. Steam sterilisation can be considered a standard by many when filling in HA or other compounds into the syringe. Therefore, it is critical to have evidence showing resistance of the syringe to steam sterilisation.

Q Can you tell us whether BD has a solution to address needs in HA dermal filler administration with respect to HA manufacturer and end-user requirements?

A Yes, we do have an optimal syringe delivery solution for HA delivery. The solution, BD Hylok™ syringe, has been commercially available since December 2018 and is currently available in a 1 mL format; the most commonly used format for HA delivery in dermo-cosmetic applications.

The BD Hylok™ syringe (see Figure 1) is a glass, prefillable syringe specifically designed to provide a robust needle connection through a patented, strongly affixed LLA during HA delivery. The LLA of BD Hylok™ is affixed using new bonding technology effectively reducing the risk of LLA rotation and disconnection during use. The syringe is designed with a New LLA thread that enables a safe and robust needle connection. Additionally, BD Hylok's intuitive screw-on tip-cap, is preferred by users over a standard clip-on tip cap as evidenced by a human factors study carried out internally by BD in 2017.

BD Hylok™ is resistant to steam sterilisation, is supplied with a technical data package to support HA manufacturer development and registration and is expected to be compatible with existing HA filling and packaging lines.

From a solution development perspective, we have been iterating BD Hylok™ over the past few years through end-user and HA manufacturer feedback and also through internal testing and validation studies. Solution developmental efforts have also been backed by qualitative and quantitative market research.

Q What performance validation has been conducted with BD Hylok™ for HA dermal filler delivery?

A BD Medical – Pharmaceutical Systems conducted a simulated-use human factors study to evaluate the usability of BD Hylok™ syringes among several routes of administration for injectable medications and products. This study aimed to assess that the connectivity of BD Hylok™ syringes is safe and effective when used by nurses and dermatologists injecting viscous product such as HA through the ID, SC and IA routes. The study also aimed to validate participant understanding of the BD Hylok™ product usage instructions in elation to optimally and securely screwing the needle on to the LLA of the syringe. The user population in this study entailed 15 nurses with experience using IV needles and IV catheters and 15 dermatologists with experience injecting patients with HA fillers for cosmetic purposes. The study design consisted of two phases, learning and validation and market peer comparison. The validation study results demonstrated that BD Hylok™ is safe and effective when used by trained intended users – nurses and dermatologists – and the intended uses, with viscous product such as HA as well as non-viscous products.

Based on performance of the BD Hylok™ syringe during the initial validation phase, no patterns of error for nurses and dermatologists during needle connectivity were observed. In the validation phase, a 100% success rate was recorded. In fact, BD Hylok™ syringe showed significantly lower failure rates compared to a market peer. LLA rotation was found to be the main cause of the significant difference between BD Hylok™ and the market peer.

In summary, in 859 injections that were performed by nurses and dermatologists in the human factors studies, no LLA rotation or disconnection was observed. And in 105 injections performed by nurses and dermatologists, no needle disconnection occurred when the needle was screwed in tightly.

Q How does BD Hylok™ perform relative to market peers after being subjected to different sterilisation modes?

A BD Hylok™ withstands both ethylene oxide (EtO) and steam sterilisation. Pull-out force – the force required to pull out the LLA – and rotational torque performance were tested after two EtO and two steam sterilisation cycles at 121°C, for 20 min. Market peers' performances were compared after one EtO and two steam sterilisation cycles at 121°C for 20 min. After EtO sterilisation, conditions were simulated in an environment where the glass syringe is prefilled with HA and the LLA subjected to forces/torque. After steam sterilisation, the resistance of pull-out force and rotational torque were calculated by subjecting the adapter to forces similar to those which it would be subjected to by end-users when screwing on the needle.

> "In 859 injections that were performed by nurses and dermatologists in the human factors studies, no LLA rotation or disconnection was observed."

Peer and competitor benchmarking showed that the BD Hylok™ LLA on average resists a pull-out force three-times higher than that of its peers (Figure 2). The rotational torque that BD Hylok™ can withstand is almost five times higher than that of its peers (Figure 3).

This robust LLA provides confidence to dermatologists and nurses to strongly screw on the needle without worrying about it disconnecting or rotating, or about consequent filler leakage and spillage concerns.

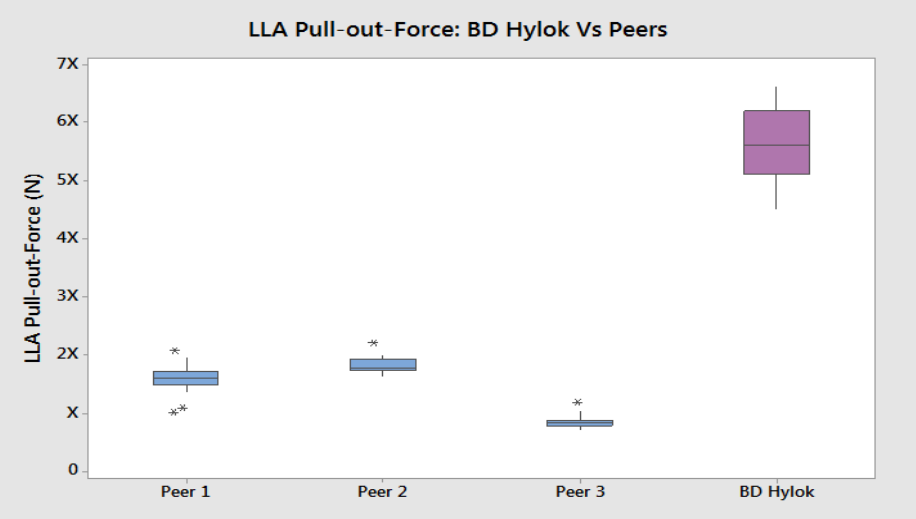

Figure 2: On average BD Hylok™ LLA resists pull-out forces three-times higher than that of its peers (BD Hylok™ and BD Hylok™ competitor syringes performance evaluation [internal reports] – Pont-de-Claix, FR: Becton Dickinson and Company; 2018).

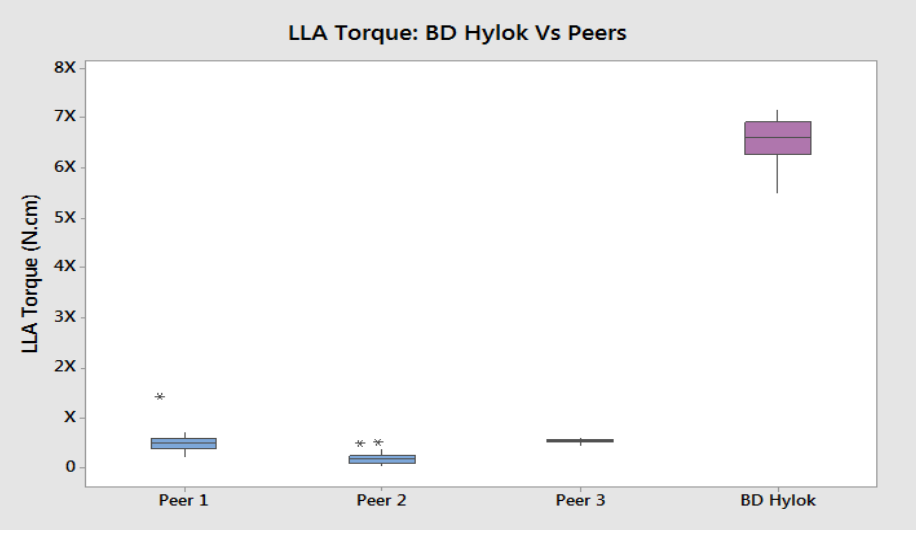

Figure 3: On average, the BD Hylok™ LLA resists rotational torque five times higher than that of its peers (BD Hylok™ and BD Hylok™ competitor syringes performance evaluation [internal reports] - Pont-de-Claix, FR: Becton Dickinson and Company; 2018).

Medical Support

- Non clinical and clinical data
- Human Factor Engineering (HFE) testing data

Regulatory Support

- Worldwide registration service
- Timely and accurate Regulatory Affairs package
- Consultative / training services
- Life cycle management strategy

Formulation and Analytics

- Extractable / leachable data set
- Analytical services

Distribution and Sales

- Logistics services deliveries
- Certificate of Analysis

Container / Device Selection and Customisation

- Early sample deliveries through BD Accelerate Program
- Compatibility with drug from mechanical and chemical standpoint
- Co-development partnering for customisation and rapid prototyping
- Functional test services
- Sample filling (Not For Human Use)

Filling, Assembly, Labeling and Packaging

- Technical support (machine and fill-finish)

Figure 4: BD's range of services complementing its product offering.

"BD's partners know that we have an extensive offering around regulatory, technical services and medical affairs, so they know that they will be provided with relevant data supporting the successful development and commercialisation of their products in BD Hylok™ syringes."

Q Thinking about the commercial development, what is the current status in terms of regulatory and technical data relative to BD Hylok™?

A As part of the offering to HA manufacturers, in addition to the BD Hylok™ product itself, we provide a robust, extensive data package to support development and registration.

The package includes but is not limited to: quality statements, human factors user studies summary, product usage instructions, performance assessment; and regulatory support to enable a smooth transition to BD Hylok™ from an existing syringe or enables adoption in case a new HA product is being launched.

BD's partners know that we have an extensive offering around regulatory, technical services and medical affairs (Figure 4). We are well positioned to provide our HA partners with relevant data supporting the successful development and commercialisation of their products in BD Hylok™ syringes, be that for initial container/device strategy or for lifecycle management.

BD

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THE DIFFERENCE OF ONE DRUG DELIVERED

SECURE IN YOUR HANDS, SAFE FOR YOUR PATIENTS*[1,2] At BD, we're dedicated to improving the delivery of injectable drugs, one patient at a time. That's why we developed the innovative **BD Hylok™** glass prefillable syringe for hyaluronic acid. The BD Hylok™ glass prefillable syringe addresses end users' and manufacturers' concerns caused by the high viscosity of hyaluronic acid, such as needle disconnection and luer-lock adapter rotation. With its strongly affixed, patented BD Luer-Lok adapter for safe and robust needle connection,[1,2,4] the BD Hylok™ glass prefillable syringe delivers superior performance[5] for end users. Discover the difference of advanced technology. **Discover the new BD.**

*No needle disconnection, no BD Luer-Lok™ Adapter rotation or disconnection[1-3]

1 BD Hylok™ Design verification results [internal report]. Pont-de-Claix, France: Becton Dickinson and Company; 2016. **2** BD Hylok Human factor study [internal report]. Pont-de-Claix, France: Becton Dickinson and Company; 2017. **3** BD Hylok™ IV connectors and needles compatibility [internal report]. Pont-de-Claix, France: Becton Dickinson and Company; 2016. **4** Hallynck, Wools, Maritan, Devouassoux. 2016. Adaptor for a needleless device and method for connecting said device thereon. U.S. 2016/0158518 filed July 22, 2014, and issued June 9, 2016. **5** BD Hylok™ and BD Hylok™ competitor syringes performance evaluation [internal reports]. Pont-de-Claix, France: Becton Dickinson and Company; 2018.

Learn more at **bd.com/InnovativeSyringe**

BD

ZAHORANSKY
PERFECTLY DIFFERENT

FROM GRANULATE TO PACKAGED PRODUCT

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

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

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

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

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

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

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

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

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

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

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

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

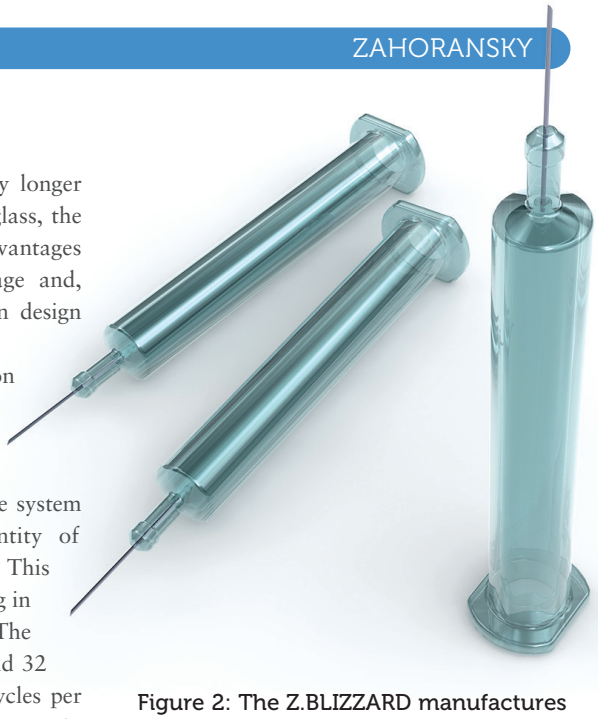


Figure 2: The Z.BLIZZARD manufactures PFS from plastics that have several advantages over their glass variants, such as the fact that the needle is over-moulded and not melted down.

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

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

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

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

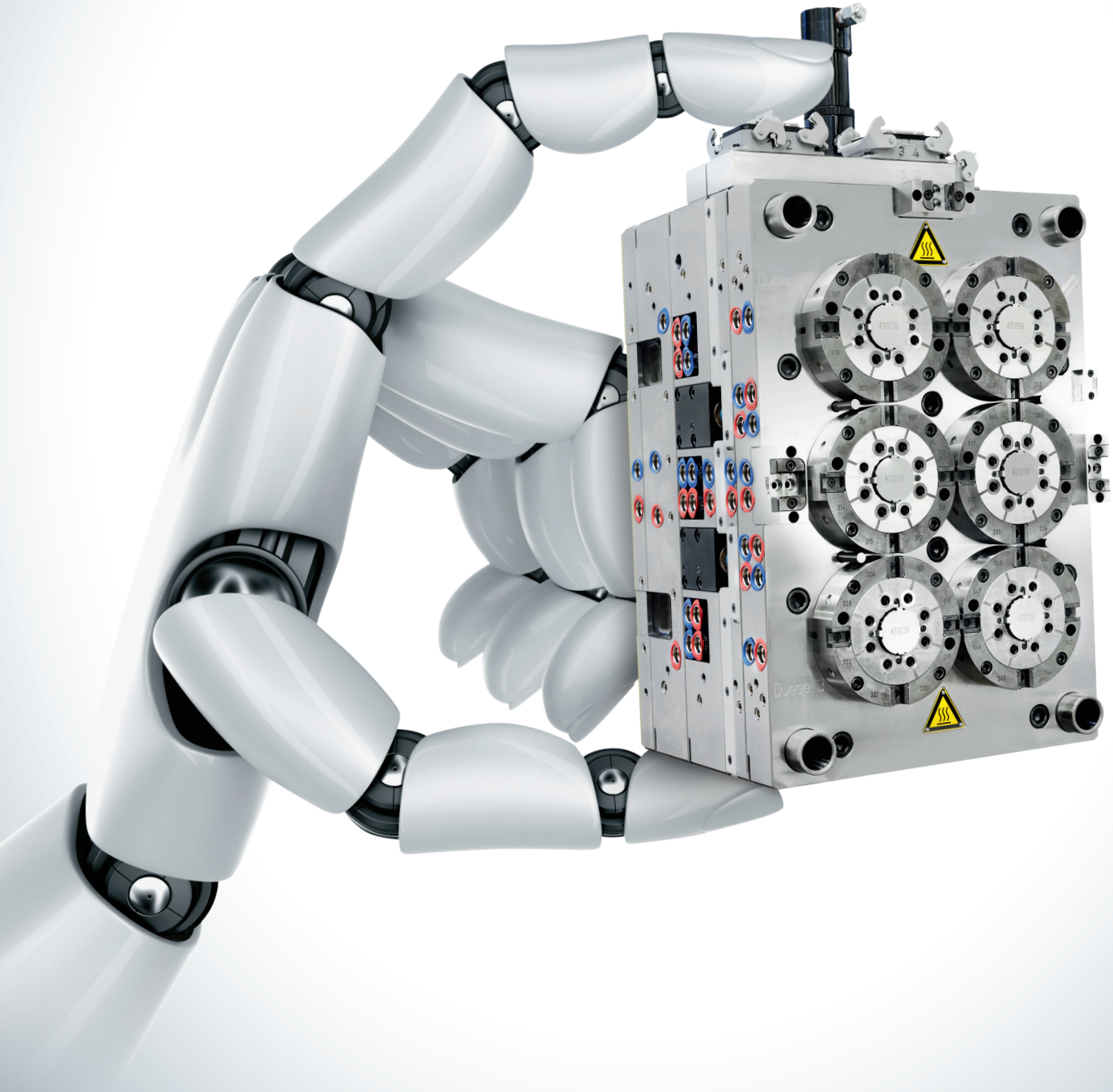
Schopferer. "We play an important role in ensuring that our customers' products meet the high-quality specifications that are required and demanded in medical technology." If the Z.MISTRAL (Figure 4), which is responsible for the downstream, and the Z.LODOS palletising system are also connected, it is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

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

ABOUT THE COMPANY

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

The One-Stop Solution Provider
for Automation & Molds



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