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DELIVERING INJECTABLES:
DEVICES & FORMULATIONS

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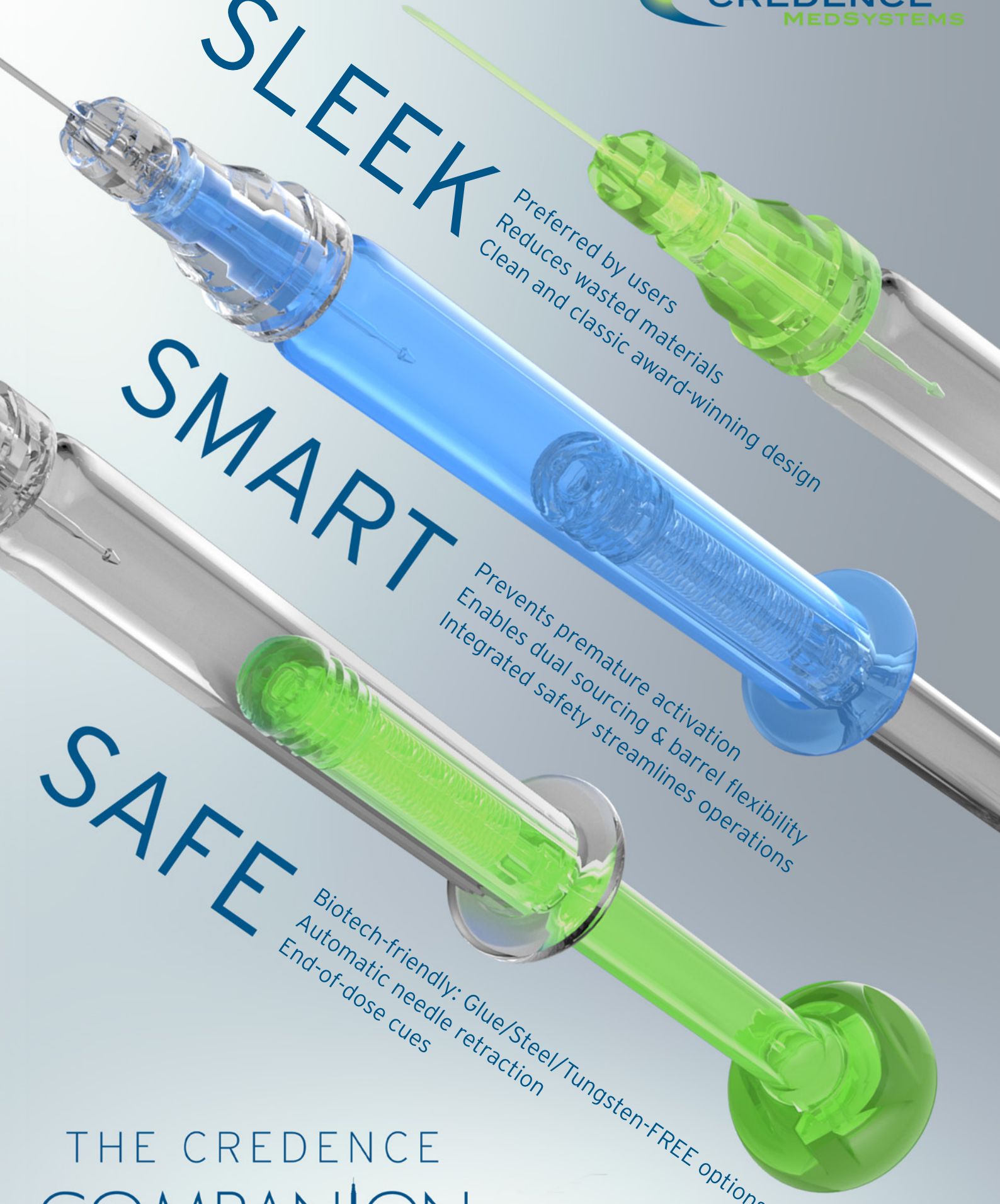

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ONdrugDelivery Issue N° 147, May 22nd, 2023

DELIVERING INJECTABLES: DEVICES & FORMULATIONS

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May/Jun	Novel Oral Delivery Systems

EDITORIAL:
Guy Furness, Proprietor & Publisher
E: guy.furness@ondrugdelivery.com

CREATIVE DESIGN:
Simon Smith, Creative Director (Freelance)
E: simon.smith@ondrugdelivery.com

SUBSCRIPTIONS:
Audrey Furness (subscriptions@ondrugdelivery.com)
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ADVERTISING:
Guy Furness (guy.furness@ondrugdelivery.com)

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COLD STORAGE AND CONTAINER CLOSURE INTEGRITY – DEMONSTRATED PERFORMANCE OF ETFE-COATED COMPONENTS

In this article, Sebastien Cordier, Technical Product Manager, PremiumCoat®; Benjamin Brocco, PhD, Marketing Manager; Estelle Verger, Business Development Senior Manager, PremiumCoat®; and Arnaud Clausse, R&D Director, all at Aptar Pharma, discuss the results of a series of tests to demonstrate that PremiumCoat® can maintain closure integrity down to -80°C.

It is no surprise that injectable biologics are becoming more prevalent on the market;[1] their effectiveness for treating complex diseases, such as cancers or autoimmune disorders, accurate administration and minimised side effects compared with traditional small molecules make them ideal to address unmet medical needs and improve patient outcomes. Advances in biotech techniques are attracting investment from the pharmaceutical industry, resulting in a wider range of options being brought to the market.

Due to their complex molecular structures and the biotech processes required to produce them, biologics are more likely to be sensitive and require extra protection from the earliest manufacturing steps all the way through to administration. To maintain the potency and safety of these drugs throughout their lifecycle, developers must ensure that their formulations are compatible with the primary packaging and drug delivery device. These validation steps remain challenging, and drug container compatibility can become an obstacle to achieving rapid time to market. The primary packaging industry has been supporting progress in this regard and has developed an array of solutions, such as laminated rubbers and advanced washing processes, that help promote drug/container compatibility.

> "Biologics are more likely to be sensitive and require extra protection from the earliest manufacturing steps all the way through to administration."

In addition to using new primary packaging technologies, drug manufacturers have investigated the importance of storage conditions for maintaining the stability of sensitive molecules. Deep-cold storage has been identified as a key strategy and proved to be pivotal during the covid-19 pandemic, with critical mRNA vaccines requiring storage at -80°C. Although the benefits of deep-cold storage for supporting long-term drug stability are undeniable, such extreme storage conditions are challenging for the primary packaging and container closure integrity (CCI).

Glass, which is the most common material used for primary containers, can be submitted to deep-cold storage without significant dimensional changes. On the other hand, rubber, which is the material of choice for closure, is sensitive to cold.

Sebastien Cordier
Technical Product Manager, PremiumCoat®
T: +33 6 3170 5278
E: sebastien.cordier@aptar.com

Dr Benjamin Brocco
Marketing Manager
T: +33 6 7404 8924
E: benjamin.brocco@aptar.com

Estelle Verger
Business Development Senior Manager, PremiumCoat®
T: +33 6 4263 1821
E: estelle.verger@aptar.com

Arnaud Clausse
R&D Director
T: +33 6 3889 0917
E: arnaud.clausse@aptar.com

Aptar Pharma
22 Avenue Des Nations
95944 Villepinte
France

www.aptar.com/pharmaceutical

"For most drugs that require deep-cold storage conditions to ensure their long-term stability, PremiumCoat® stoppers must be able to maintain CCI down to -80°C."

For standard halobutyl formulations, the glass transition temperature (at which the rubber goes from a viscoelastic state to a glass-like state[2]) is between -60°C and -80°C for Aptar Pharma's rubbers. Beyond the glass transition temperature, the rubber properties evolve, causing components to shrink and become hard and brittle.

One of the key functions of the rubber closure component is to maintain a seal with the glass – a function that is allowed by the viscoelastic properties of the material. The disruption of these viscoelastic properties may pose a risk to the CCI. Therefore, pharma companies, glass manufacturers and closure component makers must work together to ensure that the packaging parameters, such as the residual seal force (RSF), are under control and that CCI is maintained, even below the glass transition temperature of rubber.

PremiumCoat® film-coated solutions combine a market-proven ethylene tetrafluoroethylene (ETFE) film with Aptar Pharma's proprietary bromobutyl formulation. The chemical performance of these solutions has been extensively demonstrated and the ETFE film has been shown to reduce the quantity of extractables and leachables that may be transferred into the drug product significantly. For most drugs that require deep-cold storage conditions to ensure their long-term stability, PremiumCoat® stoppers must be able to maintain CCI down to -80°C.

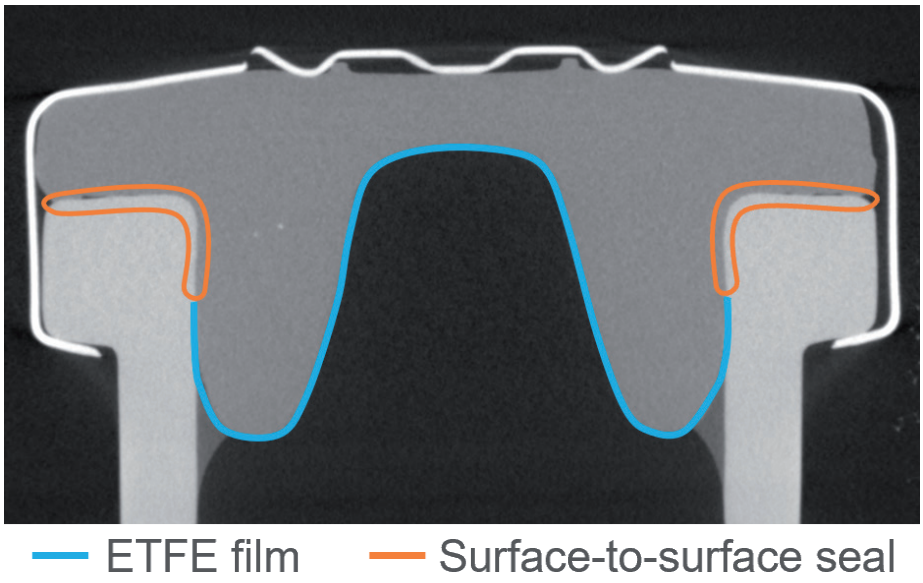

Figure 1: X-ray tomography of a PremiumCoat® stopper inserted onto a 6R ISO NBB vial. The ETFE film coating is represented in blue and does not interfere with the valve, transition or land seal area, as defined by the Parenteral Drug Association.[3]

Aptar Pharma has extensively characterised the Bromobutyl formulation used for PremiumCoat®, in which the glass transition temperature was evaluated to be at -77°C. To confirm that PremiumCoat® can maintain closure integrity and that the precisely positioned ETFE film does not interfere with CCI (Figure 1), Aptar Pharma performed a series of tests, leveraging its knowledge of rubber products, technical know-how and state-of-the-art analysis methods.

"Aptar Pharma performed a series of tests, leveraging its knowledge of rubber products, technical know-how and state-of-the-art analysis methods."

METHODS

Stopper RSF and compression: 6R ISO European blowback (EBB) and non-blowback (NBB) vials were crimped using laboratory automatic crimping equipment. Three levels of crimping force were tested and referred to as low (worst-case scenario), medium and high. The RSF was measured using dedicated measurement equipment that applies force on the crimped vial to find the force at which the stopper starts to further compress (Figure 2A). The compression of the stopper was also measured directly using X-ray tomography (Figure 2B). This analysis enabled an evaluation of the force that keeps the stopper secured on the vial's neck.

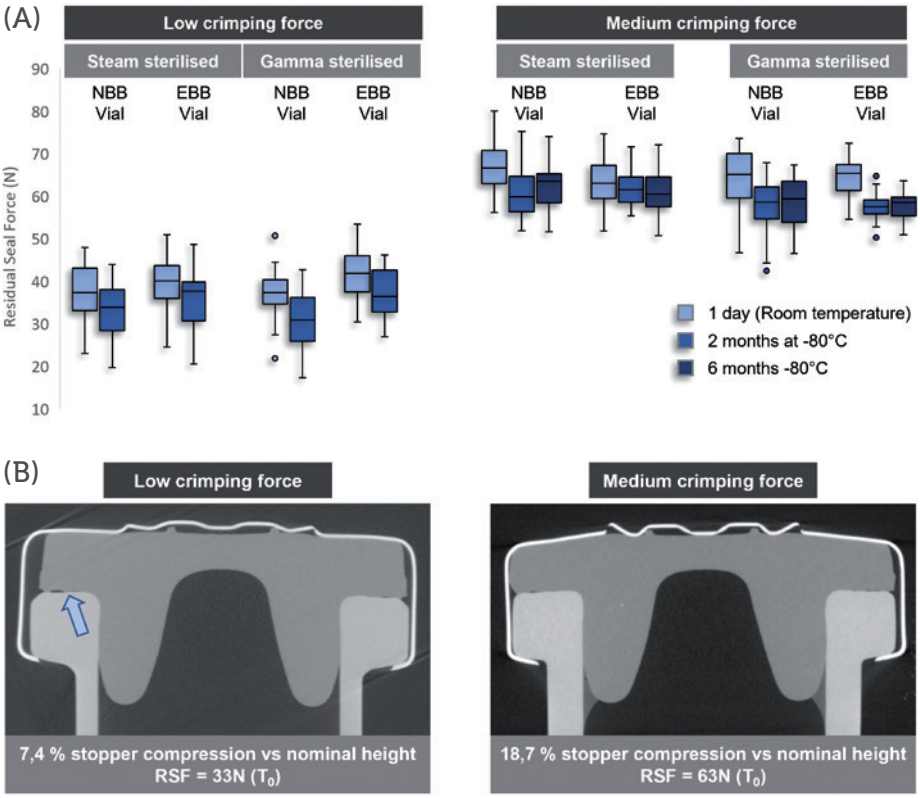

Figure 2: Comparison of the effect of low and medium crimping forces on stopper compression and RSF. A) RSF measurements were performed on 6R ISO NBB and EBB vials, using steam and gamma-sterilised stoppers, after one day at room temperature, and after two months and six months at -80°C. Two crimping forces were tested, the low crimping force representing a worst-case scenario. B) X-ray tomography performed after crimping at low (33N) and medium (61N) RSF. The compression of the stopper was calculated as a ratio of the uncompressed stopper thickness and compressed stopper thickness.

Laser headspace analysis: 6R ISO EBB and NBB vials were stoppered under vacuum (85 torr) and then crimped before being stored at -80°C (Figure 3). If, during cold storage, the stopper shrinks to the point where it does not maintain CCI, air gets inside the vial and equilibrates with the freezer's pressure. When placed back at room temperature, the stopper thaws, resealing the system and trapping the air inside. As temperature rises, the pressure inside the vial increases. Therefore, a significant increase of pressure inside the vial indicates CCI defects at –80°C.

Helium leak: The vials were pierced and connected to a helium inflow. An aspiration system was connected around the stopper. The helium flow was quantified by mass spectrometry on the stopper's side. The baseline detection of helium was measured and the helium flow measured again when the helium supply was turned on. For each vial/stopper system, the experiment was done at room temperature, -80°C and again at room temperature. For the simplicity of representation, only the data at -80°C are represented in Figure 4. A sharp increase in the helium flow at -80°C is indicative of a CCI defect.

RESULTS

Higher Crimping Forces Lead to Higher Stopper Compressions and RSF

The industrial protocol used to package drugs is of prime importance for ensuring that the drug remains protected throughout packaging, storage and delivery. The crimping force is a critical parameter that ensures that the stopper and vial's neck maintain close contact, ensuring that a proper seal is formed (Figure 1).

In the conditions of this test, Aptar Pharma observed in that storage at -80°C only had a mild reducing effect on the measured RSF, whether at low or medium crimping force (Figure 2A). In both cases, for the two vial necks tested and sterilisation methods used, the RSF remained consistent throughout the storage period, indicating that cold storage does not have a lasting negative impact on the elastic properties of the rubber.

Figure 2B further exemplifies the importance of putting the crimping force under control, as low crimping force may lead to incomplete contact between the stopper and the glass (see arrow), and potentially lead to a faulty CCI.

These data demonstrate that storage at -80°C does not significantly affect the RSF of crimped PremiumCoat® stoppers and that, when crimped at medium force, PremiumCoat® establishes full contact with the vial's neck, indicating that PremiumCoat® would maintain CCI under deep-cold storage conditions.

Premiumcoat® Stoppers Maintain CCI Down to -80°C When Crimped According to Medium Parameters

To evaluate whether PremiumCoat® can maintain CCI down to -80°C, two complementary methods were used. The laser headspace analysis measured differences of headspace pressures before and after storage at -80°C, with a significant increase of inside pressure indicating a loss of CCI. Although this method is non-invasive and does not require any modification of the vial, it does not allow the measurement of headspace pressure in real time during -80°C storage. This method is therefore completed by helium leak analyses, which requires the alteration of the glass vial for connecting the glass supply, but allows measurement to be performed continuously, even at -80°C. The combination of these two complementary methods can therefore give a complete picture of whether CCI was compromised during -80°C storage.

> "Storage at -80°C does not significantly affect the RSF of crimped PremiumCoat® stoppers and, when crimped at medium force, PremiumCoat® establishes full contact with the vial's neck, indicating that PremiumCoat® would maintain CCI under deep-cold storage conditions."

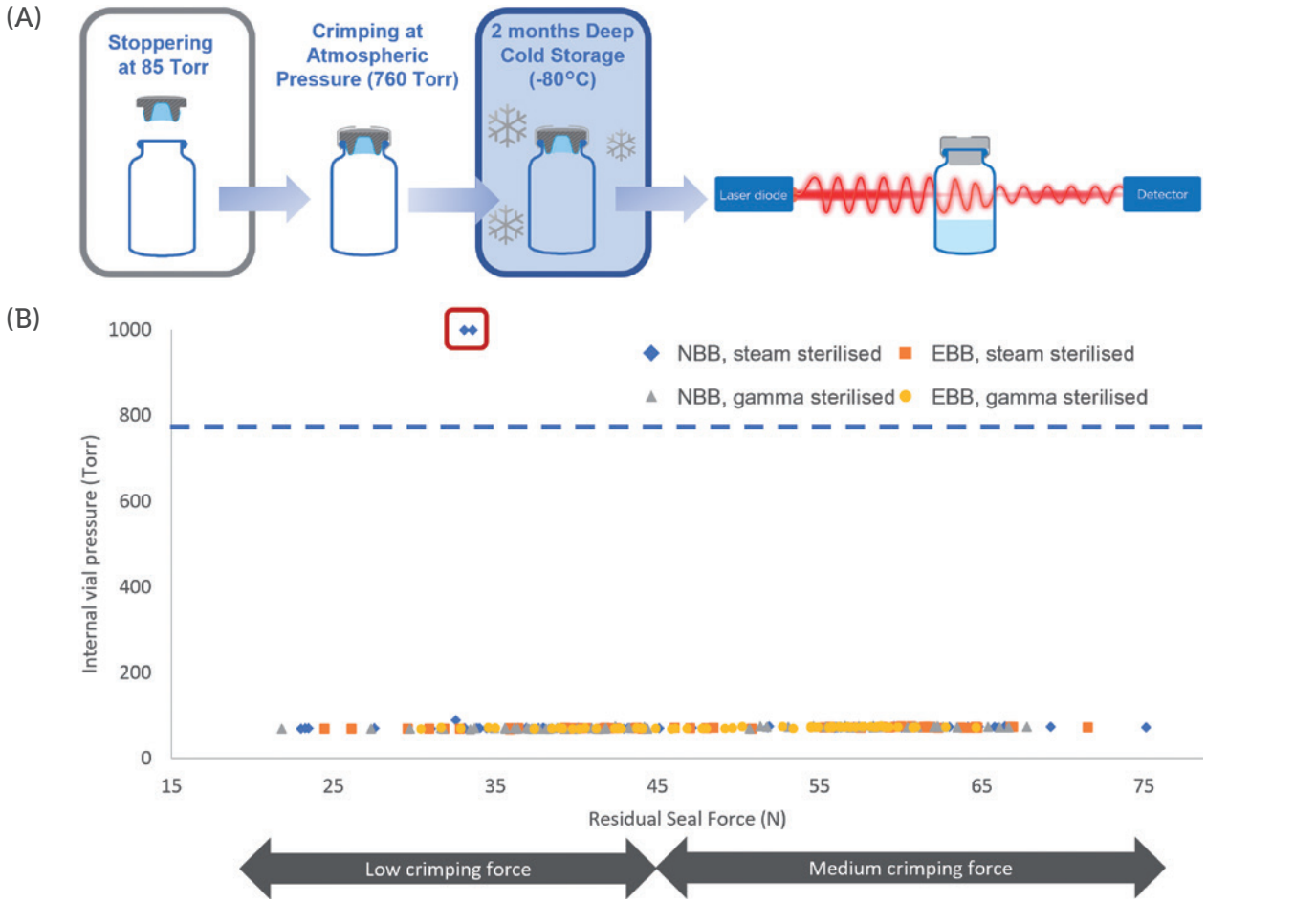

Figure 3: Laser headspace analysis. A) Representation of the laser headspace analysis experimental set-up. B) The experiment was performed using 6R ISO EBB and NBB vials. The internal pressure of the vials was measured using laser headspace analysis and the results were plotted against the measured RSF for each vial. NBB and EBB vials were tested with PremiumCoat® stoppers that had been steam or gamma sterilised. RSFs below 45N were obtained using low crimping forces and RSFs above 45N were obtained after crimping at medium force. The red box represents the two data points that are indicative of a faulty CCI.

Laser Headspace Results

Using laser headspace analysis, it was determined whether PremiumCoat® was capable of maintaining CCI down to -80°C, according to the protocol shown in Figure 3A. The data in Figure 3B indicate that only two vial/stopper couples out of 120 could not maintain CCI at -80°C. It is important to note that both CCI failures happened for vials displaying a RSF of about 30 N, which is obtained when using the lowest crimping force and is therefore a worst-case scenario. In all other cases, PremiumCoat® was able to maintain CCI.

These data indicate that, when applying the appropriate crimping force (medium), PremiumCoat® stoppers can maintain CCI down to -80°C and therefore protect the drug's integrity during deep-cold storage.

Helium Leak Results

To further confirm these results, complementary helium leak tests were performed at -80°C and the results are presented in Figure 4. As described previously, each vial/stopper system was sequentially submitted to the helium leak test at room temperature, -80°C and then again at room temperature. This protocol enabled the identification of potential leaks at room temperature or -80°C, and the last measurement ensured that, after having been submitted to -80°C, the stopper retained its visco-elastic properties for maintaining CCI after thawing.

For all the vial/stopper systems crimped at low, medium or high force, and for stoppers that were steam or gamma sterilised, no leak was observed at room temperature (data not shown). For steam-sterilised stoppers crimped at low force, a significant leak was observed at -80°C for Sample 4, where the detected helium flow increased by a factor of 1,000, with a final value of $1.5x10^2$ mbar.L/s. For all steam-sterilised stoppers crimped at medium or high force and RTU stoppers crimped at low, medium or high force, no leak was observed at -80°C. All measured flows of helium were not significantly different from the background measurement.

It is important to note that, for all the conditions tested, no leak was observed when returning the vials to room temperature after exposure to deep-cold storage conditions (data not shown). This observation is also valid for Sample 4 of the steam-sterilised stoppers crimped at low force (Figure 4), indicating that, even if a leak was observed at -80°C, the stoppers demonstrated their resilience and restored seamless CCI at room temperature (data not shown).

CONCLUSION

In this study, Aptar Pharma's technical experts used complementary methods to understand the visco-elastic properties of PremiumCoat® stoppers and tested the ability of the stoppers to maintain CCI under various conditions. By using commonly accepted evaluation methods, such as laser headspace analysis and

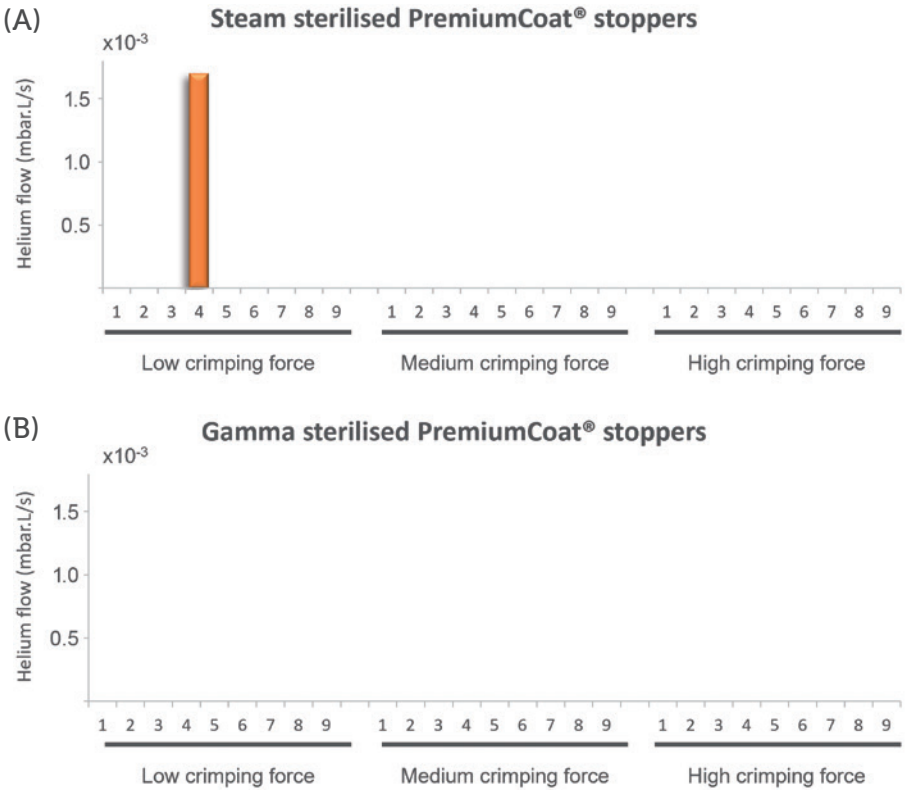

Figure 4: Helium leak test performed at -80°C, different crimping forces and for (A) steam and (B) gamma-sterilised PremiumCoat® stoppers. The data represent the helium flow measured in mbar.L/s. A sharp increase of helium flow is indicative of a leak. For all samples except Sample 4 of the steam-sterilised stoppers crimped with low force, the measured helium flow was too low to be visible on this plot and not significantly different from the background measurements.

"These data position PremiumCoat® as an ideal solution for protecting sensitive drugs that need to be stored at -80°C."

helium leak, it was demonstrated that PremiumCoat® can maintain seamless CCI down to -80°C when crimped appropriately. Although Aptar Pharma recommends crimping forces of 60 N, when used under sub-optimal conditions (30 N crimping force), PremiumCoat® was still able to maintain CCI in the large majority of cases. Taken together, these data position PremiumCoat® as an ideal solution for protecting sensitive drugs that need to be stored at -80°C.

When developing a new drug or evaluating a second-source supplier to de-risk operations, it is essential for drug developers to select the right closure components. The covid-19 pandemic emphasised the rising importance of security of supply, fast regulatory approval and cold storage. As the market is moving toward more complex and sensitive drugs, such as monoclonal antibodies, bispecific proteins and nucleic acids, primary packaging manufacturers must adapt their solutions to ensure that these drugs are appropriately protected from extractables and leachables, and meet regulatory requirements for chemical properties and ensure that the packaging remains perfectly sealed, even under the most strenuous conditions.

In addition to protecting the drug's integrity during deep-cold storage, PremiumCoat® ETFE film-coated stoppers were proven to reduce the number and quantity of extractables and leachables transferred into the drug product. Aptar Pharma's experts performed a wide variety of studies to demonstrate the chemical and functional performances of PremiumCoat® and compiled data packages for partners to better understand PremiumCoat®, de-risk their component selection and facilitate their validation process. Aptar Pharma's experts are also working in close collaboration with drug developers to provide a full range of analytical services to take the burden of packaging validation off them, so they can focus on their drug development.

"PremiumCoat® ETFE film-coated stoppers were proven to reduce the number and quantity of extractables and leachables transferred into the drug product."

ABOUT THE COMPANY

For pharma customers worldwide, Aptar Pharma is the go-to drug delivery expert, from formulation to patient, providing innovative drug delivery systems, components and active material solutions across the widest range of delivery routes, including nasal, pulmonary, ophthalmic, dermal and injectables. Aptar Pharma Services provides early-stage to commercialisation support to accelerate and de-risk the development journey. With a strong focus on innovation, it is leading the way in developing digital healthcare devices to help improve patient adherence and compliance. With a global manufacturing footprint of 14 manufacturing sites, Aptar Pharma provides security of supply and local support to customers. Aptar Pharma is part of AptarGroup, Inc.

All the data shown in this article are extracted from internal studies MDNFET001 and CET0202737.

REFERENCES

1. *Senior M, "Fresh from the biotech pipeline: fewer approvals, but biologics gain share". Nat Biotechnol, 2023, Vol 41, pp 174–182.*
2. *Kumar S et al, "Tailoring permeation characteristics of bromobutyl rubber with polyepichlorohydrin and graphene nanoplatelets". Materials Research Express, 2015, Vol 2(10), 105007.*
3. *"Identification and classification of visible nonconformities in elastomeric components and aluminium seal for parenteral packaging". PDA Technical Report No. 76, Oct 2016.*

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ABOUT THE AUTHORS

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

Benjamin Brocco, PhD, is the Global Marketing Manager for Aptar Pharma's Injectables division. He has a PhD in Biophysics and is a graduate of Grenoble Ecole de Management in France. Dr Brocco previously worked at a world-leading delivery device company, where he developed an in-depth understanding of the needs of injectables drug developers. He joined Aptar Pharma in 2020 as a marketing specialist and evolved to his current position in which he co-ordinates the marketing operations of the division and aligns Aptar Pharma's value proposition with the needs of the market.

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

Arnaud Clausse is the Global R&D Director dedicated to Injectables solutions for Aptar Pharma. As a graduate in Chemical Engineering, he has over 20 years' experience in highly technological industries. Mr Clausse joined Aptar Pharma in 2012 and has occupied technical, industrial and site management positions, leading product development and capacity expansions projects over the years. He is committed to expanding Aptar Pharma's technical capabilities and directing the innovation strategy to deliver world-class solutions to the injectables pharma market.

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ON drugDELIVERY

2023/24 EDITORIAL CALENDAR

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March	Ophthalmic Drug Delivery	Feb 1, 2024
April	Pulmonary & Nasal Drug Delivery	Mar 7, 2024
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May	Delivering Injectables: Devices & Formulations	Apr 4, 2024
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HOW PATIENT AND TREATMENT FACTORS SHAPE SUBCUTANEOUS DOSING PREFERENCES

In this article, Andreas Schneider, PhD, Innovation & Business Development Director at Ypsomed, highlights the importance of understanding the drivers of dosing preferences when it comes to choosing the right injection device for patients. Specifically, the research summarised here studies whether and how patient characteristics and treatment attributes influence the decision to use prefilled handheld autoinjectors or large-volume wearable injectors.

Advancements in subcutaneous drug delivery have led to a transformation in healthcare, with more patients self-injecting high-value biologics at home instead of receiving intravenous infusions in the hospital. As a result, choosing the optimal dosing option for medication has become a critical issue that can determine treatment adherence and health outcomes.

Patricia, a 73-year-old patient with high cholesterol, faced a dilemma when discussing the different dosing options for Repatha (Amgen, CA, US) with her cardiologist. Repatha is an injectable biologic drug to lower bad cholesterol and reduce heart attack risk. Patricia was torn between two options: a twice-weekly 15-second at-home self-injection with a handheld autoinjector or a once-a-month five-minute self-injection with a large-volume wearable device. She was worried about the hassle of injecting herself every two weeks – but felt intimidated by a device attached to her skin for a longer duration. When she asked her doctor to help her decide, he said there was no simple answer to her question.

Every patient is unique, and there is no clear guideline to predict which dosing option would work best for her. Some patients prefer the hands-free operation of the wearable large-volume injector, while others prefer the handheld autoinjector's feel of control and short injection duration.

Pharmaceutical manufacturers of high-value injectable biologics have taken up patient-centred concepts of self-care by offering more treatment choices. As such, the industry is witnessing an ever-increasing interest in wearable large-volume injectors as an alternative to the market-proven device category of handheld prefilled autoinjectors. Patients can patch these devices onto the skin and self-administer larger dose volumes over minutes or hours, without the need to hold the device against the injection site.

This emerging device category enables the administration of larger single-volume doses of biologics across chronic diseases. In so doing, wearable large-volume injectors contribute to decreasing injection frequency – a critical treatment attribute that scholars have repeatedly related to better treatment

> "The decision on which dosing option to choose can significantly influence a patient's therapy adherence, treatment outcomes and total healthcare costs."

Dr Andreas Schneider
Innovation & Business Development Director
T: +41 34 424 32 06
E: andreas.schneider@ypsomed.com

Ypsomed AG
Brunnmattstrasse 6
CH-3401 Burgdorf
Switzerland

www.ypsomed.com/yds

Handheld prefilled autoinjectors		Large-volume wearable injectors
Push-on-skin activation, held against injection site	**Handling principle**	Attached to skin, automated needle insertion and retraction
Audible start and end injection clicks & visual cues	**Injection feedback**	Advanced continuous visual and audible feedback
Seconds	**Injection time**	Minutes
0.1–5.5 mL	**Delivered volume**	2.0–10.0 mL
Mechanical, spring-driven	**Drive unit**	Electromechanical, motor-driven

Figure 1: Contrasting prefilled handheld autoinjector with large-volume wearable injector dosing options.

adherence. Moreover, these devices also allow for subcutaneous injections for therapies that require single large-volume doses beyond the capacity of handheld autoinjectors. Figure 1 contrasts the key attributes and differences between wearable large-volume injectors and handheld autoinjectors.

As patients like Patricia are taking a more active role in treatment decisions, healthcare providers are encouraged to personalise therapy options to ensure optimal medication adherence and health outcomes. However, the industry offers few answers to whether and how patient characteristics and therapy attributes drive device choices. This lack of insights is critical, as the decision on which dosing option to choose can significantly influence a patient's therapy adherence, treatment outcomes and total healthcare costs.

EXPLORING THE UNKNOWN IN PURSUIT OF ANSWERS

Recently, Ypsomed sought to answer these questions and studied how patient characteristics and treatment attributes influence their preferences for large-volume autoinjectors over prefilled handheld devices.[1] The study surveyed 191 patients with prior self-injection experience who suffer from chronic conditions such as arthritis, asthma or cancer. The online questionnaire captured patient characteristics and asked them to complete pairwise device choice tasks expressing their preference between handheld autoinjector and wearable large-volume injector dosing options. The survey assessed various patient characteristics, such as quality of life, dexterity impairment or skin irritation, using well-established standardised scales. The research design intentionally varied treatment attributes among these choice tasks – including injection duration and frequency, perceived pain and skin irritation – to contrast different options between the two device categories and unveil tipping points where device preferences changed.

DEVICE PREFERENCES DIFFER BETWEEN PATIENT GROUPS

The study asked patients to choose between two different injection devices: a handheld autoinjector for a weekly injection that causes mild pain and skin irritation or a wearable large-volume injector for a monthly injection that causes mild-to-moderate pain and skin irritation. Figure 2 illustrates the data on injection device preference by disease area. Around one-third (31.6%) favoured the large-volume wearable injector over the handheld autoinjector. Although the overall choice for this scenario remained with the handheld device, patient groups showed differences in preference. In the healthy control group, 36.4% of the participants preferred the wearable large-volume device – but this varied from 21.9% to 42.9%, depending on the chronic disease diagnosed. Notably, patients with multiple sclerosis were most likely to prefer the wearable device, while those with psoriasis were least likely.

> "Patients with multiple sclerosis were most likely to prefer the wearable device, while those with psoriasis were least likely."

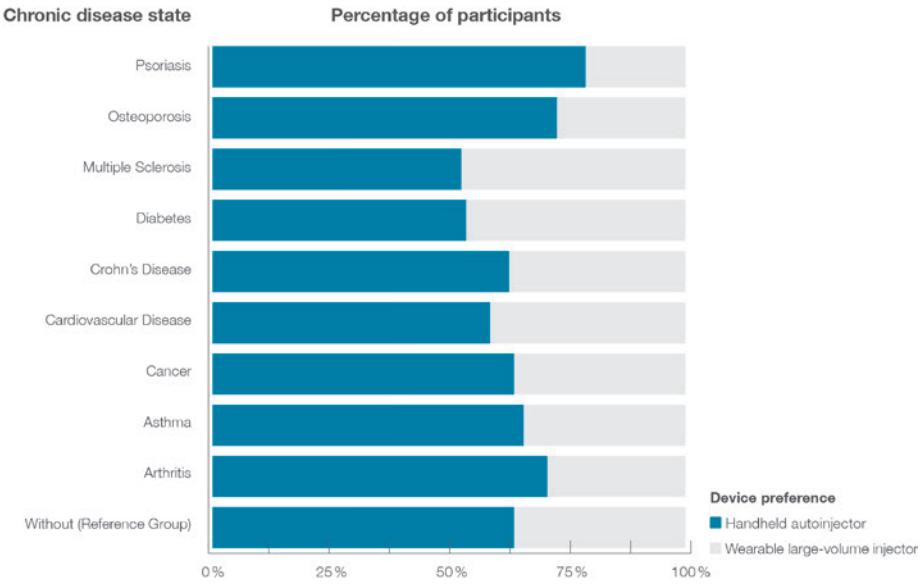

Figure 2: Device preference based on diagnosed disease state. Note: Comparison of a three-minute, weekly injection with a handheld autoinjector with a 33-minute, monthly injection with a large-volume wearable device.

"The study revealed a remarkable synergistic effect between injection frequency and duration on device preference."

EFFECTS OF INJECTION FREQUENCY AND DURATION ON PREFERENCES

Of particular interest were the effects of changing injection frequency and duration – two critical attributes of injection-based therapies. The study advanced the critical insight that stepwise decreases in injection frequency and time significantly increased the likelihood that patients preferred the emerging category of wearable large-volume devices to market-proven autoinjectors. Patients were more likely to choose a wearable large-volume injector when reducing its injection duration from more than 30 minutes to less than ten minutes, and injection frequency from biweekly to quarterly administration.

The results of this study have significant implications for drug product development. The study revealed a remarkable synergistic effect between injection frequency and duration on device preference. In fact, over two-thirds of participants preferred the large-volume wearable device when reducing injection duration to eight minutes and frequency to quarterly injections, compared with the well-established once-weekly injection using autoinjectors. Figure 3 illustrates these effects and highlights the critical inflection point where the overall preferences shift from handheld autoinjectors to wearable large-volume devices.

These findings underscore the importance of focusing on new formulations and device technologies that enable high-rate subcutaneous injections. For example, researchers may use innovative wearable large-volume injectors to accelerate the subcutaneous delivery of a drug co-formulated with permeation enhancers. By doing so, innovators can shift overall patient preferences and boost the commercial success of subcutaneously self-injected drugs.

WHY PATIENT QUALITY OF LIFE MATTERS IN CHOOSING INJECTION DEVICES

Deciphering the key drivers of patient dosing preferences is complex, as they are multifaceted and can change throughout therapy. However, the study revealed that patients with high quality of life tend to favour more frequent but shorter injections using handheld autoinjectors rather than less frequent but more prolonged drug self-administration using wearable large-volume injectors. These findings suggest that patients with better physical health find slower injections using wearable injectors attached to the abdomen or thigh more disruptive and may prefer a device that empowers them to be in full control of the process. In contrast, patients with lower quality of life appreciated the hands-free operation, automated injection process control and additional reassurance offered by wearable injectors. Notably, patients' quality of life seems to mask other individual-level characteristics on dosing preferences, such as dexterity limitations, injection experience, age or sex (see Figure 4 for an overview).

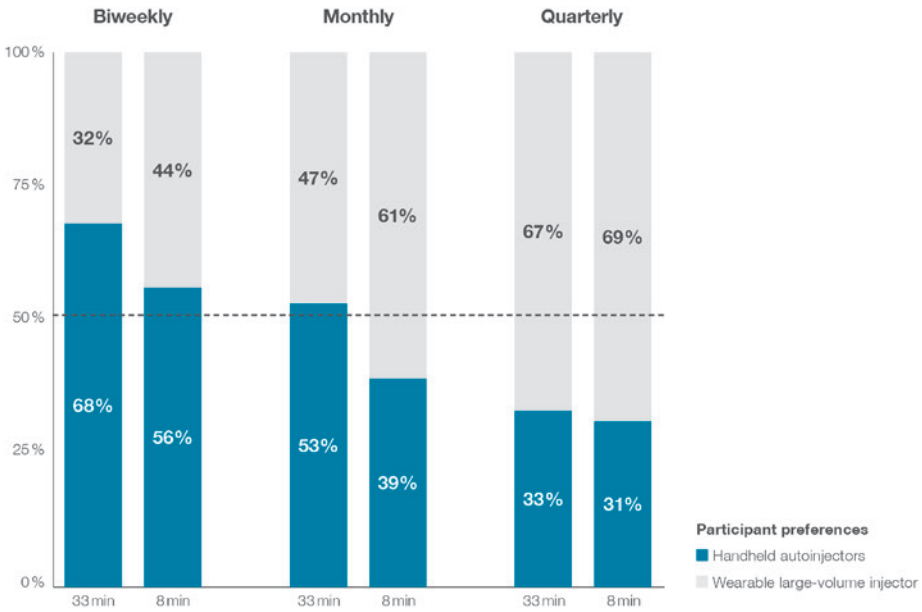

Figure 3: Device preference based on varying wearable large-volume injector injection duration and frequency. Note: The handheld autoinjector had a fixed injection duration of three minutes and a weekly injection frequency.

Patient characteristics	Effect on preference for large-volume injectors*	Regression coefficients*
Quality of life	Negative	-0.234, $p < .001$
Dexterity	None	0.011, $p > .05$
Skin sensitivity	None	-0.011, $p > .05$
Sex (male)	None	0.303, $p > .05$
Age	None	-0.009, $p > .05$
Self-injection experience	None	-0.498, $p > .05$

* Logistic regression model based on patient characteristics as predictor variables and patients' preference for wearable large-volume injector as response variable ($X^2(7) = 17.91^{**}$, $p < .01$; AIC = 227.44, Pseudo-R^2 = 0.13)

Figure 4: Effects of patient characteristics on preferences for large-volume wearable injectors.

> "Patients' quality of life seems to mask other individual-level characteristics on dosing preferences, such as dexterity limitations, injection experience, age or sex."

These insights are essential for selecting and prescribing injection-based therapies for patients. By considering a patient's quality of life and treatment preferences, healthcare providers can work with patients to choose the optimal self-injection device for their needs. Given these findings, let us return to Patricia's case and see how her cardiologist helps her navigate this decision. He understands that patients' quality of life is crucial in choosing the optimal device, so he asks about her daily activities, her overall health and how it affects her daily life.

Patricia shares that she enjoys being active and social but sometimes struggles with joint pain that limits her mobility. She also mentions that she values independence and prefers not to rely on others for help. Her doctor notes these critical factors and advises Patricia that a handheld autoinjector with shorter, more frequent injections may be the better option for her, given her desire for independence and an active lifestyle. He reminds her that adherence is vital to achieving optimal health outcomes and encourages her to follow up with him regularly to monitor progress and adjust the treatment plan as needed.

About the Study

Ypsomed, a leading manufacturer of self-injection systems for subcutaneous drug delivery, collaborated with HFC Human-Factors-Consult (Berlin, Germany) to conduct the empirical study presented in this article. As part of its commitment to advancing new insights relevant to both industry and academia, Ypsomed has established a scientific research and communications programme. The outcomes have been published in leading peer-reviewed scientific forums such as *Expert Opinion on Drug Delivery, Patient Preference & Adherence* and *Medical Devices: Evidence and Research*, and have also been presented at significant medical device and drug delivery conferences, such as the PDA Universe of Pre-Filled Syringes and Injection Devices.

ABOUT THE COMPANY

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

With over 35 years of experience in the development and manufacture of innovative injection systems, Ypsomed is well equipped to tackle digital healthcare challenges and has strategically invested in the development of connected solutions and therapy-agnostic digital device management services.

Anticipating the future needs of patients, pharmaceutical customers, payers and healthcare professionals, Ypsomed moves beyond manufacturing connected sensors. Ypsomed's smart device solutions strive to transform patients' lives by capturing therapy-relevant parameters, processing them to facilitate self-management of chronic diseases and integrating these insights with digital therapy management ecosystems.

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

ABOUT THE AUTHOR

Andreas Schneider, PhD, is Innovation & Business Development Director with Ypsomed Delivery Systems. He leads the design and development of new products, services and business models focusing on improving the self-management of chronic diseases. Dr Schneider has published numerous articles on innovation management and drug delivery and is an avid speaker on these subjects. He holds a PhD in Innovation Management from ETH Zurich, Switzerland.

REFERENCE

1. *Schneider A et al, "Understanding patient preferences for handheld autoinjectors versus wearable large-volume injectors". Expert Opin Drug Deliv, 2023, Vol 20(2), pp 273–283.*

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ADDRESSING PEPTIDE THERAPEUTICS WITH A VERSATILE PEN PLATFORM

Here, Cécile Gross, Global Category Manager, Parenteral, and Mark Tunkel, Global Services Director, both at Nemera, discuss the rising demand in peptide therapeutics and how Nemera's PenVario pen injector platform, coupled with Nemera's end-to-end service offering, has been designed to help pharma partners achieve success in this sector.

The synthesis of the first peptide therapeutic, insulin, occurred more than 100 years ago,[1] targeting diabetes mellitus. Ever since, insulin has been widely used to treat this chronic condition. To this day, pharma companies are still working on formulations to improve bioavailability, long-lasting efficacy and patient adherence.

Considering Type 2 diabetes, for over a decade, another area of interest has been the incretin system.[2] Two hormones have been identified – glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide, also known as gastric inhibitory polypeptide (GIP). Both of these hormones are rapidly broken down by the enzyme dipeptidyl peptidase-4 (DPP-4), which encourages the development of degradation-resistant GLP-1-receptor agonists and DPP-4 inhibitors.[3] Adding this family of agents to the repertoire of therapeutic blood glucose control has broadened the target patient population from diabetes to obesity. Since the first US FDA-approved GLP-1 in 2009, pharma companies have worked to reduce injection frequency, improve delivery devices and even offer alternative administration routes, such as oral delivery.

In an overview of the evolution of these diseases, in 2019, the International Diabetes Federation estimated that 463 million people between the ages of 20 and 79 are suffering from diabetes, of which 231.9 million are undiagnosed.[4] The prevalence of diabetes is projected to reach almost 11% of the global population by 2045. As for obesity, in 2022, the WHO estimated that more than 1 billion people in the world are obese, including 650 million adults.[5] In the US, the prevalence of obesity in over-20s is already more than 40%, according to the National Institute of Diabetes and Digestive and Kidney Diseases.[6]

> "Since the first FDA-approved GLP-1 in 2009, pharma companies have worked to reduce injection frequency, improve delivery devices and even offer alternative administration routes, such as oral delivery."

A DISPOSABLE PEN PLATFORM TO MEET THE DEMAND IN PEPTIDE THERAPEUTICS

In line with this growing demand and leveraging its long-standing expertise in insulin pens and GLP-1 autoinjectors, Nemera chose to develop a pen injector platform versatile enough to address the aforementioned drugs, as well as others. Now that more than 80 peptide drugs are on the market,[7] with several more in clinical

Cécile Gross
Global Category Manager, Parenteral
E: cecile.gross@nemera.net

Mark Tunkel
Global Services Director
E: mark.tunkel@nemera.net

Nemera
Immeuble Eklaa
63-65, avenue Tony Garnier
69007 Lyon
France

www.nemera.net

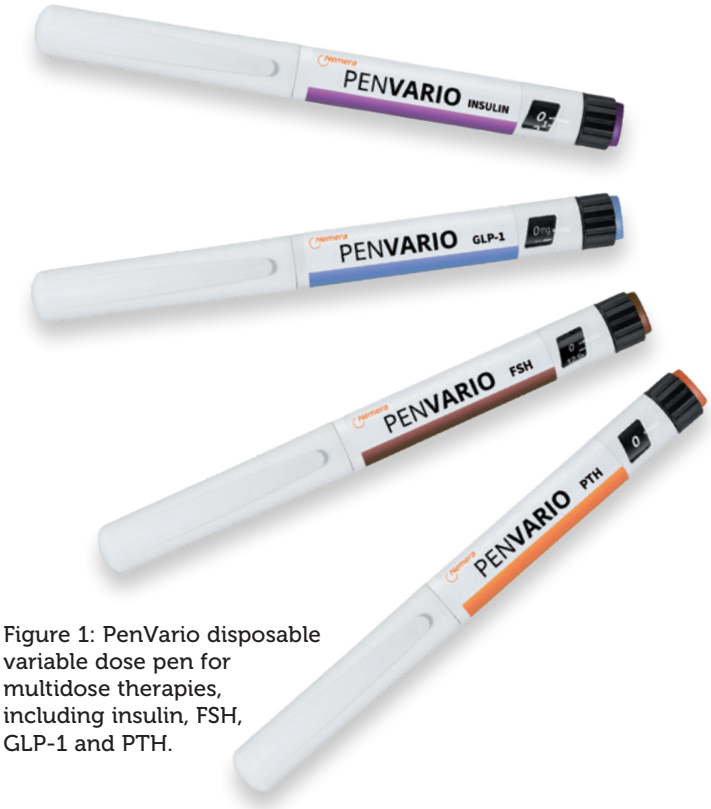

Figure 1: PenVario disposable variable dose pen for multidose therapies, including insulin, FSH, GLP-1 and PTH.

> "PenVario is a manual pen platform able to address diabetes and obesity with rapid-acting or long-acting insulins and GLP-1, osteoporosis with PTHs, such as abaloparatide, and fertility with FSHs, such as follitropin alpha."

trials, covering therapy areas such as migraine, oncology, dry eye syndrome, cardiovascular diseases and even growth disorder, to name but a few, adding a disposable, variable dose device to the already existing pen range seemed obvious.

PenVario is a manual pen platform able to address diabetes and obesity with rapid-acting or long-acting insulins and GLP-1, osteoporosis with parathyroid hormones (PTHs), such as abaloparatide, and fertility with follicle-stimulating hormones (FSHs), such as follitropin alpha. Given the differences between these target populations and regimens, each variant of the platform has been designed to match the specificities of each therapeutic area (Figure 1).

Case Study: Fertility

Although this therapeutic area receives less media attention than diabetes or, more recently, obesity, due to the controversy related to off-label use, infertility does affect a large number of people. According to a recently published WHO report,[8] its prevalence is growing, with it estimated to affect up to 17.5% of the adult population worldwide, including both women and men.

There are a few therapeutic solutions and several drugs already available for women or men suffering from infertility, mostly targeting patients between 20 and 45 years old. Ovarian stimulation is sometimes prescribed along with assisted reproductive technologies for women and spermatogenesis for men – two examples of treatments for which an injection of FSH can be required. The regimen usually implies daily injections over the course of several weeks.

Given the characteristics of such a regimen, its duration and potential psychological considerations, the delivery device needs to be as user-friendly as possible to avoid incorrect dosing. Consequently, the FSH variant of the PenVario offers a clearly visible indication of the dosage in milligrams and comes in different versions to accommodate different drug concentrations. Cap fitting and removal forces have also been fine-tuned according to this specific target population, leveraging Nemera's own human factors capabilities through an ergonomic evaluation.

INTEGRATED SERIVICES AND MANUFACTURING CAPABILITIES

For specific customer applications, Nemera can support PenVario with the human factors and patient experience activities that must be integrated to ensure an efficient development process. This ensures that the device, in combination with the drug, is appropriate, safe and effective for the target patient population. This also extends to optimising the patient experience to create competitive differentiation and ensure adherence and engagement with patients and clinical stakeholders.

Customers need to be sure that the device addresses the defined user populations. To this end, early use-related risk analysis activities can help define the human factors and usability programme. Clinical risks must be identified by conducting formative and summative usability testing for all aspects of the device and any supporting assets in alignment with the human factors programme definition, including the production of human factors engineering report documentation for use in for regulatory submissions. This process is linked to developing instructions for use, value-added packaging and digital health related add-ons to support patient engagement and adherence, as well as to extend the value of a device platform (Figure 2).

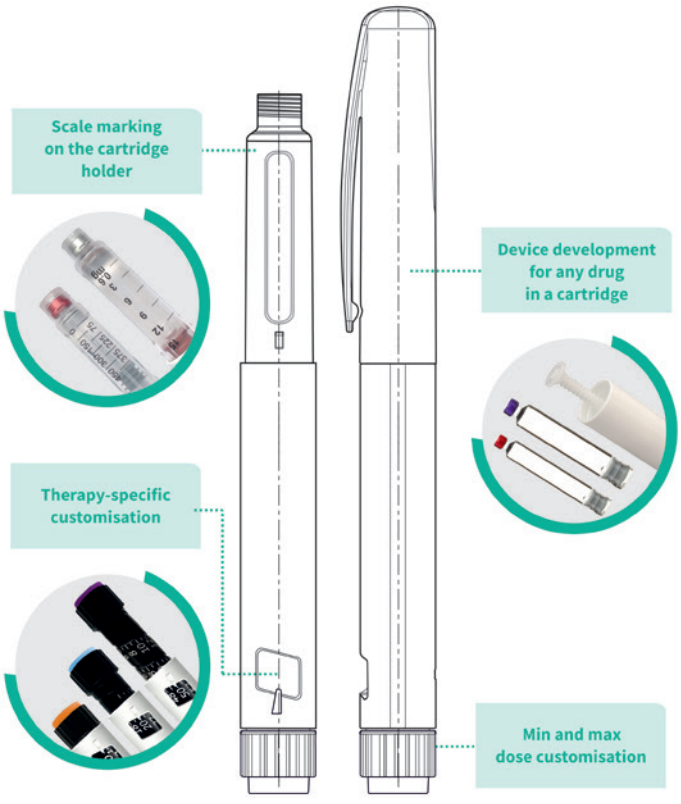

Figure 2: PenVario platform capabilities, tailored to customers' needs.

Nemera can also support regulatory strategy development and support the entire process of developing materials for submission to regulatory authorities, as well as provide laboratory and analytical services. This can also be augmented by fit-for-purpose preclinical, clinical and small-series device supply to accelerate development timelines and defer capital expenses. It is crucial that this is all completed holistically.

Furthermore, Nemera is willing to provide a fully automated industrial line to its partners. Nemera has recently invested in a new manufacturing plant (Figure 3), with the capability to produce prototypes, small series for clinical batches and large-scale automated volumes. Sporting state-of-the-art equipment, from moulding to assembly and quality control testing, this brand-new facility includes an ISO 8 cleanroom and complies with BREEAM recommendations (Figure 4); for example, heat is recovered from the process line, and the facility also segregates and sorts all waste, aiming to achieve a 100% recycling rate.

Figure 3: Nemera's brand new state-of-the-art manufacturing facility in Poland.

Figure 4: ISO 8 cleanroom compliant with BREEAM recommendations.

> "Nemera has recently invested into a new manufacturing plant, with the capability to produce prototypes, small series for clinical batches and large-scale automated volumes."

Apart from its end-to-end offering, Nemera is actively working not only with peptides and pen injectors but more globally towards holistic patient-centric solutions. In this regard, its latest move has been to join the Subcutaneous Drug Delivery and Development Consortium to be more involved in this peer-to-peer collaborative hub reflecting on how to address unmet needs.

BENEFITS OF PARTNERING WITH AN INTEGRATED PRODUCT AND SERVICE PARTNER

Nemera's pen platforms, integrated development, consulting and manufacturing services allow customers to achieve a successful regulatory submission and commercial launch of safe, effective and differentiated combination products with a single partner, applying an agile process across the device and combination product value chain. This will drive patient-centricity, reduction of risk and increased speed to market. This approach can be applied to Nemera's device platforms or with organic development and allow customers to focus on their core business.

ABOUT THE COMPANY

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

quality standards. Agile and open-minded, Nemera works with its customers as colleagues. Together with its customers, Nemera goes the extra mile to fulfil its mission.

REFERENCES

1. *Wang L et al, "Therapeutic peptides: current applications and future directions". Sig Transduct Ther, 2022, Vol 7, Article 48.*
2. *Hinnen D, "Glucagon-Like Peptide 1 Receptor Agonists for Type 2 Diabetes". Diabetes Spectr, 2017, Vol 30(3), pp 202–210.*
3. *Baggio LL, Drucker DJ, "Biology of incretins: GLP-1 and GIP". Gastroenterology, 2007, Vol 132(6), pp 2131–2157.*
4. *Buchholz K, "We should be worried about global diabetes rates. This chart shows why". World Economic Forum, Nov 2021.*
5. *"World Obesity Day 2022 – Accelerating action to stop obesity". WHO, Mar 2033.*
6. *"Overweight & Obesity Statistics". NIH webpage, accessed May 2023.*
7. *Muttenthaler M et al, "Trends in peptide drug discovery". Nat Rev Drug Discov, 2021, Vol 20, pp 309–325.*
8. *"Infertility Prevalence Estimates, 1990–2021". WHO report, Apr 2023.*

ABOUT THE AUTHORS

Cécile Gross is Marketing Global Category Manager at Nemera, focusing on parenteral devices. Ms Gross oversees the product portfolio strategy, development and lifecycle for safety system, pen injector and on-body injector platforms. She has more than two decades of experience in the medical device industry, marketing B2B technological products and implementing product lifecycle management for various kinds of devices. Ms Gross graduated in International Business and completed her initial training with a master's degree in Marketing and Management in the Healthcare Industry at the IMIS Institute (Lyon, France).

Mark Tunkel is Global Category Director, Services at Nemera. He was previously a partner at Insight Product Development, which was acquired by Nemera in 2019 and became the Insight Innovation Center. With more than 20 years of global business development experience and a deep understanding of the marketplace challenges and trends impacting the pharma industry, Mr Tunkel has advised many of the world's leading companies on their product development and innovation strategies, with an emphasis on driving realisation and the most favourable business outcomes.

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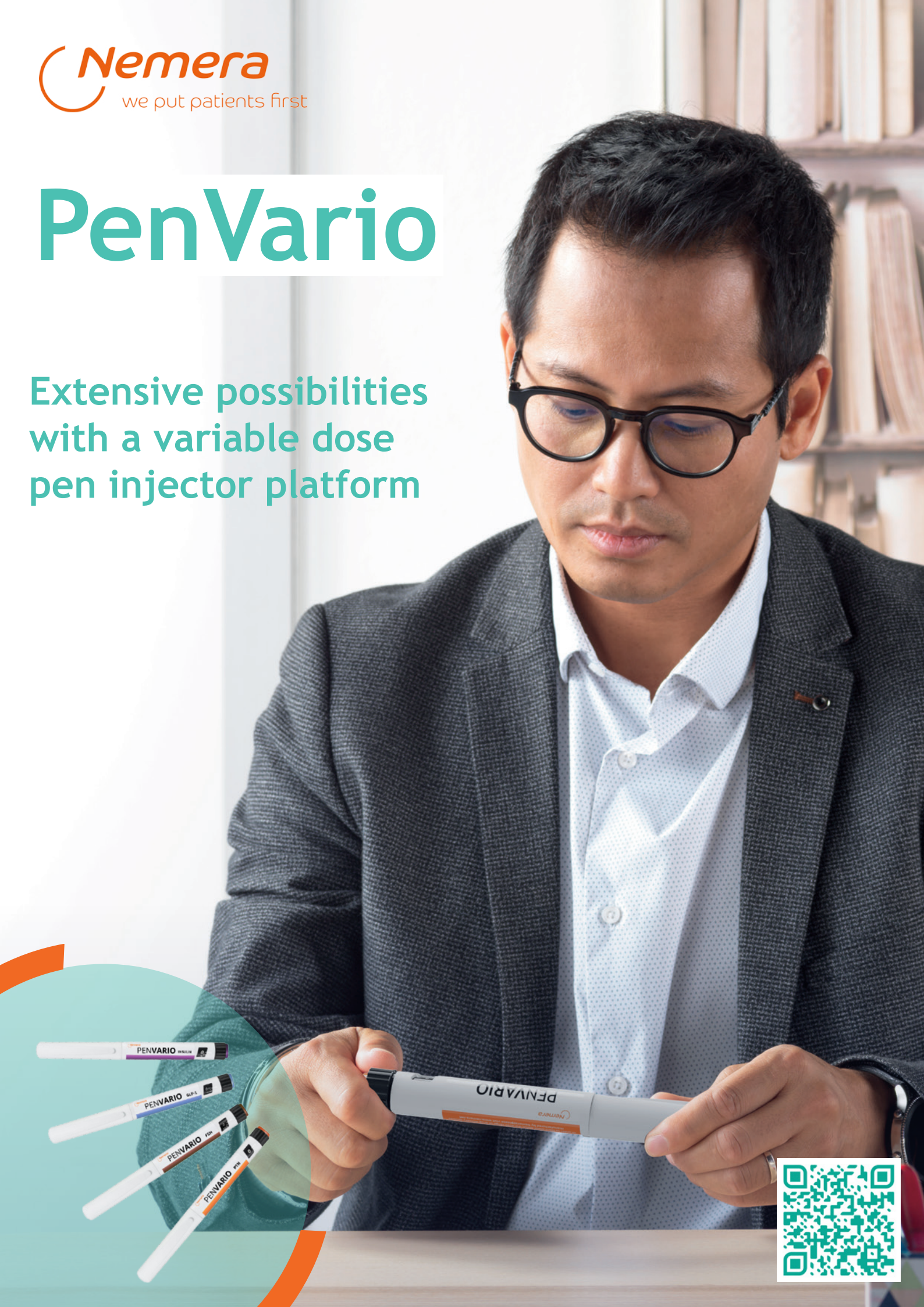

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HARNESSING HUMAN FACTORS IN CONNECTED DEVICE DEVELOPMENT

In this article, Finola Austin, Human Factors Lead at Owen Mumford, looks at the role human factors testing plays in the development of connected drug delivery devices.

User-centred product design has a crucial role to play in drug delivery device development. The safety of medical devices relies on them being used as intended, which is why regulatory agencies place great emphasis on incorporating human factors (HF) and usability engineering in the design process to minimise potential use errors and potential harm. Intuitive, easy-to-use devices also encourage patient adherence, which, in turn, may help improve therapeutic outcomes.

The increasing availability of connected drug delivery devices offers patients new opportunities to manage their medical conditions from the comfort of their own homes, with key information – such as injection date and time, dose and injection site – automatically captured and shared with their healthcare providers. In addition, notifications can help remind patients when their next dose is due and alert them to missed doses, typically via a smart phone app.

However, incorporating connectivity poses new challenges in terms of the user interface. For example, adding authentication steps to protect data privacy and security can make it more difficult to set up and use the device in question – acting as a barrier to adoption for patients who are less familiar or confident with technology. Furthermore, the right balance must be struck with notifications and patient feedback; such information can be reassuring for patients but can also act as a distraction and introduce unnecessary complexity to the injection process – making it difficult for users to navigate from a physical and cognitive perspective.

For these reasons, HF studies are more important than ever with connected drug delivery device development. They enable design and development teams to take an in-depth look at user requirements, characteristics, concerns and challenges – and identify design features to support ease of use. HF studies also explore how intended users interact with all aspects of a device interface and accessories, including buttons, switches, visual and audible indicators, labelling and instructions, as well as the size and configuration of the device.

The digital interface is another key aspect of the user interface. Its impact must be incorporated into user studies to evaluate user experience, ensure that it supports the users' needs and does not adversely affect the drug delivery process in any way.

FORMATIVE AND SUMMATIVE STUDIES

Part of the HF process involves designing formative and summative studies that evaluate intended use and test the product in the intended use environments. Participants are recruited to ensure

"Part of the HF process involves designing formative and summative studies that evaluate intended use and test the product in the intended use environments."

Finola Austin
Human Factors Lead
E: pharmaservices@owenmumford.com

Owen Mumford Ltd
Brook Hill
Woodstock
Oxfordshire
OX20 1TU
United Kingdom

www.owenmumford.com

sufficient representation of all intended user groups and their characteristics, ranging from their role (patient, caregiver), age and gender to reading age. Intended users are invited into the design process as early as possible to ensure that the concept is sensitive to their needs. This also helps to ensure that there is sufficient time to shape the design interface and mitigate potential use errors.

However, it is always a challenge to hit the sweet spot when planning formative studies, as a balance needs to be struck between prototype/device readiness, project timelines and having sufficiently representative interface(s) to ensure that the study findings are reliable and useful.

CASE STUDY

A good example of user-centred design in action is Owen Mumford's first project involving connectivity – the UniSafe autoinjector, a companion device for the UniSafe 1 mL safety device (Figure 1). A key requirement for this reusable platform device was the prevention of needle exposure before, during and after the injection process, which was achieved by using the UniSafe sharps protection feature with the UniSafe safety device inserted into the autoinjector before use. The autoinjector incorporates connectivity and is suitable for a wide range of therapy areas, which helps to support and encourage patient adherence and provides healthcare professionals with access to patient medication data. The UniSafe 1 mL autoinjector has been designed to be safe and effective when used with or without connectivity.

During the early stages of device development, the use steps were simplified by incorporating the priming function for drug delivery into the device open/close action. The team also worked closely with design engineers to create the optimum user interface while accommodating the technical requirements. The HF emphasis was on desktop ergonomics, using anthropometric data to shape the physical interface and cognitive psychology to guide display solutions. In addition, early in-house user testing was conducted with device-naive participants to gain early insights into general handling, understanding of the display and controls, and interpretation of the signals for connectivity.

LEARNING POINTS

The HF team endeavoured to conduct user studies on each part of the digital interface as soon as they had an appropriate level of fidelity. However, a challenge was posed by the fact that the development of each part of the system progressed at different rates. It was relatively easy to storyboard the overall app structure and generate a simulation via Adobe XD before writing the software. This could then be modified and iterated rapidly based on desktop analysis and the findings of user evaluations. However, the device components and electronics developed at a slower pace – including the ability to connect the device. The team compensated for this by mimicking connectivity in the app. This was constructive, but it meant that the moderator had to intervene more than desired during the early studies – which had the potential to affect the study outcomes.

Learning from the formative studies helped to evaluate the app's content and flow – Owen Mumford was committed to creating a "demonstrator" app that would allow it to consider the full impact on safe and effective use of the device. As the prototype matured, there were inevitable stops and starts in the flow of app use. This required the creation of use scenarios that had to be mocked up in isolation, simulating the appearance of connectivity in several cases.

The HF studies for the UniSafe 1 mL autoinjector were also designed to evaluate worst-case use scenarios. Participants with mixed experience were recruited and interacted with the device with no training and no direction to read the instructions. Although the team did not want the users to be preoccupied with the app, it was an intrinsic part of the evaluation. The inclusion of an app, instructions for use (IFU) and new autoinjector with no training meant that users were confronted

Figure 1: The UniSafe autoinjector is a companion device for the UniSafe 1 mL safety device.

with quite a high workload in a single usability evaluation. In the real world, the user would typically be introduced to the components by a healthcare professional and the patient might be more inclined to explore the device and app separately, in their own time.

The formative studies also helped to develop a generic IFU for the device with a layout that meets user needs and aligns with potential packaging solutions – a landscape booklet emerged as the best way to provide enough space to present the intended use steps in an easy-to-follow sequence. The team was also able to experiment with colour in the studies – participants successfully loaded and unloaded the device guided by effective use of colour on key touchpoints. This emphasised the impact of colour on user interaction while competing with different aesthetic and marketing proposals.

CONCLUSION

Incorporating connectivity into drug delivery devices is a challenging process. While connectivity brings a wealth of possibilities, it can introduce some complexity for the patient. User-centred iterative design, coupled with multiple formative studies of the physical and connected interfaces, can harness this potential and optimise ease of use. The HF study participants surprised Owen Mumford with their immediate recognition of the connected element – and effective interaction with the connected device and app.

ABOUT THE COMPANY

Owen Mumford is a medical device manufacturer with a global presence across the UK, Europe, the US and Asia, pioneering the advancement of medical technology for 70 years. The company manufactures its own brand of medical products and is a trusted partner to many of the world's largest pharmaceutical and diagnostic companies. Its leading medication administration, blood-sampling and testing solutions are designed and manufactured for the comfort, safety and dignity of patients, healthcare professionals and caregivers as a priority. Driven by its purpose to do business in the right way, Owen Mumford is one of the first medical device companies in the world to achieve B Corp certification and has set science-based targets to achieve net zero by 2045, as part of its long-established and continually evolving sustainability agenda.

ABOUT THE AUTHOR

Finola Austin is a highly experienced Human Factors Engineering manager, boasting 15 years' experience in the mentorship and management of human factors services in safety-critical industries. Ms Austin has successfully planned and delivered human factors activities for hundreds of handheld medical devices, including autoinjectors, emergency-use devices, inhalers, injection pens and lancets.

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TACKLING DESIGN CHALLENGES IN EMERGENCY-USE AUTOINJECTORS

In this article, John Burke, Senior Consultant at Team Consulting, considers the challenges that manufacturers need to overcome when designing emergency-use autoinjectors.

It seems obvious that when developing a device to deliver a potentially life-saving medication, you want to ensure it is safe, reliable and easy to use. Achieving this with an emergency-use autoinjector poses significant challenges, in part due to the fact that they need to be used in highly stressful situations by a wide range of users. To date, several on-market devices have shown various use-related issues, while technical failures have resulted in a number of devices being recalled both in Europe and the US.

To counter this, the US FDA issued new guidance in 2020 outlining their expectations in terms of essential performance requirements and device reliability. While this has added clarity for what is required, the bar has been set high. Companies seeking to bring new emergency-use devices to market are now faced with the challenge of demonstrating the 99.999% reliability required by the FDA, while also addressing known use-issues. Achieving this requires a careful balance of user-centred design, regulatory strategy and design for reliability.

"Companies seeking to bring new emergency-use devices to market are now faced with the challenge of demonstrating the 99.999% reliability required by the FDA, while also addressing known use-issues."

EMERGENCY-USE USER INTERFACES – WHAT ARE THE KNOWN ISSUES?

An essential aspect of emergency-use autoinjectors is ease of use. When looking at the devices currently available, a number of which are shown in Figure 1, there is a wide variety of different and potentially contradictory approaches to the user interface. It is therefore easy to see why confusion and user-error can occur.

One study found that only 16% of adults who had been prescribed an adrenaline (epinephrine) autoinjector knew how to use the device correctly, including parents who might need to inject their child. This issue is not limited to a single device either. Another study in 2010 compared four devices – INT01, INT02, EpiPen® (Mylan,

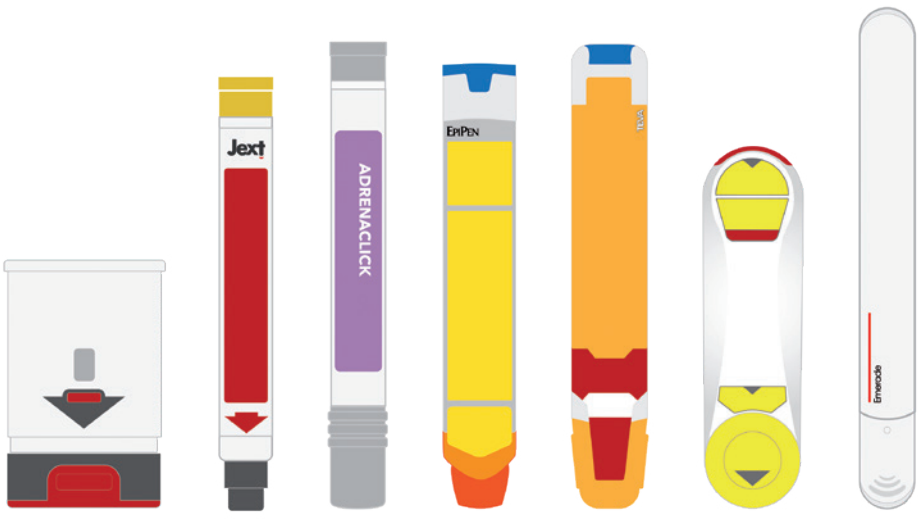

Figure 1: Currently available emergency-use autoinjectors pictured left to right: (Auvi-Q®, Jext®, Adrenaclick®, EpiPen®, Teva Generic®, Maverick®, Emerade®).

John Burke
Senior Consultant
T: +44 1799 532700
E: john.burke@team-consulting.com

Team Consulting Ltd
Abbey Barns
Duxford Road
Ickleton
Cambridge
CB10 1SX
United Kingdom

www.team-consulting.com

part of Viatris, PA, US) and TwinJect® (Verus Pharmaceuticals, CA, US) – and identified 13 different types of use error, including:

- Issues with the safety caps – removing in the wrong order, difficulty removing, or not removing at all
- Unintentional injection into the hand or digit
- Attempting to inject more than once
- Not holding for correct amount of time
- Attempting to disassemble the device
- Not injecting at all.

While the design of some of these devices has evolved since this 2010 study, there is still a variety of user interfaces among devices currently on the market.

SEQUENCE OF USE – A COMPARISON OF ON MARKET DEVICES

Figure 2 shows a comparison of four on-market emergency-use devices – Auvi-Q® (Kaléo, VA, US), Jext® (ALK, Berkshire, UK), Adrenaclick® (Meridian Medical Technologies, MI, US) and Emerade® (Medeca Pharma, Uppsala, Sweden) – that clearly highlights some of the differences in their sequences of use and the potential root causes of user error:

1. **Remove the device from its protective case:** Even with this simple step, several known use issues have occurred. During formative studies, users of the Auvi-Q® struggle to understand what to do with the case or lack the physical capability to remove the device from its tight-fitting sleeve. In other studies focused on different devices, there have been instances where users mistakenly believed the device was unlocked and ready to go once it had been removed from its protective case.
2. **Unlocking the device:** The Auvi-Q® and Emerade® devices are both unlocked by pulling a safety feature or cap off the needle end of the device. Jext®, however, has a safety release that is pulled off the opposite end of the device, while Adrenaclick® requires the user to pull caps off both ends of the device (note the order is important here too – first the front and then the back).
3. **Administering a dose:** All four devices actuate by firmly pushing the needle end against the skin to release the internal mechanism and start the injection. A common use issue that arises at this step is users holding the device in the wrong orientation. With more "traditional" devices, such as EpiPen® and Jext®, removing the safety release also leaves a round hole in the top of the device, which can result in accidental thumb injection. It should be noted that incorrect orientation is not limited to this type of device and has also been observed within studies evaluating devices with a more contemporary two-step interface as well. Various factors can impact this, including form-factor, any on-device instructions or cues, the use of colour and packaging and labelling.
4. **Full dose delivery:** Once the device has been activated, the user needs to hold the device in place for between 3 and 10 seconds (depending on the device) before removing. Some devices have an indicator, but they are typically small and hard to see, while Emerade's is under a peelable label. The Auvi-Q® device talks the user through the process and provides a clear audible countdown, which can be helpful.

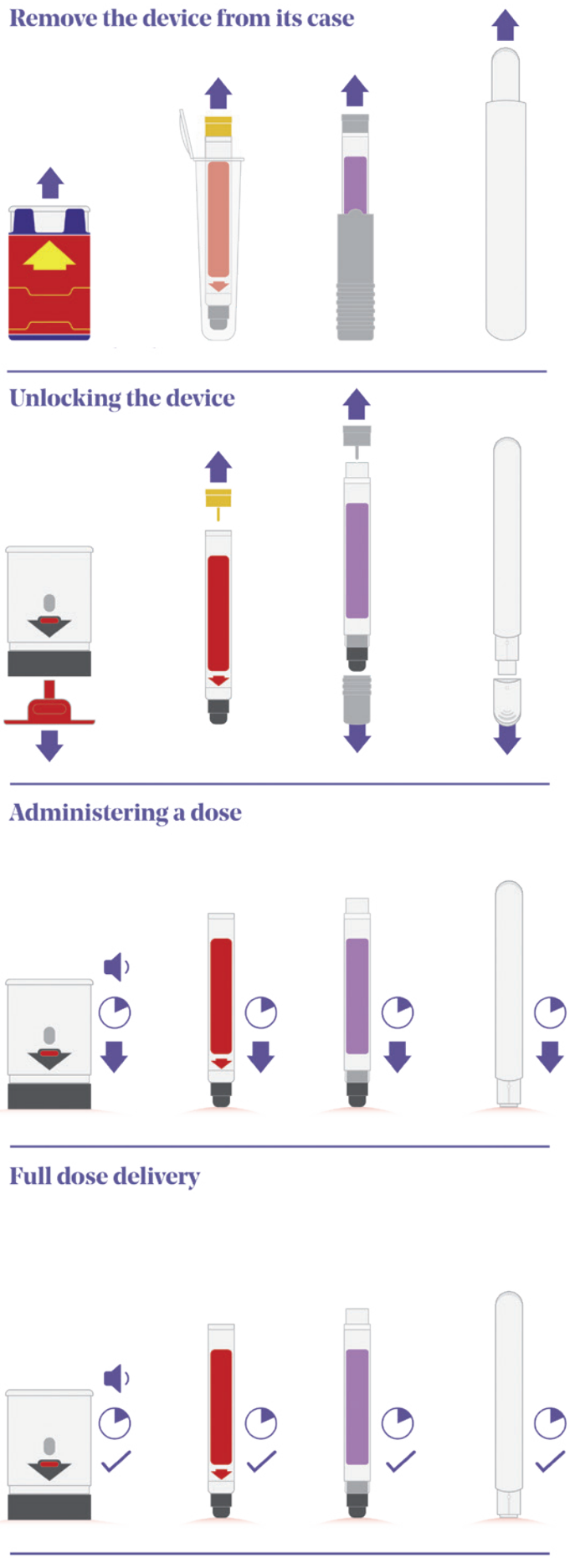

Figure 2: A comparison of emergency-use autoinjectors, pictured left to right (Auvi-Q®, Jext®, Adrenaclick®, Emerade®).

When ease of use is paramount, this variety in user-interfaces places additional demands on the user, so it is hardly surprising to see use errors. A standardised sequence of use could help reduce the instances of use-error; however, it is important to note that this approach can introduce its own challenges as well.

Can a Contemporary "Two-Step" Approach Apply to Emergency-Use Autoinjectors?

In the last five years, a simple "two-step" user interface has become popular among autoinjectors used to treat chronic conditions such as rheumatoid arthritis, Crohn's disease and psoriasis. There are, of course, outliers, but the benefits of a single, intuitive interface are clear. The FDA and other regulatory bodies have also become familiar with the approach and endorse the idea of standardisation.

It seems logical therefore that, if you were developing a new emergency-use autoinjector, you would shift to this more contemporary two-step approach. Not only is it proven in other applications and fast becoming industry standard, it would help remove some of the known use-errors associated with traditional devices.

The challenge is that millions of users have already been trained and are familiar with existing emergency-use devices. Any changes made to existing devices presents a potential risk. This does not mean it is the wrong thing to do, but every effort needs to be taken to reduce the risk of misuse due to established mental models or previous device experience.

DESIGNING FOR USABILITY

Regulatory Strategy

The regulatory strategy a device manufacturer adopts will have an impact on the user interface of their product. This is particularly apparent for generic device design. Currently, many emergency-use devices contain drugs that have already been approved for use in the US. Section 505(j) of the Federal Food, Drug, and Cosmetic Act enables companies to demonstrate "sameness" to a reference listed drug (RLD) and leverage some existing safety and efficacy data, helping to save on clinical trials or other expensive studies. For this to apply, however, the drug product must be "therapeutically equivalent" and the accompanying device similar to the RLD, so that prescribing doctors and users can be confident in its use.

> "Generic device manufacturers must carefully balance the challenges of ensuring enough similarity to the existing device, while simultaneously tackling the known use issues that may accompany it."

In addition to 505(j), the FDA has issued specific guidance on the design of generic adrenaline autoinjectors. The guidance does not state that the design should be identical, however the FDA is clearly conscious that manufacturers are not designing in a vacuum and that users may have experience or existing mental models around existing (potentially flawed) devices. What the FDA will not accept is manufacturers not addressing areas of the device that are known to cause confusion or issues – they will want to see evidence that these risks have been effectively mitigated.

> "What the FDA will not accept is manufacturers not addressing areas of the device that are known to cause confusion or issues – they will want to see evidence that these risks have been effectively mitigated."

In 2018, the FDA approved the first generic adrenaline injector from Teva Pharmaceuticals (Tel Aviv, Israel) as an ANDA under 505(j). Notably, the device has several key differences in the user interface to the RLD. For example, the sequence of use has changed from two steps to three with the introduction of a twist of cap covering the needle end, while the blue safety release differs somewhat from the RLD as it peels off from one side rather than pulling straight up.

Generic device manufacturers must carefully balance the challenges of ensuring enough similarity to the existing device, while simultaneously tackling the known use issues that may accompany it.

The Importance of Human Factors Engineering

Regardless of the regulatory strategy chosen, it is essential to have an effective human factors engineering (HFE) programme that runs

in parallel with the design and engineering activities in accordance with IEC 62366-1. By having HFE as an integral part of the process from the outset, it is possible to optimise the device design, identify flaws and mitigate use errors. Every touchpoint is an opportunity to improve the usability of the device and its full ecosystem, from the physical device design, labelling and instructional information through to the packaging and more.

By including HFE through the entire development process, an HFE summary report can be submitted to the regulators that shows how the design has been optimised to minimise the potential for use error.

User capability studies can inform the specification limits, which, in turn, form the basis of essential performance requirements (e.g. the force to remove the cap or actuate the device). These need to be very carefully considered, as they form the target the manufacturer will be held to from a reliability standpoint. If the limit is too high, there is a risk that users may not be physically capable of performing the task. If the range is too narrow, it may be impossible to demonstrate the required level of reliability consistently.

Designing for Reliability – FDA Draft Guidance

Once the user interface has been considered and optimised, the next challenge is reliability. The FDA draft guidance on the reliability of emergency-use injectors, published in April 2020, has brought some clarity about what the FDA expects. The guidance describes the application of a scored fault tree analysis (FTA), alongside traditional development activities and approaches for achieving a reliability of 99.999% with a 95% level of confidence for the device. FTA is a well-established risk analysis and trouble-shooting tool that uses a top-down approach, starting with the main fault/effect and working down to potential root causes. Typically, an initial FTA is developed early in the development process, after which predicted probability can be applied based on simulation, design analysis, initial testing and informed manufacturing assumptions.

The required level of reliability to be demonstrated is understandably high. Device manufacturers should not underestimate the challenge of achieving and demonstrating that their device meets these requirements.

THE SUSTAINABILITY FACTOR

So far, this article has focused on two main areas: usability and reliability. There is, however, another important design consideration: sustainability. In practice, many emergency-use injectors are never used, with the majority expiring and being disposed of before they are required. It therefore makes sense to consider the environmental impact of decisions around the design, assembly and supply of components. From experience in conducting lifecycle analysis – a tool used to determine the carbon footprint of component manufacture and transportation – the greatest impact on device development is likely to come from:

- Supply change management, especially air travel
- Cold chain storage
- Device/packaging size
- Device architecture
- Drive (spring vs gas)
- Integration of electronics
- Shelf life
- Possibly shifting from glass primary packaging to copolymer or cyclic-olefin polymer.

These are all important considerations that should be factored in alongside designing for usability and reliability.

SUMMARY

Developing an emergency-use autoinjector is particularly challenging because of several issues:

- **Usability** – These products need to be used safely and effectively, every time; however, the usability of some of the devices currently available leaves a lot to be desired and known use errors persist. Adding to this is the challenge of shifting away from these potentially flawed interfaces due to existing mental models and the prior experience and training of users. To resolve this there is a clear need for a rigorous, effective HFE programme.
- **Reliability** – In terms of reliability and achieving "five nines", while the FDA draft guidance provides clarity, the bar has been set very high. Conforming to this will significantly impact and shape the development of emergency-use devices.
- **Sustainability** – Finally, while it is critical not to compromise on the two key drivers above, it is also important to consider how the environmental impact of these single-use devices can be reduced, given their relatively short life and the number that end up in landfill.

Moving forwards, device manufacturers must balance each of these factors carefully to develop devices that are safe, effective and reliable, while minimising their carbon footprint.

ABOUT THE COMPANY

Team Consulting is a world-class partner in drug delivery device design and development. For over 37 years its multidisciplinary team of experts have applied the latest approaches in design theory, engineering ingenuity and human factors to deliver products that are not only regulatory compliant, but loved by end users. Working with leading pharma companies and innovative start-ups across the globe, Team Consulting thrives on helping its clients deliver the right technologies for their drug delivery needs.

ABOUT THE AUTHOR

John Burke specialises in the design and project management of medical devices, with a particular focus on the development of parenteral drug delivery devices. A designer by training with a strong grounding in medical design and regulatory focused human factors, he regularly attends user studies in both Europe and the US. On projects he seeks to balance technical, user and commercial requirements to produce simple elegant solutions. Over the years, Mr Burke has worked on a range of parenteral device developments with leading pharma companies in both Europe and the US and has a good knowledge and understanding of the market, current devices and trends.

ENSURING PATIENT SAFETY AMIDST MEDICAL DEVICE REGULATION DELAYS WITH PMS

Here, Timothy Bubb, Technical Director at IMed Consultancy, discusses the five steps to setting up an effective post-market surveillance process.

In late 2022, EU Health Commissioner Stella Kyriakides identified a need for "additional measures to address the structural problems" relating to the implementation of the Medical Device Regulation (MDR) and proposed delaying MDR enforcement by three to four years to prevent product shortages and give the market time to implement new measures.[1] The Commission has since formalised the Kyriakides' suggestion and implemented regulation changes to extend the transition period for higher-risk devices until the end of 2027 and for medium- and lower-risk devices until the end of 2028.[2]

Whilst this delay recognises the risk of setting a conformity deadline before the market and assessment systems are fully prepared, it does not resolve the threat for many existing and new medical devices of not being able to enter – or of being forced out of – the EU market.

A Challenging Scenario for Drug/Device Combination Products

This is therefore a particularly tough situation for many players in the flourishing drug delivery devices market, driven by an increasing level of chronic diseases, groundbreaking innovation and technological advancements in manufacturing. Indeed, as many new drugs require innovative delivery devices, there is a growing need for safe, advanced drug delivery devices to complement the approval of new drugs and the fast-growing advanced therapeutic medicinal products area.

With the aim of increasing patient autonomy, many drug/device combination products, such as prefilled syringes and implantable infusion pump systems, are designed to be used directly by patients to increase convenience through self administration – and, in some cases, even complete automation of drug therapy delivery. This makes monitoring device usage and performance to ensure patient safety all the more important.

MDR Requirements Related to Patient Safety

Therefore, even in the midst of these delays, ensuring patient safety is paramount for manufacturers. Fortunately, this can be facilitated by clearly identifying and aligning with the new or enhanced requirements under the MDR that are closely related to patient safety and already enforceable. For example:

- Post-market surveillance (PMS)
- Periodic safety update report
- Post-market clinical follow-up
- Person Responsible for Regulatory Compliance (PRRC) – unless selling only legacy devices.

As PMS requirements under the MDR have been applicable since May 26, 2021 for all medical devices sold into the EU, regardless of a device's MDR CE-marking status, now is the time to address those requirements.

> "As many new drugs require innovative delivery devices, there is a growing need for safe, advanced drug delivery devices to complement the approval of new drugs."

SETTING UP AN EFFECTIVE PMS PROCESS

With the objective of striving to prevent problems rather than seeking to resolve them once they occur, the MDR gives special focus to proactive post-market surveillance. By placing special emphasis on gathering clinical and safety-related data after completion of the CE certification process, approval and market access, it

Timothy Bubb
Technical Director
T: +44 1295 724286
E: tim@imedconsultancy.com

IMed Consultancy Ltd
Bloxham Mill Business Centre
Barford Road
Bloxham
Banbury
Oxfordshire OX15 4FF
United Kingdom

www.imedconsultancy.com

clearly highlights the importance of putting in place and maintaining regular, careful assessments relating to the device's performance.

Step 1: Connecting with Users and Patients

Thanks to modern technology, manufacturers can assess any potential issues with their product by connecting with patients and users of medical devices in a two-way conversation. For example, certain patient groups may experience specific side effects or discomfort. Additionally, this conversation may assist in identifying how devices are used outside of their intended use – a particularly important aspect as manufacturers must be fully aware of this to ensure they are not complicit in any off-label use. If off-label use of a device is discovered, manufacturers must notify users and take steps to remedy it. This is a scenario that could involve healthcare professionals and necessitate education and training on the device's intended use.

Finding off-label use does not always have to be bad – in fact, if the manufacturer collects sufficient clinical, safety and performance data to enable a conformity assessment and approval, it may provide an interesting insight that enables the formulation of new claims regarding the device and novel market segments in which to sell it.

Step 2: Monitoring Social Media Channels

Linked to step 1, this activity is crucial for obtaining information directly from patients and social media users who talk about their real-world experiences. Monitoring social media also plays an essential role in ensuring that marketing and communications departments adhere to the company's compliance and messaging, particularly regarding off-label use. Comments written in the wrong context – such as "So glad to hear that!" – could easily be interpreted as support for off-label use, causing legal and reputational harm.

Step 3: Tracking Competitor Device Performance

This is good business practice and also helps evaluate "clinical benefit" and "state of the art", which are important new elements of the regulations. Competitors' performance can be tracked to show appropriate surveillance, in compliance with the new regulations, and provide fresh data for ongoing clinical evaluation. If complaints or potential issues are found with a device that is similar or performs the same function, there is the opportunity to fix common problems before they spread and put patient safety at risk.

Step 4: Surveying Published Literature

Medical device manufacturers must regularly analyse published work that is relevant to their device market or to similar products. This is to gather information regarding the device's use, performance and safety profile. Key clinical evidence can be found in scientific and medical literature that may highlight potential risks or even provide more convincing evidence of a product's clinical benefits. Specialist trade publications that cover the target application market of the device, together with more general nursing, medical or healthcare titles, are also good sources of intelligence as they offer practical, real-life opinions from users and patients, and provide general insights regarding off-label use.

Step 5: Periodically Re-Evaluating the Risk Data for Each Device

When launching products, manufacturers prepare very precise risk management documents. But many fail to update them regularly with new statistics and data. Ideally, this activity should be done on a regular basis because repeated use in the real world uncovers new information. Best practice suggests that a review and update of risk management data should be done at least once a year – and more frequently for higher-risk and novel devices.

GETTING PMS PROCESSES IN PLACE

These five steps for effective PMS need to be regularly monitored by specialist teams with suitable skills to identify any issues before they become a problem or cause preventable patient harm. Therefore, although transition arrangements may be delaying the urgency for MDR certification, now is the perfect time to make headway in establishing solid systems and processes to protect devices from potential non-conformities, safeguard users and patients, and help generate the required safety and performance data needed for successful MDR approval of existing medical device product portfolios.

An immediate, plug-in solution aimed at easing the considerable pressures on busy teams is to enlist the support of specialist consultants who are experts in satisfying post-market obligations and can provide ample reassurance that manufacturers are meeting their obligations and are compliant.

ABOUT THE COMPANY

Founded in 2012, IMed Consultancy offers a wide range of regulatory and compliance services to the medical technology industry, supporting medical device manufacturers through all stages of the product lifecycle from concept and design consultancy through to PMS activities. IMed Consultancy's team of skilled and experienced medical regulatory professionals offers an outstanding yet flexible service covering regulatory affairs, UK Responsible Person (UKRP) and EU Authorised Representative (EUAR) services, PRRC, and quality assurance in medical devices, including Class III active and implantables, companion diagnostics, software as a medical device (SaMD) and *in vitro* diagnostics (IVDs). With extensive hands-on problem-solving expertise, IMed Consultancy's remit is truly global, ensuring that client devices are successfully launched and maintained in total compliance in the UK, EU, US and internationally.

REFERENCES

1. *"Opening Remarks by Commissioner Stella Kyriakides at the EPSCO Council-Implementation of the Medical Devices Regulation". Speech, European Commission, Dec 9, 2022.*
2. *"Regulation (EU) 2023/607 of the European Parliament and of the Council of 15 March 2023 amending Regulations (EU) 2017/745 and (EU) 2017/746 as regards the transitional provisions for certain medical devices and in vitro diagnostic medical devices". Official Journal of the EU, Mar 15, 2023.*

ABOUT THE AUTHOR

Timothy Bubb has more than 10 years' experience in quality assurance and regulatory affairs roles, with breadth and depth of knowledge across regulatory, engineering, clinical, design and development, and quality assurance disciplines. He has a passion for empowering innovation in medical devices and brings insight and pragmatism to projects bringing complex lifesaving and life-enhancing products to market.

DESIGNING FOR USABILITY IN EMERGENCY-USE COMBINATION PRODUCTS

In this article, Thomas James, Lead Mechanical Engineer at Key Tech, highlights the importance of early user engagement, as well as continuous refinement of information and workflow design, for efficient development of drug-device combination products for emergency use.

Designing a drug-device combination product can be exceptionally difficult, and reliability is one key aspect that must always be considered and refined in any proper risk management programme. Reliability becomes more important still when a combination product is intended for emergency-use scenarios. Although that bar is high – 99.999% high, to be precise – for any given critical-to-function technical requirement, performance against that bar will be (conveniently) both measurable and verifiable from relatively early on in the development process.

However, when it comes to the usability of these devices, whether they are autoinjectors for administration on the playground, dosing aids in a sterile field or novel delivery devices being used at the bedside, a deep understanding and consideration of the wide range of use-risk scenarios needs to be established long before formal development begins to ensure a commensurate degree of use-related reliability. Unfortunately, these variables can be a bit more complicated to bench test.

The importance of early application-specific user engagement is essential to a successful emergency-use device development programme. Looking past the user's physical capabilities and into their preferences, instincts and expectations can help the development team understand exactly what the most sensitive use steps are – and how to best get ahead of those opportunities for error. By widening the view to the full drug delivery journey, from unboxing to disposal, it quickly becomes evident just how valuable each user touchpoint is along that journey. Furthermore, pointed iteration around information and workflow design can play a surprisingly significant role in conveyance of safe and effective device use to the end user, even in these high-stress scenarios.

> "By widening the view to the full drug delivery journey, from unboxing to disposal, it quickly becomes evident just how valuable each user touchpoint is along that journey."

USER CHARACTERISTICS: BEYOND THE NUMBERS

Understanding the foreseeable user groups, including both patients and caregivers (often one and the same) is a first step towards establishing a human-factors-based starting point for device requirements. Fortunately, published sources covering generic demographic capabilities may guide the technical requirements, such as activation forces or grip diameters. In many cases, however, they do not provide enough insight into creating requirements or informing design strategies that are tailored specifically towards those populations. In these cases, a dedicated, well-designed investigation may be necessary to better understand user preferences and intuitive, population-specific administration practices. As an example, in patients with decreased mobility, an assessment of self-injection location preference and instinctive device handling techniques would be a valuable set of inputs to guide downstream architecture exploration and definition.

User Literacy and Device Use

User characteristics encompass more than physical measurements and force capabilities. Assumptions about user literacy can be particularly risky in emergency-use products. For example, an impaired user administering naloxone or a child with a

Thomas James
Lead Mechanical Engineer
T: +1 410 385 0200
E: tjames@keytechinc.com

Key Tech Inc
40 East Cross Street
Baltimore
MD 21230
United States

www.keytechinc.com

"When healthcare professionals are involved, there is a high risk of use-step transference from other devices they have previously encountered."

rescue inhaler may not fully comprehend written on-device instructions, particularly those with precise clinical language. In fact, reading comprehension of even the most well-read, measured and methodical users can be greatly impacted by the stress of an emergency scenario. Although it would be highly valuable, it is very difficult to recruit for a formative study with exclusively <5th percentile participants in the "performance under pressure" category. Whilst it is a nuanced scenario, on-device symbols and co-ordinated colour motifs can often help guide correct use among (even temporarily) mixed-literacy users.

User Expectations and Instincts

Expectations around device usage and workflow are a double-edged sword in emergency settings – and often in unexpected ways. Frequently, the lay caregivers with the least device experience can, in fact, be some of the most successful users, as they have very little in the way of preconceived notions of intended workflow. When healthcare professionals (HCPs) are involved, there is a high risk of use-step transference from other devices they have previously encountered. Developers must carefully consider product appearance, workflow and use setting to avoid this potential pitfall. If a product looks like an inhaler but does not work like an inhaler, it should be no surprise to the development team when use errors are encountered in early HCP engagements and formative studies.

Counterintuitively, intentionally manipulating the device form and workflow away from HCPs' expectations can be an effective approach to improve correct use, as it helps to keep the users on their toes during the workflow. Of course, taking that strategy to an extreme can be dangerous, as users can often be intimidated during their first use of an unfamiliar device.

In instances where user instincts play a particularly significant role in device interactions, dedicated handling models with distinct forms or functions can help inform which specific device concept characteristics are driving those transference behaviours. From there, the development team can thoughtfully consider how best to either avoid or leverage those user instincts for successful device use.

UNDERSTAND THE DRUG JOURNEY – AND OPTIMISE ALL OF IT

A comprehensive understanding of the entire drug delivery journey, from preparation to administration and disposal, is crucial to ensure that emergency-use combination products effectively capitalise on every moment of user interaction. To achieve this, developers must document and analyse each step along this journey, challenging the interface points and identifying any unique environmental or use considerations specific to each step.

Product Retrieval and Unboxing Experience

When product retrieval is part of the emergency-use scenario, understanding the locations and the ways in which the product is stored is critical, as the storage conditions frequently vary greatly from the conditions during administration. Taking an autoinjector as an example, while the administration environment may have one temperature and humidity range, if the product is refrigerated prior to use, it is very unlikely that the user will be able to "let it warm up for 30 minutes" before administration, which is common practice in self-administration for management of chronic conditions. Whilst this readily translates to power-pack design requirements to handle potentially elevated viscosities and deeper characterisation of break-loose glide force, for example, it also elevates the criticality of effective in-process feedback solutions, due to the range of resultant injection times that the user needs to successfully navigate.

Developers must consider scenarios such as the risk of opening the box before use, as can happen with co-packaged drug-device combination products, as the use risk of potentially separating the instructions for use (IFU) from the product quickly becomes relevant. Similarly, in situations where the product requires sterile compounding, ensuring that necessary information reaches the user administering the product is essential, often through on-device labelling. Effective functional packaging, with consistent and targeted information design on the outer carton, IFU and sterile barriers, can help establish correct use practices even in those unfortunate cases when the user disregards and discards the IFU.

Circling back to the drug delivery journey, it is important to consider each use step not only as a challenge but also as an opportunity. The unboxing and preparation experiences, for example, are often overlooked by engineering teams during architecture development, but they play a significant role in communicating proper device use to the user. In many cases, these "non-critical" steps may take longer than the actual device use. For example, if 30 seconds of interaction with external packaging precedes a 10-second injection, three-quarters of the opportunity to communicate with the user is during the external packaging touchpoints.

There should be a dedicated focus during product architecture development to optimise the information and workflow design of unboxing and preparation to stack the deck in the user's favour. It is incredibly valuable to trial this "full workflow" experience in front of users as well. Evaluating a concept's effectiveness is one obvious reason why but, furthermore, providing realistic device packaging goes surprisingly far towards helping users to settle into simulated-use scenarios, which are notoriously difficult to produce.

In-Process Feedback and Workflow Design

In chaotic emergency-use settings, planning for multiple feedback mechanisms is vital. For example, a single audible feedback source may be insufficient in a noisy industrial environment, so visual or tactile feedback should also be implemented. Fortunately, some features can provide multiple types of feedback – an end-of-dose "click" in an autoinjector often comes with a tactile sensation for free.

In many emergency-use systems, mechanical lockouts are often a necessary feature to mitigate risks such as premature dose delivery. However, not all use steps are tightly coupled to internal mechanisms of the device, and therefore it can be extremely difficult to poka-yoke those steps to mechanically "enforce" correct use.

"In chaotic emergency-use settings, planning for multiple feedback mechanisms is vital."

For example, consider a dual-chamber injector that reconstitutes at the point of care. Guiding the user through a process such as "confirm that all particulates have dissolved, then invert the pen and continue with a priming step" is not easily handled by internal cams and triggers. In these instances, functional labels that force interaction (e.g. "inspect and then tear along the perforation") can be used to briefly capture the attention of a user who had been racing through the device use steps up to that point. To ensure that that moment of attention is as effective as possible, eye-tracking glasses can help evaluate if on-device labelling and critical features are in line with the user's instincts, which allows the designer to make the most effective use of that high-value on-device real estate.

Functional labels offer the added benefit of rapid iteration and evaluation of different information design strategies, as they can often be revised and reprinted on the fly by a nimble design team. This capability allows for quick adjustments during early use studies and helps calibrate the designer's ability to put themselves in the user's shoes (or scrubs) as the product development cycle continues back at the office until the next in-person device evaluation.

CONCLUSION

Efficient development of drug-device combination products for emergency use demands a deep appreciation of user characteristics, expectations and instincts, as well as a comprehensive analysis of the entire drug delivery journey from unboxing to disposal. Early user engagement and continuous refinement of information and workflow design are crucial for guaranteeing safe and effective device use. Focusing on user preferences, instincts and expectations throughout the entire device process allows designers to craft a smooth user experience, significantly reducing opportunities for human error, even in the most stressful settings.

"Focusing on user preferences, instincts and expectations throughout the entire device process allows designers to craft a smooth user experience."

ACKNOWLEDGEMENTS

The author would like to acknowledge Mariano Mumpower and Chet Larrow of Key Tech (Baltimore, MD) for their collaboration on risk-based architecture development strategies in early-stage product development, in addition to their first-rate technical and usability design expertise. Credit is also due to the continued partnership on these methods with Marty Coyne and Chris Franzese of Matchstick (Boonton, NJ), who bring with them comprehensive clinical expertise and industry-leading user-engagement methods.

ABOUT THE COMPANY

Key Tech is an end-to-end product development firm specialising in the design of complex electromechanical devices and systems for medical applications. It is 100% employee owned and located in downtown Baltimore (MD, US). Key Tech employs 75 engineers and designers focused on transforming complex technologies into simple, intuitive solutions.

ABOUT THE AUTHOR

Thomas James is a Lead Mechanical Engineer at Key Tech, where he is responsible for both the innovation and development of novel drug preparation and delivery devices. During his tenure at the company, he has contributed to several in-clinic and at-home infusion and injection systems, ranging from low-cost emergency-use disposables to highly accurate and flexible advanced-functionality delivery systems. Mr James also serves on Key Tech's business development team, focusing on the pharmaceutical and drug delivery industry. He holds a BSc in Mechanical Engineering from the University of Maryland (MD, US).

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STRATEGIES FOR TEST METHOD VALIDATION OF DRUG DELIVERY PLATFORMS

In this article, Deepu Asok, Manager, Small Molecule Portfolio Ops & Analytics, at Pfizer, discusses the importance of test method validation for drug-device combination product development and how a common mistake is to design the validation process for a specific device rather than to accommodate the potential variety of a device platform.

With the recent rise in use of biologics for treating chronic diseases, the relevance and application of injectable drug delivery systems are on the rise. The global injectable drug delivery devices market reached a value of nearly US$39.9 billion (£32.1 billion) in 2022 and is expected to grow to $58.1 billion by 2027 at a rate of 7.5%.[1] As more therapies shift towards self-administration in an at-home setting, the need for innovative injection devices is on the rise.

> "When a design is established based on specified design inputs, it becomes the responsibility of the device manufacturer to confirm that the design outputs meet the predefined acceptance criteria."

This rising demand has forced both device and drug manufacturers to think in terms of delivery platforms instead of one-off delivery devices. However, this means that manufacturers must become creative when designing their studies to gather evidence about the safety and effectiveness of these delivery platforms. A key element to ensure the success of those studies is the test methods used to verify the safety and efficacy of the devices. The strength of the data rests upon the foundation of the test method validation (TMV), which establishes that the test methods are robust, repeatable and fit for purpose.

WHAT IS TEST METHOD VALIDATION?

When a design is established based on specified design inputs, it becomes the responsibility of the device manufacturer to confirm that the design outputs meet the predefined acceptance criteria. The aim of design verification is to ascertain that design outputs not only fulfil the requirements detailed in the design input document(s) but also evaluate the efficacy of risk controls. Pursuant to this, test methods function as the tools for generating data for design verification tasks. Similar to any tool, the data gathered from them are only as reliable as the tool itself. If a tool is defective, it will produce inaccurate measurements, which, in turn, will lead to incorrect conclusions. Therefore, it is essential to validate test methods to guarantee repeatable and reproducible results; this is vital for the success of any product development project.

A standard TMV process involves designing a study wherein multiple operators conduct a study where they gather test data using the proposed test method. The study will also involve multiple trials on the same (in the case of non-destructive tests) or similar (in the case of destructive tests) test articles. Once gathered, the test results are analysed for variability within the same operator's data and between that collected by different operators. As long as the total variability falls within the range of the acceptable variability limits previously established, the method is deemed suitable for gathering design verification data to be used in the submission.

Conducting TMV studies for multiple test methods can involve a significant amount of time and resources. The whole process involves significant planning and preparation, including standalone supporting documentation, such as TMV plans, protocols and summary reports.

Deepu Asok
Manager, Small Molecule Portfolio Ops & Analytics
T: +1 785 236 9331
E: deepu.asok@pfizer.com

Pfizer Inc.
375 N Field Dr
Lake Forest
IL-60045
United States

www.pfizer.com

"One of the common mistakes that people make when conducting TMV is that they design their validation plans around the product, not the platform."

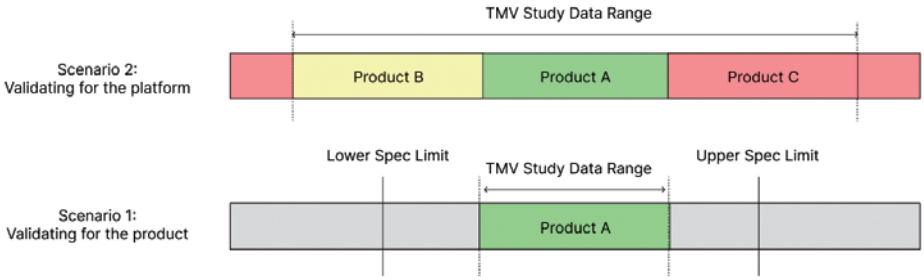

Figure 1: Scenario 1 shows the limitations in the validated data range when using just a single product or part for TMV studies. Scenario 2 shows how using several parts or products within a TMV study provides a wider validated range for the test method.

A common mistake lies not in the execution of such studies but rather in not thinking holistically about the larger needs of the organisation and future device platforms.

THINK IN PLATFORMS, NOT PRODUCTS

One of the common mistakes that people make when conducting TMV is that they design their validation plans around the product, not the platform. For example, executing the TMV using a specific prefilled syringe (PFS) or autoinjector design that the developer plans to file for the immediate submission. Then, a few months later, they realise that there is a new PFS design that needs TMV as well. However, it may not be possible to use the previous TMV study, as the validated range is specific to the product that was included in that study and the new product's performance data falls outside that validated range.

In this case, there is no other choice but to repeat the TMV study for the same test methods, but this time with the new product design. This could require a significant investment in terms of time and effort that could have been saved if the TMV was strategically designed to cover future design variations within that injectable device category. After all, all PFSs must adhere to the same test methods prescribed in ISO standards, such as ISO 11040, 7886 or 11608.

INCLUDE PRODUCT VARIANTS IN THE ORIGINAL TMV STUDY

To avoid this problem of having to repeat TMV studies, try to include multiple product variations within the same study. For example, if there is a 5, 10 and 15 mL version of a syringe, think of ways to design a test method that be used for all these variants. As shown in Figure 1, this can extend the validated range of a test method. Including at least two more product variants, one for a lower data range and one for a higher data range, will establish a validated test method that can be used for multiple design verification studies in the future.

INCLUDING CHALLENGE PARTS IN TMV STUDIES

As discussed, it would be beneficial to include multiple product variations within the same TMV study to avoid the need for future repetition of work. However, during early studies, it may be challenging to obtain different variations of the injectable device. In such cases, the concept of challenge parts can be invaluable.

Challenge parts are custom-engineered test articles that simulate the form and mechanical function of the product family under investigation. For example, when validating the break-loose and extrusion force of a PFS with only one available variant, an engineered sample can be created to replicate the syringe's form and function, such as a piston-barrel system. This sample can then be designed to encompass a broader range of break-loose and extrusion forces than the product intended for verification.

By adopting this challenge parts approach, the validated range of the test method can be extended, while also incorporating the final product to be tested during design verification testing in the comprehensive validation study (Figure 2). However, it is important to ensure that the product that will ultimately be tested during design verification testing is included when conducting TMV studies with challenge parts.

DESIGNING UNIVERSAL TEST FIXTURES

One of the key elements of a test method is the test fixture that is used to hold or manipulate the test article. Instead of designing a fixture around the specific dimensions of an injectable device, it is valuable to develop a design that can accommodate potential variations of future designs. For example, a PFS can come in different shapes, materials and form factors. It could be one with a Luer or non-Luer tip design, one with a glass flange or an add-on flange adaptor, or one with or without a safety device. It is possible to design a fixture that can be adjusted to accommodate these variations without significantly altering the physics of the testing mechanism.

This can be achieved either by designing fixtures that can be adjusted to accommodate the variations in form factor or by using replaceable adapters that can be swapped in and out based on the changes in device design. For example, one of the most common test methods for PFSs is needle-shield removal force, which is often tested by constraining the syringe body and using a pull fork to

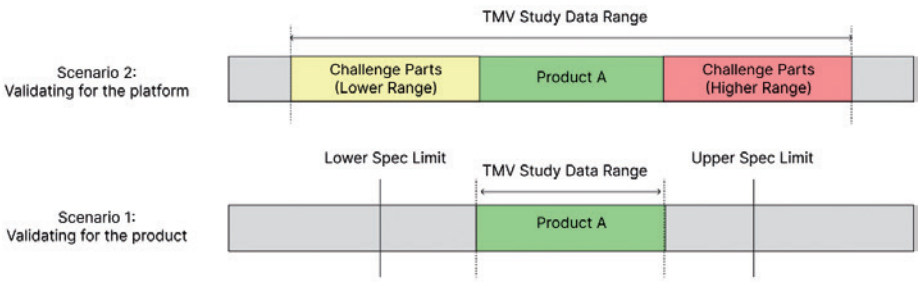

Figure 2: Scenario 1 shows the limitations in the validated data range when using just a single product or part for TMV studies. Scenario 2 shows how using engineered challenge parts within a TMV study provides a wider validated range for the test method.

pull the needle cap out and measure the force using a universal testing machine. In this case, pull forks can be designed to accommodate the variations in needle shield diameters and use replaceable syringe-holder adaptors to include more than one size of syringe in the TMV study.

LEVERAGING EXISTING TEST METHODS

In some scenarios, it may be possible to leverage existing validated test methods instead of starting from scratch. However, it is important to establish a detailed rationale explaining how these test methods are substantively similar. The primary emphasis should be placed on looking at the differences, if any, and explaining how those differences would not impact the validity of the test method. The five key factors that contribute to the repeatability and reproducibility of test methods are equipment, fixtures, procedure, operator and environment. While leveraging previous test methods, make sure to include a side-by-side comparison of these five factors and justify any identified differences that would not impact the test results (Table 1).

Test Method Attribute	Test Method 1	Test Method 2	Rationale for Differences (if any)
Equipment	Equipment A	Equipment B	
Fixture	Fixture A	Fixture B	
Operator	Operator Profile A	Operator Profile B	
Procedure	Procedure A	Procedure B	
Environment	Environment A	Environment B	

Table 1: Sample table for analysing the differences between the key factors for two test methods.

1. **Equipment:** The measurement equipment used is a crucial element of test method validation. If a different model is used, it is necessary to establish that the new equipment is substantively similar to the original one. For example, Instron (MA, US) and ZwickRoell (Ulm, Germany) are two popular makes of equally capable universal testing machines that are used in the industry. By providing a comparison, including a detailed analysis of the two pieces of equipment's capabilities, operating ranges and precision, it is possible to justify leveraging a TMV study that used one piece of equipment to support testing performed using the other.
2. **Fixtures:** The primary purpose of a test fixture is to constrain the test article in place during the testing process. While using existing test methods, it is important to ensure that there is no significant difference in the fixture mechanism that could impact the results. For example, the repeatability of the test data gathered could vary when holding a syringe using a simple adjustable jaw-type fixture versus a custom-designed syringe-holder fixture.
3. **Procedure:** The test operators must strictly follow the same procedure during TMV and design verification testing. When using existing TMV studies, any deviations from the original procedure must be scrutinised to ensure that they do not impact the validity of the test method. For example, a change in the testing speed for a syringe extrusion force from 100 mm/min to 300 mm/min could produce different test results. However, it does not impact the validity of the test method as a whole as long as the new data is still within the previously validated range.
4. **Operator:** The operator's level of skill and training play a significant role in any test method. When using a validated test method, it is essential to ensure that the operators will receive substantively equivalent or more training and supervision than the operators involved in the TMV study.
5. **Environment:** Environmental factors, such as temperature, humidity and vibration, can impact test method parameters. Careful analysis of any differences in the environment between the original TMV study and the new study must be carried out to identify any potential impact. For example, a study that was validated in a carefully controlled R&D lab may not produce the same results when performed in a manufacturing environment with extreme environmental conditions.

"Embracing a strategic approach to TMV by focusing on platforms rather than individual products can significantly enhance the efficiency and adaptability of the validation process."

CONCLUSION

Embracing a strategic approach to TMV by focusing on platforms rather than individual products can significantly enhance the efficiency and adaptability of the validation process. By adopting strategies such as designing universal fixtures, incorporating challenge parts and leveraging existing test methods, manufacturers can reduce the development cycle time for drug delivery devices. This accelerated development ultimately enables them to bring life-changing therapies to patients more quickly, improving patient outcomes and addressing urgent healthcare needs while staying ahead in the rapidly evolving world of injectable drug delivery systems.

ABOUT THE COMPANY

Pfizer is a global pharmaceutical corporation headquartered in New York, with its research headquarters in Groton (CT, US). Pfizer is among the world's largest pharma companies. It is listed on the New York Stock Exchange, and its shares have been a component of the Dow Jones Industrial Average since 2004.

REFERENCE

1. *"Reportlinker.com announces the release of the report: Injectable Drug Delivery Devices Global Market Report 2023". Press Release, Reportlinker.com, February 10, 2023.*

ABOUT THE AUTHOR

Deepu Asok is Manager, Small Molecule Portfolio Ops & Analytics, at Pfizer, with over nine years of experience in combination product development, focusing on injectable drug delivery systems. His expertise covers development of needle-based injection systems, including PFSs, pens, autoinjectors and wearable injectors, and the test method validation for parenteral drug delivery systems. Currently, he manages the portfolio operations for Pfizer's value-add and innovative small molecule portfolio.

INTEGRATED DRUG PRODUCT DEVELOPMENT AND MANUFACTURING

Here, Andrea Allmendinger, PhD, Chief Scientific Officer; Michael Adler, PhD, Director Drug Product Design; and Hanns-Christian Mahler, PhD, Chief Enablement Officer, all at ten23 health, highlight the importance of integrated drug product development, considering aspects such as formulation, device, container closure system, manufacturing processes and usability, as well as considering the quality target product profile and clinical phase-appropriate technical development strategy.

The ultimate goal of the technical development and manufacture of parenteral products is to develop and supply safe, effective, patient-friendly and competitive medicines for patients. These sterile products must meet regulatory and compendial requirements, as well as related quality aspects, to support clinical studies and deliver for the market after product launch.

Drug substance development of biologics focuses on establishing cell-derived manufacturing processes, yielding purified, efficacious molecules with a certain impurity profile (process- and product-related impurities), however, sterile product manufacturing does not end here. Drug substance manufacturing is followed by sterile (typically aseptic) drug product manufacturing, also referred to as "fill-finish" processing, as an integral part of manufacturing operations. Fill-finish processing is associated with different complex, often underappreciated challenges to supply the final sterile drug product.

This article focuses on the interplay between drug product formulation, primary packaging and drug product manufacturing processes. It highlights how to approach and design the overall technical development to commercialise the final product and avoid lengthy and costly delays by anticipating failure modes and developing mitigation strategies.

> "Drug substance manufacturing is followed by sterile drug product manufacturing, also referred to as fill-finish processing."

TECHNICAL DEVELOPMENT ROAD MAP

State-of-the-art development of parenteral dosage forms comprises the development of formulation and manufacturing processes using appropriate primary packaging materials and possibly devices, and developing and using appropriate analytical methods according to quality-by-design (QbD) principles. QbD is a systematic approach to development that starts with predefined objectives and emphasises product and process understanding based on sound science and quality risk management as described in the ICH Q8 and Q9 guidelines.

Following QbD principles, technical product development starts with the end product in mind, which is summarised in the target product profile (TPP). The TPP typically describes the product in detail and includes aspects such as indication, patient population, treatment duration, delivery

Dr Andrea Allmendinger
Chief Scientific Officer
E: andrea.allmendinger@ten23.health

Dr Michael Adler
Director Drug Product Design
E: michael.adler@ten23.health

Prof Hanns-Christian Mahler
Chief Enablement Officer
E: hanns-christian.mahler@ten23.health

ten23 health AG
Mattenstrasse 22
4058 Basel
Switzerland

www.ten23.health

"The content of a product's TPP and QTPP are typically defined according to patient needs based on the benefit and potential risks to the user or patient population, but also according to market projections, competitive market advantage and regulatory and compliance expectations."

mode/route of administration, dosage form, regimen, efficacy, side effects and therapeutic modality. The quality target product profile (QTPP) links the TPP with expected quality and product aspects, and comprises dosage form, delivery systems, dosage strength, container closure system, route of administration, shelf life, storage temperature, purity and compendial compliance (such as sub-visible and visible particle levels), among other aspects.

The content of a product's TPP and QTPP are typically defined according to patient needs based on the benefit and potential risks to the user or patient population, but also according to market projections, competitive market advantage and regulatory and compliance expectations. As an example, a subcutaneous (SC) application will have a higher user acceptance, and therefore probably higher market penetration, when developed for self-administration and supplied in a prefilled syringe, autoinjector or on-body device compared with a vial presentation due to a significantly higher ease of use. Another example is the higher acceptance for intravitreal injections if dosing frequencies are kept to a minimum.

CLINICAL PHASE-APPROPRIATE TECHNICAL DEVELOPMENT APPROACH

To support clinical and preclinical toxicological studies, a technical development strategy is typically designed by considering a clinical phase-appropriate approach (Figure 1). While, during early clinical and preclinical studies, a high degree of flexibility is required with respect to the applied dose and likely the route of administration, ideally, the final drug product formulation in the final primary container should be used for pivotal studies before product launch.

The therapeutic dose is typically unknown for entry into human (EIH) studies, due to only having limited pharmacodynamic and pharmacokinetic data available from pharmacological and toxicological studies, sometimes with limited applicability of *in vitro* or *in vivo* (animal) tests to the human situation. Therefore, the effective clinical dose needs to be defined in dose escalation studies in humans. In particular, the intended starting dose must be aligned between technical and clinical disciplines. As a result, the drug product configuration must be chosen anticipating changes to the dose regimen.

Vial configurations are a very flexible configuration if developed in combination with an appropriate formulation, allowing for a broad range of fill volumes and different administration options, such as intravenous (IV) or SC injection, dilution in infusion bags followed by infusion or injection via an injection pump. This can be useful, as several drug product strengths and configurations may have to be manufactured during clinical development in order to supply the changing demands and needs of clinical studies.

It is worth noting that each change in drug product configuration, such as a change in fill volume or container closure system (CCS), will require the submission of an amendment to the regulatory dossier. Changes are also associated with additional stability studies, and the impact and potential relevance of these changes on clinical studies needs to be technically assessed in detail and considered with respect to the development timelines and costs.

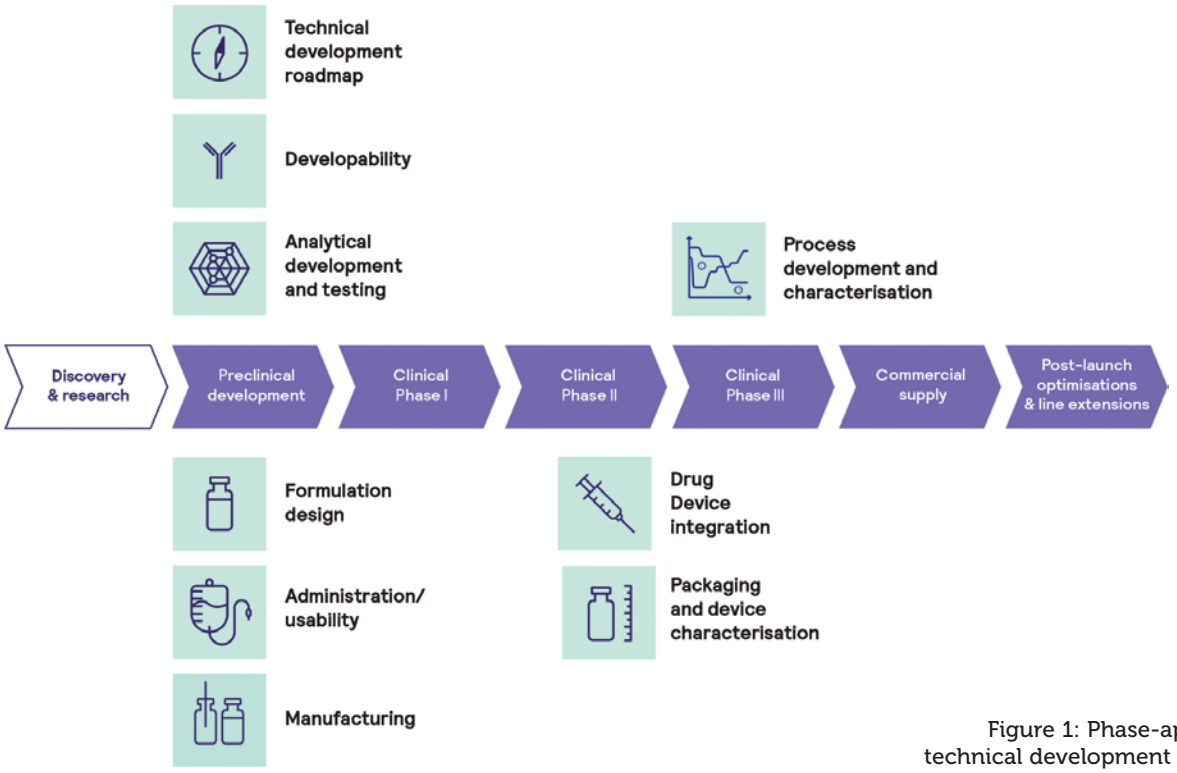

Figure 1: Phase-appropriate technical development approach.

"For biologics, an adequate formulation needs to be developed as early as possible to stabilise the protein and ensure adequate shelf life to support clinical studies."

Many molecules entering the clinical development phase will not make it to market because of an unfavourable risk/benefit balance, such as a lack of efficacy, poor safety findings or an inferior clinical read-out compared with the expected standard of care. Therefore, it is desirable to opt for a lean and cost-conscious development and manufacturing approach until proof of concept (PoC) has been shown. However, reaching the market as fast as possible cannot compromise product quality at any point, with the highest priority being patient safety.

Especially in drug substance development, major changes may occur during technical development, requiring a fine balance between "speed" and "representativeness". Product specifications as documented in the QTPP are typically linked to clinical exposure and variability during clinical testing.

For biologics, an adequate formulation needs to be developed as early as possible to stabilise the protein and ensure adequate shelf life to support clinical studies. However, little is known at this stage of development about product stability during manufacture and storage, as well as about the compatibility of the product with manufacturing and administration materials. Platform-based approaches to formulation and primary packaging are often recommended so that developers can build on existing knowledge and experience, which can – but does not have to – then be refined at a later stage of development.

Some companies prefer a lyophilised formulation over a liquid for EIH studies to maximise product stability. However, the higher manufacturing costs and lower end-user convenience of lyophilised formulations mean that it is likely that the drug developer will want to switch to a liquid formulation at a later point in development. Changing from a lyophilised to a liquid product also creates some specific technical challenges, as new stability studies for the liquid formulation are required and can be expected to show higher degrees of degradation compared with the lyophilised dosage form.

In such cases, the post-change product is expected to be less stable than the pre-change product. With a lack of clinical exposure to relevant impurities and degradants in early-stage clinical testing, this approach not only requires a significant effort to make the change in late-stage development, but also bears a risk of requiring further preclinical, or even clinical, studies to evaluate any potential safety liabilities of the post-change product.

SWITCHING FROM VIAL TO DRUG-DEVICE COMBINATION PRODUCT

The route of administration should be defined in the TPP/QTPP. For injectables, SC application, in combination with a ready-to-use injection device, is typically preferred over IV application, especially for chronic diseases, as well as increasingly for oncology treatments. This can provide benefits such as enabling at-home delivery, shorter administration, self-administration and flexibility for the user. However, the development of drug-device combination products is cost intensive and comes with additional technical risks, meaning that it is typically pursued during later clinical phases.

For EIH, a traditional vial configuration provides maximum flexibility to react to the needs of the clinical dosing schedule, especially as the dose range is unknown for Phase I studies. For known and established vial configurations, the technical risks are rather low, in large part due to the pre-existing knowledge about their use. In early-stage development, leveraging extensive formulation and process development know-how and experience can provide a significant advantage towards defining and making the right experiments using the right methods, which can provide a boost in quality and time compared with generating hundreds of formulation combinations or data points from a blank slate. Another consideration is that fewer stability data at intended storage temperatures are required for regulatory submission for early clinical phases.

The switch from a vial format to the drug-device combination product is associated with numerous technical risks; comparability needs to be demonstrated between the two dosage forms, including comparative stability studies. However, many technical and analytical endpoints can be expected to be different when assessing the product in the vial versus in a syringe. Manufacturing vial and prefilled syringe or cartridge presentations on the same filling line can avoid technical transfers and thereby minimise technical and comparability risks, as well as costs and delays to project timelines.

Clinical bridging when switching from a vial format to a combination product is ideally performed prior to the start of pivotal studies to minimise any risks associated with the switch. Switching configurations during the pivotal phase is still possible when pursuing accelerated development options; however, additional clinical study arms may be needed.

Switching the route of administration during clinical development, such as from IV to SC, in addition to introducing a combination product, adds further complexity to both the technical and clinical development road maps, requiring extra clinical bridging studies, such as bioavailability and safety studies, as well as technical comparability studies if the API concentration or formulation is adapted.

CCS AND DEVICE SELECTION – SELECTING THE RIGHT PARTNERS

Selection of the appropriate CCS and injection device for a formulation, such as a prefilled syringe, autoinjector, pen or on-body injection device, depends on the target patient population and indication, intended use or user preference, to name only a few potential considerations. Besides

"The switch from a vial format to the drug-device combination product is associated with numerous technical risks; comparability needs to be demonstrated between the two dosage forms, including comparative stability studies."

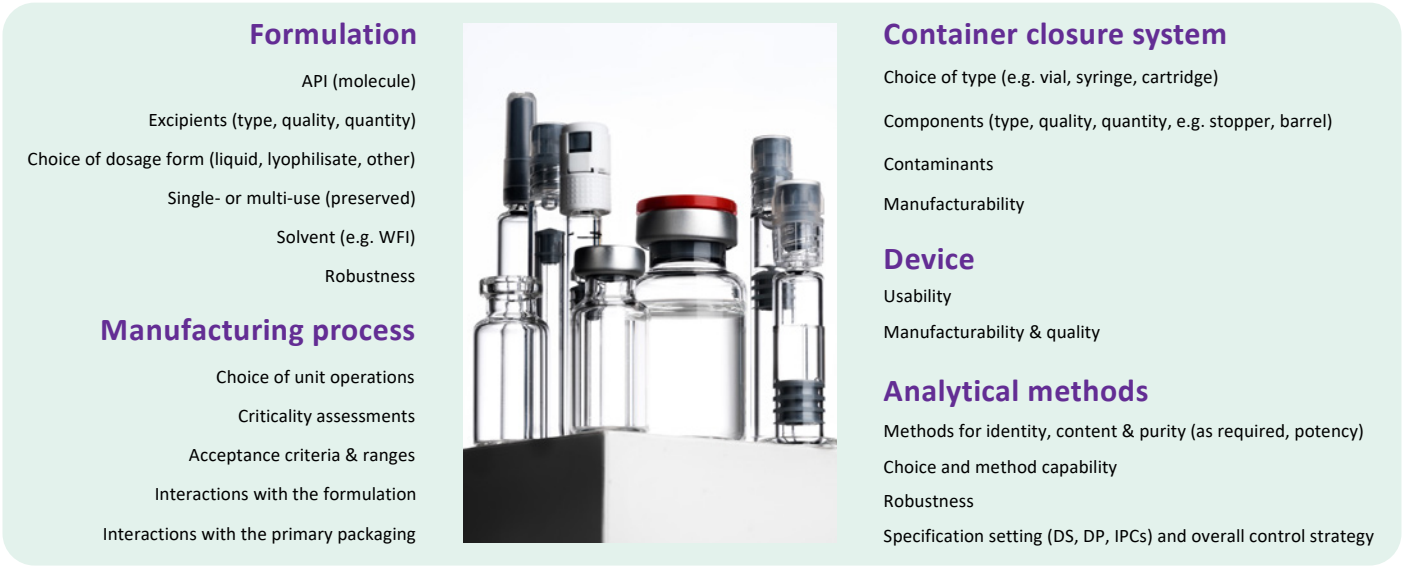

Figure 2: Considerations for integrated drug product development.

usability aspects, technical challenges during drug product development and manufacturing must be evaluated when selecting the appropriate CCS and device. Technical challenges comprise product compatibility with the primary packaging components, product stability, compliance with compendial tests (such as particulates) and functionality.

Functionality and usability are interlinked with the product formulation, particularly so with its viscosity and its visco-elastic behaviour, as well as with manufacturability and choice of unit operations and specific process set-up. Of course, the design of the appropriate needle, including its size, shape, type and supplier, is key. Novel CCSs should be assessed for container closure integrity in detail, using the most sensitive methods, such as helium leakage, and not relying on crude, probabilistic tests, such as dye ingress testing.

The criticality of the entire CCS's material attributes should be studied in detail, considering the respective interplay between parts, including dimensional variances. For example, the variability of a plunger stopper's elasticity in a syringe barrel may significantly impact the quality of the stopper setting during fill-finish operations.

The CCS should initially be chosen to cover a range of fill volumes and viscosities and provide a reproducible injection time per dose strength to allow some flexibility during product development. Selection of the appropriate device and CCS must also consider the pros, cons and associated risks of selecting a new device versus an established CCS.

From a technical perspective, an integrated and holistic development approach, including formulation sciences, manufacturing operations and primary packaging and device component performance and quality testing, is recommended (Figure 2). Selecting the right partners according to their capabilities is essential for transferring product knowledge and facilitating troubleshooting activities. Even better, the groups developing the formulation, choosing the primary packaging and device, setting up and defining the manufacturing process, handling the fill-finish facility and managing quality control and assurance should be within the same company and entity.

Strategy and project timelines must be synchronised between all teams and specifications and test methods need to be aligned to ensure lean technical transfer from development to manufacturing. Additionally, troubleshooting activities can be approached holistically to save time, cost and resources, as well as, most importantly, to avoid errors. In summary, it is recommended to select a partner for manufacturing with very strong development capabilities and expertise.

THE ART AND SCIENCE OF DRUG PRODUCT DEVELOPMENT

Previously, formulation development has sometimes been considered as a by-product of drug substance development, with focus on a few biophysical parameters, such as unfolding or melting temperature of the molecule. However, appropriate formulation development based on expert knowledge using relevant analytical methods and endpoints can resolve many challenges along the supply chain, as a drug product must be manufacturable, shippable, stable during intended or accelerated storage and easy and safe to administer, as well as fulfilling compendial requirements and related quality aspects.

To succeed, a drug product formulation should be developed as soon as possible – ideally, before entering into preclinical and clinical studies, considering all product aspects, such as the target product profile, the intended manufacturing process, its primary packaging and, last but not least, usability by the patient and healthcare professionals.

Early-Stage Development and Manufacturing

The extent and timelines for early-stage formulation development studies generally depend on the molecule. Whilst platform formulations are well established for monoclonal antibodies and antibody fragments, formulation screening is usually recommended for complex molecules, which typically include pH/buffer and excipient screens. Excipients must be safe and non-immunogenic within the dose ranges used, approved for parenteral use and available in a parenteral grade. Information from developability assessments and forced degradation testing, such as by pH, oxidation, light stress, isoelectric point or hydrophobicity, can be helpful to guide the design of the formulation screens.

To define the target concentration for high-concentration protein formulations, it is important to study the relationship between viscosity and protein concentration, the visco-elastic behaviour and the potential

need for viscosity-reducing agents prior to the excipient screen. The target protein concentration for the excipient screen is then based on the outcome of the viscosity assessment. It is typically a compromise between injectability, manufacturability and acceptable injection volume to achieve the desired dose.

As the formulation components can interact with the components of the CCS, formulation development studies should be performed using representative CCSs, which are typically vial configurations for early-phase clinical studies. Examples of such interactions include the precipitation of inorganic material, which results from leaching of bivalent ions with formulation components, and the occurrence of glass surface defects over time, such as delamination.

Potential protein degradation pathways include chemical degradation, such as deamidation, and physical degradation, such as soluble aggregation or the formation of proteinaceous sub-visible or visible particles. Therefore, it is important to use a broad, relevant analytical method panel, including detection and counting of visible and sub-visible particles beside chromatographic and electrophoretic methods for protein purity.

Biophysical methods, such as thermal stability by differential scanning fluorimetry or colloidal stability by dynamic light scattering, have not been proven to be fully predictive for stability yet. Therefore, these methods can support but not replace the need for short-term stability studies and the application of a broad stability-indicating analytical method panel. A forced degradation study should be performed prior to formulation development to establish stability-indicating methods for protein quality. Potency methods are rarely suitable for formulation development studies, especially in early-stage trials, due to their inherent variability, meaning that they may not capture differences in the stability of different formulations.

"The manufacturing processes for early-phase clinical supplies should make use of prior knowledge when setting up the unit operations and when defining target process parameters by using established product-independent process parameters, such as capping pressure, or by using platform CCSs."

The manufacturing processes for early-phase clinical supplies should make use of prior knowledge when setting up the unit operations and when defining target process parameters by using established product-independent process parameters, such as capping pressure, or by using platform CCSs. This eliminates the need for extensive process development studies prior to process implementation, with the added advantage of shortening timelines and saving API and cost. Platform manufacturing processes are generally applicable to platform molecules for which a sound formulation development has been performed, including short-term stability, freeze-thaw stability and shaking stress stability studies. The data from these studies aims to look for potential liabilities, which may impact manufacturability.

For more challenging molecules and formulations, such as high-viscosity formulations, process development studies should look at manufacturability with regard to freeze-thaw stability, compatibility with filter and other process materials, filter binding of API and surfactant, filling pump compatibility and temperature, ambient light and oxidation sensitivity. It is recommended to perform these studies using appropriate small-scale models in laboratories, rather than trying to perform development studies in costly GMP facilities.

Late-Stage Development and Manufacturing – Before Start of Pivotal Phase

Late-stage development starts prior to pivotal clinical trials with formulation optimisation studies that define a formulation in its final CCS in a format suitable for commercialisation. The aim is to optimise stability and thus maximise shelf life by adjusting formulation parameters based on existing long-term stability data of the early-stage formulation. In many cases, the API concentration and dosage strength may also be adjusted during formulation optimisation based on information from clinical dose-finding studies.

The final CCS and device is selected with consideration of the intended route of administration, injection volume, solution viscosity and manufacturability, amongst other factors. Injectability is impacted by solution viscosity, needle gauge and the properties of the primary packaging components according to Hagen-Poiseuille's law. Additionally, siliconisation of the device or stopper hardness may impact injection forces.

"Especially when considering ready-to-use containers and closures, it is important to understand how well particle contamination is prevented and controlled by the manufacturer, as particles cannot be removed during the manufacturing process of the drug product."

Especially when considering ready-to-use containers and closures, it is important to understand how well particle contamination is prevented and controlled by the manufacturer, as particles cannot be removed during the manufacturing process of the drug product. Prior to the introduction of a new CCS, container closure system qualification needs to be performed to ensure container closure integrity, which maintains sterility of the drug product. Additionally, it is essential to assess the compatibility of the formulation with the primary packaging components prior to switching, for example, from a vial used for early-phase clinical trials to a prefilled syringe for late-phase clinical trials or post-approval lifecycle management.

As prefilled syringes and cartridges are far more complex and have more materials in contact with the drug product than a vial, incompatibilities resulting in protein adsorption, protein degradation and formation of proteinaceous sub-visible or visible particles can occur. Prefilled syringes require lubrication to ensure functionality during the product's shelf life. Traditionally, glass syringes use silicone for that purpose. Siliconised primary packaging components typically release silicon oil droplets into the formulation, resulting in an increase in sub-visible particles.

It is important to characterise the sub-visible particle population with methodologies such as flow-imaging microscopy. This enables differentiation of silicon oil droplets from proteinaceous particles, which is valuable as some protein formulations are sensitive to silicon oil, resulting in proteinaceous particles. Such studies are also helpful when changing from a vial to a delivery device, given that this results in higher sub-visible particle counts are expected, yet, typically, not of any clinical significance.

There are further challenges relating to the use of syringes, as residual tungsten in glass prefilled syringes has been reported to lead to protein aggregation and protein oxidation. Radicals in gamma irradiated cyclo-olefin polymer syringes may also result in protein aggregation. Furthermore, cyclo-olefin polymers are permeable to oxygen, which can lead to oxidation of the API or other formulation components. In cases where oxidation is a critical quality attribute, such as with therapeutic proteins that contain a methionine in their binding regions, oxidation events can significantly diminish product efficacy.

In general, incompatibilities can result in a change in product quality leading to underdosing, a shorter shelf life or even requiring a safety assessment. Thus, it is prudent to plan compatibility studies with the selected final CCS and device well ahead of introducing it in late-phase clinical studies so that alternatives can be identified in case of incompatibilities without impacting the overall project timelines.

During development of a prefilled syringe with a staked-in needle, the risk of needle clogging needs to be assessed. Needle clogging can occur due to water vapour transmission from product solution in the needle through the rigid needle shield. Needle clogging is especially critical for high-concentration protein formulations as the solution in the needle can solidify. The impact of a solidified plug is partial or no delivery of the dose and a failure in design verification testing. A careful selection of the prefilled syringe components can mitigate the risk of needle clogging.

Functionality testing of devices is required during formulation development to assess if, and to what extent, break-loose and glide forces change dependent on storage condition and time. Injection forces testing must also address the user capabilities as evaluated in human factors studies. In siliconised prefilled syringes and cartridges, the release of silicon oil from the barrel dependent on storage time might result in an increase in break-loose and glide forces or an increase of injection time for autoinjectors. This impact can result in a failure in design verification and lead to out-of-specification results for stability.

> "For the final manufacturing process, a thorough risk assessment should be performed according to ICH Q9 – for example, a failure modes and effects analysis – to identify potential critical process parameters."

Ideally, the manufacturing site for early-phase clinical supplies can support the transition from the early-phase CCS, such as a vial, to the late-stage and commercial CCS, such as a prefilled syringe or cartridge. The manufacturing process can essentially remain unchanged apart from the filling operation, which saves time and cost for a technical transfer, as well as minimising the risk of comparability failures. Filling parameters need to be optimised and tubing and needle diameter need to be adequately chosen to ensure fill weight accuracy in manufacturing. Furthermore, the stoppering process parameters, for example, the vacuum setting in the case of vacuum stoppering, might need to be determined depending on prior knowledge and formulation characteristics.

The implementation of filling processes for innovative CCSs, such as prefilled syringes for intravitreal injection and cartridges as well as for formulations with challenging formulation properties, may require specific expertise and know-how. The challenges involved with novel CCSs are manifold, such as fill weight accuracy for low fill volumes or bubble-free stopper setting.

Late-Stage Development and Manufacturing – During Pivotal Phase

During pivotal clinical studies, the robustness of the formulation should be tested to assess the impact of formulation parameters on product stability over its shelf life, such as protein and surfactant content or pH. During routine manufacture, various parameters of the formulation are expected to vary within the predefined ranges, such as pH or concentration, therefore, it must be ensured that the product quality remains acceptable. Depending on the results of such a formulation robustness study, the drug product release specification can either be supported by the stability data or it may need to be tightened to ensure quality throughout the intended shelf life. Furthermore, container and closures extractables and leachables studies should be initiated during pivotal studies, in conjunction with ICH stability studies, which need to be submitted in the biologics license application or market authorisation application.

For the final manufacturing process, a thorough risk assessment should be performed according to ICH Q9 – for example, a failure modes and effects analysis – to identify potential critical process parameters. As a result, process characterisation studies should be performed to evaluate the impact of the manufacturing unit operation, as well as any associated potential critical process parameters and their ranges, including time out of refrigeration, ambient light exposure and extractables and leachables of product contact materials, on critical quality attributes and process performance.

These studies should identify critical and non-critical process parameters and enable the definition of target and acceptable process parameter ranges. Based on the results of process characterisation studies, necessary and meaningful in-process controls and respective acceptance criteria or alert limits can be defined, as

> "The impact of transportation on product quality can be assessed by transport simulation studies, which simulate mechanical stress during air and ground transportation in a lab-scale set-up."

summarised in the overall control strategy. After successful process characterisation, the risk assessment is usually updated and the process performance qualification campaign can be executed as prerequisite for a biologics licence application or market authorisation application submission.

To enable an impact assessment on product quality after temperature deviations during transport, it is recommended to perform a temperature excursion study. High and low temperature excursions are simulated and their impact on product stability is tested. Furthermore, the impact of transportation on product quality can be assessed by transport simulation studies, which simulate mechanical stress during air and ground transportation in a lab-scale set-up. The impact of reduced pressure during air transportation on potential stopper movement in prefilled syringes and cartridges, which might impair sterility, can be tested at lab scale with an appropriate vacuum chamber. It is key to appropriately define representative worst-case samples when performing such studies, for example, the air bubble size will typically be relevant for prefilled syringes.

CONCLUSION

Given the many pitfalls and challenges covered in this article, it is obvious that the development and manufacturing of a drug-device combination product goes far beyond the identification of a stable, high-concentration protein formulation or the ability to successfully fill a GMP batch of sterile product. It requires the expertise and experience to select a formulation, container closure system and suitable device, as well as to define appropriate manufacturing processes and product use, considering all possible interactions and failure modes.

ABOUT THE COMPANY

As a contract design and manufacturing organisation, ten23 health is appropriately positioned to anticipate and mitigate the technical challenges when developing formulation and manufacturing processes for injection devices. ten23 offers integrated development of formulation services, analytical development and product characterisation, device selection and testing and drug product process design and characterisation. ten23 also provides fill-finish manufacturing of complex and high-precision containers at its GMP fill-finish facility.

ABOUT THE AUTHORS

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

Michael Adler, PhD, is currently Director Drug Product Design at ten23 health in Basel (Switzerland). He has over 20 years of industry experience at different pharmaceutical companies, including Abbott (now AbbVie), Roche, Lonza and ten23 health. He has vast experience in early and late-stage formulation and drug product manufacturing process development for both liquid and lyophilised dosage forms. His area of expertise also covers process transfer, process characterisation and validation and commercial support for biological drug products, including combination products and small-molecule parenterals. Dr Adler has driven development of monoclonal antibodies and novel antibody-derived formats, fusion proteins, PEGylated proteins, synthetic peptides and oligonucleotides for intravenous, subcutaneous, intravitreal and intrathecal delivery. He has extensive knowledge with regards to regulatory registration activities, as well as health authority interactions for the US, Europe and elsewhere. Dr Adler studied Pharmacy at the University of Heidelberg (Germany) and holds a PhD in Pharmaceutical Technology from the University of Erlangen-Nürnberg (Germany).

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

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- Sterile drug product development for different modalities
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- Syringe development, manufacturing, testing
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ten 23 health AG
Mattenstrasse 22
4058 Basel, Switzerland
contact@ten23.health

MITSUBISHI GAS CHEMICAL

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

In this article, Tomohiro Suzuki, Associate General Manager at of Mitsubishi Gas Chemical, reviews the advantages that OXYCAPT™, the company's multilayer material for vials, offers to biologics and gene and cell therapies, and discusses the results of recent tests into low-temperature storage and dimethyl sulfoxide resistance.

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

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

Figure 1: OXYCAPT multilayer plastic vial.

At present, the company is conducting additional studies into extractables, container closure integrity at cryogenic temperature and other properties, the results of which will be shared at the next opportunity.

In recent news regarding OXYCAPT Syringe, MGC signed a LOI with Becton Dickinson (BD) in May 2022 and have started earnest discussions to apply our multilayer technology to next-generation PFS for

Tomohiro Suzuki
Associate General Manager
T: +81 332 83 4913
E: tomohiro-suzuki@mgc.co.jp

Mitsubishi Gas Chemical Company, Inc
Mitsubishi Building
5-2 Marunouchi 2
Chiyoda-ku
Tokyo 100-8324
Japan

www.mgc.co.jp/eng

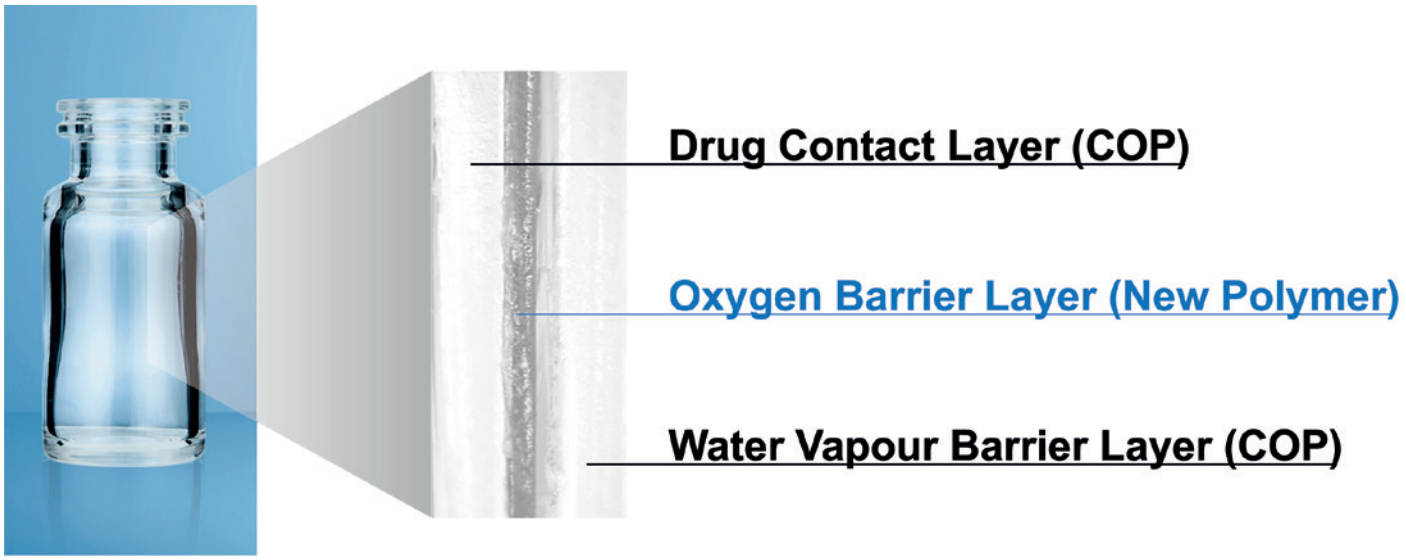


Figure 2: Multilayer structure of OXYCAPT.

biologics. Therefore, we have tentatively stopped introducing the current version of OXYCAPT Syringe to customers. We believe this collaboration will be helpful for the pharmaceutical companies to safely develop novel & sensitive future drugs.

OXYCAPT OVERVIEW

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

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

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

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

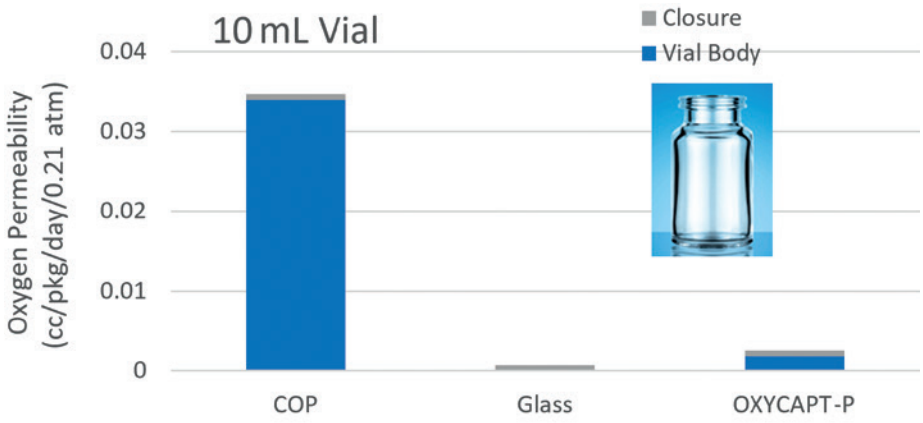


Figure 3: Oxygen permeability comparison of a typical COP, glass and OXYCAPT-P.

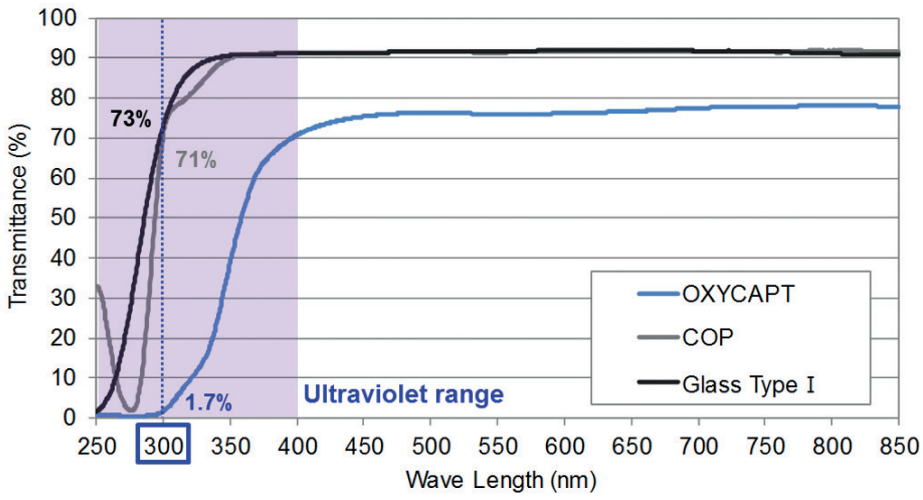


Figure 4: UV light transmittance comparison of a typical COP, Type 1 glass and OXYCAPT.

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

Studies have shown an extremely low level of extractables from OXYCAPT. One study was conducted to confirm the levels of volatile, semi-volatile and non-volatile impurities from OXYCAPT. Water and four solutions (50% ethanol, sodium chloride, sodium hydroxide and phosphoric acid) were selected and impurities were measured by gas chromatography mass spectrometry (GC-MS) and liquid chromatography-UV spectroscopy-mass spectrometry (LC-UV-MS) after 70 days at 40°C. Compared with the control, impurities were not detected in the OXYCAPT containers. A second study confirmed that inorganic extractables levels from OXYCAPT were similar to those from COP, which is well known for being an extremely pure polymer with a better extractables profile than Type 1 glass (Figure 5). Lower levels of inorganic extractables are known to contribute to better pH stability in drug products.

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

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

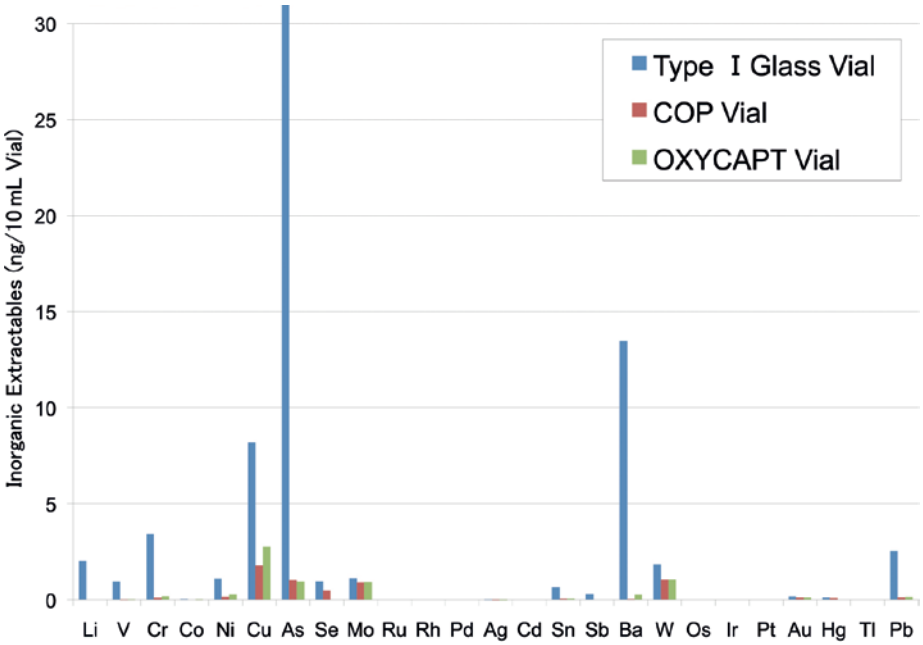


Figure 5: Comparison of inorganic extractables found in COP, Type 1 glass and OXYCAPT.

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

Table 1: MGC's OXYCAPT product portfolio.

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

The primary target market for OXCAPT is the therapeutic application

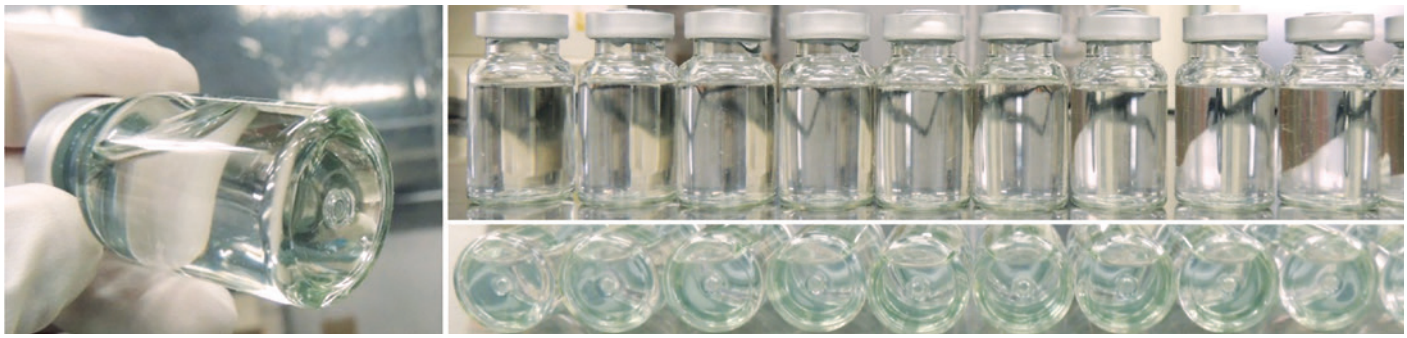


Figure 6: No breakage, leakage or layer separation was found after the quick defrosting test (-80°C to 40°C).

"Some drug developers have recently started evaluating the OXYCAPT vials for their gene and cell therapies; the RTU vial is sterilised by gamma radiation, making it ideal for protein-based drugs."

of biologics. As mentioned in ICH Q5C (Stability of Biotechnological/Biological Products), oxidation is one of the causes of protein instability. As such, the oxygen and UV barrier properties of OXYCAPT will definitely contribute to the stability of biologics stored within. Furthermore, some drug developers have recently started evaluating the OXYCAPT vials for their gene and cell therapies; the RTU vial is sterilised by gamma radiation, making it ideal for protein-based drugs.

OXYCAPT AT VERY LOW TEMPERATURES

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

A further test was conducted where the vials were stored in a freezer at -80°C for one-week, six-month and 24-month periods. After being removed from the freezer, the vials were immediately dropped onto a steel plate from a height of 1.5 m. No breakage or leakage was detected in any of the vials for any length of time in cold storage.

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

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

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

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

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

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

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

Table 3: DMSO resistance of OXYCAPT.

DMSO RESISTANCE

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

CONCLUSION

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

ABOUT THE COMPANY

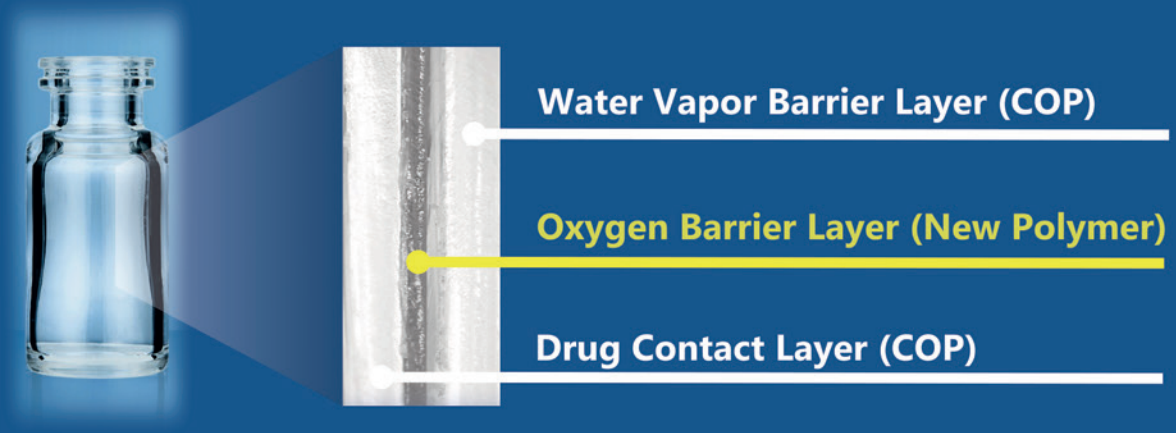
Mitsubishi Gas Chemical is a major chemical products manufacturer, operating across a wide range of fields, from basic chemicals to fine chemicals and functional materials. In 2012, MGC established a new division as a centre for continually creating new businesses. In the field of drug delivery, the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

ABOUT THE AUTHOR

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

OXYCAPT™ Multilayer Plastic Vial

Multilayer Structure



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

2, 6, 10, 20mL Vial

Nest & Tub for Vial

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MITIGATING CONTAINER CLOSURE INTEGRITY CHALLENGES FOR INJECTABLES

Based on an article also published in Express Pharma, May 2023.

In this article, Eugene Polini, Technical Key Account Manager at Datwyler Sealing Solutions, discusses the importance of container closure for the parenteral drug market, including some of the consequences of compromised container closure and what steps manufacturers can take to ensure that primary packaging systems remain sealed for a product's entire shelf life.

PRIMUM NON NOCERE

"First, do no harm", the Hippocratic Injunction, is the often-official motto of healthcare providers, organisations and associations around the world and sets the bar for the global pharmaceutical industry. Patient safety should always come first. However, this philosophy is not just for guiding the practices of medical professionals and drug developers; it extends all the way down to the healthcare sector's expectations for every component, instrument and process in the development and manufacture of medicine. Injectable therapies are often highly sensitive drugs and require the most rigorous protective measures to ensure that unwanted particles, microbes and oxidants do not jeopardise formulation integrity.

> "Injectable therapies are often highly sensitive drugs and require the most rigorous protective measures to ensure that unwanted particles, microbes and oxidants do not jeopardise formulation integrity."

These high standards are not attainable without a serious commitment to container closure integrity (CCI). CCI is the ability of a container closure system to maintain the sterility of the pharmaceutical products contained therein throughout its shelf life. It is also a regulatory requirement for container closure designs. In the case of parenteral drugs, CCI aims to avoid adulteration of the drugs packaged in vials, syringes and cartridges (Figure 1). Even though these types of packaging systems are hermetically sealed, there are still many risks to mitigate.

Figure 1: Parenteral drugs packaged in vials.

Eugene Polini
Technical Key Account Manager
E: eugene.polini@datwyler.com

Dätwyler Holding AG
Gotthardstrasse 31
6460 Altdorf
Switzerland

www.datwyler.com

WHY IS CCI CRITICAL?

CCI is subject to many threats from the ambient environment. When it comes to sterile packaging, standard industry preference is for a terminal sterilisation process, wherein the entire packaging system is sterilised at the end of production. Alternatively, drug manufacturers can package drugs with components that have been sterilised individually, then assembled and filled aseptically by filtering the drug product through a 0.2 µm filter. However, drugs filled and packaged using either method are still subject to the risks posed by CCI failure.

Loss of Aqueous Solvent

If the drug is in an aqueous medium, any hole in the vial can accelerate vaporisation, which can translate to a loss of solvent. Not only can this issue compromise the formulation and patient health, but the disappearance of a labelled ingredient can land drug manufacturers on the wrong side of the law; it is illegal to sell a mislabelled drug in most countries around the world.

Oxidation

Oxygen is, obviously, a potent oxidiser and must be excluded from parenteral packaging systems. Otherwise, the presence of oxygen can lead to the breakdown of fats, lipids, proteins and other ingredients, compromising the drug formulation and its therapeutic impact. In a 5 mL vial, there is typically 3 mL of liquid drug product and 2 mL of gas sitting above it. Therefore, drug manufacturers typically fill the excess space with either nitrogen or argon to exclude any oxygen from the system.

A leak would cause equilibration between the contents of the container and the outside environment. The oxygen-rich environment outside the vial will seep into the vial interior and equilibrate so the atmosphere is 18% oxygen both outside and inside the vial at the same barometric pressure. This can lead to oxidation of the API and inhibit the therapeutic efficacy of the dose.

Introduction of Microbes

A leak in a vial can let in more than just oxygen. There is also the threat of intrusion by microbes, which can be highly dangerous, depending on the microbe and the condition of the patient's immune system. Even the pressure change of a storm could create the conditions not only to pull out, but also to push in material if there is a leak.

Figure 2: Every small component of a primary packaging system, stoppers, plungers and caps alike, has a critical role to play in preserving drug integrity.

WHAT CAN DRUG MANUFACTURERS DO TO MINIMISE THESE RISKS?

First, it must be remembered that every small component, such as stoppers, plungers and caps, has a critical role to play in preserving CCI as part of the parenteral drug packaging system (Figure 2). Stoppers are placed at the top of syringes, vials and cartridges to seal the barrels of these containers. Plungers glide through the barrel of syringes to deliver injectable drugs smoothly and effectively. Caps often top off vials and are comprised of both metal and rubber components. All must be designed with painstaking care to ensure compatibility with the drug product they interact with. With those in place, there are many assessments, practices and technologies available to help drug manufacturers enhance CCI.

Paper Analysis

In this process, analysts compare drawings of components to drawings of the vials and syringe barrels to ensure that there is enough compression and interference between the elastomer and the glass or plastic package to create a seal. Furthermore, they check to make sure there is not too much interference or compression, which can compromise machinability during assembly. For syringes, they must also check break-loose and glide forces for the same factors. The fit should not be too tight or too loose; it must be just right. Typically, the target is approximately 2% compression between the rubber and the walls of the package, but optimal results may vary. For a stopper, more compression is desirable, whereas a plunger requires less to ensure mobility up and down the barrel of the vial.

> "It must be remembered that every small component, such as stoppers, plungers and caps, has a critical role to play in preserving CCI as part of the parenteral drug packaging system."

Many vials are now made with blowback features – small, recessed rings inside the neck of the vial – that allow the rubber to relax into them, which helps to prevent back pressure popping the stopper off. A matching feature can be added to the stopper, such as a protuberance that is designed to snag into the recess. However, problems can arise when the blowback feature is mismatched with the stopper design, so these features must be carefully considered and tolerances included. More recently, there was a movement to make blowback tolerances and dimensioning for these features clearer at the specification stage, which would enable drug manufacturers to better identify potential mismatches during paper analysis.

Dry Lab Work

Dry lab, or exploratory developmental, work consists of a series of practical physical tests. The pop-up test is one example; a vial is filled with water and a stopper is placed loosely on top. This system is then frozen, after which the stopper is inserted to observe whether it pops out due to

positive pressure as the system thaws. The cold gas in the headspace after sealing starts to warm up, increasing the pressure and potentially popping the stopper off. This test is an effective way to assess for stopper and vial compatibility.

CCI Testing

Following dry lab work, the system's CCI is tested with more advanced instrumentation. Typically, these tests use the final drug product, minus the API, to ensure that the package is robust and shows no leakage over the temperature range that the drug product will experience through its lifecycle. This may include cold-chain testing for cryogenic or cold storage, which is often a challenging barrier to success due to the effect of extreme cold on elastomeric components. For example, some drugs must stay at liquid nitrogen temperature (-185°C) to maintain viability. However, rubber and plastic materials take on the attributes of glass at those temperatures, making it difficult to achieve an adequate seal, and requiring alternative approaches.

Residual Seal Force Testing

Residual Seal Force Testing can help elucidate the residual spring left in the elastomeric closure's flange. The flange compresses as vertical force is applied during capping. By locking the skirt in a metal furl during sealing, the energy in the rubber flange is captured and keeps the rubber in a state of compression, which aids in keeping the system sealed throughout the product's lifespan. Measuring residual seal force can test if the capping force is too great, which may create a wrinkle or fold and, ultimately, a product leak. This testing can help drug manufacturers find the sweet spot for capping force as a measure to maximise seal integrity.

Shelf Studies

Shelf studies occur after the drug product is manufactured and include repetitive CCI testing at frequent intervals throughout its proposed shelf life. Typically, the manufacturer will put up three lots of drug product in its packaging. Then, at periods of 0, 1, 2, 3, 6, 12 and 18 months, these samples are tested for, among other things, the quality of their CCI. This assessment gives drug manufacturers a good idea of how the drug will fare over time in storage.

> "No matter where drugs are manufactured, pharmaceutical companies are still subject to the CCI standards of the markets they serve."

INTERNATIONAL CONSIDERATIONS

No matter where drugs are manufactured, pharmaceutical companies are still subject to the CCI standards of the markets they serve. This can complicate the manufacturing process, as pharmacopoeias vary by region. For example, Japan has extremely strict regulations around sterility for closures compared with other markets, requiring significant R&D efforts to develop elastomeric closures that met the standard.

As another example, The US FDA prefers deterministic CCI testing over the probabilistic CCI testing of the past. This preference is due to the fact that probabilistic methods are more subjective and contain more qualitative methodology, whereas deterministic methods are quantitative and non-destructive while still providing actionable insights. As a result, there is greater certainty with deterministic testing methodologies.

As such, it is critical that drug manufacturers comprehend the differences between the markets they serve and work closely with suppliers that understand the nuances of different regional regulations.

ABOUT THE COMPANY

Datwyler focuses on high-quality, system-critical elastomer components and has leading positions in global markets such as healthcare, mobility, general industry and food and beverages. With its recognised core competencies and technological leadership, the company delivers added value to customers in the markets it serves. With more than 20 operating companies, sales in over 100 countries and more than 7,000 employees, Datwyler generates annual sales of more than US$1,000 million. Within the healthcare solutions business area, Datwyler develops, designs and manufactures solutions for injectable packaging and drug delivery systems to facilitate customers to create a safer medical environment. With more than 100 years of history, Datwyler is a reliable partner, now and in the future. The company has been listed on the SIX Swiss Exchange since 1986 (security no. 3048677).

ABOUT THE AUTHOR

Eugene Polini graduated with a Bachelor's of Science degree in Biology from Villanova University (PA, US). After finishing his undergraduate study in 1983, he joined West Pharmaceutical Services, where he served in a number of technical, quality and customer support roles. In 1999, Mr Polini graduated with a Master's in Business Administration degree from St. Joseph's University (PA, US). He has over 30 years of experience working with primary parenteral packaging systems, from R&D to quality control and technical sales support. Mr Polini joined Datwyler in 2017 as a Technical Key Account Manager, working side-by-side with Key Account Managers and focusing on technical sales management and mitigating technical issues for Datwyler's largest clients.

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