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Apr/May	Drug Delivery & Environmental Sustainability
May	Injectable Drug Delivery: Formulations & Devices
Jun	Connecting Drug Delivery
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Aug	Industrialising Drug Delivery
Sep	Wearable Injectors
Oct	Prefilled Syringes & Injection Devices
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Nov	Pulmonary & Nasal Drug Delivery
Dec	Connecting Drug Delivery
Jan 2023	Skin Drug Delivery: Dermal, Transdermal & Microneedles
Feb	Prefilled Syringes & Injection Devices

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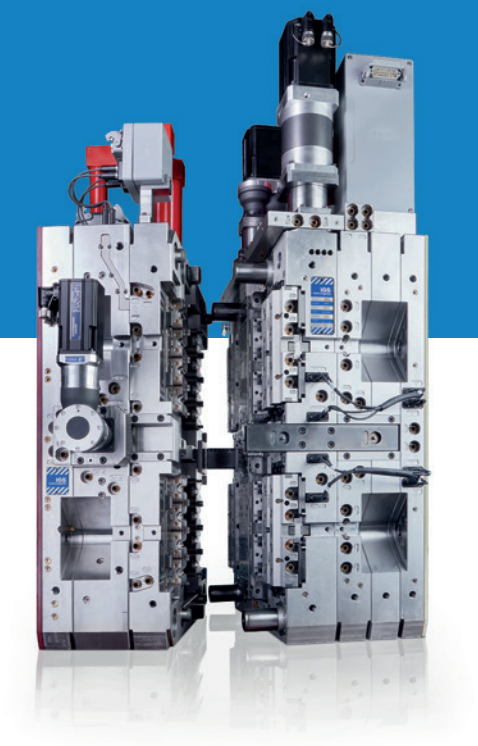

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HOW MODEL BASED DEFINITION REVOLUTIONISES THE PRODUCTION OF MEDICAL DEVICES

Here, Rob Doorakkers, Chief Innovation Officer, at IGS GeboJagema, looks at the advantages of the company's Model Based Definition process and its ability to improve the quality of medical device production.

The requirements for medical devices are constantly evolving. This includes ISO norms and government regulations, of course, but patients today are also looking for greater convenience. Modern devices are becoming easier for patients to use, yet often more complex to produce.

In short, the challenge for manufacturers is to further improve the quality of increasingly complex medical devices. IGS GeboJagema engineers and manufactures injection moulds for drug delivery devices, such as syringes, autoinjectors and inhalers. The key to delivering quality can be captured in a single word: precision. When the company manufactures moulds for medical devices, it works with tolerances as low as a few microns. This need for extreme precision has been a major factor in IGS GeboJagema's decision to implement a new approach in its factory: Model Based Definition (MBD).

> "MBD is the cornerstone of a new way of working that improves product quality and allows for a leaner workflow throughout the production process."

Put simply, MBD is the use of 3D models that contain all relevant product data, instead of 2D drawings. At first glance, the main advantage of MBD might seem to be that it saves time in the design department, but while it is true that MBD removes the time-consuming need to create 2D drawings, this is just one of the many advantages of using MBD.

In fact, MBD is the cornerstone of a new way of working that improves product quality and allows for a leaner workflow throughout the production process. That should be the main reason to adopt MBD.

For decades, the manufacturing industry has used 2D drawings and wrestled with the resultant interpretation and communication problems. Although processes based on 2D drawings are deeply rooted in most companies, these drawings must be interpreted by individuals, meaning errors are unavoidable.

With MBD, every step in the production process uses 3D data. It allows one to aim to automate as much programming as possible in computer-aided manufacturing (CAM) – Model Based Manufacturing (MBM) – and metrology – Model Based Inspection (MBI). This not only minimises human error, but also improves product quality and optimises every step of the production process, from design and manufacturing to programming and inspection. These should be the main drivers to develop a new way of working using MBD – it is integral to an Industry 4.0 strategy.

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> "It is vital that this model is 100% accurate, as every other step in the production process depends on it; any inaccuracies in this product model will result in inaccuracies in the final FEM."

This article discusses how MBD changes the workflow in every step of the production process. From design and logistic technical engineering (LTE) to MBM, the tool shop and model-based inspection.

DESIGN

MBD starts with the design department delivering an optimal 3D CAD file, called a functional engineering model (FEM). The FEM needs to be a 100% accurate model of the actual steel part. Crucially, it should also include all the product manufacturing information (PMI). All information necessary to build a tool should be added to the FEM, such as preload, venting gaps, mounting clearances and so on. The FEM should be 100% nominal, which means no unsymmetrical tolerances; only +/- tolerances can be used (Figure 1).

Creating a perfect FEM starts with a model of the final plastic product. It is vital that this model is 100% accurate, as every other step in the production process depends on it; any inaccuracies in this product model will result in inaccuracies in the final FEM. This means the product designer should invest sufficient time in preparing the model of the plastic product. This file should then be delivered in the toolmaker's preferred settings or, if possible, as a native CAD file. The product designer can also add PMI data, such as tolerances or surface finish information, to this product model, which can then also be included in the FEM. Colour coding is one way of adding PMI data to the FEM, as discussed below.

This new way of working requires a shift in mindset at the design department, as it changes the way it has operated for decades. It takes a little more time to add the PMI to the FEM, but because 2D drawings are no longer required, this change in approach results in a 20–25% time reduction during the design phase. Moreover, it lays the foundation for numerous advantages in subsequent stages of the production process, as will be discussed later in this article.

Adding PMI to the Functional Engineering Model

One way of adding Product Manufacturing Information to the FEM is to use a colour coding system that creates different appearance states (i.e. visualisations in the CAD application) for different types of information (Figure 2). One appearance state shows the colours indicating the required tolerances. Each surface area is assigned its own colour, which corresponds to the tolerance given to the surface (Figure 3). A second appearance state displays the assigned surface finishes, such as electrical discharge machining (EDM) texture or Plastics Industry Association (previously SPI) standard finish.

While designing the FEM, the tool designer can add the required colour (i.e. tolerance and/or surface finish) to the model right away. Currently, this information is often processed days or weeks later when the 2D drawing is prepared, which can lead to errors if the

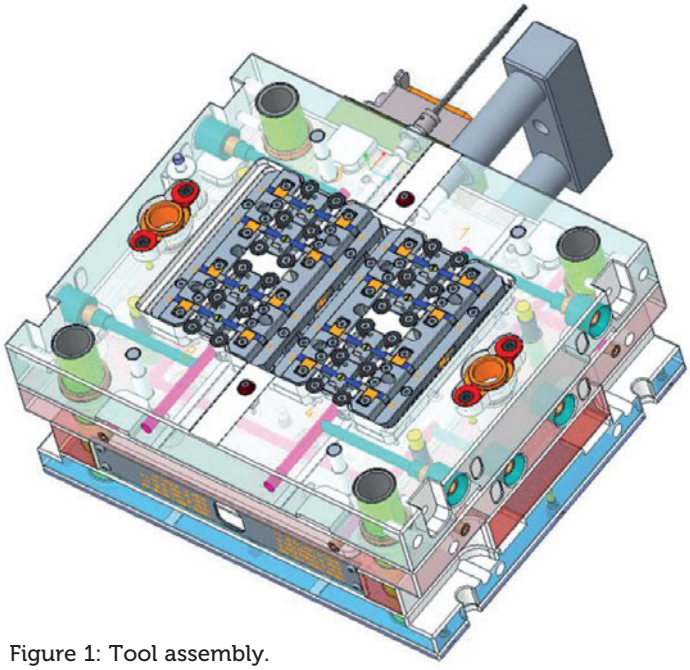

Figure 1: Tool assembly.

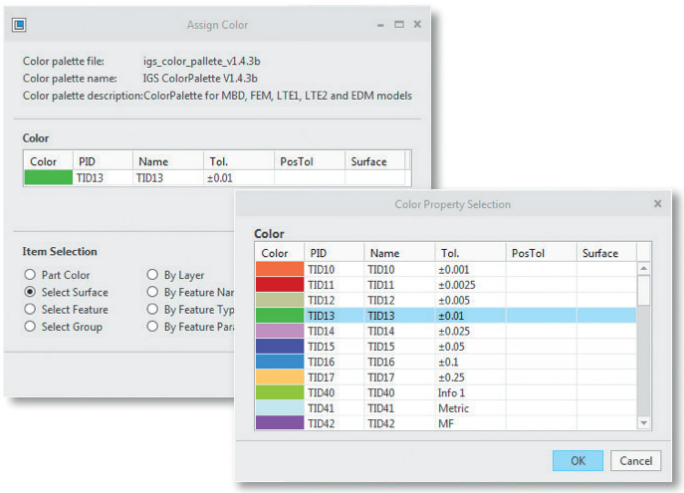

Figure 2: Colour-coding system.

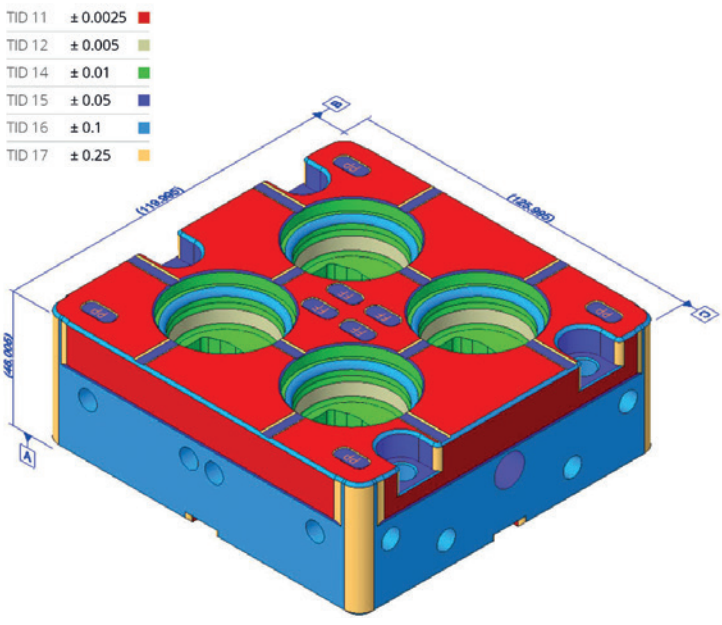

Figure 3: FEM model. The colours indicate the required tolerances.

tool designer misremembers the original idea or if the 2D drawing is created by a different member of the design team. Immediately adding the information during the tool design removes the risk of such errors occurring and significantly reduces drawing failures due to human error.

Moreover, this change in approach makes it possible to start the manufacturing phase sooner. In the old approach, the CAM programmers had to wait until the 2D drawings had been prepared. In the new MBD approach, the FEM has all the necessary information to start programming (Figure 4).

LOGISTIC TECHNICAL ENGINEERING WITH MBD

The LTE team prepares the workflow of the manufacturing departments. They determine the production steps necessary to manufacture the FEM (i.e. the actual steel components used for mould assembly). To do this, the LTE team also uses the MBD strategy and prepares 3D CAD manufacturing models. These manufacturing models are based on and linked to the FEM. Any modifications to the "parent" FEM will automatically be applied to "child" manufacturing models as well. The LTE team has full control over the manufacturing models, but cannot make any changes to the original FEM.

First, the LTE team creates a soft steel manufacturing model in which extra allowance is added, holes are closed, extra features can be included and so on. This means the department will create a 100% accurate model of what will be manufactured in soft steel before it goes into heat treatment. This model can then be manufactured with an overall standard tolerance.

A second manufacturing model is used for hard part manufacturing. The area that should be finished in each of the manufacturing steps is highlighted in this model. It allows the team to add notes, additional dimensions, change tolerances (if required for manufacturing purposes) and more.

A big advantage of this working method is that the workflow is captured within the 3D CAD files and stored in the data management system covered by version management. This allows any replacement or repeat work to be started very quickly and ensures the same manufacturing strategy will be used to create identical parts (Figure 5).

ADVANTAGES IN CAM PROGRAMMING VIA MBM

MDB saves the most time in CAM programming, via the MBM strategy. By aiming to automate 75% of programming, the skills of the program engineers are freed up to improve output. For example, they can optimise the programs in order to improve quality of the most critical parts in the tool and reduce runtime on high-volume production.

Automated programming is possible because the PMI data has been added to the FEM during the design phase. CAM programs cannot read PMI data on 2D drawings. But, through colour recognition, CAM software can determine the tolerances that have been assigned to the holes, chambers, outer boundary and other features in the FEM. Using that PMI, the software can determine the optimal standard strategy for tools to manufacture the cores and cavities.

By preparing standard strategies for milling and lathing, tool shops will be able to use automated programming for 75% of their workload. The main reason for this is to minimise human

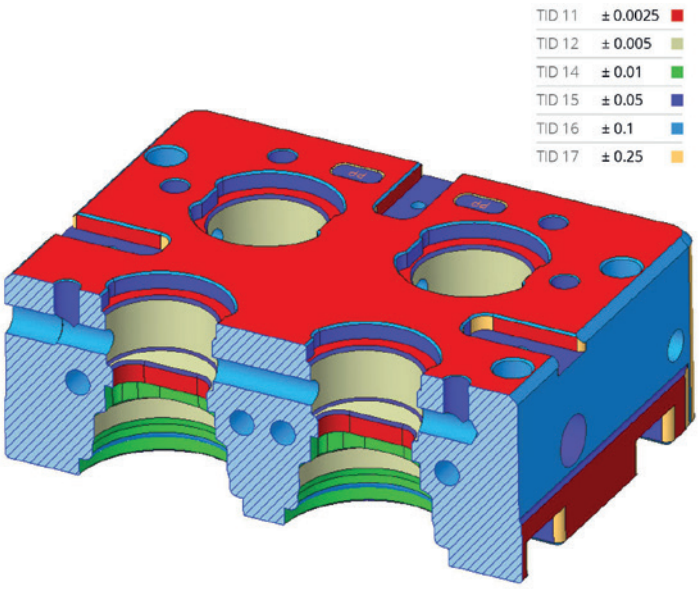

Figure 4: The FEM has all the necessary information to start programming.

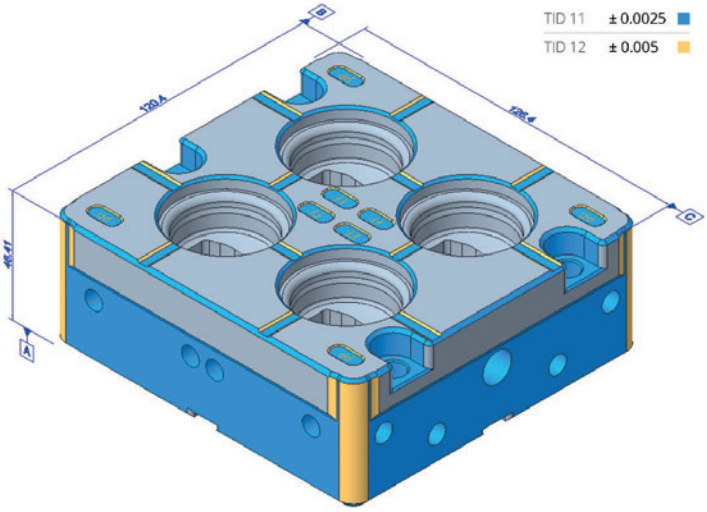

Figure 5: All allowances are in the 3D model. The workflow is captured within the 3D CAD files.

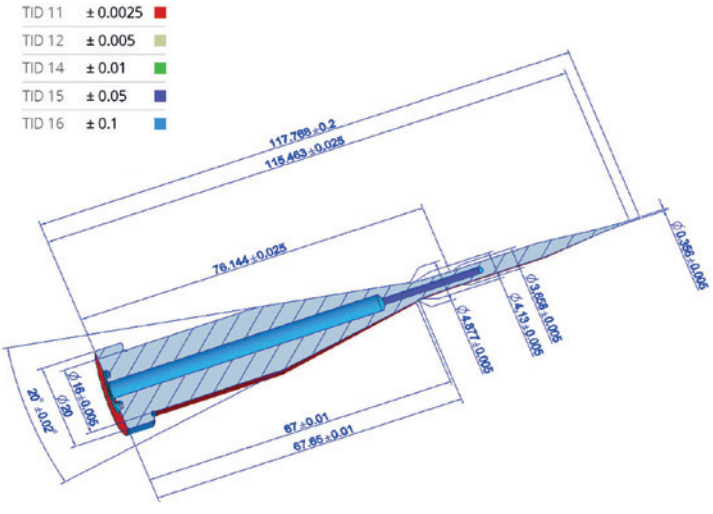

Figure 6: In fully annotated files, operators do not need to measure in the FEM to find the information they need.

"Standardised methods of working create a better workflow and allow program engineers to put more effort into the non-standard and critical parts."

errors and deviations in strategy. These standardised strategies create a recognised, standardised manufacturing method within the tool shop. All this helps to improve quality and output. Standardised methods of working create a better workflow and allow program engineers to put more effort into the non-standard and critical parts.

The goal of this new way of working is not to reduce the number of program engineers, but to create more CAM programs with the same number of people. Over the years, it has become clear that CAM capacity determines the output of the manufacturing departments. With MBD, it should be possible to increase output and create extra machine hours.

MBD IN THE TOOL SHOP

As we move into an Industry 4.0 environment, we need to go paperless and supply digital information to all departments. This is true for both the fully automated and the non-automated activities in the tool shop. Viewable files can be created to present all PMI data from the FEM model.

For automated activities, one can work with minimally annotated files, meaning just a coloured 3D file showing the applied colours for tolerances and surface finishes, as well as some specific notes. In the viewable file, buttons are created to highlight colours that indicate a tolerance or surface finish, which helps improve readability and reduces human error. The operator can measure real dimensions within the 3D file.

The second option is to create fully annotated files showing visual PMI data. This tends to be easier for non-automated activities, as the operators are provided with dimensions and notes on the viewable file, meaning that the operators do not need to measure in the FEM to find the manufacturing information they need. Of course, these fully annotated files are more time-consuming to create than minimally annotated files and will require some extra work in the design or LTE departments (Figure 6).

FAST AND EASY PROGRAMMING AND METROLOGY USING MBI

All the advantages of CAM programming apply to metrology as well, where automated programming also increases efficiency significantly. As in previous steps, a 3D CAD file is prepared (the MBI file). The MBI file is also a "child" of the FEM and it re-uses the PMI data from the colour-coded FEM model. All metrology points are added to the MBI file, and standard datum plans are used to align it with the actual steel components.

Because geometrical tolerances have been added to the FEM through colour coding, it is no longer necessary to apply geometric dimensioning and tolerancing as notes. By staying within the boundaries of the geometrical tolerances, requirements in terms of parallelism or squareness will also be covered.

The metrology points required to measure the FEM are also added to the MBI file. Next, the co-ordinate measuring machine uses these metrology points in the MBI file to generate the metrology reports. Because these metrology points are also part of the FEM, they are stored in the data-management system and controlled with version management. This ensures identical metrology output for any repeat or replacement work in the future.

ADOPTING MBD: WHAT ARE THE PROS AND CONS?

For any company in the manufacturing industry that wants to move towards an Industry 4.0 production environment, MBD is a must have. It is a vital tool for improving a production workflow.

Organisations looking to adopt MBD should keep the following in mind:

1. Preparing the FEM requires more time, as the PMI needs to be added.
2. Extra time is required in the LTE department to prepare the 3D manufacturing models.
3. There is a risk of error when people on the shop floor need to measure directly in the FEM instead of having the dimension available on a drawing.

However, the advantages of MBD are significant. The main reasons to adopt MBD are:

1. MDB improves product quality by minimising human error. This not only reduces the number of rejects but also prevents those rejects from disrupting planning and scheduling.
2. MDB exclusively uses 3D files for automated programming steps in CAM and quality assurance. This allows for more efficient use of programming software and manufacturing equipment and optimises production processes.
3. The entire production process is stored within the FEM and is ready for repeated production.

In short, MBD offers significant benefits and contributes to assembled and complex products with a better fit.

ABOUT THE COMPANY

IGS GeboJagema is a high-precision mould maker that designs, manufactures, validates and maintains moulds for products where extreme precision is vital, from glasses and contact lenses to asthma inhalers, insulin pens and blood diagnostic devices. IGS GeboJagema specialises in collaborating with medical original equipment manufacturers early in the product lifecycle, allowing its exceptional engineering team to develop innovative moulding solutions.

ABOUT THE AUTHOR

Rob Doorakkers is Chief Innovation Officer at IGS GeboJagema, where he focuses on optimising production processes, continuously improving product quality and finding innovative solutions to solve the most challenging technical challenges. Mr Doorakkers has over 30 years of experience in the injection moulding and manufacturing industry.

DRUG DELIVERY DEVICE TRENDS FOR 2022

In this article, Tom Oakley, Director of Drug Delivery Device Development, Springboard, looks at some of the current trends in the drug delivery industry and projects some of the key factors that will influence drug delivery decision making in 2022.

The drug delivery industry depends on innovation, and keeping abreast of the latest trends can help us predict the future. Springboard is in the privileged position of being at the centre of many of the most exciting drug delivery device developments and has compiled the following list of top trends for 2022.

CONTINUED COVID-19 DIVIDEND

Countries around the world are still struggling to manage waves of covid-19 infections. The highly infectious Omicron variant has undone some of the progress made by the vaccination campaigns conducted in the wealthier economies. Nevertheless, the suffering and disruption brought by covid-19 has led to some profound changes and benefits for the healthcare industry, which Springboard has termed "the covid-19 dividend" (Figure 1).

Before covid-19, political leaders may have considered vaccine strategy to be primarily concerned with public health. However, the continuing threat of covid-19 is likely to remind them of the vital role healthcare plays in national security and economic welfare too. National governments and supranational organisations, such as the European Union, seem to announce new vaccine procurement deals almost daily.

> "We can be confident that funding into vaccine development, and the devices to deliver vaccines, will continue to be high for the foreseeable future."

The US Vaccines National Strategic Plan (published on January 19, 2021) says that "there remains a significant need for new and improved vaccines and vaccination strategies, such as the development of new vaccines against vector-borne diseases, a more broadly protective universal influenza

Figure 1: The ongoing covid-19 crisis has led to some profound beneficial changes in the healthcare industry, which Springboard has termed "the covid-19 dividend".

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vaccine, and improved strategies for maternal immunisation. Developing new vaccines includes modernising the [US] domestic vaccine enterprise to be highly responsive, flexible, and scalable; improving capacity for agile and rapid responses to emerging influenza threats; and developing more broadly protective vaccines."[1] Therefore, we can be confident that funding into vaccine development, and the devices to deliver vaccines, will continue to be high for the foreseeable future.

Vaccines are not the only area of healthcare in great demand due to covid-19 and the heightened awareness of other potential pandemics that has come with it. Diagnostics (point of care and laboratory), critical care equipment and personal protective equipment are likely to benefit strongly from the covid-19 dividend too.

RENEWED DEMAND FOR RE-USABLE DEVICES

Many categories of drug delivery device can be developed as either:

1. Disposable
2. Part re-usable and part disposable (Figure 2).

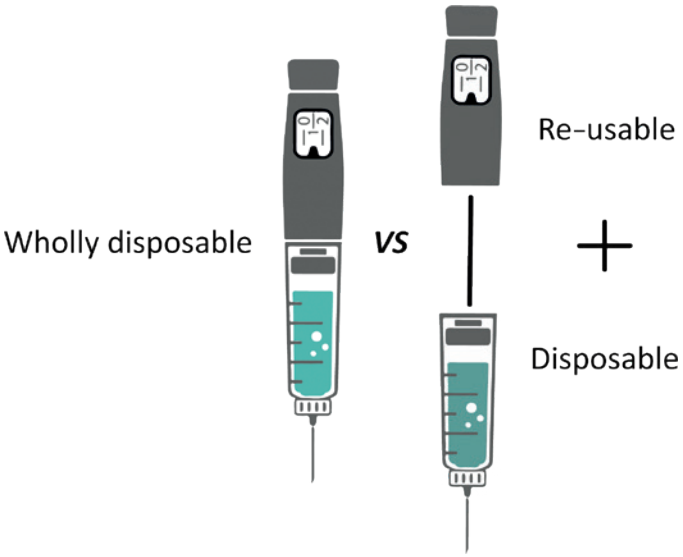

Figure 2: A wholly disposable versus a part disposable, part re-usable pen injector.

There seems to be a trend whereby pioneering devices tend to be partly re-usable, after which wholly disposable versions appear and take a share of the market. Examples include:

- Pen injectors, where the earliest model (NovoPen, Novo Nordisk) was re-usable and then disposable models (FlexPen, Novo Nordisk; SoloSTAR, Sanofi; KwikPen, Eli Lilly; FlexTouch, Novo Nordisk; etc) appeared.

"Many of the devices Springboard is being asked to develop at the moment suggests that the pendulum is swinging back towards partly re-usable devices."

- Dry powder inhalers, where the earliest models (Aerohaler, Boehringer Ingelheim; Spinhaler, Fisons; etc) were re-usable[2] and then disposable models (Turbuhaler, AstraZeneca; Diskus, GSK; Ellipta, GSK; NEXThaler, Chiesi; etc) appeared.

Many of the devices Springboard is being asked to develop at the moment suggest that the pendulum is swinging back towards partly re-useable devices. Drivers are likely to include:

- Patients and other stakeholders are becoming more sensitive to the environmental impact, especially from plastic waste, of fully disposable devices. Sustainability is discussed in more detail below.
- The current generation of devices tends to be more complicated and costly than the previous generation. For example, on-body injectors are likely to have more components and mechanisms, and therefore have a higher built-in cost than prefilled syringes, safety systems and autoinjectors. The economics of fully disposable devices sets an upper limit on their cost.
- Many new devices have a "connectivity" aspect. The electronics and batteries that are typically involved lend themselves to re-usable modules.

LAUNCH OF MORE RECYCLING SCHEMES

Used drug delivery devices often create biohazard waste that needs to be incinerated and typically some plastic waste as well. Pharmaceutical companies and device manufacturers are looking for ways to reduce the waste going to landfill, and one of the strategies is return-to-manufacturer schemes.

GSK ran a return-to-manufacturer scheme for its inhalers from 2011 to 2020. Sources indicate that take-up was not as high as GSK wanted, although more than two million inhalers were recycled by the scheme. GSK has said that it "believes there needs to be a focus on a wider, joint-working approach across industry, rather than our own standalone approach."[3]

"Pharmaceutical companies and device manufacturers are looking for ways to reduce the waste going to landfill, and one of the strategies is return-to-manufacturer schemes."

Nevertheless, some manufacturers are piloting new schemes, for example:

- Novo Nordisk's PenCycle pilot was launched on November 1, 2021. If successful, it could be expanded to cover the whole of the UK and could recycle many of the 2.5 million FlexPen and FlexTouch devices sold in the UK each year.[4]
- Chiesi's inhaler recycling scheme started in February 2021 and covers any inhaler from any manufacturer. It could reduce the waste caused by the 73 million inhalers prescribed each year in the UK.[5]

We can expect to see more recycling schemes announced in 2022 if these pilots are successful.

> "There have been some innovations over recent years, such as using nitrogen dioxide, but it takes time to validate processes, adapt designs for new sterilisation methods and overcome the risk aversion that is pervasive in the pharmaceutical industry."

NOVEL STERILISATION TECHNOLOGIES

Ethylene oxide and gamma irradiation methods account for the majority of medical device sterilisation. However, ethylene oxide has a relatively long cycle time (including aeration time to reduce sterilant concentration) and the sterilant is explosive and carcinogenic. On the other hand, gamma radiation can damage materials, turning transparent materials yellow or brown, and crosslinking certain useful engineering polymers such as polytetrafluoroethylene (PTFE) and polypropylene. Gamma radiation can also damage drugs and electronics, and a global shortage of cobalt-60 is limiting capacity.[6]

There have been some innovations over recent years, such as using nitrogen dioxide (Noxilizer, MD, US), but it takes time to validate processes, adapt designs for new sterilisation methods and overcome the risk aversion that is pervasive in the pharmaceutical industry. However, demand for alternative sterilisation methods will persist through 2022 and beyond.

SUMMARY

More than at any other time, in 2022, the world recognises the need for high quality, accessible and sustainable healthcare. We are likely to see remarkably high levels of investment in vaccines, diagnostics, critical care, personal protective equipment and reducing environmental impact.

If you have questions or would like to discuss any points, please do not hesitate to contact the author.

ABOUT THE COMPANY

Springboard specialises in developing devices from concept to manufacture for regulated markets. The company is expert at creating innovative yet robust designs and solving difficult technical problems quickly. Springboard does not have internal projects so it is as fast and cost effective as possible, and the intellectual property belongs to its clients.

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ABOUT THE AUTHOR

Tom Oakley leads engineering and scientific teams developing new injection devices, pumps and inhalers. He has been the named inventor on dozens of patents throughout his 20 years' experience in industry. Mr Oakley is a regular speaker at various international conferences on innovation and medical device development, and mentors engineering and MBA students on innovation and device development at the Cambridge University Engineering Department and the Judge Business School (Cambridge, UK). He read Engineering at Cambridge University before becoming the Choate Fellow in Human Physiology and Pathology at Harvard University (MA, US).

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COMPUTATIONAL MODELLING OF INJECTION-RELATED TISSUE RESPONSES IN DRUG DELIVERY

Here, Olivia Jefferies, Junior Device Development Engineering Student, Oval Medical Technologies, Elizabeth Margerison, PhD, Marketing Manager, Oval Medical Technologies, and Asmita Khanolkar, Senior Director, Cambridge Pharma, introduce Oval's work on using ultrasound scanning and finite element analysis to construct a model of how tissue compresses under use of an autoinjector across patient demographics, and how this may provide insights into improved autoinjector design for more accurate injection depths, improving patient outcomes.

INTRODUCTION

At the global level, trends continue to move medical care from hospital to the home, resulting in a growing need for at-home care for both chronic and crisis medications. This is leading to further growth areas for autoinjectors to deliver drugs and biologic products, as autoinjectors have usability advantages over other drug delivery methods, such as manual injections. Autoinjectors can enhance safety, improve dosing accuracy and improve patient compliance, especially in self-administration settings. With this significant growth, research is necessary to understand the relationship between body morphology, injection force and needle length. This can help to improve both the patient experience and the effectiveness of drug delivery devices.

Oval Medical Technologies offers a variety of autoinjector technology platforms (Figure 1), with both subcutaneous and intramuscular capabilities, to deliver a wide range of challenging novel drug formulations with high viscosities and a wide range of delivered volumes. With challenging novel formulations, complex molecules, large dosages and new delivery sites, optimising delivery along with the formulation is key for successful clinical outcomes.

> "Oval has developed a force-sensing ultrasound methodology for physiological analysis that enables needle lengths to be specified safely and effectively."

A key part of successful drug administration is that the injection reaches the correct anatomical tissue. Several factors may affect the depth of injection achieved when using an autoinjector, including both injector- and patient-related factors. In addition, it is necessary to understand that the injection-related tissue responses during delivery and their correlation with patient physiology factors. Oval has developed a force-sensing ultrasound methodology for physiological analysis that enables needle lengths to be specified safely and effectively (Figure 2). This is done via characterising skin-to-muscle depth (STMD) and skin-to-bone depth (STBD) for different population groups and injection sites (Figure 3). In addition, the effects of tissue compression can be established with the use of an autoinjector.

Furthermore, finite element analysis (FEA) is used to model tissue compression in each of the tissue compartments at various injection sites, the results of which

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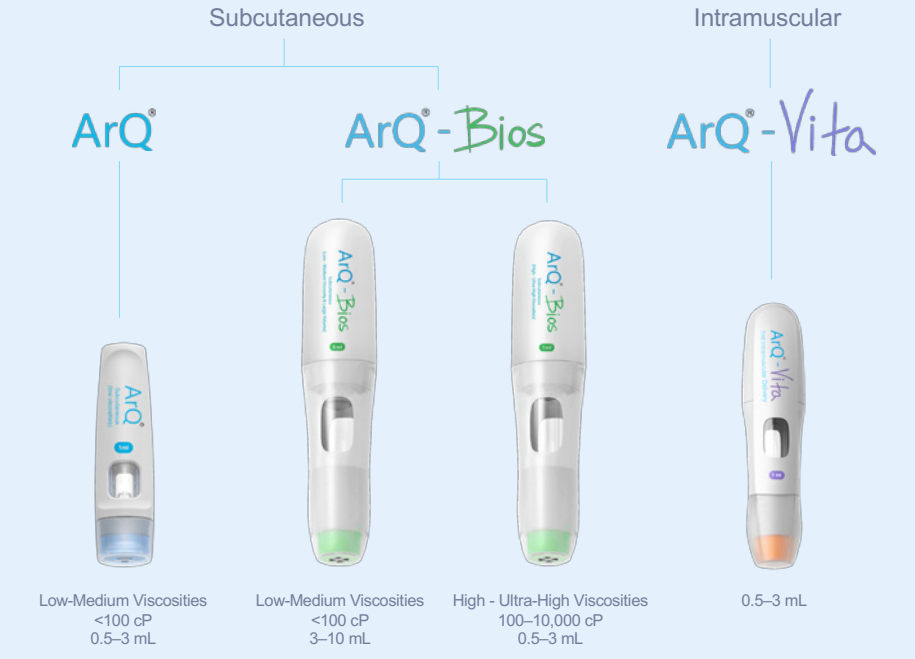

Figure 1: Subcutaneous and intramuscular delivery technologies from Oval.

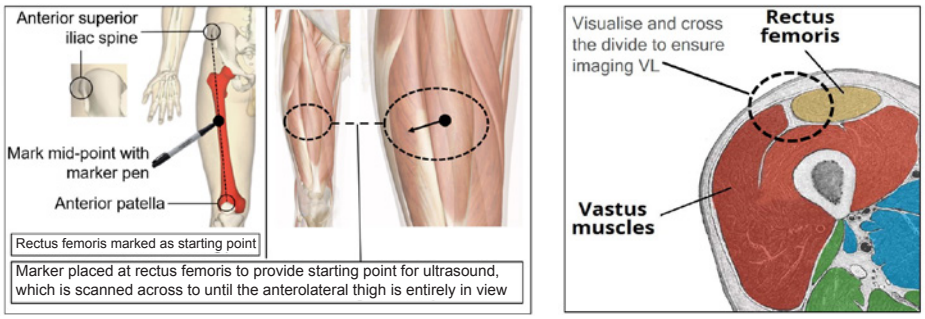

Figure 2: Identification of location for ultrasound imaging (anterolateral thigh).

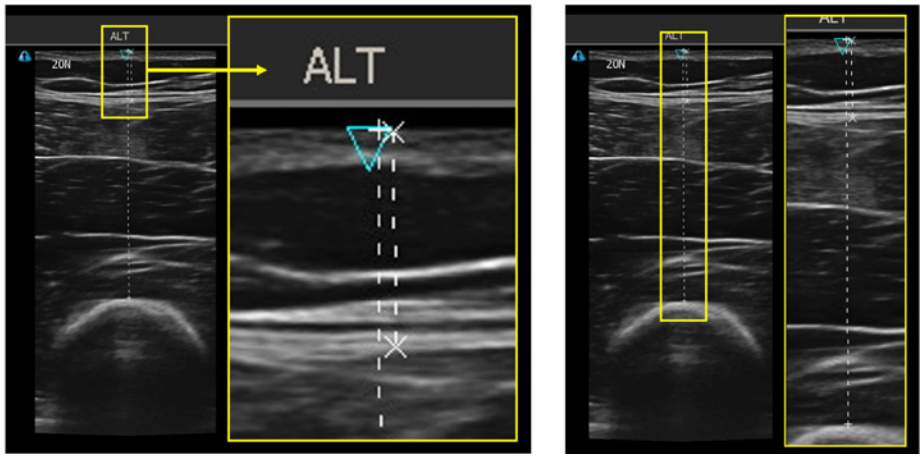

Figure 3: Ultrasound images of the thigh, indicating the skin, subcutaneous tissue, muscle and bone. Left image represents STMD and the right image is STBD.

"Consideration of the anatomical injection depth should be taken into account during the design of a drug delivery device to ensure optimal delivery of the drug, which is determined by the exposed needle length."

can be verified using Oval's ultrasound technique. While already used extensively in other engineering fields, such as civil and aeronautical engineering, FEA is being increasingly applied within the medical field. It opens the door to many innovative and interesting methods and applications within research and design.

INJECTION SITE

The recent trend of moving treatments from hospitals to the home has been facilitated by a change from intravenous to subcutaneous and intramuscular routes of administration. This trend is driving the increasing demand for autoinjectors and, in many cases, facilitates self-administration by patients. Subcutaneous delivery can be administered in the leg, abdomen or arm. For intramuscular delivery, there are five main sites:

- Thigh (vastus lateralis, rectus femoris)
- Gluteal (ventrogluteal, dorsogluteal)
- Arm (deltoid).

The vastus lateralis (VL) is the largest of the four muscles forming the quadricep, located in the thigh. Its main function is to control the movement of the knee, working with surrounding tissue to stabilise the joint. The significant work done by the VL requires high levels of vascularisation; the femoral artery and other branching arteries, such as the profunda femoris, are key blood supplies. This makes the VL an ideal site for intramuscular injection, including for crisis medication. The thigh consists of different tissue structures, including:

- Skin (dermis and epidermis)
- Subcutaneous tissue
- Muscle, (vastus lateralis, rectus femoris, etc)
- Bone (femur).

For gluteal intramuscular injections, the ventrogluteal and dorsogluteal sites are shown in Figure 4. The selection is based on the formulation, dose volume, viscosity and patient considerations, such as thickness of subcutaneous fat layer.

IMPORTANCE OF NEEDLE LENGTH

Consideration of the anatomical injection depth (subcutaneous or intramuscular) should be taken into account during the design of a drug delivery device to ensure

optimal delivery of the drug, which is determined by the exposed needle length. Characterisation of the needle length requires an understanding of the STMD and STBD at the site of injection. Insufficient knowledge about tissue behaviour and compression can result in the drug being delivered into the incorrect tissue, which can have devastating consequences for the patient.

In crisis applications, autoinjectors are used for delivering adrenaline during anaphylactic shock. The pharmacokinetic (PK) properties of adrenaline require a high blood plasma concentration (C_{max}); therefore, intramuscular administration is recommended into the VL. If adrenaline is delivered for the subcutaneous tissue, there may be a lag in the C_{max} (Figure 5). Again, this can have devastating consequences for the patient.

On the other hand, the lag in C_{max} means that long-acting injectables, such as insulin, are best administered subcutaneously. If the drug is delivered into the muscle, there will be a spike in blood plasma concentration; for insulin, this can cause the patient to become hypoglycaemic and reduce the length of time the drug is effective.

In the case of intramuscularly administered long-acting injectables, controlled release of the API is managed by adjusting solubility in a carrier. Due tothe extended periods between administrations, it is essential that the drug is delivered to the correct depth in the muscle tissue, or it can result in the failure of the therapy.

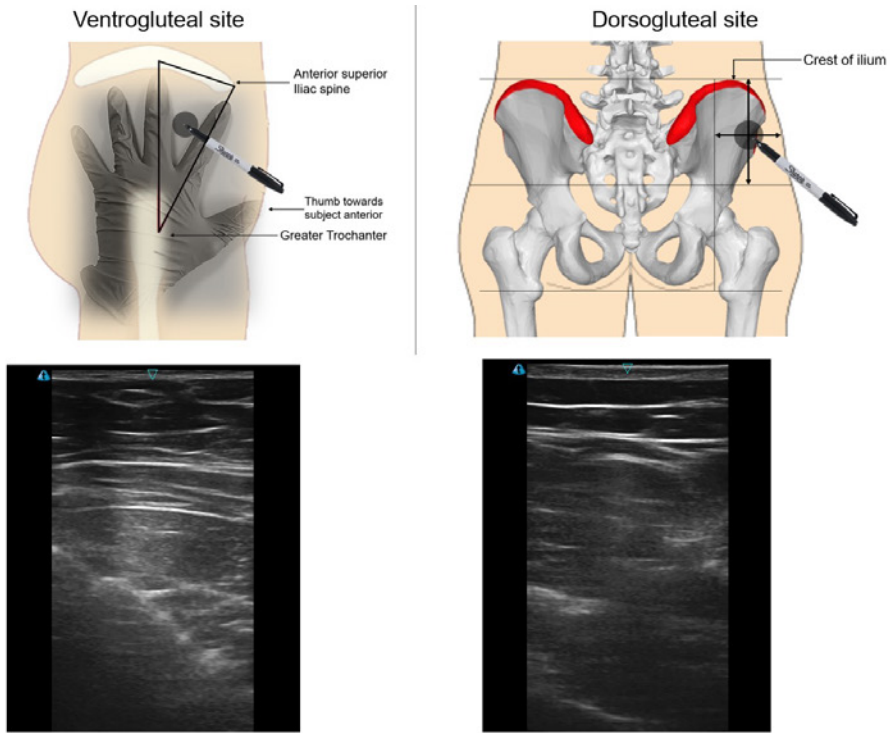

Figure 4: Identification of gluteal locations and sample ultrasound images.

> "Human tissues are highly complex, with interesting mechanical properties and structures; it is important to understand the architecture and physical characteristics of the tissue in question to ensure the accuracy of an FEA model."

POPULATION DISCREPANCIES

The distribution of subcutaneous tissue varies between males and females, with men commonly carrying it around their abdomen and women around their buttock and thighs. When considering an intramuscular injection into the VL, the chances of women receiving an erroneous subcutaneous injection are increased. Likewise, for a male targeting a subcutaneous injection into the quadriceps, a lack of subcutaneous fat may lead to an intramuscular injection. Therefore, variations in tissue thickness must be considered when designing an FEA simulation study. Other factors, such as weight and age, are characteristics that can lead to dissimilarities between patients.

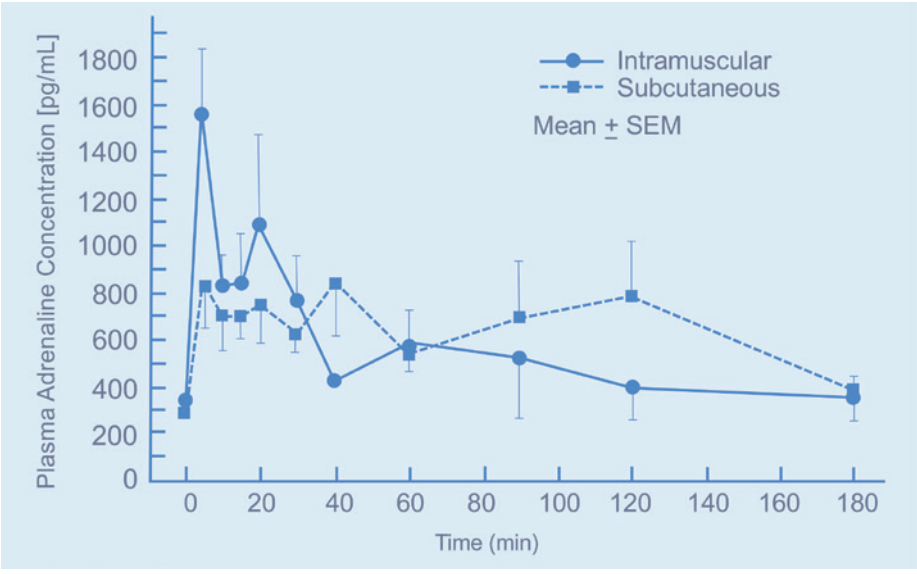

Figure 5: Plasma adrenaline concentration for intramuscular and subcutaneous injection over time.[1]

TISSUE MECHANICS

Human tissues are highly complex, with interesting mechanical properties and structures; it is important to understand the architecture and physical characteristics of the tissue in question to ensure the accuracy of an FEA model. Human tissue is a hyper-viscoelastic material, meaning that deformation is highly non-linear, significant and time-dependent. Within the context

of an FEA simulation, the tissue should be considered as solely a hyperelastic material, because the rate at which the load is applied remains constant.

Many variables can affect the structure and mechanical properties of human tissue, including age, sex and injury. For simplicity, the current model does not consider the difference these properties may have on the tissue, nor does it consider natural variation between subjects. Although, where possible, material properties were found for males and females individually.

TISSUE CHARACTERISATION WITH ULTRASOUND

A clinical study used ultrasound and a load cell to collect images of the anterolateral thigh and plot a force-time graph during compression of the tissue (Figure 6). Data collected from the ultrasound study assisted in developing the model and material characteristics. STMD, STBD and tissue deformation data during application of the probe were acquired using live imaging and load cell monitoring.

FINITE ELEMENT ANALYSIS

ABAQUS CAE 2021 (ABAQUS, CA, US) was used to create six models of human tissue, each representing a different patient group – both male and female for small, medium and large participants, categorised by BMI. This ensured that the data collected accounted for differences between sexes and the effect of tissue thickness on tissue compression. The surface area of the external load in the model matched the ultrasound probe used to gather the ultrasound data. The leg was modelled as a cylinder and then partitioned according to the tissue thickness calculated from the ultrasound study. Partitioning of the model into the individual tissue layers allows for the different material properties to be applied to each partition.

For the FEA simulation study, materials were considered to be homogenous and isotropic. Initially, linear elastic material properties were applied to the individual tissue layers to verify that the model works while keeping computation time to a minimum. Once verified, the model was tailored by applying hyperelastic material properties to the individual layers, allowing the model to consider the large deformations observed in ultrasound footage.

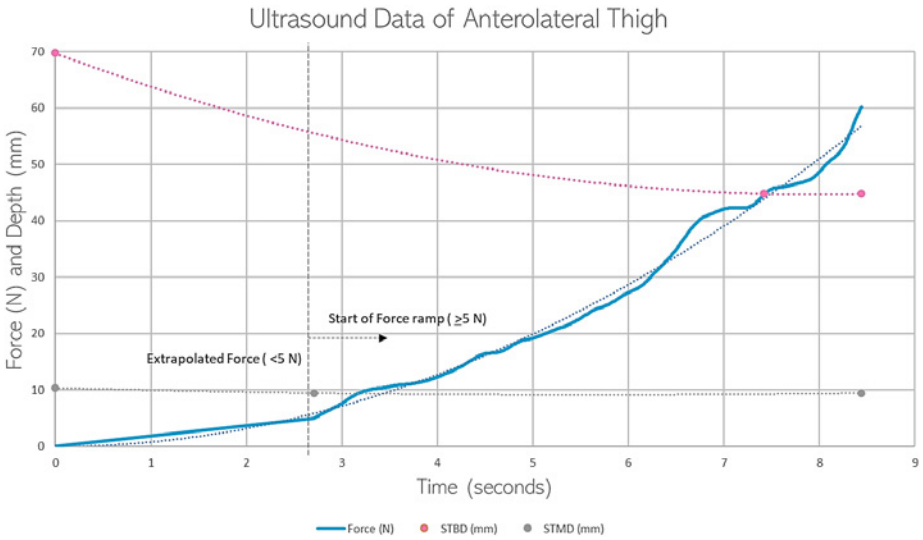

Figure 6: Graph showing an anterolateral thigh ultrasound measurement.

Various interactions were used to detail how the load simulating the ultrasound probe and human tissue behaved in relation to one another during the simulation. A standard contact-to-contact interaction was placed on the top surface of the human tissue and the outer surfaces of the probe. This allowed the tissue to deform when in contact with the probe. To simplify the model, only 1/8th of the leg was taken and symmetrical boundary conditions were applied to the model to represent the entire leg fully during calculation. The behaviour of bone was mimicked using a boundary condition not allowing for any displacement of the central partition. Finally, a displacement condition was implemented to represent axial translation of the probe onto the injection site.

The model used a varied hex mesh that decreased in size as it converged towards the probe location. This helped to balance computation time with accuracy – a finer mesh results in more calculations, therefore increasing the accuracy, but also results in a significantly longer computation time. Hence, it is advantageous to have a non-uniform mesh distribution across the model that becomes more accurate around the point of contact.

The results showed that each tissue behaves differently when a compressive force is applied; muscle accounts for the majority of tissue compression, with compression of the skin and subcutaneous tissue being minimal to non-existent. Figure 7 shows the small female muscle compressed by 13.75 mm, subcutaneous tissue by 1.25 mm

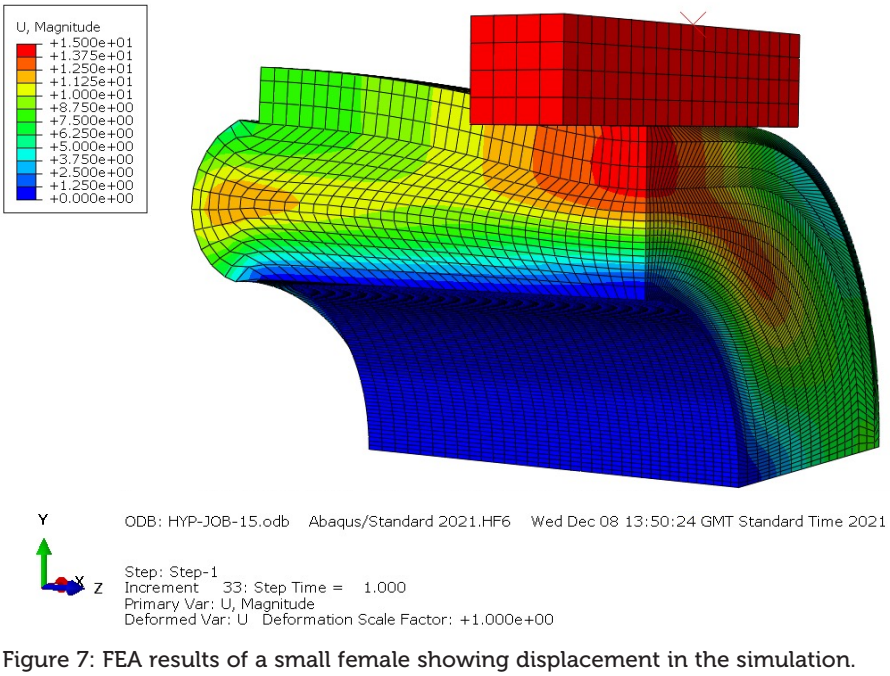

Figure 7: FEA results of a small female showing displacement in the simulation.

and skin by 0 mm. It can also be seen that the high compression and Poisson's ratio caused significant perpendicular movement of the tissue.

CLINICAL ULTRASOUND VERIFICATION

The ultrasound video footage was sampled to acquire tissue compression over time during application of the ultrasound probe. The load cell data was sampled to acquire force data over time during application, and the two were aligned with respect to one another to assess tissue compression at different forces. These data were used to verify the FEA model, ensuring that the model is representative of how real tissue behaves.

Similar to the FEA results, the ultrasound data showed that the muscle is responsible for the majority of tissue compression when the load is applied. It also showed that the muscle reaches a point of maximum compression, after which increasing force will not affect tissue compression. These data were used to guide the compression depth in the FEA model.

The force-displacement graph of the ultrasound mirrors that of the FEA, with only slight variability between the exact data values. To improve the similarity between the FEA data and ultrasound data, the tissue material properties will be iteratively changed to become more accurate. The change in material properties is intended to absorb the effect that surrounding tissues have on compression, for example, the tension of muscle or blood pressure.

"Similar to the FEA results, the ultrasound data showed that the muscle is responsible for the majority of tissue compression when the load is applied."

CONCLUSION

The FEA simulation has shown the potential of FEA to create accurate models of human tissue, although further development of the model would be required before the results can be used as part of an autoinjector design. Unlike ultrasound, FEA can be used to understand the effect of skin doming on tissue thickness for different needle hole diameters. It can also be used to help improve the understanding of what data and participants are required, in terms

ABOUT THE AUTHORS

Olivia Jefferies, Junior Device Development Engineering Student, Oval Medical Technologies, is pursuing studies in Product Design Engineering (MEng) at Loughborough University (UK). Her academic advisors are Yang Liu (Senior Lecturer in Healthcare Engineering) and Simin Li (Senior Lecturer in Mechanics of Biomaterials) at Loughborough University. She is passionate about solving design-engineering problems with innovative and advanced solutions that help improve the lives of others. Her recent project at Oval involved studying the effects of topical pressure on the compression of tissue structures using FEA.

Elizabeth Margerison, PhD, Marketing Manager, Oval Medical Technologies, has an MSc in Biological and Medicinal Chemistry and a PhD in Immunology and Infectious Diseases. She has worked in the pharmaceutical and medical device industries for over 20 years, working as project manager in many disease areas and has experience in managing clinical trials. Her passion lies in improving clinical outcomes by ensuring medicines are effective, safe and convenient to use and in the application of novel technologies to enhance the patient experience. Dr Margerison is involved in multiple early user clinical research studies providing valuable insights in optimising drug delivery for various population groups.

Asmita Khanolkar, Senior Director, Cambridge Pharma, SMC Ltd, has an MSc in materials science and engineering from Worcester Polytechnic Institute in Worcester (MA, US). With over 24 years of manufacturing experience, specialising in the medical device and pharmaceutical industry, she has managed various device projects from concept to commercial launch. Her product portfolio includes single-use, wearable and implantable devices, and drug-device and device-biologic combination products for drug delivery, biotech and pharmaceutical applications. Ms Khanalkar has held various engineering and management roles in new product development, manufacturing engineering, advanced quality planning, operations, supply chain and product lifecycle management. Her current responsibilities include a corporate leadership role as subject matter expert supporting multiple sites with bringing complete solutions to customers.

of sex and size, to gather the necessary data for clinical trial design.

Using data from such studies, Oval has optimised its intramuscular and subcutaneous platforms to align the activation force with known tissue compression, thereby optimising needle length for various injection sites, population groups and challenging applications. The correlation between delivery performance and needle depth consistency over various time points and conditioning scenarios has been proven in technology and PK studies. Ensuring the correct needle length leads to more successful injections, creating a more patient-centric autoinjector.

The potential to use FEA to simulate novel and interesting situations opens exciting research and design opportunities that can improve on the current knowledge base surrounding the use of autoinjectors and, ultimately, the usability of devices.

ABOUT THE COMPANIES

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

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

SMC Ltd, with more than 33 years of experience, provides product services from initial concept to the final packaged device, including program management, design and development, product manufacturing, clinical/commercial manufacturing, electronics integration, and global supply chain management. SMC has global GMP manufacturing sites in the US, the UK, Costa Rica and India.

Cambridge Pharma specialises in pharmaceutical services, sterile fill-finish batches of lot sizes 100 -10,000 units for a range of presentations including its own primary containers, as well as syringes, cartridges and vials. It works with a wide variety of formulations including small molecules, proteins, peptides and biologics. Its flexible, broad service offering allows clients to develop the fill-finish process including container closure integrity method development and testing, analytical methods for quality control release, and stability testing.

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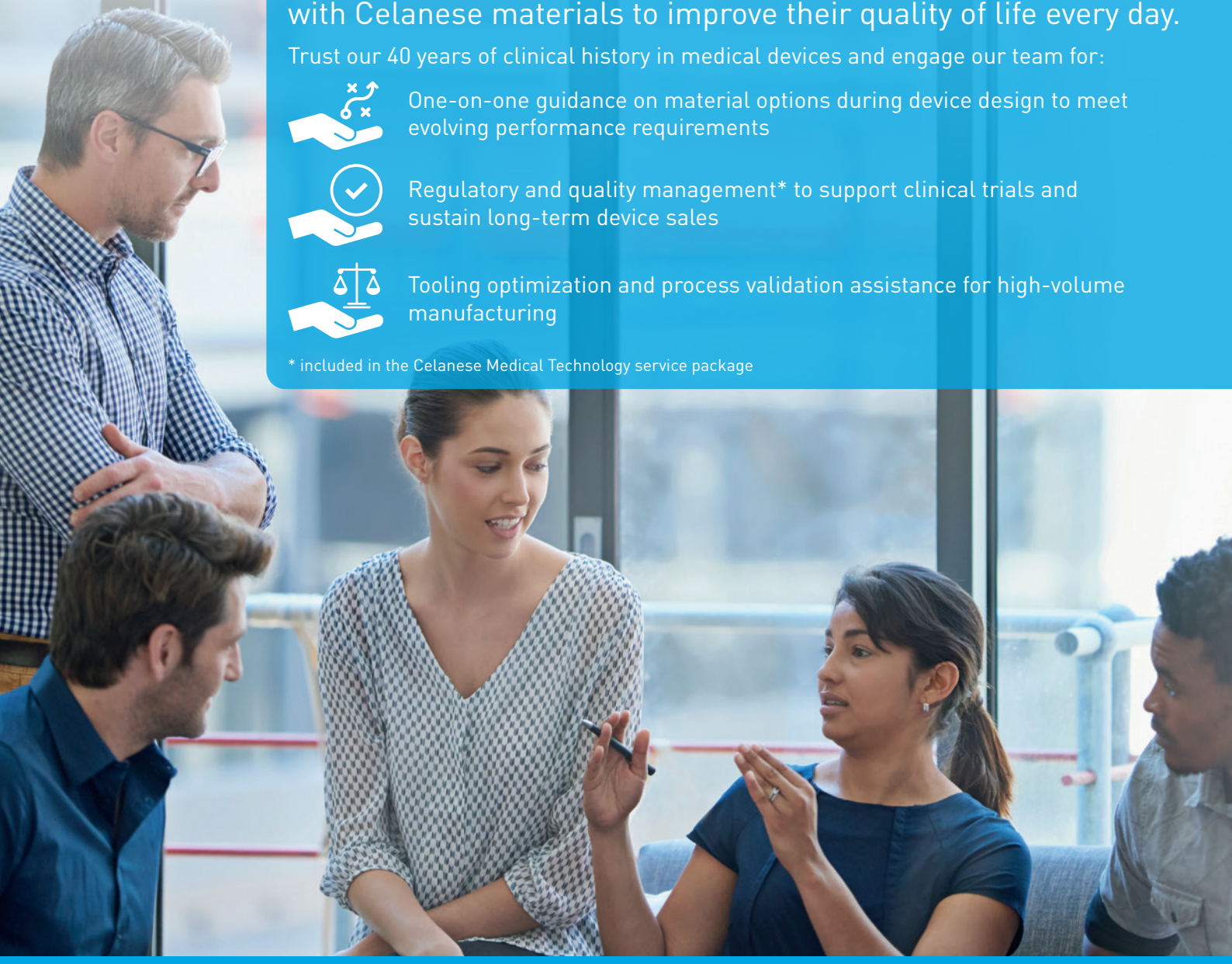

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A VIEW ON THE USE OF APROTIC SOLVENTS IN PARENTERAL DRUG FORMULATIONS

In this article, Michael Neely, Consultant to Xeris Pharmaceuticals, presents a review and discussion of the status of aprotic solvents as a solubilising vehicle for parenteral drug formulations in the context of the industry's increasing interest in biologic drugs.

A review of the literature surrounding aprotic solvents produces but a scant bibliography citing their use in parenteral drug formulations, and a look at the current array of marketed drug products shows that only a very few employ such solvents. Given the potential benefits that non-aqueous systems might present to certain types of drug formulations, especially for biologics susceptible to water-mediated degradation, the dearth of industry experience invites some speculation as to why the approach has not been more widely explored. To try to explain this observation, there are several questions whose answers may be revealing. Relevant questions include:

- How much do formulators know about aprotic solvents and their properties?
- Are there prevailing assumptions in academia and industry about the safety and suitability of aprotic solvents for parenteral administration?
- Is existing equipment for formulating and packaging in the pharmaceutical industry a deterrent to alternative approaches?
- To what extent are non-aqueous solvents compatible (or incompatible) with existing parenteral filling equipment and packaging systems?
- What additional formulation modifications might be necessary to make aprotic formulations stable, safe and effective?
- How do regulatory agencies view aprotic solvents, and what additional risks or delays might the use of these solvents introduce to the approval process?

Biomolecules, such as proteins and peptides, comprise a large segment of new drugs currently in development. While recent research on formulation approaches for these drugs has been heavily focused on non-parenteral routes of administration, biomolecules remain most readily amenable to parenteral delivery. Accordingly, for developers looking to achieve rapid market entry, drugs that require precise dosing, or for APIs that are very high cost where alternative delivery routes are economically infeasible, parenteral formulation remains the most viable option.

Protein- and peptide-based drugs are often packaged and distributed as lyophilised products. This is because these molecules are susceptible to several water-mediated degradation pathways, such as hydrolysis, as well as various pH-dependent oxidation or reduction reactions that affect their amino acid side chains. When concentrated in aqueous solution, certain peptides are also prone to forming insoluble aggregates. Lyophilisation renders these molecules stable for extended periods of time, making them suitable for commercial distribution in the pharmaceutical supply chain. A downside is that lyophilised drugs require reconstitution prior to administration, which presents additional handling requirements, a potential risk of contamination and can easily result in over- or under-dilution. Moreover, once reconstituted, many of these drugs have a very short shelf life, and some must be administered immediately or discarded.

"While recent research on formulation approaches for these drugs has been heavily focused on non-parenteral routes of administration, biomolecules remain most readily amenable to parenteral delivery."

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"So why are there so few examples of marketed drugs formulated in aprotic solvents, given the rise in biomolecule drug candidates and the many potential advantages and benefits such solvents offer with these molecules?"

The rationale for considering a non-aqueous solvent for parenteral delivery of protein or peptide drugs includes considerations of several factors, including:

- Stability
- Solubility
- Safety
- Efficacy
- Compatibility with containers, closures and injection devices
- Manufacturability
- Regulatory approval
- Patient acceptance.

Until very recently, the only non-aqueous polar solvent that could be found in commercial parenteral formulations is N-methyl pyrrolidone. This solvent is typically present at concentrations of around 30–60% in several extended-release depot injection drugs containing peptide drug substances. More recently, formulations of the sugar-regulating peptide hormone, glucagon, have been approved for marketing using dimethyl sulfoxide (DMSO) as the solvent. In this unique formulation, DMSO proved to be a superior solvent because it eliminated water, and thereby water-mediated degradation. This allowed for an increased drug concentration and reduced injection volume due to greater solubility of the active, eliminated aggregation as a degradation pathway, and has proven to be shelf-stable for upwards of 24 months at room temperature.

So why are there so few examples of marketed drugs formulated in aprotic solvents, given the rise in biomolecule drug candidates and the many potential advantages and benefits such solvents offer with these molecules? A value proposition is the net of benefits less risks and, when risks are not well known or well understood, their perceived magnitude is increased. A lack of familiarity with aprotic solvents, specifically of their physical, chemical and toxicological properties, is probably one reason why they may not have received first line consideration.

"Many formulators may look at DMSO as a vehicle unsuitable for parenteral injection. However, a review of the literature shows that it has very low toxicity and, in clinical experience, is proving to be well tolerated in subcutaneous injections."

Many formulators may look at DMSO as a vehicle unsuitable for parenteral injection. However, a review of the literature shows that it has very low toxicity (it has a no-observed-adverse-effect level greater than 10 mg/Kg) and, in clinical experience, is proving to be well tolerated in subcutaneous injections. DMSO is widely available in United States Pharmacopoeia and European Pharmacopoeia grades from several suppliers. Moreover, the literature suggest that DMSO has antimicrobial properties that could be beneficial in sterile fill or aseptic processing operations.[1,2]

Whatever the reasons behind the reluctance to include aprotic solvents in a formulation approach, the lack of activity in this area of inquiry appears to have created a vacuum in the realm of intellectual property development, and the adage "nature abhors a vacuum" has proven true once again. A review of patents granted over the past half decade shows that a small handful of companies have begun to explore and develop the opportunities afforded by aprotic solvents as parenteral formulation vehicles. Indeed, a total of 13 US and 93 Ex-US patents claiming use of aprotic solvents as formulation solvents and/or the medical use of such formulations have been granted to a single company, Xeris Pharmaceuticals. Other patents have been issued claiming aprotic solvents as specific formulation components.

A look at some of the current patents shows that another issue with adoption of aprotic solvents might be that using them is not as simple as just substituting the aprotic solvent for water. It also appears to be critical that additional stability-promoting formulation components must be included to ensure the desired shelf life of the drug product is achieved. Such formulations result in a drug molecule that retains its structure and functional characteristics once it is introduced to the *in vivo* aqueous environment.

It will be interesting to see whether and how this technological opportunity manifests in the pharmaceutical industry as the pace of discovery and development of protein- and peptide-based biomolecules continues to increase.

ACKNOWLEDGEMENTS

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ABOUT THE COMPANY

Xeris Pharmaceuticals is a specialty pharmaceutical company that leverages novel formulation technology platforms to develop and commercialise ready-to-use liquid-stable injectables. The company

is focused on creating medicines that are easier to use, including its Gvoke® glucagon injection, which uses Xeris's technology to deliver ready-to-use solutions for patients and caregivers alike.

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ABOUT THE AUTHOR

Michael Neely retired in 2015 after a 42-year career in the pharmaceutical industry. He currently serves in a consulting role for business development at Xeris Pharmaceuticals. His experience spans multiple disciplines, including pharmaceutical manufacturing, research and development, business development and marketing.

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FROM VIAL TO PREFILLED SYRINGE: MIGRATING A DRUG PRODUCT PRESENTATION

Martin Gonzalez, PhD, Senior Manager, Formulation and Process Development at Pfizer CentreOne, discusses some of the most relevant engineering activities that are necessary to transfer a product successfully from a vial into a prefilled syringe presentation.

There is a growing trend for pharmaceutical companies to ask their CDMOs to support the conversion of an existing product presentation into a different final container type – more specifically, to provide options for moving a drug product from a vial presentation into a prefilled syringe (PFS).

WHY TRANSITION FROM A VIAL TO A PFS?

There are many reasons why a drug developer may be interested in converting a drug product currently provided in a vial form into a PFS. It is sometimes driven by quality requirements to preserve product safety or potency. However, more often than not, the desire to create more patient-centric administration formats and to extend patents is underpinning the move.

In addition, the decision is increasingly being driven by a desire to create more convenient drug products, easing or tailoring administration to the therapeutic need. When an injectable's intended use is during emergency surgery, in doctors' surgeries or in a variety of at-home care scenarios, simple and/or more rapid administration is often required. Ease of use can positively impact patient compliance, which is one of the longest standing problems in healthcare. PFSs (Figure 1) remain one of the fastest-growing classes of drug delivery device, due to advances in technology and the increased development of parenteral drugs.[1]

Figure 1: PFSs remain one of the fastest-growing classes of drug delivery device.

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Figure 2: A vial fill line usually uses in-house processed glass before the vial enters the aseptic fill suite.

The core rationale for switching from a vial to a PFS is that it helps businesses manage the brand lifecycle of their products, offers significant benefits to healthcare providers (HCPs) and patients, and can help cut manufacturing and product costs. Manufacturers increasingly need to innovate to retain market presence or strengthen their market share for an indication.

On the manufacturing front, vials are sometimes overfilled to ensure the full dose is retrievable for administration to the patient. This is not necessary with PFSs, as they inherently improve dosing control, significantly reducing drug product waste. As a result, PFSs have lower manufacturing costs overall.

COMPARING GLASS VIAL AND PFS PROCESSING

Glass Vials

Commodity Preparation

Vial and PFS fill lines are inherently different. A vial fill line (Figure 2) usually uses in-house processed glass before the vial enters the aseptic fill suite hosting the filler inside a restricted access barrier system (RABS). The glass vials are received at the facility from the glass manufacturer "as is". Once received, inspected and released, the vials are transferred to a washing-depyrogenation continuous operation tunnel. There, vials are washed with chilled water for injection, drained and dried out with filtered air or nitrogen gas before entering a depyrogenation oven where they are dry heated at temperatures in the range of 275–350°C. They then move to cooling stations under filtered air or nitrogen gas to reduce their temperature to near room temperature. Depending on the vial size, the washing-depyrogenation line speeds can vary to accommodate the fill line output and to obtain a correct depyrogenation process.

Common issues noted with this process include:

- Introduction of particulate matter
- Increased glass delamination, usually detected after product has been placed on stability for months or years
- Incorrect washing-depyrogenation tunnel speed set-up leading to surface scratches resulting in high numbers of rejected units.

Vial Feeding into Fill Suite

Once vials are washed-depyrogenated, they move to a Class II/Grade B classified area accumulation table. From there, vials enter the RABS to be filled (Class I/Grade A area) and capped, then moved to visual inspection stations or into lyophilisers through HEPA carts or an automated loading-unloading systems (ALUS). The fill process is performed under air or nitrogen atmosphere, depending on the drug product needs. Vapour hydrogen peroxide (VHP) is used to sanitise the line, followed by a period of venting/aeration to remove potential VHP traces. In some cases, a manual decontamination process is used, and steam-sterilised change parts are fitted prior to the introduction of vials into the RABS. For liquid products, the vials are fully capped and crimped, then moved to visual inspection stations for a manual, semi-automated or automated visual inspection process. If the product is lyophilised, the vials are partially capped, placed in carts (manually or into ALUS carts) and loaded into lyophiliser chambers. Visual inspection occurs after the product has been lyophilised, capped and crimped.

PFS

Commodity Preparation

PFSs come as a sterilised, pre-processed, nested commodity. PFS manufacture has improved tremendously over the last couple of decades and now provides a very consistently high-quality product. Rejection limits due to cosmetic factors have been significantly lowered, mostly because each PFS glass barrel is isolated from its neighbours, which are all inserted in a template inside a plastic tub.

The manufacturer's processing of PFSs involves the washing, siliconisation and sterilisation processes using gamma irradiation. In addition, the tubs are single- or double-bagged with plastic wraps. Once the PFSs arrive at the CDMO manufacturing site, they are typically released for manufacturing, usually by undergoing a few more tests than a vial would undergo. Units are tested for sterility, correct needle attachment, unclogged needle and tip cap removal force, on top of the testing common to vials (dimensions, type of glass determination, hydrolytic resistance and cosmetic defects). There is no further processing for the PFSs before heading to the fill line at this point, as opposed to the washing-depyrogenation required for glass vials.

> "To transition a drug product from a vial into a PFS, developers must first consider the physicochemical properties of the drug product and the impact on its quality as it is in contact with the different components of the container closure."

PFS Feeding into Fill Suite

Feeding the commodity into the fill suite is where the process differs the most between glass vials and PFSs. To insert the nested PFS (tubs) into the fill line, the tub – which usually comes double-bagged – must be disinfected first.

In a grade B/C area, the outer bag is removed, then it enters the RABS filler system through a conveyor belt where the inner bag is removed under a class I/grade A area, and then it goes into the electron-beam (E-beam) tunnel. A conveyor belt takes the tub through a path inside the E-beam tunnel where low-energy electrons bombard the surface, killing any biological entity present, and then the tub's Tyvek® lid is removed. The removal of the outer bag can still allow micro-organisms to be carried into the aseptic area, and the purpose of the low-energy E-beam treatment of the tubs is to inactivate any such contaminating micro-organisms. A simple schematic of an E-beam/RABS fill-finish system is shown in Figure 3.

In manual operation modes (where operators remove the outer bag and place the tub on the conveyor), bioburden numbers of around 100 colony forming units (CFUs) per tub are common (Bachmann and Harper, 2007). But in automated operations a dramatic reduction of CFU count is usually found. The radiation dosage is established, considering the material comprising the outer surfaces of the tub, as well as any effects on the PFS constituent materials inside the tub. The physical and chemical properties of polymers are affected by irradiation, and the radiation dosage should be selected so that its effects are minimised while ensuring proper sterilisation.

MOVING DRUG PRODUCT FROM VIAL INTO PFS

Analytical Requirements

To transition a drug product from a vial into a PFS, developers must first consider the physicochemical properties of the drug product and the impact on its quality as it is in contact with the different components of the container closure. When evaluating a new container closure, in this case a PFS system, screening studies for suitable parts are needed. There are many factors involved during the selection process:

- Nature of the drug product (small molecule or biologic)
- Formulation composition (high salt concentration and high solution pH prompts glass delamination)
- Sensitivity to oxygen in the headspace or oxidants, such as tungsten traces present in some PFS types (can affect a biologic's potency and purity)
- Headspace volume (affecting plunger stopper movement during shipping, thus compromising closure integrity)
- Siliconisation levels (affecting device functionality or promoting aggregate formation on sensitive biologics)
- Container closure integrity testing using suitable methods. High voltage leak detection might sometimes not be suitable for biologics, but fine for small molecules.

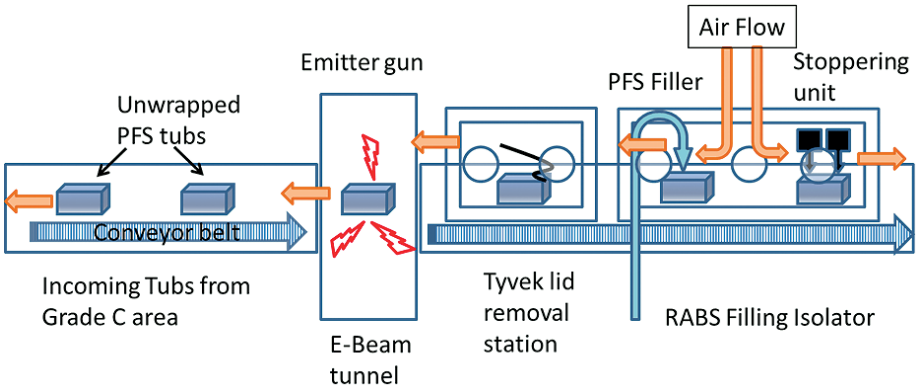

Figure 3: A schematic of an E-beam/RABS fill-finish system.

> "Establishing as early as possible what experimental materials are available and the associated timescales will ensure a smoother roll-out."

Headspace analysis by frequency modulated infrared spectroscopy (e.g. LIGHTHOUSE) are both high-throughput methods. Dye ingress or pressure decay could be easily implemented for most container formats but are low-throughput and destructive methods that can only test a few units, rather than an entire lot.

Availability of analytical test methods is important to carry out suitability studies of the different commodities (glass barrel, plunger stopper type, etc). Ancillary facilities and equipment (stability chambers, compounding capabilities for lab batch scales, specific analytical instrumentation) are also necessary, otherwise delays could happen when transferring samples to a third-party testing facility or the pharmaceutical company's own laboratories.

Engineering and Commodities

Screening activities are carried out in process development laboratories, while engineering/machinability trials are required to test the selected parts in the specific fill line with the exact commodities. The screening activities to select product-contact parts are, under normal circumstances, completed within 4–6 months. It is then that the programme can proceed to machinability or commodity suitability trials in the fill line. When starting these types of screening studies, it is vital to check commodity availability with the vendor. Establishing as early as possible what experimental materials are available and the associated timescales will ensure a smoother roll-out. It also helps define the extent of the design of experiments space to carry out.

A manufacturing subject matter expert team provides the necessary knowledge to select the right parts that will be needed to process the commodities and will lead the activities to completion.

Some of the critical activities to perform are dependent on the current fill line configuration:

- If nitrogen blanketing is needed, a full vacuum stoppering retrofit or a vacuum-assisted stoppering process could be installed. Some coated plungers might be prone to wrinkling when inserted into the barrel, so additional trials might be needed to set up the fill line correctly. These activities can be completed in around 5–6 months after receiving the necessary parts from the filler's

manufacturer. Scoping out the project needs might take some additional time – up to three months in some cases.

- If a change in PFS size is needed (e.g. if the line is set to 1–2.25 mL), then going to a different (e.g. 5 mL) syringe size will require change parts to run them. It's important to consider having multiple sets to facilitate quick line turnaround for line set-up and as safety back-ups.
- Fabricating and delivering the vibrating plunger sorting bowl takes around 25–28 weeks. This requires the plunger stopper to be identified before ordering the fabrication.
- Vendor installation of required change parts, developing the filler format recipe, installing and fitting change parts, and ensuring solution volume accuracy and plunger placement requirements often takes one or two weeks to complete.
- If the PFS fill line is equipped with E-beam capability (most are) and tub size change is required (e.g. going from a 10 x 10 PFS distribution format to an 8 x 8 type, or from a 4" high to a 6" high tub size), the controlling software and the handling parameters will need to be programmed to handle the new tub size/format.
- Trial testing of the sorting bowl requires approximately 50,000 plungers. For the change parts trials, another 70,000 PFS/plungers/rods sets are needed as well.
- Automated (or manual) inspection activities also need to be considered at this time. Developing an automated container inspection process will require thousands of samples to carry out feasibility and recipe development studies. These activities normally take a few months (three to four) to complete.

All new line parts will require new validation activities, so it is best to involve validation teams as early as possible to ensure a correct and appropriate approach is applied. Additionally, project timelines can be impacted by commodity supply lead times. To initiate engineering/machinability trials, a sizeable quantity of PFSs, plungers and rods are needed. A lead time of 8–10 months for parts is not unheard of. Engaging with the vendor at an early point might ensure the timely supply of the required quantities.

> "Adopting a new final container takes concerted efforts from product development, incoming quality, chemistry quality, engineering, manufacturing, validation, procurement and regulatory teams."

BRINGING AN IMPROVED PRODUCT TO MARKET TAKES A VILLAGE

Adopting a new final container takes concerted efforts from product development, incoming quality, chemistry quality, engineering, manufacturing, validation, procurement and regulatory teams. Seamless co-ordination within the CDMO and the pharmaceutical company is paramount, since the whole process – all the way up to adopting a new container closure (or conversion to another) – could easily take up to two years. This is just to the point of manufacturing clinical trial material/registration batches to place on formal stability programmes to ensure the selected container is suitable for the shelf life of the drug product.

ABOUT THE COMPANY

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

Pfizer CentreOne was founded in 2015 when Pfizer CentreSource, a global leader in speciality APIs, and Hospira One2One merged. Backed by Pfizer resources, the company delivers technical expertise, global regulatory support and long-term supply.

REFERENCE

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ABOUT THE AUTHOR

Martin Gonzalez has a PhD in Biophysical Chemistry and over 25 years of experience in formulation development and manufacturing processes for biologics and synthetic drug products. He joined Pfizer CentreOne Contract Manufacturing Services in June 2013. Having previously worked as a scientist at the US NIH's National Heart, Lung, and Blood Institute, Dr Gonzalez has extensive expertise in plasma-derived proteins, polypeptides, enzymes, vaccines and recombinant proteins and antibodies. This expertise has made him a subject matter expert in protein formulation, product development and lyophilisation, manufacturing troubleshooting, delivery devices and final container selection.

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VOICE-ACTIVATED USER INTERFACES IN DRUG DELIVERY DEVICES CAN ENHANCE COMPLIANCE AND OUTCOMES

Here, Salvatore Forte, Innovation Manager at Flex, looks at the evolution of voice-activated interfaces in medical devices, particularly autoinjectors, and the advantages for patient compliance and quality of care.

One of the major challenges that medical device makers face is properly leveraging technological innovations to design medical devices that are more patient-centric and can ease the patient experience when self-administering at home. One of the main drivers for designing more intuitive medical devices has been the evolution of user interfaces, particularly for automated drug delivery devices. In the last decade, battery-operated autoinjectors have progressively transitioned from having bulky mechanical buttons to large touchscreen displays as the primary user interface in a conscious attempt to create a smartphone-like user experience. But graphical user interfaces do not necessarily lead to devices that are simpler to use and, if not carefully designed, can ultimately overwhelm the patient and limit device acceptance.

> "The covid-19 pandemic has dramatically increased the demand for touchless interfaces to limit spreading infection, with voice clearly becoming the primary method by which to deploy hands-free interaction with any sort of device."

Many industries have been positively affected by voice technology, with voice assistants widely deployed in smart products across multiple markets. Everyone is accustomed to smart consumer products with voice recognition capability in their home. Moreover, the covid-19 pandemic has dramatically increased the demand for touchless interfaces to limit spreading infection, with voice clearly becoming the primary method by which to deploy hands-free interaction with any sort of device.

This is paving the way to implementation of voice-enabled drug delivery devices, with new autoinjectors that could be equipped with a voice user interface (VUI). Delivering a more user-friendly human-machine interaction would transform at-home care. The patient can talk to an autoinjector and expect it to execute specific tasks according to the spoken commands, such as starting or suspending the injection and adjusting speed settings. Additionally, the voice user-interface could be used to establish a dialogue with the autoinjector, which, via miniature speaker, could query the patient for health conditions either before or after the injection and collect the feedback by voice (Figure 1). This would set new autoinjectors aside from traditional drug delivery devices, supplementing them with patient monitoring capabilities. The autoinjector could record data on how the patient responds to therapy, and the physician could use those contextual insights to adjust the treatment, if necessary, in real-time.

Of course, there are challenges with voice-controlled autoinjectors, and this article addresses the technological solutions to achieve optimal audio performance by careful design. Machine learning, sensor fusion and audio edge-processing can, together, ensure accurate voice-detection as well as mitigate risks of errors in noisy environments.

CHALLENGES AND TECHNICAL SOLUTIONS

Embedded Voice-Recognition for Edge Processing

The are several challenges at the system-level to fulfil a successful voice-recognition implementation that not only works well

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Figure 1: Autoinjector voice-interface. Assisted injection process and collection of patient feedback on health status.

"In recent years, advancements in artificial intelligence and machine-learning algorithms have been driving innovation in the voice processing space, becoming key to enabling embedded voice implementation."

from the user viewpoint but also meets the technical requirements for integration in battery-powered autoinjectors. These are normally built around small microcontrollers, with limited processing capability and memory resources. When analysing the spectrum of voice-enabled products currently available in the marketplace, one can easily confirm that the majority are based on complex voice solutions that can interpret full natural speech. They require high computational power and therefore can only operate remotely in the cloud.

However, in recent years, advancements in artificial intelligence and machine-learning algorithms have been driving innovation in the voice processing space, becoming key to enabling embedded voice implementation. Today, highly efficient keyword recognition models can fit in small microcontrollers (e.g. the ARM Cortex M) to assist domain-specific device tasks. They can recognise up to dozens of command words, giving them an adequate vocabulary with which to deploy meaningful use cases for injection devices, such as controlling the operation of the built-in device's motor.

"Voice-enabled autoinjectors must be able to recognise words spoken by the user with a high level of accuracy, even in the presence of background noise, and mitigate the risks of errors that might lead to hazardous consequences for the patient."

Such machine learning models can run as embedded software while requiring minimal computational power (as low as 100 MHz) and memory footprint (down to hundreds of kB) to function. Moreover, data can be processed entirely at the device-edge, requiring no connection to external voice services in the cloud. This solves data privacy and security concerns by keeping users' voice data locally on the device and never transferring it out. This eliminates the need to embed connectivity hardware and services in the device, which ultimately leads to lower system cost.

Command sets and languages can be personalised upon training the machine-learning model to fulfil the needs of different market regions. It is also possible to have a single VUI that natively implements multiple language models, rather than having single product variants that only support one language. Command models corresponding to each language can be deployed as binary files that are compiled together with the main application software and executed as single firmware on the device's microcontroller.

Audio Front-End Design for Ambient and Motor Noise Cancelling

Reliability is equally important, and commitment to safe products remains essential in the healthcare industry. Voice-enabled autoinjectors must be able to recognise words spoken by the user with a high level of accuracy, even in the presence of background noise, and mitigate the risks of errors that might lead to hazardous consequences for the patient. This is not trivial because electromechanical autoinjectors are normally exposed to a high level of interference noise, coming not only from the environment (home settings are often far from quiet) but also that generated by the device itself – mostly the motors and the movement of any associated mechanical gears. The latter adds to environmental noise interference and can drastically overwhelm the voice content. Obviously, VUIs need a clean speech signal to correctly recognise voice commands.

To address this, it is crucial to look at the solution holistically. Designers must figure out how to improve the acoustic performance of the audio-capturing system as a whole. This can be accomplished with proper arrangement of both hardware and signal processing software technologies, which must operate seamlessly on the device to ensure accurate voice recognition performance. Starting with the hardware (Figure 2), the autoinjector can accommodate multiple microphones to implement audio beam forming and enable

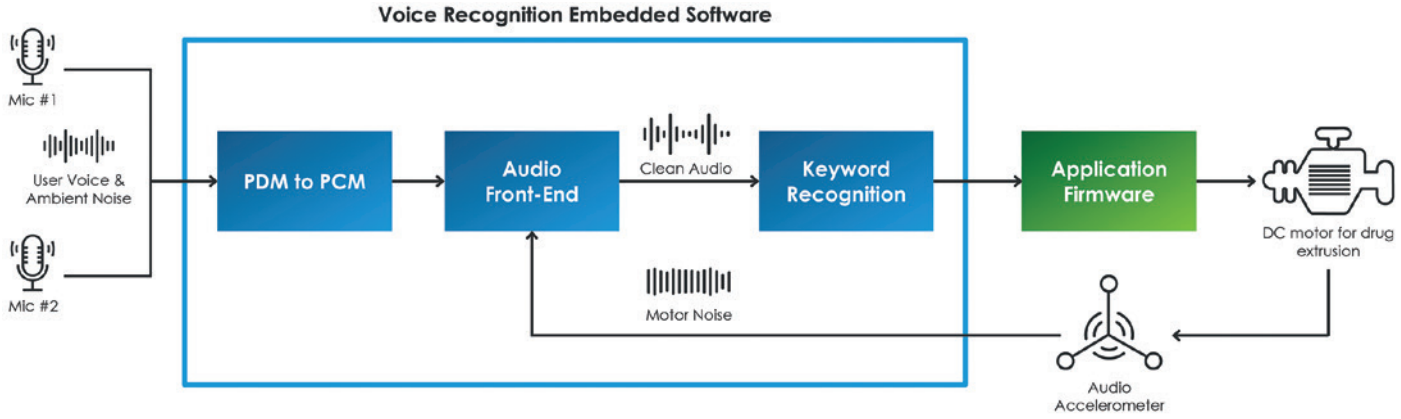

Figure 2: Block diagram of the voice-processing system.

directional voice capturing. There is no need to push for complicated hardware architecture, and two microphones are more than sufficient to achieve reliable source localisation to help to discriminate voice from sounds coming from other directions. In addition, a micro-electromechanical accelerometer can be used to perform some sensor fusion and implement a robust noise-cancelling strategy. An accelerometer can pick out the noise that propagates as mechanical vibrations through the autoinjector's plastic enclosure, and which is generated by the motorised needle and drug extrusion systems.

The software framework is just as important to get best performance from the voice-enabled system. The acoustic front-end (AFE) must reject all ambient and motor noise to deliver a clean audio signal with enhanced voice clarity to the keyword recognition engine. The AFE is made up of a suite of algorithms that are used together to pre-process the audio input stream (both the microphone and accelerometer data sets), including data-format conversion, digital filtering, automatic gain control and adaptive interference cancelling, among others. Response time is crucial for accurate performance, and the AFE can be parametrised and hand-tuned to adjust the response according to the specific interference sounds that the device would normally experience throughout its operation. These algorithms must quickly adapt to changing noise conditions, and recover quickly from instantaneous transition that happens, for instance, when the device is changing injection speed, which obviously would result in a different signal's frequency spectrum.

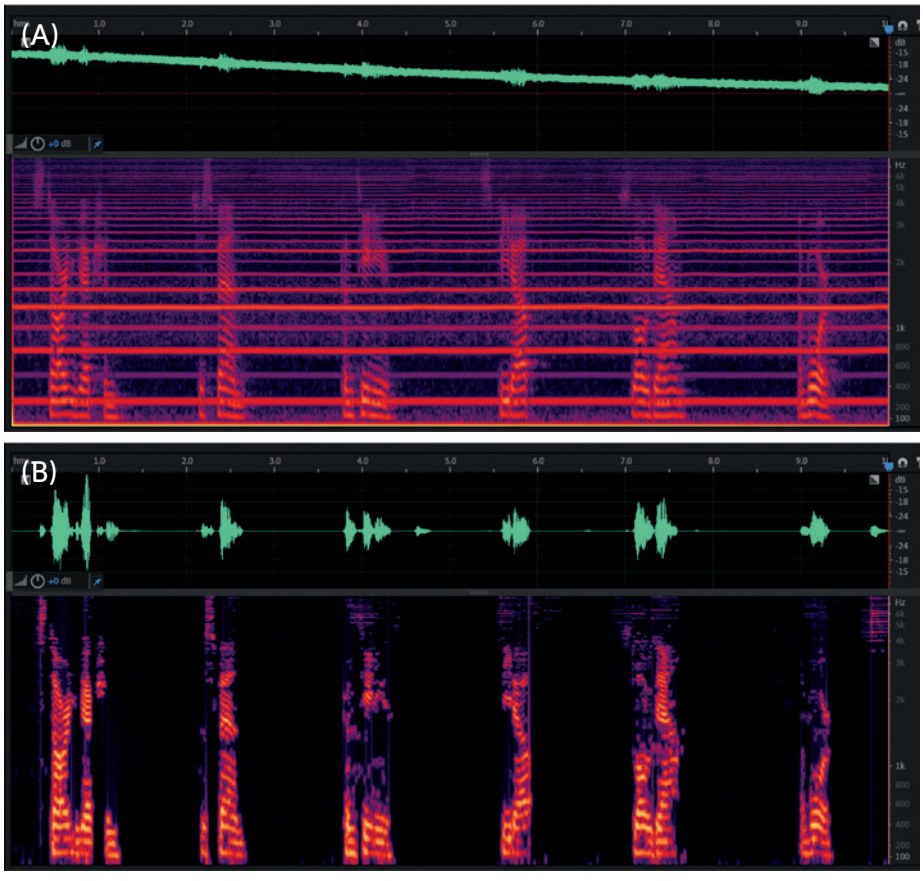

Figure 3: Spectrogram of user's voice without (A) and with (B) AFE for noise cancelling. Autoinjector motor operating at maximum speed (68 db(A) noise level).

ENGINEERING CHARACTERISATION: KEYWORDS-RECOGNITION ACCURACY PERFORMANCE

Figure 3 shows the spectrograms of the audio signals recorded by a reference platform of an electromechanical autoinjector that embeds a complete VUI. The device can respond to a predetermined set of keywords. In this example, the autoinjector was being interrogated with a set of six different vocal commands (*Start Injection, Suspend, Continue, Slow Down, Speed Up, Abort*) that were spoken by the user while the device's drug-extrusion motor was powered to run at full speed. This verified the accuracy of the system in recognising the keywords while the device was exposed to the worst-case noise scenario. The measured sound pressure level of such background noise was 68 db(A). Moreover, the tests were performed with the AFE both disabled and enabled to evaluate how it affects the statistics while it is executed to clean up the audio input stream and reject background noise. Figure 3A shows what the microphones sense when the AFE software is disabled, with noise spread across the full spectrum and non-distinguishable voice content. The keyword recognition performance is negatively affected by the presence of such high-level noise, with a success rate of 52%

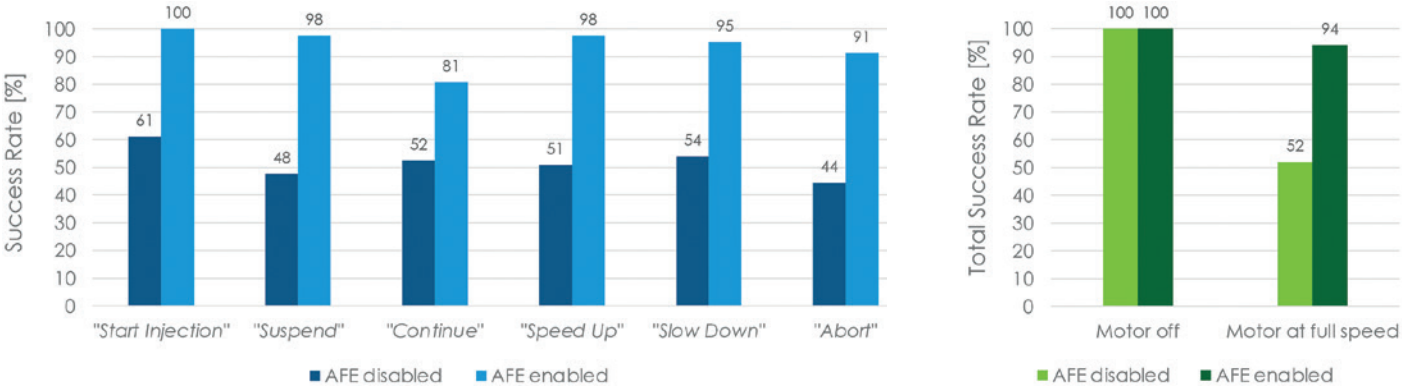

Figure 4: Keywords recognition accuracy. Test performed on 20 US-native subjects (ten male, ten female) with autoinjector's motor operated at full speed (noise level 68 dB(A)).

if no signal processing is performed. Conversely, Figure 3B shows what happens when the AFE is enabled to clean up the audio input stream, with the noise components that were visible before now completely eliminated, thereby providing the keyword recognition model with intelligible user voice. The keyword recognition success rate of the voice engine greatly improves when the AFE is enabled, resulting in a score of 94% (Figure 4).

CONCLUSIONS

Autoinjectors are often perceived as cumbersome devices and difficult to deal with for self-administration therapy at home. This tends to limit compliance and adherence to the treatment, so there is a clear demand for simpler-to-use devices with more user-friendly interfaces. Voice-recognition technology can address this demand. Using a VUI enhances device usability and delivers a more engaging patient experience, which, in turn, promises to improve patient compliance and the overall quality of care. Technology advancements in artificial intelligence and low-power processing have enabled lightweight implementations that fit minimal hardware platforms with small microcontrollers. This sets the stage for successful implementation of new voice-enabled autoinjectors.

ABOUT THE COMPANY

Flex provides sketch-to-scale solutions, delivering innovative design, engineering, manufacturing, real-time supply chain insight and logistics services to a wide range of industries. Flex Health Solutions is a global leader in the design and manufacture of medical products for pharmaceutical and medtech companies. This includes the design and commercialisation of more than 75 regulated medical devices, from pens and autoinjectors to pumps and inhalers. The company's approach is supported by FDA-registered and ISO 13485-compliant facilities and a world-class quality system.

ABOUT THE AUTHOR

Salvatore Forte is Innovation Manager at Flex, leading an R&D engineering team in the company's Design Center in Milan. Mr Forte has a solid technical background in analogue and digital electronics, specialising in embedded system design for power-sensitive medical devices, such as wearable health monitors, disposable point-of-care and automated drug delivery. He holds an MS degree in Electrical Engineering from University of Naples Federico II (Italy).

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SO FAR SO GOOD: MAINTAINING THE MOMENTUM OF PROGRESS FOR SUSTAINABLE POLICIES

In this article, Michael Earl, Director of Pharmaceutical Services at Owen Mumford, discusses the highlights of a review undertaken by Owen Mumford into how the pharmaceutical industry is faring on environmental, social and governance standards, noting that while the industry is performing above average overall, there remain some key areas for improvement.

The pharmaceutical sector is working hard to reduce its carbon footprint, eliminate pollution, conserve water and use sustainable components. Similarly, upstream suppliers and partners for combination drug delivery products are stepping up to ensure that the whole supply chain improves its environmental, social and governance (ESG) standards. As a key delivery device partner for pharma companies, Owen Mumford has reviewed the current state of play on ESG compliance in the industry across the top 25 companies reporting ESG scores. We summarise the highlights here, with the intention of contributing to the industry's current understanding, underlining the achievements made to date and signposting some of the key areas for improvement.

SUSTAINABILITY IN PHARMACEUTICALS – THE CURRENT STATE OF PLAY

Around the COP26 Summit in 2021, The Association of British Pharmaceutical Industries (ABPI) published a report entitled "Drive to Net Zero: How Pharmaceutical Companies Are Helping the Fight Against Climate Change".[1] The study reflected similar reviews covering the pharmaceutical industry in the US, the EU and parts of Asia. It describes a number of examples of leading pharma companies that are achieving significant sustainability targets or promising to reach ambitious goals over the next two decades. Those goals can be categorised into four distinct areas of sustainability policy:

- **Carbon emission** issues focused on energy use reduction, sustainability and overall net-zero targets
- **Water sustainability** concentrated on reduced manufacturing consumption and the elimination of pharmaceutical waste from the water system
- **Waste management improvements** zeroed in on packaging and more effective product recovery and disposal
- **Sustainability by design** covering both green chemistry and chemical recovery and reuse, as well as reusable delivery devices.

"As a sector, biopharma outperformed the overall company average in each of the report's key measurement categories: measurement and reporting; ambition and targets; governance, strategy and action plan; and achievement."

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"No company can claim to be part of a sustainable ecosphere unless its whole supply chain (including distribution channels) is moving in lockstep and to similar standards – exemplified by the rules on Scope 3 emissions which specifically reference the supply chain in total."

Corroboration of this positive industry view was seen in the October 2021 Climate Reporting Performance report from EcoAct,[2] which states that three biopharmaceutical giants feature in the global top 20 companies for sustainability. As a sector, biopharma outperformed the overall company average in each of the report's key measurement categories: measurement and reporting; ambition and targets; governance, strategy and action plan; and achievement.

Owen Mumford has conducted its own analysis of the pharmaceutical industry, across a set of ESG factors that are extremely specific to the sector and the supply chain that serves it. This latter point is important, as no company can claim to be part of a sustainable ecosphere unless its whole supply chain (including distribution channels) is moving in lockstep and to similar standards – exemplified by the rules on Scope 3 emissions which specifically reference the supply chain in total.[3]

Owen Mumford sees this pressure come down the line from its pharma clients and is taking a collaborative approach to increase attention to ESG aspects for combination products across sourcing, manufacturing, packaging and distribution. A good example is the contentious area of disposable plastic devices in drug delivery. While alternatives, such as degradable plastics, are under constant review, immediate progress is being made by reducing the number of disposable components in delivery devices. At Owen Mumford, this kind of sustainability by design is already visible in the development of its reusable autoinjector range, providing pharma partners with environmental progress in their supply chain.

VARIANCE AND SIZE – TWO PRELIMINARY POINTS

Before getting into the specifics of the industry review, there are two overarching observations that are worth pointing out. First, although the industry as a whole achieves an ESG score of 61% in the EcoAct review mentioned prior – significantly above the all-industries average of 53% – the performance of individual companies varies significantly. The study revealed a variance of over 40% between the top performers and those who are at an earlier stage in their journey. As such, the industry cannot be complacent until the industry average is accompanied by a narrower band of variation. Equally, it appears that neither geography nor size is a major factor. The top performing smaller firms are only a few percentage points short of the top performing giants, all spread across the world. This implies that corporate will and commitment to ESG improvements are almost as important as large budgets with which to achieve them.

"The industry cannot be complacent until the industry average is accompanied by a narrower band of variation."

MEASURING REAL TARGETS

Owen Mumford's review considered not only where ESG policies had been put in place and published, but also where a pharma company had publicly set hard targets (where appropriate) – as the saying goes, "handsome is as handsome does". Given that ESG credentials (including hard targets) are ever more frequently forming part of every tender, proposal and partnership requirement up the supply chain, it is logical to conclude that pharmaceutical companies will themselves want to demonstrate to customers, policymakers and healthcare system stakeholders not only company ambitions, but evidence of hard actions and achievement thresholds.

As just one example of what key supply chain partners are doing, Owen Mumford is pursuing a number of science-based targets, including a net-zero deadline (2045), reusable device development, renewable energy use in manufacturing and office environments, freight journey minimisation, zero waste to landfill (achieved) and various others.

FOUR POSITIVE ACHIEVEMENT AREAS

The most mature areas where hard targets have been publicly set were energy, water, waste and air emissions. Pharmaceutical manufacturing is energy intensive,[4] and the most developed energy policies focused on a combination of renewable energy sources, self-generation and energy efficiency via reduction of energy requirements in the manufacturing process.[5] Manufacturing energy efficiency can be focused on either production lines or industrial buildings – in both cases, overall savings in the region of 25% were typical and were often much higher.[6]

Water, of which the pharma sector is a major consumer,[7] focused not only on reducing consumption – itself a worthy and socially important aim – but also on cleaning and reprocessing water (either for reuse or putting back into the water grid). Health and water are closely interconnected, so managing its use – not only in-house but also throughout the supply chain – helps avoid potential risks. One international generics giant aims to achieve 100% water "neutrality" by 2025 by reusing water, recycling wastewater and capturing rainwater. The review showed that around 50% of pharma companies have set hard targets in this category.

28% of pharma companies have set targets to reduce their waste emissions by at least one quarter. Some companies are attempting to avoid reliance on landfills for waste disposal, while others are pursuing a zero-waste approach. Indeed, a commercial incentive may be coming into play as increasing commodity prices encourage pharma companies to recognise waste as a source of scarce resource.

Air emissions are a major focus with almost 70% of pharma companies pursuing specific targets. Not only are they looking at carbon emissions reduction, but also the release of gaseous pollutants. Typical pollutants to be filtered include acidic gases, basic gases, dust and aerosols, pharmaceutical "actives" and volatile organic compounds.

"While 84% of companies have a policy on pharmaceuticals in the environment and 36% have a policy on the related issue of anti-microbial resistance, almost none have actual targets in these areas."

CONTAMINATION AND PACKAGING – A WORK IN PROGRESS

As well as these highly developed areas of ESG compliance and specific target setting in the pharmaceutical industry, there are other areas of surprisingly low commitment to measurable outcomes, at least to date. In particular, while 84% of companies have a policy on pharmaceuticals in the environment and 36% have a policy on the related issue of anti-microbial resistance, almost none have actual targets in these areas. The AMR Alliance, an industry initiative to address anti-microbial resistance in all its aspects, notes that, "Manufacturing emissions from both the production of APIs and their formulation into drugs is another source of environmental emissions. In regions like Europe, only trace levels of antibiotics in the environment can be attributed to waste from production but in countries where discharges are not well controlled some studies have found very high levels of active residues in the discharge vicinity of antibiotic factories."[8] A variety of studies confirm this issue, which is just one of several when it comes to safeguarding the environment from pharmaceutical contamination.[9] Clearly this area is a work in progress.

More surprising (and less complex) is the issue of packaging. While 76% of pharma companies have a policy on this front, only 13% of companies studied in the review had translated policy into actual targets. This is a little perplexing, as it is an area that other sectors have long since addressed, and one in which it is a relatively straightforward task to define goals. Packaging can be converted to sustainable alternatives – where clinically acceptable – and companies can also address weight and packaging efficiency to reduce the burden on shipping. A few leaders have pinned their colours to the mast, with specific targets set, especially around rebalancing the use of plastics versus recycled/sustainable paper – objectively assessing where replacement brings a net environmental gain and where the original packaging should be retained. It is likely that this area will become widespread rapidly over the course of the next few years.

CONCLUSION

A variety of independent studies have clearly indicated that the pharmaceutical industry is above average when it comes to ESG compliance, initiatives and recognised measurements. Many of those measurements specifically scrutinise the imposition of standards throughout a pharmaceutical manufacturer's supply chain and distribution channels. However, there are several areas revealed in the Owen Mumford review where hard target commitments should be developed over the next few years to enhance the industry's positive position on ESG standards further.

ABOUT THE COMPANY

Owen Mumford is a major healthcare company and device manufacturer that commercialises pioneering medical products in its own brand and custom device solutions for the world's major pharmaceutical and diagnostic companies. Owen Mumford's goal is to enhance access to diagnostics, encourage adherence to treatment and reduce healthcare costs, making a world of difference to a world of people.

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ABOUT THE AUTHOR

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

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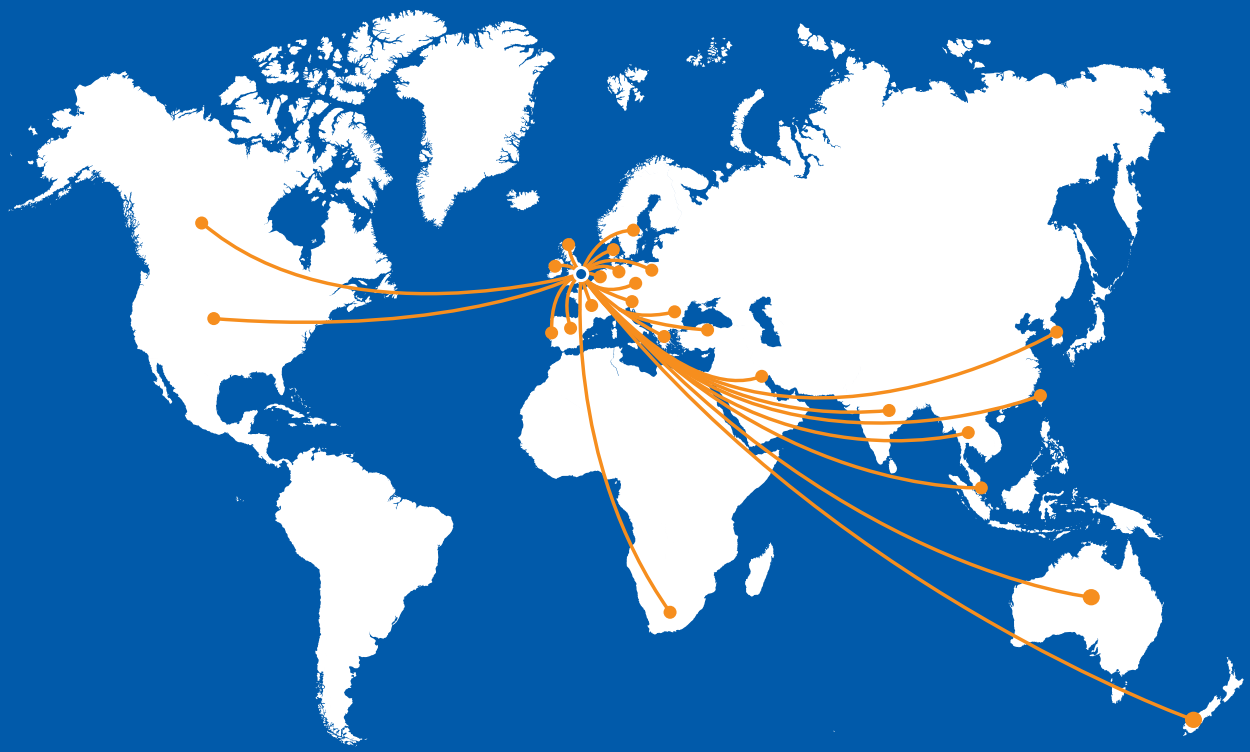

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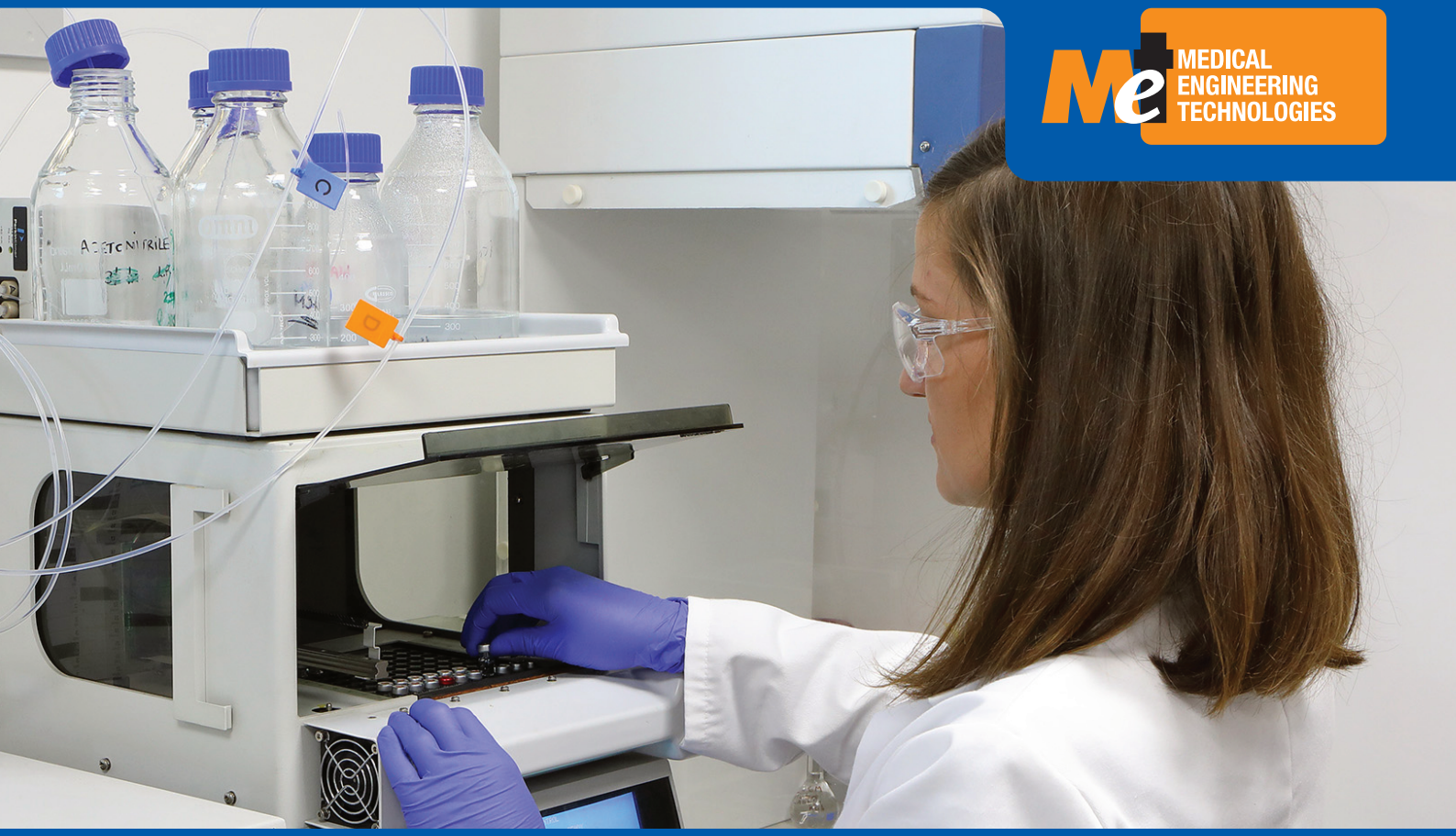

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2022/23 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
March 2022	Ophthalmic Drug Delivery	Deadline passed
April	Pulmonary & Nasal Drug Delivery	Mar 17, 2022
April/May	Drug Delivery & Environmental Sustainability	Mar 24, 2022
May	Delivering Injectables: Devices & Formulations	Apr 7, 2022
June	Connecting Drug Delivery	May 5, 2022
July	Novel Oral Delivery Systems	Jun 2, 2022
August	Industrialising Drug Delivery	Jul 7, 2022
September	Wearable Injectors	Aug 4, 2022
October	Prefilled Syringes & Injection Devices	Sep 1, 2022
Oct/Nov	Drug Delivery & Environmental Sustainability	Sep 15, 2022
November	Pulmonary & Nasal Drug Delivery	Oct 6, 2022
December	Connecting Drug Delivery	Nov 3, 2022
January 2023	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Dec 1, 2022
February	Prefilled Syringes & Injection Devices	Jan 12, 2023

TAKING INTEGRATED NEEDLE SAFETY SYSTEMS FOR PREFILLED SYRINGES TO THE NEXT LEVEL

Here, Michelle Deutsch, Head of Product Management for Glass Prefilled Syringes at SCHOTT Pharma, and John Merhige, Chief Commercial Officer at Credence MedSystems, discuss the needle safety requirements of prefilled syringes and consider how SCHOTT TOPPAC® and syriQ® PFS with Credence Companion® technology combine to meet these challenges, while ensuring the device meets sustainability demands.

Needle safety and usability is a greater challenge than ever for new types of medication in new types of surroundings. Today's mass vaccination programmes highlight the increasing importance of needle safety and enhanced usability in drug delivery systems. Enabling both successful dose delivery and protection from sharps injuries is critical.

Multidose vials, commodity syringes and user-activated needle safety devices offer the first level of protection and usability, while single-dose, prefilled syringes (PFSs) and passive safety devices represent a step-change in safety, convenience and flexibility. Additionally, a superior PFS safety device should feature easy integration with fill-finish lines and environmental sustainability. User-centric design and an awareness of the complex issues facing modern pharmaceutical manufacturers are key to the successful delivery of such solutions.

PARTNERING TO ADDRESS THE CHALLENGE: SCHOTT AND CREDENCE

SCHOTT and Credence MedSystems have collaborated to meet today's stringent requirements for safety and usability. SCHOTT's technological expertise in glass and polymer primary packaging, combined with Credence's award-winning innovation talents, have combined to create an integrated PFS system that closes the gaps in existing offerings and opens up new possibilities in flexibility, convenience and usability. The integration of SCHOTT and Credence products and competencies has enabled a broad choice of PFS safety options – materials, components, design options – with expert support.

> "Multidose vials, commodity syringes and user-activated needle safety devices offer the first level of protection and usability, while single-dose, PFSs and passive safety devices represent a step-change in safety, convenience and flexibility."

THE CHALLENGES IN DETAIL

The US Needlestick Safety and Prevention Act was passed in 2000, when it was estimated that over 600,000 needlestick injuries

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"The right approach should improve the shortcomings of today's traditional safety syringes while also offering advantages in usability and sustainability."

occurred in the US alone.[1] In 2010, an EU mandate addressed the danger of accidental sharps injuries with legislation on the issue, coming into force from 2013. In 2011, ISO 23908 was created to set out test methods and performance parameters for evaluating the performance of sharps injury protection devices.

Today, with user injury rates continuing to be much higher from active compared with passive safety devices,[2] it is hardly surprising that authorities have demonstrated a strong preference for passive safety devices. New vaccines are coming onto the market, the move to home-based care continues and more dual chamber applications are entering the pipeline. The need to accelerate the move to patient and user needle safety has never been clearer. PFSs and passive safety devices are the obvious solution.

Given the pressing need, it is not surprising that conventional "add-on" safety devices are being challenged by "integrated" alternatives, where the safety mechanism is incorporated into the syringe before delivery to the fill-finish suite. However, as new technologies are developed to address the shortcomings of conventional approaches, usability must be enhanced rather than hindered.

Premature activation of the safety mechanism can be a recurring failure mode in both traditional and recently introduced developmental safety systems. This is a significant disadvantage because once activated during transport or use, the syringe is no longer able to inject the drug, leading to the waste of potentially costly and scarce medications. Activation failures and limitations on the angle of injection are other drawbacks associated with some needle safety mechanisms.

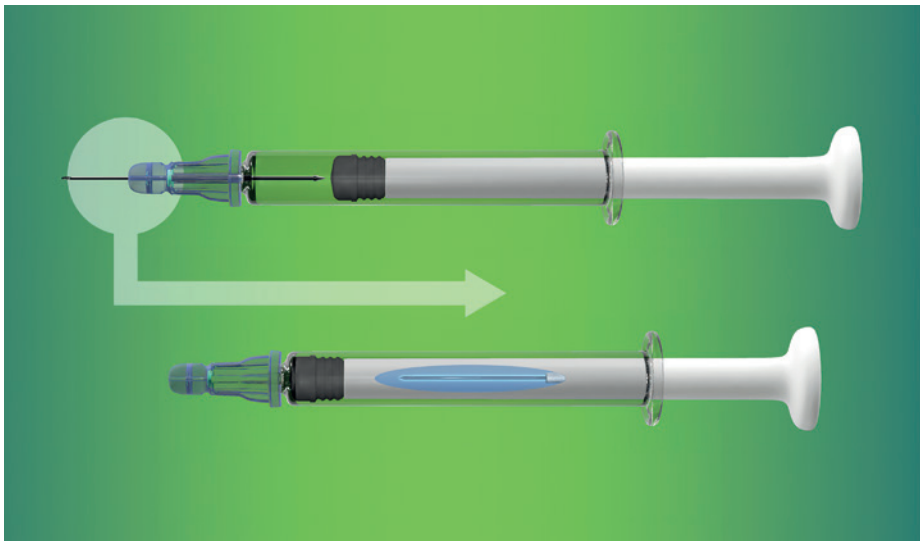

Figure 1: At the end the injection, the user receives an audible and tactile cue that the dose has been delivered, the needle has been retracted into the plunger rod and the syringe is prevented from re-use.

The right approach should improve the shortcomings of today's traditional safety syringes while also offering advantages in usability and sustainability. Additionally, it is critical to identify an approach that is flexible enough to support full drug platforms as well as the needs of specific drugs.

CREDENCE COMPANION®: COMBINING ENHANCED SAFETY AND USABILITY WITH OPERATIONAL EFFICIENCY

The Companion® safety syringe system has been developed to overcome challenges with both existing and in-development approaches, as well as to offer enhanced safety and usability features, while benefitting from compatibility with existing PFSs and other primary package components. Its performance robustness has been demonstrated in rigorous evaluations and customer assessments, including, among other verification activities, drop testing and retraction reliability studies (Figure 1).

"Companion® incorporates different cues to support a user-friendly experience. In addition to an audible click marker, tactile and visual indicators combine to mark the end-of-dose and the needle safety."

Companion® incorporates different cues to support a user-friendly experience. In addition to an audible click marker, tactile and visual indicators combine to mark the end-of-dose and the needle safety. In conventional approaches, complex external structures can obscure the view of the syringe, but Companion® features a streamlined design that provides a clear view of the syringe barrel and drug product. This has the advantages of allowing users to perform the common syringe techniques that Companion® supports – air bubble purging and aspiration – and confirm full drug delivery and needle retraction. Both customer-sponsored and Credence's own human factors testing has consistently shown a higher user preference for Companion® compared with alternative approaches.

Besides these usability advantages, a design that eliminates the complex add-on structure delivers further advantages in fill-finish processing. Companion® is compatible with existing nest and tub configurations, allowing for high-speed processing through fill-finish lines. Additional production steps and scrap associated with the mounting of conventional add-on devices can be eliminated, offering pharmaceutical manufacturers the opportunity to innovate and implement more efficient equipment configurations and processing flows.

While Companion® therefore has the advantage of supporting industry-standard processing, packaging and equipment, it also incorporates its own value associated with the control of undesirable added residuals. Its needle assembly is mounted on standard glass and polymer

syringe barrels without the use of glue, removing an unwanted material. Tungsten-free and stainless steel-free options are also available. Superior fit with the existing fill-finish landscape, the ability to integrate with a broad portfolio of PFSs and critical differentiating features combine to make Credence Companion® the ideal safety device for SCHOTT PFSs (Figure 2).

syriQ® AND SCHOTT TOPPAC® SYRINGES: PROVEN SOLUTIONS

An industry leader in pharmaceutical packaging, SCHOTT offers customers a choice of PFS to meet the needs of drugs across a range of market segments. syriQ® glass syringes and SCHOTT TOPPAC® prefillable syringes made of cyclic olefin copolymer (COC) can be found in traditional and modern vaccines, sensitive biologics, cosmetics and intravenous applications in homecare, clinical, hospital and operating room settings across the world. SCHOTT PFSs are at the forefront of cutting-edge vaccine programmes and biologic drug delivery. The engineering teams behind this work lead the way in applying packaging science to solving the human health challenges of today.

"The advantages of Credence Companion® combined with syriQ® glass and SCHOTT TOPPAC® polymer prefillable syringes create a powerful primary packaging value proposition, taking the safety and usability of injectables administration to the next level."

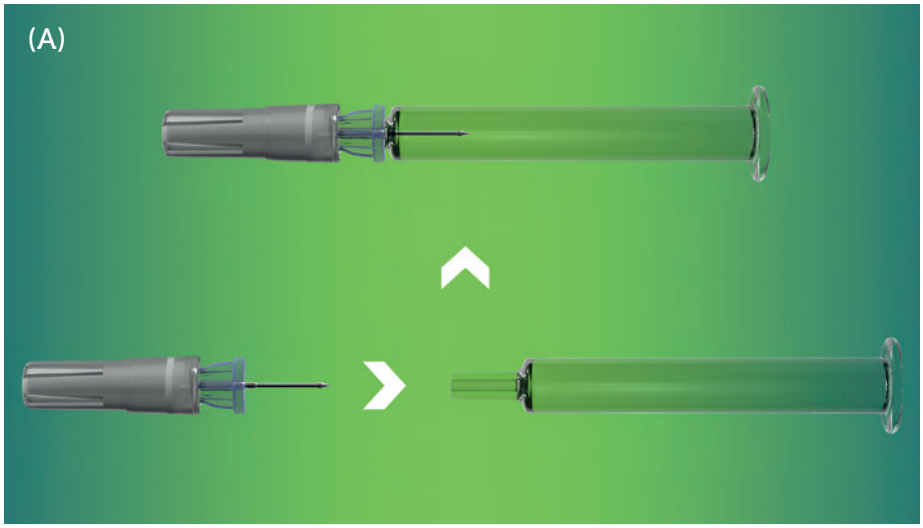

Figure 2: The Companion® needle assembly is integrated with SCHOTT PFSs (A) and delivered to the filling suite in the preferred presterilised nest and tub configuration ready for filling (B).

syriQ®

The full syriQ® portfolio offers all the advantages of SCHOTT FIOLAX® glass tubing, with the FIOLAX® Controlled Hydrolytic Resistance syringe barrel option offering additional resistance against leachables and the attack of aggressive buffers. Ultra-low tungsten options prevent potential protein agglomeration in sensitive drugs.

Homogeneous low-silicone layers applied with state-of-the-art diving nozzle technology ensure that break-loose gliding forces remain consistent over the ageing process for a range of plunger stoppers. Ongoing particulate reduction programmes and major investments in new washing lines and camera inspection systems have supported increasingly tighter acceptance quality limits across the full syriQ® portfolio. syriQ® is bolstered by multiple suppliers for raw materials and access to world-class internal materials expertise gained across a range of glass product lines.

The advantages of Credence Companion® combined with syriQ® glass and SCHOTT TOPPAC® polymer prefillable syringes create a powerful primary packaging value proposition, taking the safety and usability of injectables administration to the next level.

SCHOTT TOPPAC®

Rapidly gaining acceptance in new market segments, polymer PFSs have long been a staple in applications demanding a PFS in sizes and configurations less suitable to glass syringes. Polymer syringes have also stood out for their specific advantages when delivering highly viscous injectables and their regulatory acceptance in intravenous drug delivery.

The manufacturing process for COC PFSs generates no heavy metals and requires no adhesives, resulting in a product that contains no tungsten, guarantees no ion leaching and maintains a consistent product pH over time. SCHOTT TOPPAC® syringes feature silicone-free

oil. Like the syriQ® portfolio, they are verified with a choice of plunger stoppers. SCHOTT TOPPAC® syringes support different sterilisation modalities – gamma, e-beam and X-ray – and their COC material lends itself to highly flexible design.

The combination of SCHOTT TOPPAC® and Companion® technology is a breakthrough – the first prefillable syringe made of COC to be commercially available with a staked needle and integrated passive safety device. With this comes the important potential benefit of extending sharps injury protection to user populations in a wider range of applications. An additional breakthrough stemming from this combination of leading technologies is evident in applications requiring point-of-care reconstitution of large volume pharmaceuticals. Integrating the Credence Dual Chamber Reconstitution technology with larger SCHOTT TOPPAC® barrels (e.g. 10 and 20 mL) results in a safe and convenient method to reconstitute and deliver large volumes, and leverages the weight and break-resistance of polymer syringes.

THE FREEDOM TO CHOOSE WITH CONFIDENCE AND SUSTAINABILITY

Credence Companion® and SCHOTT syringes will be integrated using a flexible approach that can support a wide range of drugs, administration routes and patient populations. A versatile portfolio of prefilled safety syringes is planned to support syriQ® glass syringes from 0.5 to 3 mL and SCHOTT TOPPAC® polymer syringes from 0.8 to 20 mL, with needles for either glass or polymer from 22 to 32G including both 1/2 and 5/8th needle lengths. The system will also lend itself to adaptation for autoinjector use.

The Credence Companion® and SCHOTT prefilled safety syringes will use familiar, existing components and materials – glass, polymer, siliconisation technologies and closure components – already used in standard syriQ®, syriQ BioPure® glass and SCHOTT TOPPAC® polymer syringes, reducing the burden of change management. As well as existing syringe components and materials, the integrated Companion® and SCHOTT syringe safety system will also be built around existing packaging and equipment, working seamlessly with industry-standard SCHOTT syringe nests and tubs and supporting easy integration with existing fill-finish lines. Familiar tubs containing the nested safety syringe will be delivered to the fill-finish site together with plunger rods to complete the assembly following a standard manufacturing and supply chain flows. Equipment changes will not be required to process the Companion® PFS.

The streamlined, flexible design of Companion® results in an environmental footprint that approximates that of a standard "naked" PFS and is a significant improvement compared with conventional add-on systems. Compared with a leading add-on safety syringe system, Companion® reduces the weight of added components by 58%, uses 38% of the plastic, occupies 47% of the volume pre-use and occupies 33% of the volume post-use, according to an internal Credence study (ENG-0141). Lighter, smaller and using less plastic, the Companion® system can provide pharmaceutical manufacturers with sustainability and cost advantages; the integrated Companion® and SCHOTT syringe can reduce the burden on in-plant material processing, the size of secondary packaging, cost of shipping and space needed in cold storage (Table 1).

Sustainability Category	Advantage of Companion® Compared with Leading Add-On Device
Weight of Added Components*	Weight of added components reduced by 58%
Polymer/Plastic Consumption	Weight of Polymer/Plastic used reduced by 62%
Pre-Use Volume Occupied by Device	3D Footprint reduced by 53%
Post-Use Volume Occupied by Device	3D Footprint reduced by 67%

*Incremental to baseline syringe, stopper and needle shield

Table 1: Companion® sustainability advantages: 1 mL long syringe (Credence internal study ENG-0141)

SCHOTT PFS, integrated with Companion® technology, minimises disruption to existing injectables manufacturing and supply chain flows, allowing pharmaceutical manufacturers to innovate without the burden of significant change management, resulting in a more environmentally sustainable safety syringe option.

UPGRADING INTEGRATED SAFETY SYSTEMS TO THE NEXT LEVEL

Integrated safety systems have a vital part to play in preventing sharps injuries and supporting positive clinical use experiences. They also offer important opportunities for drug lifecycle management and product differentiation. Choosing the right safety system, especially for multiple drugs or an enterprise platform, is not a trivial decision. Reliable partners, ease of integration, environmental sustainability and a product that offers the flexibility to support a wide range of different drugs are all critical selection criteria. The integrated Companion® and SCHOTT syringe safety system (Figure 3) can deliver all of these advantages, from stability testing through launch, with a range of creative, versatile formats and with the assurance of SCHOTT as a full system supplier.

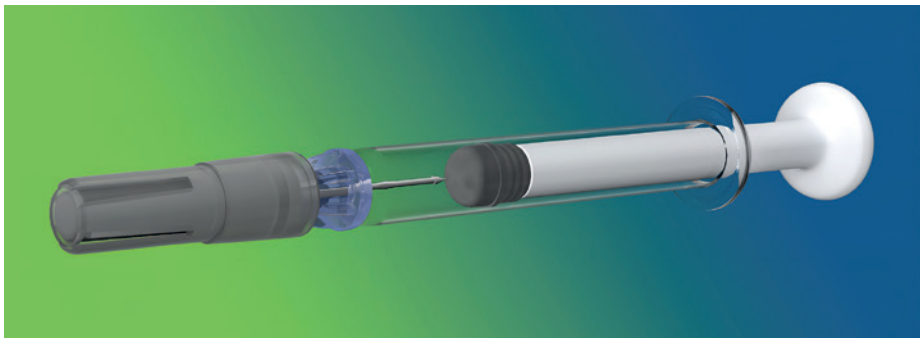

Figure 3: Credence Companion® on SCHOTT prefilled 1 mL long syringe.

ABOUT THE COMPANIES

SCHOTT Pharma helps people around the world protect, access and use the medicine they need as safely and

conveniently as possible. As a market leader in primary packaging made of glass and polymer, SCHOTT is safeguarding and advancing the integrity of injectable solutions and more. The company is a pioneer with unsurpassed quality, safety and reliability.

Credence MedSystems is a developer of drug delivery systems that solve unmet market needs for the pharmaceutical industry. Credence's philosophy of Innovation Without Change allows pharma manufacturers to impress and protect their end users while preserving their existing processes, sourcing strategies and preferred primary package components. The Companion® family of syringe systems includes proprietary needle retraction technology, syringe re-use prevention and other critical safety and usability features. The Dual Chamber Reconstitution platform offers single-step mixing and injection for medicines that require reconstitution at the time of delivery. The Credence Connect™ brings digital connectivity to any syringe and has the potential to impact chronic disease management and clinical trial compliance. Metered dose systems and other novel devices address the needs of specific therapeutic markets, such as ocular therapies and cosmetic applications.

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ABOUT THE AUTHORS

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John A. Merhige is Chief Commercial Officer at Credence MedSystems, leading the company's commercial activities and external collaborations. Previously, Mr Merhige was Vice President, Market Development at Sanofi. Mr Merhige graduated from Dartmouth College earning a BA, a BE in mechanical engineering and a Masters in Engineering Management from Dartmouth's Thayer School of Engineering and Tuck School of Business (NH, US).

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MDR COMPLIANCE: PLANNING FOR POST-MARKET CLINICAL FOLLOW-UP

In this article, Celeste Maksim, PhD, Chief of Staff, Clinical and Post-Market Practice at RQM+, discusses best practices for drug delivery device manufacturers when conducting post-market clinical follow-up activities, as mandated by the EU Medical Device Regulation.

While the EU Medical Device Regulation (MDR) came into force in May 2021, many manufacturers benefitted from the option to renew their certificates under the previous Medical Device Directive (MDD), granting them an extended period to transition to MDR compliance, ending in 2024. However, some requirements already applied to all manufacturers, regardless of whether or not they are taking advantage of the extension; Article 120 of the MDR states that post-market requirements will apply to MDD-certified devices even during the transition period. Post-market activities are extensive under the MDR and require ongoing attention. This article will focus on post-market clinical follow-up (PMCF), which falls within the MDR's post-market surveillance (PMS) plan.

The aim of PMCF is firstly to confirm the safety and performance of a device, including the clinical benefit, if applicable, across the span of its expected lifetime. It also helps to address risk by identifying previously unknown side-effects, monitoring the identified side-effects and contraindications, and identifying and analysing emergent risks on the basis of factual evidence. The conclusions of this analysis are then used to demonstrate the continued acceptability of the product's benefit-risk ratio. Furthermore, PMCF activities can identify possible systematic misuse or off-label use of the device.[1]

Pharmaceutical companies must be aware of PMCF requirements, particularly if they:

- Manufacture medical devices
- Partner with or supply to companies that manufacture medical devices
- Manufacture a drug that is sold pre-packaged in a delivery device.

STRATEGY

As PMCF is a long-term activity that must be carried out throughout the lifecycle of a device, it is paramount to establish sound strategies and clear processes for it as soon as possible. Ideally, strategies should take a holistic approach, incorporating all relevant departments within an organisation. PMCF is likely to require significant resources, even for legacy devices that have been on the market for a long time, and input will be required from multiple departments and functional areas within the company. Therefore, it is important to involve each department in discussions and decision-making, making them aware of the rationale for PMCF activities and the potential business damage of non-compliance.

> "A recommended approach is to stratify the clinical evidence to determine the appropriate PMCF activity and identify the objectives, primary endpoint and acceptance criteria for each product."

The available activities for PMCF include randomised clinical trials, registry studies, retrospective patient chart reviews, literature reviews, end-user surveys and focus groups; appropriate activities need to be carefully selected from this list. A recommended approach is to stratify the clinical evidence to determine the appropriate PMCF activity and identify the objectives, primary endpoint and acceptance criteria for each product. Transparency with all stakeholders should minimise the potential side-effects of compartmentalising activities within the company.

It is also helpful for all departments to understand how data links together throughout the post-market lifecycle. Gantt charts by document and data input/source have proven helpful for optimising strategies, and for understanding the resource requirements for ongoing MDR compliance. For example, discuss with safety and

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complaint handling teams how complaints will be handled prior to conducting a complaints-related PMCF activity.

PROCESSES

New clinical data obtained through PMCF should be fed into ongoing clinical evaluation, and post-market documents need to be regularly updated. Inconsistent procedures and data organisation will inevitably make PMCF compliance a much greater challenge than it needs to be. Data should be presented in a standardised manner across all devices, medical indications and target populations, making it easier to evaluate existing clinical data, contextualise and track changes, and prioritise.

Crucially, standardised processes should support a notified body review, as they produce a consistent clinical story across all documents in the submission, and in documents supporting ongoing compliance. Processes may need some adjusting once they have been tried out, so it is good practice to test processes with some representative high-priority devices first. This helps to gauge whether the proposed templates, forms and processes will work well across the company.

PRIORITISATION

It may not be realistic for a company to achieve PMCF compliance for their entire product portfolio overnight. As a result, they may need to assess the quality and relevance of existing clinical evidence and determine which devices are closest to meeting PMCF compliance requirements and which need more work. They can then decide which devices to prioritise while also considering revenue, certificate expiration timelines, likely lifecycle, market strength and the number of devices in need of data remediation. If there is not enough time to carry out the most appropriate PMCF activity for a device, manufacturers can demonstrate how this will be remedied over a multi-year period and which activities will be employed. In some cases, it may be possible to obtain PMCF clinical data during notified body review, which can then be used to answer post-submission queries from the notified body.

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> "Manufacturers should ensure that their data clearly support the intended use of the device, demonstrate clinical benefit and support the indications and claims."

DATA & DOCUMENTATION

PMCF must be based on what the regulation refers to as "sufficient clinical evidence". What exactly the regulation means by "sufficient" can be a source of confusion for manufacturers. The amount of data required varies depending on the risk class of the device, the indication, claims, available data to support the device and any recent changes in clinical practice or the device itself. Manufacturers should ensure that their data clearly support the intended use of the device, demonstrate clinical benefit and support the indications and claims. They can also compare the outcomes achieved with similar devices on the market that are considered state of the art treatment options, to determine whether they have sufficient clinical data.

It is critical to be able to provide a strong rationale for why the available data should be considered "sufficient". A common remark from notified bodies is that manufacturers are not providing enough detail on decisions in their documentation. All decisions, however obvious, should be explicitly rationalised and supported with all relevant data, documentation, regulatory references and statistical rationales.

COMPLIANCE URGENCY

The expectations placed on the quality and quantity of data are higher under the MDR. To meet these expectations, best practice is to plan thoroughly from the outset. With notified bodies under severe pressure, it is advisable for manufacturers to complete outstanding compliance tasks as soon as possible. A high volume of MDD certificates are expected to expire in 2024, which may then lead to delays in notified body reviews. Timely compliance will allow manufacturers to benefit from the attention of a notified body before the rush of submissions expected in two years' time. Although notified bodies cannot offer consultancy or advice, manufacturers can liaise with them post-submission to understand their queries and the meaning of any non-conformities raised.

The advice provided in this article is intended to help manufacturers plan for high-quality submissions that require minimal remediation and to implement best practices in their PMCF activities.

ABOUT THE COMPANY

RQM+ is a leading international provider of regulatory, quality and clinical consulting services for medical device and diagnostics manufacturers. RQM+ delivers transformative solutions to clients by providing collective knowledge and expertise, fuelled by passion for client success. RQM+ experts are collaborative, laser-focused on client needs and committed to delivering high-value solutions that exceed expectations.

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ABOUT THE AUTHOR

Celeste Maksim, PhD, is Chief of Staff, Clinical and Post-Market Practice a RQM+. She is RAC-certificated, has a PhD in analytical chemistry and has over a decade of experience in regulated industries, including pharmaceuticals, medical devices, and *in vitro* diagnostic products. Dr Maksim's main focus at RQM+ is on building and managing PMS & PMCF/PMPF services.

NEW BD SCF™ PREMIUMCOAT® 1MLL PLUNGER STOPPER: GLIDING TOWARDS DE-RISKED COMBINATION PRODUCT DEVELOPMENT

Here, Victoria Meyer, Senior Global Strategic Marketing Manager at BD Medical – Pharmaceutical Systems, introduces the BD SCF™ PremiumCoat® 1mlL Plunger Stopper and explains how the product's role is critical in determining combination products' exposure to extractables and leachables.

The complexity and sensitivity of biopharmaceutical drugs require that specific care be taken in their development, manufacture and administration.

Because of the potentially heightened risk of unexpected interactions between the biologic drug product and its primary packaging, particular care must be taken when evaluating and selecting device materials and components. The price of unforeseen interactions can be steep, including potential product launch delays, as well as possible product recalls in the case of a combination product experiencing functional or safety challenges post-launch.[1]

> "As a component of a combination product in constant contact with the biologic drug, the plunger stopper plays a critical role in determining the combination product's exposure to extractables and leachables."

As a component of a combination product in constant contact with the biologic drug, the plunger stopper plays a critical role in determining the combination product's exposure to extractables and leachables. Co-solvents, surfactants, chelating agents, bulking agents, pH modifiers and other formulation ingredients typically used to stabilise biologic drugs can have an impact on the leaching of organic compounds from rubber stoppers.[2]

As injection device designs evolve to accommodate a broadening range of challenging drugs, often requiring the mitigation of high injection forces for delivery, the plunger stopper has the potential to contribute to the combination product's functional characteristics, including glide force, efficacy and safety. The choice of plunger stopper can also impact processibility and manufacturing, determining the component's behaviour and functional performance during the assembly phase, as well as its compatibility with existing assembly lines.

All these considerations contribute to the plunger stopper playing an important part in the development and assembly of combination products for self-injection. It also means that the choice of plunger stopper is an important step in helping to de-risk the development and launch of biologic combination products.

BD SCF™ PREMIUMCOAT®* 1mlL PLUNGER STOPPER FOR PREFILLED SYRINGES

BD has partnered with Aptar Pharma to develop the BD SCF™ PremiumCoat® 1mlL Plunger Stopper: a sterile, clean and

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"BD draws upon decades of collaboration with pharma industry leaders and understands the importance of meeting drug requirements and quality criteria to provide patients with innovative injectable therapies while helping pharmaceutical companies mitigate product development and commercialisation risks."

ready-to-fill plunger stopper for prefilled syringes for use in the development of combination products. 1mlL refers to the 1 mL "long" configuration of prefillable syringe for which the stopper has been developed.

BD draws upon decades of collaboration with pharma industry leaders and understands the importance of meeting drug requirements and quality criteria to provide patients with innovative injectable therapies while helping pharmaceutical companies mitigate product development and commercialisation risks. BD chose to partner with Aptar to leverage a commercialised rubber and film coating formulation, which has been proven in the market since 2015, thus minimising development risks. BD fully processes, tests and inspects the BD SCF™ PremiumCoat® 1mlL Plunger Stopper to help limit risks, such as foreign matter contamination, and to support successful integration with BD glass prefillable syringes.

The BD SCF™ PremiumCoat® 1mlL Plunger Stopper features a bromobutyl rubber formulation (6720GC) and incorporates an ethylene tetrafluoroethylene (ETFE) film coating.[3] The BD SCF™ PremiumCoat® 1mlL Plunger Stopper helps reduce the risk of drug-container interaction by aiming to limit extractables and leachables.[4] With this proven formulation and film coating incorporated into the BD SCF™ PremiumCoat® 1mlL Plunger Stopper, pharma partners have access to a plunger stopper solution attuned to the needs of their pipeline of sensitive drugs.

REDUCING GLIDE FORCE BY UP TO 65%**

Patient needs are a central consideration in the development of any combination product. Innovation may be required to meet a variety of challenges regarding patient and caregiver ability to deliver a biologic into the subcutaneous tissue via injection.[5] As biologics are developed with high viscosities, ease of manual injection can become compromised due to the force required to inject using a syringe.[6] Developers of combination products can mitigate some of these challenges by considering primary and secondary components that can support glide force – an important element of the injection force required to deliver viscous biologic products. As a key component of combination drug delivery systems, the BD SCF™ PremiumCoat® 1mlL Plunger Stopper aims to improve delivery performance by reducing glide force and variability and helping to reduce injection time and variability with a combined prefillable syringe and disposable autoinjector solution, such as the BD Neopak™ Glass Prefillable Syringe and the BD Intevia™ 1 mL Disposable Autoinjector.

This improved functional performance aims to support the injection of high viscosity drugs in a more effective and predictable way. Testing conducted by BD shows that the BD SCF™ PremiumCoat® 1mlL Plunger Stopper was able to reduce glide force by up to 65% and reduce glide force variability by up to 53%.[7**] At the same time, activation force remains equivalent to the alternative plunger stopper.[7+¥]

"BD considers plunger stoppers as an important component of an entire solution for combination products that, by design, ensures closure integrity, functional performance and reduced risk of drug-container interaction."

THREE-RIB DESIGN FOR ENHANCED CONTAINER CLOSURE INTEGRITY

BD considers plunger stoppers as an important component of an entire solution for combination products that, by design, ensures closure integrity, functional performance and reduced risk of drug-container interaction. Contributing to this performance is the BD SCF™ PremiumCoat® 1mlL Plunger Stopper's three-rib design, which reduces occurrences of no contact between the ribs of the plunger stopper and the barrel. This consistent and improved contact between the BD SCF™ PremiumCoat® 1mlL Plunger Stopper ribs and the barrel supports container closure integrity to help protect the drug in a combination product.[3]

MANUFACTURING FLEXIBILITY WITH ENHANCED PROCESSABILITY AND ASSEMBLY

The BD SCF™ PremiumCoat® 1mlL Plunger Stopper can be assembled using either a long insertion vent-tube or a vacuum-assisted short insertion tube assembly process, supporting flexibility during assembly. A study conducted by Bausch + Ströbel (Ilshofen, Germany) using high speed lines and a vent tube assembly process demonstrated that the BD SCF™ PremiumCoat® 1mlL Plunger Stopper performed well below the requirements for temperature[8] and reduced glide force.[7] Specifically, the BD SCF™ PremiumCoat® 1mlL Plunger Stopper demonstrated glide forces of 20 N, four times below the maximum requirement of 80 N. Assembly testing with the BD SCF™ PremiumCoat® 1mlL Plunger Stopper also determined that the temperatures generated using the same assembly process were below 40°C, which is well below the 60°C requirement, which further supports processability performance on Bausch + Ströbel manufacturing lines. Finally, there were no undesirable defects, such as wrinkles, detected with the BD SCF™ PremiumCoat® Plunger Stopper processing during the study,[8] all of which can impact final assembly of a combination product.

PROCESSING AND INSPECTION – ENSURING TIGHT SPECIFICATIONS

BD processes and inspects the BD SCF™ PremiumCoat® 1mlL Plunger Stopper to limit foreign matter contamination. The six-step process incorporates washing, siliconisation (Silicone LIVEO™ 360 Viscosity 1000 cSt), drying and quality controls, one of which is the BD Visioguard™ 100% camera inspection process.

"With the evolution of treatments for new and existing diseases, pharmaceutical organisations are also evolving and developing sensitive vaccines, such as those for covid-19."

Packaging includes both the Transfer Door Sterile Clean Fill (TSCF) and Bagged Sterile Clean Fill (BSCF) processes for optimum compatibility with manufacturing lines. The sixth and final step consists of sterilisation, using low-dose 12–25 kGy irradiation.

SYSTEM INTEGRATION SUPPORT DATA

The importance of pairing components with a drug is paramount as combination products seek to reconcile the viscosity, concentration and volumes associated with biologics with delivery parameters and patient requirements. To help de-risk drug-device development, BD aims to be a solutions partner that can assure and support the performance of the combined delivery system throughout development and commercial launch.

BD offers system data for delivery solutions to help support combination product development, registration and time to market. BD provides relevant technical and regulatory data for BD products, including plunger rods, backstops, plunger stoppers, prefillable syringe barrels and secondary components, such as disposable autoinjectors and safety shielding solutions. This includes system data that show specific performance metrics, such as the glide force of the BD SCF™ PremiumCoat® 1mlL Plunger Stopper when combined with the BD Neopak™ Glass Prefillable syringe and the BD Intevia™ 1 mL Disposable Autoinjector, providing insights to further de-risk development of combination products.

Packages include data on functionality, extractables level (leachables on request), processability and device integrability.

A SOLUTION FOR SENSITIVE VACCINES

With the evolution of treatments for new and existing diseases, pharmaceutical organisations are also evolving and developing sensitive vaccines, such as those for covid-19. New sensitive vaccine formulations can lead to different requirements during combination product development that can also create challenges for manufacturers. To address this need, BD is in the project initiation process of the BD SCF™ PremiumCoat® Plunger Stopper 1–3 mL for sensitive vaccine applications.

AN INNOVATIVE PLUNGER STOPPER FOR BIOLOGICS BASED ON MARKET-PROVEN TECHNOLOGY

Commercialising a combination product comes with many challenges. The BD SCF™ PremiumCoat® Plunger Stopper, whether in the 1 mlL or 1–3 mL format, aims to help limit drug-component interaction while improving delivery system performance.

While the BD SCF™ PremiumCoat® 1mlL Plunger Stopper offers new levels of product performance, processability and manufacturability, pharma partners can choose that performance with confidence because of the proven track record of the PremiumCoat® rubber formulation and ETFE film coating.

**PremiumCoat is a registered trademark of Aptar Pharma.*
*** When compared with an identical system combined with BD SCF™ FluroTec®∞ plunger stopper.*
∞FluroTec is a registered trademark of West Pharmaceutical Services, Inc.
+ Glide force and glide force variability was tested with BD Neopak™ Glass Prefillable Syringes and BD SCF™ PremiumCoat® plunger stopper system.
¥ Mean value, gliding test performed at nominal design space, in BD Neopak™ Glass Prefillable Syringe 1mlL 27G filled with water for injection. Test after ageing.

ABOUT THE COMPANY

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

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ABOUT THE AUTHOR

Victoria Meyer has worked at BD for more than 14 years across several business units in various commercial roles including sales, sales operations and regional marketing. Mrs Meyer is currently the Senior Global Strategic Marketing Manager, responsible for leading 1 mL product platforms across the BD Biologics portfolio. In this role, she closely partners with Research & Development and other cross-functional teams to define, develop and deliver programmes, data sets and system solutions to pharmaceutical customers to help support combination product development. Mrs Meyer earned her Master's degree in Business Administration from Columbia Business School (NY, US) and holds an undergraduate degree in economics from the College of the Holy Cross (MA, US).

THE DIFFERENCE OF ONE DRUG DELIVERED

WITH A GLOBAL LEADER IN PREFILLABLE DELIVERY SYSTEMS. BD partners closely with leading pharmaceutical companies to support their success from drug development to launch and beyond. With a broad portfolio of innovative drug delivery systems, a global perspective and regulatory insights, a BD Medical–Pharmaceutical Systems team can partner with you to match the optimal solutions to your product. In addition to prefillable syringes, our technologies include self-injection systems, safety and shielding solutions—which we can customize and develop to meet your precise technical requirements and the demands of your business. You can also count on our depth of regulatory knowledge, product development, medical expertise and responsive support. Discover the confidence of working with the right partner. **Discover the difference of BD.**

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EVOLVING ANALYTICAL METHODS: ADVANCES IN MOLECULE CHARACTERISATION

In this article, Eliza Lee, Lead Scientist at Samsung Biologics, discusses some of the modern analytical techniques available for the characterisation of modern biologics, and how CDMOs equipped with these techniques are able to support pharmaceutical development.

Comprehensive analytical assessments of structure and function are essential in order to compliantly bring a molecule to market. With recent technological advances, it is possible to characterise molecules and their interactions more thoroughly than ever before. Moreover, these robust analytical methods are often required by regulatory bodies as part of a successful filing for commercial manufacturing. It is therefore essential for CDMOs to remain at the forefront of analytical technologies (Figure 1).

> "Executing these finicky assessments accurately can prove challenging for even the most experienced teams. Fortunately, advances in the design and development of commercially available analytical products and kits have enabled highly accurate analyses with rapid run times."

Researchers and developers are under constant pressure to deliver results from increasingly thorough analytical assessments and analyses during drug development. Characterising the structure and activity of today's more complicated biotherapeutic molecules requires highly sensitive informatics systems and analytical technologies. To meet this demand for insightful and high-fidelity data, researchers and developers must use numerous advanced analytical technologies to deliver sophisticated assessments in the most effective and cost-efficient way.

Figure 1: It is key for CDMOs to be able to carry out the robust analyses required by regulators to help pharma partners successfully see their products to market.

UNDERSTANDING THE MOLECULE – BEGIN WITH ACTIVITY AND FUNCTION

Assessment of molecular function is necessary for determining whether the desired cellular or immune responses are likely to be stimulated *in vivo*. Therefore, functional assays play an essential role in understanding a molecule's potency.

The assays used to analyse molecular function must reflect cellular and immune system responses, which may involve complex, sophisticated feedback-controlled interactions and reactions. As such, executing these finicky assessments accurately can prove challenging for even the most experienced teams. Fortunately, advances in the design and development of commercially available analytical products and kits have enabled highly accurate analyses with rapid run times.

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ELISA – How Potent is the Molecule?

Best practice for researchers during early-phase development is to use binding assays, such as enzyme-linked immunosorbent assays (ELISAs), also known as enzyme immunoassays (EIAs), to examine the potency of their biological molecule. This is frequently the preferred initial assay when starting biomolecular analysis.[1]

The ELISA is a plate-based technique designed to detect and quantify soluble substances that are used to elucidate interactions between highly specific antibodies and antigens indirectly. The assay facilitates conditions where the interaction of interest immobilises the participating molecules onto the wells of a microplate. After washing and removing unbound components, a substrate is added to the microplate wells, which reacts with reporter enzymes linked to antibodies. This reaction produces a quantitative signal which is proportional to the dose-dependent interaction.

The use of an ELISA to determine potency has many benefits, including high specificity, sensitivity and efficiency, as well as a simple procedure. Another advantage is the shorter timelines required for development and qualification, which can help to accelerate investigational new drug (IND) filing times. However, depending on the mode of action (MoA) of the molecule, some projects may necessitate additional cell-based assays.

Cell-based Assays – What Does the Molecule do to Cell Systems?

Antigen-specific ELISAs allow for analysis of interactions under highly controlled conditions but may not accurately represent interactions *in vivo*. Molecules that have an MoA that can affect the functioning of entire systems within a cell may require cell-based assays to suitably assess their impact.

There are many cell-based assays that can be deployed. Assessment of cell viability (by determining the ratio of live and dead cells) and cell proliferation (by examining how the molecule impacts cell division over time) are two common examples. Other key cell-based assays for analysing molecule activity include cell signalling, cytotoxicity and cell apoptosis.

Cell-based assays can also be used to measure the effect of anticancer drugs. Depending on the type of analysis used, the results of this assay could act to support technical transfer as well as support chemistry, manufacturing and controls (CMC) development.[2]

UNDERSTANDING THE MOLECULE – DETERMINE THE SAFETY PROFILE

Analytical tools are essential for ascertaining whether a molecule, or other component present within the finished biopharmaceutical, is safe for use. Biological and chemical contaminants must be removed, or confirmed to be present only at a level that will not affect the patient. Without these assessments, untested drugs could cause toxicity, carcinogenic reactions, immunogenic reactions or other adverse events.

PCR: Have the Biological Contaminants Been Removed?

Polymerase chain reaction (PCR) assays are an effective and efficient method of making many copies, or "amplifying", small segments of DNA.[3] As high concentrations of DNA are not abundant in biological systems, using DNA as a substrate in analytical assays has previously been nearly impossible. With the advent of PCR in 1993, low concentrations of DNA can be amplified to levels suitable for use in *in vitro* assay analyses (Figure 2). Laboratory and clinical techniques, including diagnosis of genetic disorders, fingerprinting DNA and detection of bacteria or viruses, are now all supported by PCR.

Figure 2: PCR techniques enable DNA concentrations to be amplified to suitable levels for analysis.

> "The actives and compounds in a biologic formulation are likely to have contact with a broad range of materials during manufacture."

Quantitative PCR can be used to amplify specific segments of contaminant DNA that may be present at specific stages of the molecule manufacturing process, such as residual host cell DNA (HCD). The reaction is run over a specific timeframe, after which the amount of amplified DNA can be determined, which is proportional to the amount of contaminant present. Both the WHO and US FDA have stringent guidelines for the concentration of acceptable HCD.

Reverse-transcriptase PCR (RT-PCR) is commonly used to identify the presence of viruses. Some viruses carry their genetic information in the form of RNA rather than DNA, meaning conventional quantitative PCR cannot be used to detect their presence. Instead, RT-PCR, which includes a step where RNA is converted to DNA by the enzyme reverse transcriptase, is necessary. Viral clearance analysis is required to ensure that process purification steps have removed potentially contaminating viruses that could be introduced during manufacturing or from raw materials.

Analysing the Presence of Leachables and Extractables: Have Chemical Contaminants Been Removed?

Most biopharmaceuticals are in liquid form throughout the manufacturing process, and remain that way until they are aseptically filled and finished into primary containers for parenteral delivery. As a result, the actives and compounds in a biologic formulation are likely to have contact with a broad range of materials during manufacture.

All materials and surfaces that have been in contact with the formulation must be analysed to determine if any interactions have occurred. Some extractable and leachable compounds can impact the quality of therapeutic biological proteins by altering their physicochemical properties. Their presence in the formulation could also have the potential to cause toxic, carcinogenic or immunogenic effects in patients.

Figure 3: The Samsung Biologics site in Incheon, Republic of Korea, includes all the facilities necessary to support pharma using robust platform methods and analytical technology.

Researchers must seek a full and comprehensive understanding of the presence and possible effects of all extractables and leachables in the final formulation. Without achieving this early in development, stability and contamination risks could severely disrupt the drug development and manufacturing programme.

Capillary Electrophoresis: What is the Size and Charge of the Molecule?

In the development and manufacturing of many biological molecules, it is important to determine the molecule's stability and identify physiochemical modifications. Previously, techniques such as sodium dodecyl sulphate–polyacrylamide gel electrophoresis (SDS-PAGE) and isoelectric focusing (IEF) were used to assess size variation (associated with stability) and charge variation (associated with physiochemical modifications) respectively. These methods are time-consuming and labour intensive.

Over the past decade, more accurate and cost-effective capillary electrophoresis (CE) methods have replaced SDS-PAGE and IEF. These include capillary electrophoresis SDS (CE-SDS) and capillary IEF (cIEF), both of which are capable of producing more robust and reproducible results compared with their predecessors.

NOVEL ANALYTICS: HOW CAN WE ANALYSE NOVEL MOLECULES?

Poorly characterised complex molecules, such as fusion proteins, recombinant proteins and multi-specific antibodies, pose novel analytical challenges. Evaluating critical quality attributes (CQAs) is particularly difficult for complex molecules. Their analysis therefore necessitates the use of novel techniques.

Better characterisation of novel molecules can be achieved by optimising commonly applied analytics such as CE methods and high-performance liquid chromatography (HPLC). Careful optimisation of run conditions can ensure reproducibility and robustness in methods determining molecule characteristics.

Optimisation is also required in methods for quantifying surfactants, such as polysorbate 80 (PS80). Although these techniques have improved in recent times, driven in part by the interest regulators have taken in providing more formulation characterisation information in their guidance, optimisation is needed to raise their robustness and reproducibility.

Glycan analysis is another important technique that is now frequently required for providing information on more complex proteins, such as *in vivo* half-life, effector function and immunogenicity. Glycosylation can be challenging to study because it occurs heterogeneously; branching and single sites with multiple glycan structures present are commonly observed. Although quantitative glycosylation can provide reproducible

> "The importance of operational optimisation in analytical method development is increasing in parallel with the advancement of analytical technologies."

and robust data, it is labour intensive and time-consuming. On the other hand, high-throughput glycan analysis is much faster, but may only provide qualitative results. It is best practice to choose which glycolysis analysis to use based on data needs. In particular, considerations should be given to how the target molecule's protein activity will be affected by glycosylation at each stage of the process.

THE IMPACT OF OPTIMISING ANALYSIS

CDMOs, equipped with robust platform methods, are now able to assess product quality more effectively than ever before (Figure 3). The importance of operational optimisation in analytical method development is increasing in parallel with the advancement of analytical technologies. Moreover, this approach facilitates timely, cost-effective discovery, particularly when high-throughput analysis is integrated into analytical platform methods. As a result, biopharmaceutical drugs can move quickly through clinical trials to patients.

ABOUT THE COMPANY

Samsung Biologics (KRX: 207940.KS) is a fully integrated CDMO offering state-of-the-art contract development, manufacturing and laboratory testing services. With proven regulatory approvals, the largest capacity and the fastest throughput, Samsung Biologics is an award-winning partner of choice and is uniquely able to support the development and manufacturing of biologic products at every stage of the process while meeting the evolving needs of biopharmaceutical companies worldwide.

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Eliza Lee is a Lead Scientist at Samsung Biologics, a leading CDMO. With over 14 years of extensive experience in the fields of R&D and biopharma, Ms Lee plays a significant role in leading the company's analytical programme management, from method development to release and stability, as well as extended characterisation. Ms Lee acquired her Bachelor of Bioengineering degree from the University of California, Berkeley (US).

MITSUBISHI GAS CHEMICAL

PHOTO-STABILITY TESTS OF EPINEPHRINE

In this article, Yoshiko Sakuma, Researcher, and Tomohiro Suzuki, Associate General Manager, both at Mitsubishi Gas Chemical, provide an overview of OXYCAPT multilayer vial and syringe, with a particular emphasis on the advantages of OXYCAPT as a container for adrenaline, as demonstrated by recent studies conducted by MGC.

Mitsubishi Gas Chemical (MGC) is a leading company in the field of oxygen barrier and absorbing polymer technologies. Building on these technologies and experiences, MGC launched OXYCAPT™, a new multilayer plastic vial and syringe (Figure 1), in 2019. The material consists of three layers – the drug contact layer and the outer layer are made of cyclo-olefin polymer (COP), and the oxygen barrier layer is made of MGC's novel polyester (Figure 2). OXYCAPT offers many advantageous properties, including:

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

MGC has conducted a series of studies to confirm these excellent properties. This article will provide both a more detailed overview of OXYCAPT's properties and insight into a study focusing on the photostability of adrenaline in OXYCAPT, Type 1 glass and COP.

Figure 1: The OXYCAPT multilayer plastic vial and syringe.

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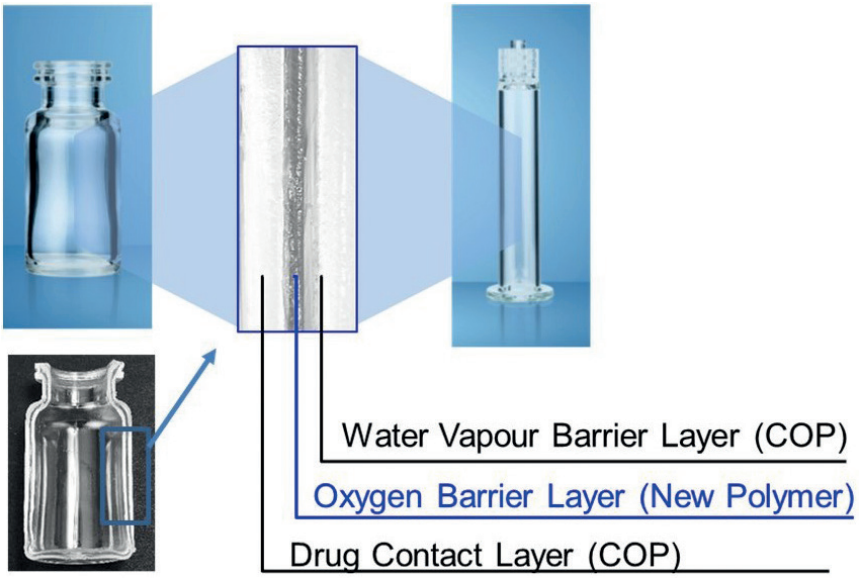


Figure 2: Multilayer structure of OXYCAPT.

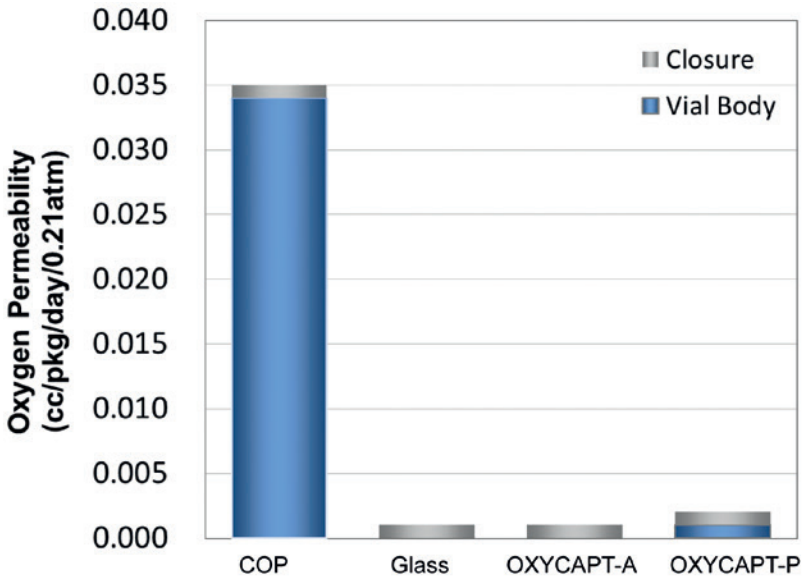


Figure 3: Oxygen permeability comparison of a typical COP, glass, OXYCAPT-A and OXYCAPT-P.

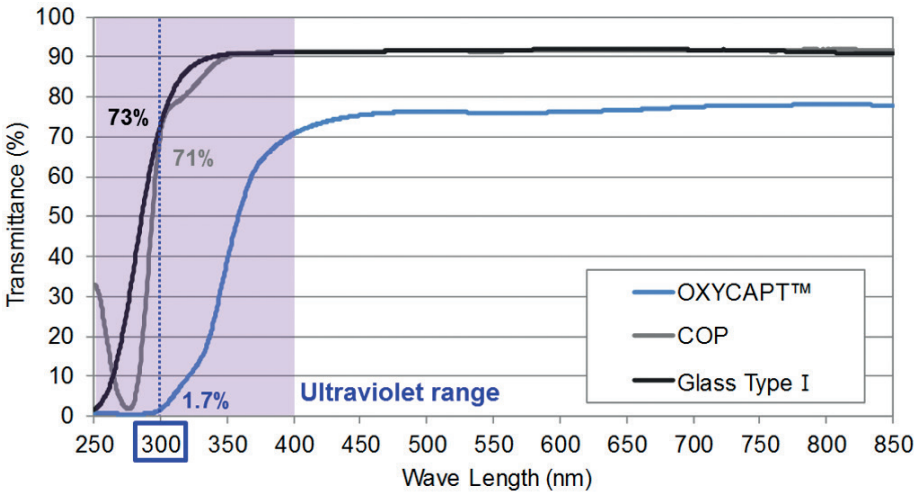


Figure 4: UV light transmittance comparison of a typical COP, Type 1 glass and OXYCAPT.

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

PROPERTIES OF OXYCAPT VIAL & SYRINGE

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

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

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

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

from COP, which is well known for being an extremely pure polymer, and with a better extractables profile than Type 1 glass. Lower levels of inorganic extractables are known to contribute to better pH stability in drug products.

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

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

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

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

Table 1: MGC's OXYCAPT product portfolio.

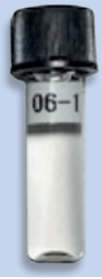
Packages	Glass	COP	OXYCAPT-P	Control (not stored)
Vial				
Syringe				

Table 2: Visual inspection of adrenaline.

OXCAPT'S SUITABILITY FOR ADRENALINE

The primary target market for OXCAPT is the therapeutic application of biologics. As mentioned in ICH Q5C (Stability of Biotechnological/Biological Products), oxidation is one of the causes of protein instability. As such, the oxygen and UV barrier properties of OXYCAPT will contribute to the stability of biologics stored within. Additionally, MGC believes that OXYCAPT is well suited to emergency adrenaline, which is well known as an oxygen-sensitive drug, because OXYCAPT combines both an oxygen barrier equivalent to Type 1 glass and the breakage resistance of a polymer. Furthermore, some drug developers have recently started evaluating the OXYCAPT vials for their gene and cell therapies; the RTU vial is sterilised by gamma radiation, making it ideal for protein-based drugs.

> "MGC believes that OXYCAPT is well suited to emergency adrenaline, which is well known as an oxygen-sensitive drug, because OXYCAPT combines both an oxygen barrier equivalent to Type 1 glass and the breakage resistance of a polymer."

In order to verify the suitability of OXYCAPT for this purpose, photostability tests on commercially available adrenaline drug products were carried out using OXYCAPT, Type 1 glass and COP containers. In this study, OXYCAPT-P, Type 1 glass and COP vials and syringes were filled with 1 mL preparations of 0.1 mg/mL adrenaline under nitrogen atmosphere. The preparations were stored under light at 4,000 lux/hour at 40°C for 12.5 days, resulting in a total radiation dose of 1.2 million lux.

After exposure to radiation, the investigation examined colour change and residual adrenaline in the preparations. The colour change was evaluated by visual inspection and the residual adrenaline was evaluated by ultra performance liquid chromatography (UPLC). The impurities generated by oxidation of epinephrine were identified by liquid chromatograph time-of-flight mass spectrometry (LC-TOF-MS). Commercially

"In order to verify the suitability of OXYCAPT for this purpose, photostability tests on commercially available adrenaline drug products were carried out using OXYCAPT, Type 1 glass and COP containers."

available adrenaline that had not been exposed to light was used as a control.

Although no colour change was observed in OXYCAPT™ and Type 1 glass containers, browning was observed in the adrenaline contained in COP. As the oxygen and ultraviolet barrier properties of COP containers is known to be very poor, it can be assumed that the UPLC in COP deteriorated as a result of oxygen and UV light (Table 2).

UPLC analysis showed that no significant difference in adrenaline concentration was observed between each container compared with the control and that the rate of residual adrenaline was 98–102% (Figure 5). Although the colour of the adrenaline in COP containers turned brown, no significant difference in the quantity of residual epinephrine was observed by UPLC analysis. Therefore, it can be assumed that the adrenaline in COP containers turned brown due to slight oxidation.

Additionally, some peaks representing impurities were found on the chromatographs of all the containers that were not detected in that of the control (Figures 6 & 7). The area of the COP vial's peaks was the largest and that of Type 1 glass the smallest (Table 3). By LC-TOF-MS analysis, the impurities were identified as adrenaline sulfate, oxo-adrenochrome, adrenochrome and leuko-oxo-adrenochrome. Furthermore, a high level of methyl-substituted adrenaline-o-quinone was detected.

"These latest results have contributed to the ongoing studies verifying OXYCAPT's superior properties for containing biologics."

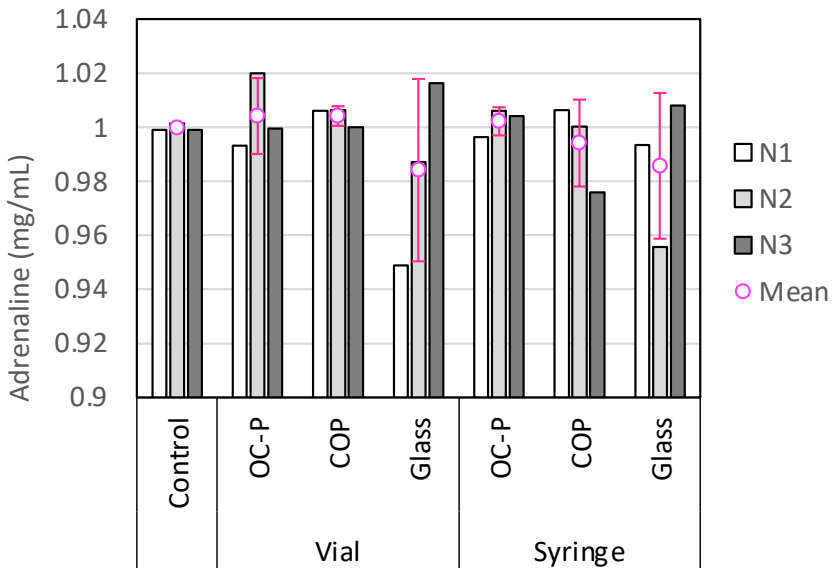


Figure 5: Concentration of adrenaline.

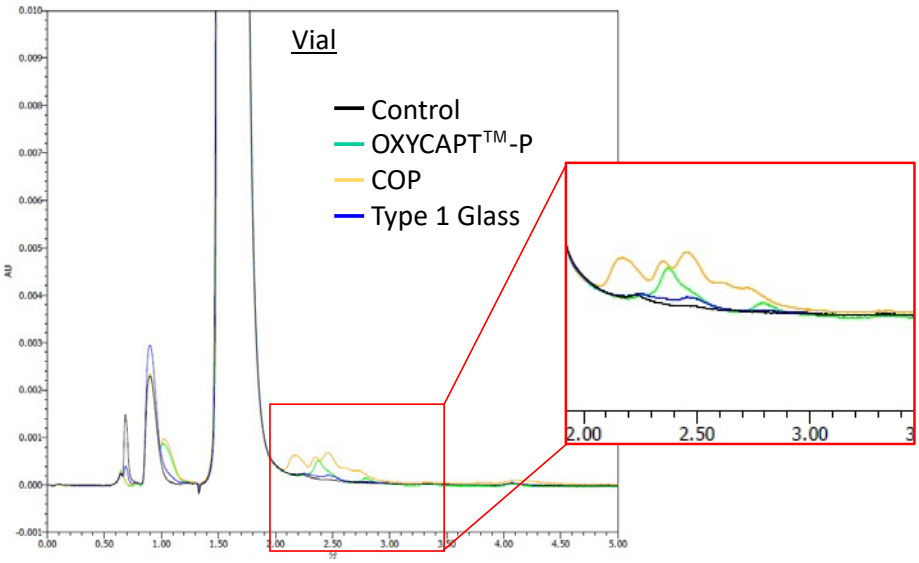


Figure 6: Impurities recognised on a chromatogram of vials.

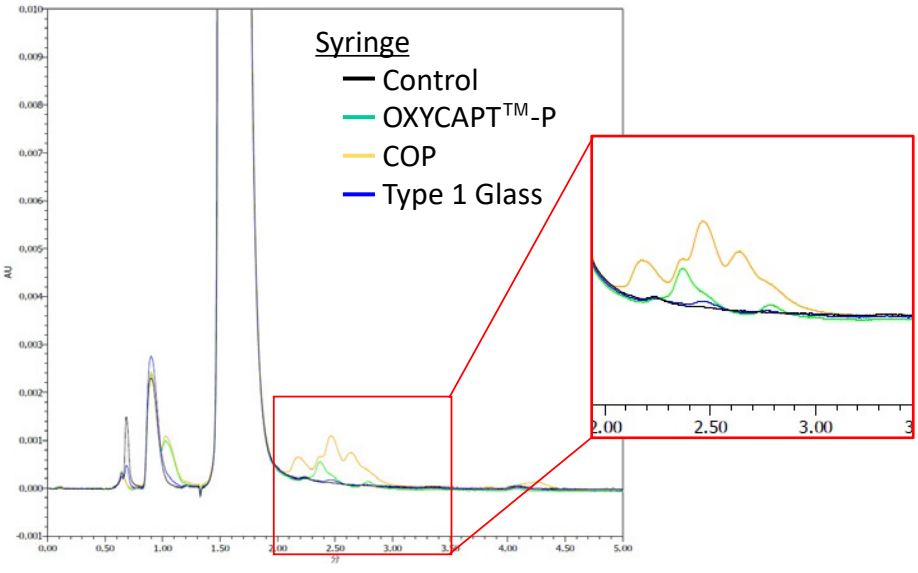


Figure 7: Impurities recognised on a chromatogram of syringes.

CONCLUSION

These latest results have contributed to the ongoing studies verifying OXYCAPT's superior properties for containing biologics, and adrenaline in particular. 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 light barrier. MGC believes that OXYCAPT offers a multitude of benefits to the rapidly growing field of biologics and gene/cell therapies.

ABOUT THE COMPANY

Mitsubishi Gas Chemical (MGC) 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 OXYCAPT plastic vial and syringe as an alternative to glass containers.

Container	Material	Ratio of impurity's peak area (%)[1]
Vial	OXYCAPT-P	0.15
	COP	0.43
	Glass	cannot calculate[2]
Syringe	OXYCAPT-P	0.16
	COP	1.38
	Glass	cannot calculate[2]

[1] N = 3, RT = 2–3 min,[2] Peak was too small to calculate

Table 3: Impurity ratios of adrenaline preparations after exposure to light.

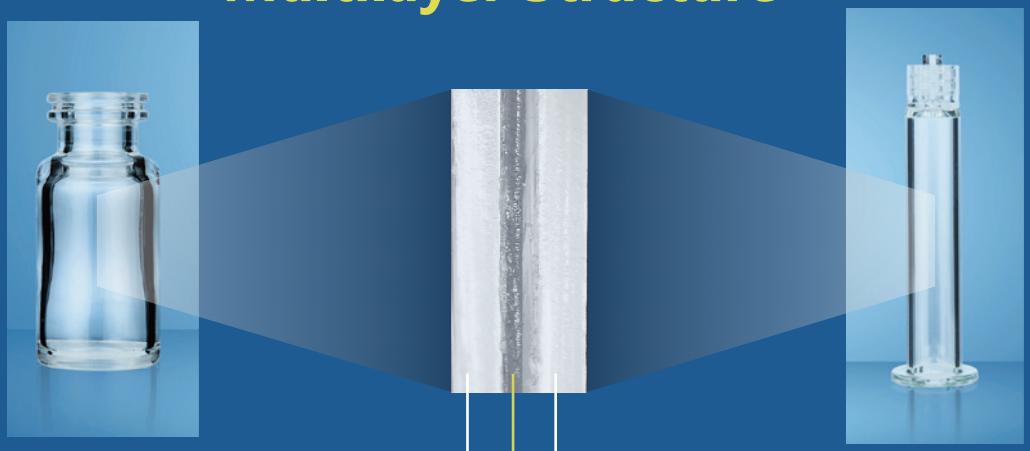
ABOUT THE AUTHORS

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

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

OXYCAPT™ Plastic Vial & Syringe

Multilayer Structure



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

2, 6, 10, 20mL Vial

Nest & Tub for Vial

1, 2.25mL Syringe

Nest & Tub for Syringe

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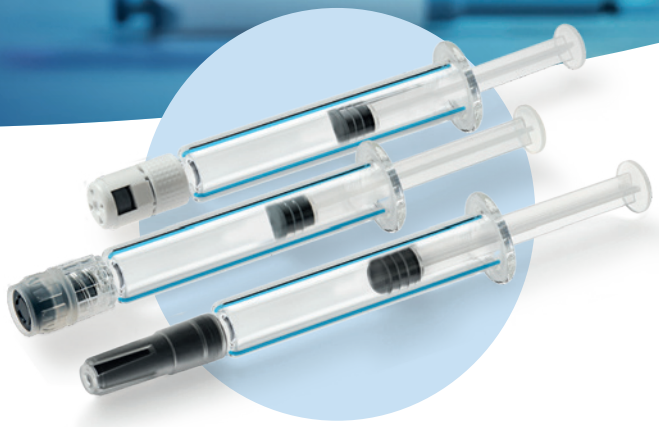
Alba®

A breakthrough solution for your gamechanger biologics



As pharmaceutical partners embrace the potential of biologics, we have developed our proven syringe platform, Alba®, to enable the optimisation of your opportunity.

We know your challenges, including the increased viscosity and stability of biologics and the relative injection forces required for effective delivery. And we have responded. **The Alba® syringe is now available also in a 2.25 ml format**, meeting the requirements of high-value and large volume biologics. Combining our cross-linked coating technology with dimensional, geometrical accuracy, and enhanced glide capability; this platform significantly reduces the release of sub-visible particles and inorganic extractables.

Easily integrated into automatic drug delivery devices, such as spring-based autoinjectors, and optimized for smooth self-administration, Alba® meets the needs of our pharma companies and their end users in equal measure.

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